EUROPEAN RESPIRATORY journal

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Task force report

European Respiratory Society Guideline on various aspects of quality in lung cancer care

Torsten Gerriet Blum, Rebecca L. Morgan, Valérie Durieux, Joanna Chorostowska-Wynimko, David R. Baldwin, Jeanette Boyd, Corinne Faivre-Finn, Françoise Galateau-Salle, Fernando Gamarra, Bogdan Grigoriu, Georgia Hardavella, Michael Hauptmann, Erik Jakobsen, Dragana Jovanovic, Paul Knaut, Gilbert Massard, John McPhelim, Anne-Pascale Meert, Robert Milroy, Riccardo Muhr, Luciano Mutti, Marianne Paesmans, Pippa Powell, Paul Martin Putora, Janette Rawlinson, Anna L Rich, David Rigau, Dirk de Ruysscher, Jean-Paul Sculier, Arnaud Schepereel, Dragan Subotic, Paul Van Schil, Thomy Tonia, Clare Williams, Thierry Berghmans

Please cite this article as: Blum TG, Morgan RL, Durieux Vérie, *et al*. European Respiratory Society Guideline on various aspects of quality in lung cancer care. *Eur Respir J* 2022; in press (https://doi.org/10.1183/13993003.03201-2021).

European Respiratory Journal

European Respiratory Society Guideline on various aspects of quality in lung cancer care

Torsten Gerriet Blum[1], Rebecca L. Morgan[2], Valérie Durieux[3], Joanna Chorostowska-Wynimko[4], David R Baldwin[5], Jeanette Boyd[6], Corinne Faivre-Finn[7], Françoise Galateau-Salle[8], Fernando Gamarra[9], Bogdan Grigoriu[10], Georgia Hardavella[11], Michael Hauptmann[12], Erik Jakobsen[13], Dragana Jovanovic[14], Paul Knaut[1], Gilbert Massard[15], John McPhelim[16], Anne-Pascale Meert[10], Robert Milroy[17], Riccardo Muhr[1], Luciano Mutti[18], Marianne Paesmans[19], Pippa Powell[6], Paul Martin Putora[20], Janette Rawlinson[21], Anna L Rich[5], David Rigau[22], Dirk de Ruysscher[23], Jean-Paul Sculier[10], Arnaud Schepereel[24], Dragan Subotic[25], Paul Van Schil[26], Thomy Tonia[27] , Clare Williams[6] and Thierry Berghmans[28]

1. Department of Pneumology, Lungenklinik Heckeshorn, HELIOS Klinikum Emil von Behring, Berlin, Germany

2. Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Canada

3. Bibliothèque des Sciences de la Santé, Université Libre de Bruxelles (ULB), Brussels, Belgium

4. Department of Genetics and Clinical Immunology, National Institute of Tuberculosis and Lung Diseases, Warsaw, Poland

5. Department of Respiratory Medicine, Nottingham University Hospitals, City campus, Nottingham, United Kingdom

6. European Lung Foundation, Sheffield, United Kingdom

7. Division of Cancer Sciences, University of Manchester and The Christie NHS Foundation Trust, United Kingdom

8. Department of Biopathology, MESOPATH/MESOBANK Cancer Center Leon Berard, Lyon, France

9. Sektion Pneumologie, Klinikum St. Elisabeth, Straubing, Germany

10. Intensive Care and Oncological Emergencies & Thoracic Oncology, Institut Jules Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles (ULB), Brussels, Belgium

11. Department of Respiratory Medicine, King's College Hospital London, UK, and Department of Respiratory Medicine & Allergy, King's College London, United Kingdom

12. Institute of Biostatistics and Registry Research, Brandenburg Medical School Theodor Fontane and Faculty of Health Sciences Brandenburg, Neuruppin, Germany

13. Department of Thoracic Surgery, Odense University Hospital, Odense Denmark

14. Internal Medicine Clinic „Akta Medica", Belgrade, Serbia

15. Faculty of Science, Technology and Medicine, University of Luxembourg and Department of thoracic surgery, Hôpitaux Robert Schuman, Luxembourg

16. Lung Cancer Nurse Specialist, Hairmyres Hospital, NHS lanarkshire, United Kingdom

17. Scottish Lung Cancer Forum, Glasgow Royal Infirmary, Glasgow, Scotland

18. Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy, SHRO/Temple University, Philadelphia, USA

19. Data Centre, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium
20. Departments of Radiation Oncology, Kantonsspital St. Gallen, St. Gallen, and University of Bern, Bern, Switzerland
21. British Thoracic Oncology Group (advocate steering committee member), NCRI Lung subGroup (consumer), and European Lung Foundation LC Patient advisory group, Sandwell, UK
22. Iberoamerican Cochrane Center, Barcelona, Spain
23. Maastricht University Medical Center, Department of Radiation Oncology (Maastro Clinic), GROW School for Oncology and Developmental Biology, Maastricht, The Netherlands; Erasmus Medical Center, Department of Radiation Oncology, Rotterdam, The Netherlands
24. Pulmonary and Thoracic Oncology, Univ. Lille, Inserm, CHU Lille, Lille, France
25. Clinic for Thoracic Surgery, University Hospital Zurich, Zurich, Switzerland
26. Department of Thoracic and Vascular Surgery, Antwerp University Hospital, Edegem (Antwerp), Belgium
27. Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland
28. Thoracic Oncology, Institut Jules Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles (ULB), Brussels, Belgium

Corresponding author:
Thierry Berghmans
Institut Jules Bordet
Rue Héger-Bordet, 1
B-1000 Brussels
Tél: +3225413111
e-mail: thierry.berghmans@bordet.be

Abstract

This ERS guideline is dedicated to the provision of good quality recommendations in lung cancer care. All the clinical recommendations contained were based on a comprehensive systematic review and evidence syntheses based on eight PICO questions. The evidence was appraised in compliance with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. Evidence profiles and the GRADE Evidence to Decision frameworks were used to summarize results and to make the decision-making process transparent. A multi-disciplinary task force panel of lung cancer experts formulated and consented the clinical recommendations following thorough discussions of the systematic review results.

In particular, we have made recommendations relating to the following quality improvement measures deemed applicable to routine lung cancer care: 1) avoidance of delay in the diagnostic and therapeutic period, 2) the integration of multi-disciplinary teams and multi-disciplinary consultations, 3) the implementation of and adherence to lung cancer guidelines, 4) the benefit of higher institutional/individual volume and advanced specialisation in lung cancer surgery and other procedures, 5) the need for pathological confirmation of lesions in patients with pulmonary lesions and suspected lung cancer, histological subtyping and the molecular characterisation for actionable targets or response to treatment of confirmed lung cancers, 6) the added value of early integration of palliative care teams or specialists, 7) the advantage of integrating specific quality improvement measures, and 8) the benefit of using patient decision tools.

These recommendations should be reconsidered and updated, as appropriate, as new evidence becomes available.

Introduction

In 2020, lung cancer ranked first among all new cancer diagnoses worldwide and third within the European Union while remaining on top of cancer death and health care cost statistics [1-4]. Beyond figures, lung cancer is associated with a high rate of comorbidities and imposes an enormous burden on patients as well as their caregivers and professionals [5]. A previous ERS task force provided a first comprehensive snapshot of the management of lung cancer care throughout Europe. While substantial variation in terms of available infrastructure, implemented pathways and related outcomes was surveyed, underlying evidence on quality of lung cancer care appeared limited regarding evidence level, scope and comparability according to the concomittant narrative review [6]. Subsequently, an ERS statement paper on harmonised standards for lung cancer registration and lung cancer services in Europe was published [7].

Scope and objectives of the guideline

The objectives of our guideline are to present a robust and comprehensive evidence base on relevant quality-defining aspects of lung cancer care and to present evidence-based recommendations promoting quality improvement. This document should set an initial standard for provision of high-quality recommendations and concurrently a starting point for future quality improvement research in lung cancer care. Future periodical updates and adaptions will ensure that all relevant indexed literature in this field will be detected and appraised according to high methodological standards [8-10]

Specialists in lung cancer care who manage adult lung cancer patients are the target audience of this guideline. General internists, primary care physicians, emergency medicine clinicians, (lung) cancer nurses and other allied healthcare professionals, as well as policy makers may also benefit from this guideline. The guidelines published by the European Respiratory Society (ERS) incorporate data obtained from a comprehensive and systematic literature review of the most recent studies available at the time. Health professionals are encouraged to take the guidelines into account in their clinical practice. However, the recommendations issued by this guideline may not be appropriate for use in all situations. It is the individual responsibility of health professionals to consult other sources of relevant information, to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and the patient's caregiver where appropriate and/or necessary, and to verify rules and regulations applicable to drugs and devices at the time of prescription.

Methods

Guideline development

This guideline was developed following the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) approach [8-10].

A multidisciplinary task force panel was constituted by the two task force co-chairs (T. Berghmans, T. Blum) with representatives from respiratory medicine, medical oncology, thoracic surgery, radiotherapy, pathology, radiology/nuclear medicine, palliative care, and quality management. Further, a lung cancer nurses, a statistician, two librarians, and representatives of the European Lung Foundation (ELF) and their Patient Advisory Group were involved together with two ERS methodologists (T. Tonia and D. Rigau). The ERS lead methodologist (T. Tonia) ensured that all the methodological requirements were met, with assistance from the other methodologist. J. Chorostowska-Wynimko and R. Morgan were nominated as third task force co-chair and external co-lead methodologist in May 2020 to facilitate the finalization phase of this task force.

Panel meetings were held face-to-face and online via web conferences. A total of eight clinical questions were generated using the PICO format (Patients, Intervention, Comparison, Outcomes) and systematic reviews were conducted to answer these specific questions. The cut-off date for literature searches was 5th January 2021.

Disclosure of potential conflicts of interest

All panel members disclosed their conflicts of interest, according to ERS policies. None of the co-chairs or other panel members declared any conflicts of interest related to this guideline.

Systematic review

One experienced librarian from Université Libre de Bruxelles, Brussels (Belgium) designed and ran search strategies using MeSH terms and keywords for each clinical question, in collaboration with the methodology working group (T. Berghmans, T. Blum, D. Rigau, T. Tonia). The search focused on identifying randomized controlled trials (RCTs) and observational studies within the scope of the eight PICO questions. For inclusion, studies needed to provide lung cancer-specific data in lung cancer or mixed patient cohorts allowing comparison between intervention and control groups to establish the efficacy and safety of the intervention being studied. Eight separate searches in Medline including update searches between April 2016 and January 2021 retrieved a total of 6,281 articles; after removal of duplicates and exclusion of citations that did not meet the inclusion criteria, a total of 244 references were included in the initial evidence summaries. Data were extracted from RCTs and observational studies as described in the online supplement. Observational studies were considered for inclusion in the evidence tables if RCTs were not available or of lower certainty of evidence. Meta-analyses on outcomes of interest were performed only if pooling of study patient cohorts was clinically meaningful. For aggregation methods, a fixed-effects method was used in case of absence of detection of heterogeneity of studies. Otherwise, random-effects models were applied.

If meta-analyses were not meaningful, the effect strength of studies were considered individually based on ***our own individual four-stage evaluation scheme***.

Assessment of the level of evidence and degree of recommendations

The panel selected twelve outcomes of interest for each of the eight PICO question *a priori*. The importance of outcomes was rated on a 9-point scale (ranging from "not important" to "critical" for decision-making) and only outcomes rated as important or critical for clinical decision making were included in the GRADE evidence profiles. We followed the GRADE approach to assess the confidence in the evidence (quality) and the degree of recommendations. The GRADE methodology was used to assess the body of evidence at the outcome level rather than the study level with risk of bias assessment at study level performed as described by Cochrane for RCTs [11] and GRADE for observational studies [12]. Some outcomes were addressed using a narrative format due to the lack of comparable studies.

The certainty of evidence was rated on 4 levels (high, moderate, low or very low) based on the GRADE methodology [13]. The overall quality of evidence was then rated as the lowest of the critical outcomes, except where the evidence for all of the critical outcomes favoured the same alternative and where the quality of evidence for outcomes that are considered key to clinical decision took precedence [14]. GRADE evidence profiles were generated for each clinical question, followed by GRADE evidence to decisions frameworks integrating evidence assessments as well as the balance of benefits and harms, values and preferences, resource use, health equity, acceptability, and feasibility as basis for the recommendations. Recommendations are reported as strong or conditional after considering the quality of the evidence, the balance of desirable and undesirable consequences of compared management options, the assumptions

about the relative importance of outcomes, the implications for resource use, and the acceptability and feasibility of implementation. Of note, GRADE methodology allows making strong recommendations despite low or very low quality of evidence in certain defined constellations, so-called ***paradigmatic situations***. Based on these formats, the panel formulated the clinical recommendations and decided on their strength by consensus, or, if required, by voting. Following the GRADE approach, strong recommendations are worded as "we recommend", while conditional recommendations are worded as "we suggest" [15].

Online supplement A provides additional comprehensive information on 1) details of methodology (including own individual four-stage evaluation scheme and paradigmatic situations according to GRADE) as well as 2) search questions based on PICO format, 3) rating of outcomes, 4) Medline search strategies, 5) eligibility criteria for study inclusion, and 6) PRISMA flow charts for all eight PICO questions.

Recommendations

General remarks

For all eight PICO questions, our systematic literature searches retrieved very heterogeneous, sometimes limited pieces of evidence. As expected within the scope of this quality of care research, the evidence was mainly based on observational studies while RCTs were rare. To overcome heterogeneity and to allow meaningful aggregation of studies, we formed subgroups within PICO questions narrowing patient populations and/or interventions.

Online supplement B presents detailed insights into the full GRADE outcome-based evidence rating and the evidence to recommendations-process. This includes for each of the eight PICO questions 1) a general summary of the evidence, 2) an outcome-based rating of the quality of evidence and GRADE evidence profiles in specific subgroups, and 3) GRADE evidence to decision (EtD) frameworks.

The recommendation section of this main document provides the essence of this complex and extensive GRADE process. **Table 1** offers an overview of the underlying evidence and the GRADE-based evidence rating per outcomes sorted according to the eight PICO questions and their respective subgroups. **Table 2** summarises the 13 formal, graded recommendations made within the guideline as well as implementation considerations and research needs which were all consented unanimously among the task force panellists. The following sections include for each of the eight PICO questions a discussion of the available evidence as well as the expert and patient representative opinions of this task force panel. These two pillars compile the rationale for our GRADE-based recommendations.

PICO-questions *PICO-subgroups* -outcomes per subgroup	Total number and type of included studies (total number of patients) per outcome	Effect strength (for single studies, meta-analyses, or aggregation based on own individual four-stage evaluation scheme in studies ineligible for meta-analysis) and effect direction per outcome	Quality of evidence per outcome
PICO 1: In patients with lung cancer (or those suspected of having lung cancer), should shorter rather than longer cancer care time intervals be used (e.g. time from diagnosis to treatment)?			
subgroup 1: NSCLC, stage I/II, surgical resection, treatment interval with shorter waiting times (vs. longer waiting times)			
-overall survival	8 OBS (341,915 pts.)	Meta: 7 (244,924 pts.); HR 0.89, 95% CI 0.85-0.94; ➔shorter waiting times	very low ⊕○○○
-30-day mortality	2 OBS (32,006 pts.)	Meta: 2 (32,006 pts.); OR 0.81, 95% CI 0.71-0.93; ➔shorter waiting times	very low ⊕○○○
-90-day mortality	1 OBS (4,984 pts.)	1 (4,984 pts.); OR 0.80, 95% CI 0.62-1.03; ➔shorter waiting times	very low ⊕○○○
-accuracy of staging	4 OBS (33,649 pts.)	S: 1 (27,022 pts.); T: 3 OBS (6,627 pts.); ➔shorter waiting times	very low ⊕○○○
subgroup 2: NSCLC, stage I/II, all treatment modalities, treatment interval with shorter waiting times (vs. longer waiting times)			
-overall survival	8 OBS (670,006 pts.)	Meta: 4 (132,673 pts.); HR 0.73, 95% CI 0.64-0.84; ➔shorter waiting times	very low ⊕○○○
subgroup 3: NSCLC, stage III, all treatment modalities, treatment interval with shorter waiting times (vs. longer waiting times)			
-overall survival	6 OBS (48,693 pts.)	Meta: 4 (44,163 pts.); HR 0.999, 95% CI 0.84-1.18; ➔shorter waiting times	very low ⊕○○○
subgroup 4: NSCLC, stage IV, all treatment modalities, treatment interval with shorter waiting times (vs. longer waiting times)			
-overall survival	5 OBS (37,306 pts.)	Meta: 2 (24,289 pts.); HR 1.14, 95% CI 0.93-1.40; ➔longer waiting times	very low ⊕○○○
subgroup 5: ALK-positive NSCLC, stage IIIB/IV, ALK-TKI, treatment interval with shorter waiting times (vs. longer waiting times)			
-overall survival	1 OBS (442 pts.)	1 (442 pts.); HR 0.49; 95% CI 0.27-0.88; ➔shorter waiting times	very low ⊕○○○
subgroup 6: SCLC, all stages, all treatment modalities, treatment interval with shorter waiting times (vs. longer waiting times)			
-overall survival	2 OBS (67,933 pts.)	L. 2 (67,933 pts.); ➔longer waiting times	very low ⊕○○○
PICO 2: In patients with lung cancer (or those suspected of having lung cancer), should a multi-disciplinary team (MDT) or certain disciplines be involved during lung cancer care rather than no involvement of an MDT or certain disciplines?			
subgroup 1: All lung cancer types, all stages, all treatment modalities, MDT involvement (vs. no MDT involvement)			
-overall survival	11 OBS (43,118 pts.)	Meta: 4 OBS (9,916 pts); HR 0,62, 95% CI 0,58-0,66; ➔MDT involvement	very low ⊕○○○
-accuracy of staging	4 OBS (30,052 pts.)	L: 1 (988 pts.); M: 1 (3,855 pts.); S: 1 (593 pts.); T: 1 (24,616 pts.); ➔MDT involvement	very low ⊕○○○
-pathological confirmation	2 OBS (4,043 pts.)	Meta: 2 (4,043 pts.); OR 2.42, 95%, CI 1.75-3.35; ➔MDT involvement	very low ⊕○○○
-receipt of curative treatment	6 OBS (32,998 pts.)	Meta:4 (7,789 pts.); OR 1.88, 95% CI 1.15-3.05; ➔MDT involvement	very low ⊕○○○
-receipt of any tumour-specific treatment	5 OBS (30,866 pts.)	Meta: 2 (4,669 pts.); OR 2.70, 95% CI 2.35-3.12; ➔MDT involvement	very low ⊕○○○
-quality of life	1 RCT (88 pts.)	T: 1 (88 pts.); ➔MDT involvement	moderate ⊕⊕⊕○
-patient satisfaction	1 RCT (88 pts.)	T: 1 (88 pts.); ➔MDT involvement	moderate ⊕⊕⊕○
subgroup 2: NSCLC, all stages, all treatment modalities, MDT involvement (vs. no MDT involvement)			
-overall survival	3 OBS (144,014 pts.)	Meta: 3 (144,014 pts.); HR 0.76, 95% CI 0.61-0.94; ➔MDT involvement	very low ⊕○○○
-30-day mortality	1 OBS (1,222 pts.)	1 (1,222 pts.); OR 1.23, 95% CI 0.47-3.20; ➔no MDT involvement	very low ⊕○○○
-accuracy of staging	1 OBS (1,222 pts.)	1 (1,222 pts.); OR 3.56, 95% CI 2.49-5.10; ➔MDT involvement	very low ⊕○○○
-receipt of curative treatment	2 OBS (1,356 pts.)	Meta: 2 (1,356 pts.); OR 1.26, 95% CI 1.001-1.59; ➔MDT involvement	very low ⊕○○○
subgroup 3: NSCLC, all stages, surgical resection, MDT involvement (vs. no MDT involvement)			
-overall survival	3 OBS(2,375 pts.)	Meta: 2 (1,555 pts.); HR 0.77, 95% CI 0.50-1.15; ➔MDT involvement	very low ⊕○○○
-30-day mortality	2 OBS (1,060 pts.)	L: 1 (240 pts.); T: 1 (820 pts.); ➔MDT involvement	very low ⊕○○○
-morbidity	1 OBS (820 pts.)	1 (820 pts.); OR 1.0, 95% 0.57-1.77; ➔MDT involvement	very low ⊕○○○
-accuracy of staging	1 OBS (277 pts.)	1 (277 pts.); OR 8.09, 95% CI 4.07-16.08; ➔MDT involvement	very low ⊕○○○
-pathological confirmation	1 OBS (1,278 pts.)	1 (1,278 pts.); OR 1.8, 95% CI 1.55-2.09; ➔MDT involvement	very low ⊕○○○
-receipt of curative treatment	3 OBS (48,033 pts.)	Meta: 2 (1,418 pts.); OR 2.55, 95% CI 1.92-3.40; ➔MDT involvement	very low ⊕○○○
-receipt of any tumour-specific treatment	1 OBS (140 pts.)	1 (140 pts.); OR 8.86, 95% CI 3.75-20.96; ➔MDT involvement	very low ⊕○○○
subgroup 4: NSCLC, stage III/IV, all treatment modalities, MDT involvement (vs. no MDT involvement			
-overall survival	4 OBS (965 pts.)	Meta: 3 (722 pts.); HR 0.75, 95% CI 0.62-0.90; ➔MDT involvement	very low ⊕○○○
-accuracy of staging	2 OBS (352 pts.)	Meta: 2 (352 pts.); OR 2.06, 95% CI 1.37-3.10; ➔MDT involvement	very low ⊕○○○
-receipt of curative treatment	1 OBS (98 pts.)	1 (98 pts.); OR 1.68, 95% CI 0.2-14.33; ➔MDT involvement	very low ⊕○○○
-receipt of any tumour-specific treatment	2 OBS (341 pts.)	Meta: 2 (341 pts.); OR 1.67, 95% CI 1.05-2.66; ➔MDT involvement	very low ⊕○○○
PICO 3: In patients with lung cancer (or those suspected of having lung cancer), should guidelines or standard operating procedures (SOP) for lung cancer care be implemented or adhered to rather than non-implementation of or non-adherence to these guidelines or standard operating procedures?			
subgroup 1: All lung cancer types, all stages, all therapies, guideline implementation (vs. no guideline implementation)			
-overall survival	3 OBS (>38,661 pts.)	M: 1 (38,661 pts.); S: 1 (no figures); T: 1 (no figures); ➔guideline implementation	very low ⊕○○○
-30-day mortality	2 OBS (>38,661 pts.)	L: 2 (>38,661 pts.); ➔guideline implementation	very low ⊕○○○
-accuracy of staging	1 OBS (38,661 pts.)	L: 1 (38,661 pts.); ➔guideline implementation	very low ⊕○○○
-receipt of curative treatment	1 OBS (38,661 pts.)	T: 1 (38,661 pts.); ➔guideline implementation	very low ⊕○○○
-receipt of any tumour-specific treatment	1 OBS (38,661 pts.)	L: 1 (38,661 pts.); ➔guideline implementation	very low ⊕○○○
subgroup 2: NSCLC, all stages, surgical resection with or without neoadjuvant/adjuvant therapies, guideline adherence (vs. no guideline adherence)			

-overall survival	5 OBS (835,464 pts.)	L-T depending on guideline recommendations: 5 (667,861 pts); ➔guideline adherence vs. 1 (single subgroup: 167,603 pts.); HR 1.25, 95%CI 1.09-1.30; ➔CON	very low ⊕○○○
-30-day mortality	2 OBS (1,662 pts.)	L: 1 (916 pts.); T: 1 (746 pts.); ➔guideline adherence	very low ⊕○○○
-morbidity	1 OBS (916 pts.)	1 (916 pts.); OR 0.8, 95% CI 0.4-1.4; ➔guideline adherence	very low ⊕○○○
subgroup 3: All lung cancer, all stages, all treatment modalities, guideline adherence (vs. no guideline adherence)			
-overall survival	2 OBS (43,131 pts.)	L: 2 (43,131 pts.); ➔guideline adherence	very low ⊕○○○
subgroup 4: NSCLC, unresectable stage III, chemo- and/or radiotherapy, guideline adherence (vs. no guideline adherence)			
-overall survival	1 OBS (45,825 pts.)	1 (45,825 pts.); HR 0.70, 95% 0.68-0.72; ➔guideline adherence	low ⊕⊕○○
subgroup 5: NSCLC, all stages, chemotherapy, guideline adherence (vs. no guideline adherence)			
-overall survival	2 OBS (2,753 pts.)	T: 2 (2,753 pts.); ➔guideline adherence	very low ⊕○○○
subgroup 6: SCLC, all stages, all treatment modalities, guideline adherence (vs. no guideline adherence)			
-overall survival	1 OBS (404 pts.)	1 (404 pts.); L: 5/6 recommendations; T: 1/6 recommendation; ➔guideline adherence	very low ⊕○○○
PICO 4: Should patients with lung cancer (or those suspected of having lung cancer) receive lung cancer-specific diagnostic or therapeutic procedures in hospitals/from professionals with higher volumes of activity/with a higher grade of specialization for these procedures rather than receiving them in hospitals/from professionals with lower volumes of activity/with lower grade of specialization for these procedures?			
subgroup 1: All lung cancer, all stages, higher hospital volume of surgical resections (vs. lower hospital volume)			
-overall survival	18 OBS (448,402 pts.)	L: 12 (275,995); M: 3 (57,643 pts.); T: 3 (154,764 pts.); ➔higher hospital volume	very low ⊕○○○
-in-house mortality	12 OBS (434,948 pts.)	L: 9 (388,079 pts.); S: 2 (26,731 pts.); T: 1 (20,138); ➔higher hospital volume	very low ⊕○○○
-30-day mortality	31 OBS (1,745,923 pts.)	L: 19 (965,608 pts.); M: 4 (364,835 pts.); S: 5 (384,345 pts.); T: 3 (31,135 pts.); ➔higher hospital volume	very low ⊕○○○
-60-day mortality	2 OBS (42,838 pts.)	L: 1 (2,084 pts.); M: 1 (40,754 pts.); ➔higher hospital volume	very low ⊕○○○
-90-day mortality	6 OBS (600,425 pts.)	L: 4 (457,203 pts.; M: 1 (139,802 pts.); S: 1 (3,420 pts.); ➔higher hospital volume	very low ⊕○○○
-morbidity	7 OBS (75,972 pts.)	due to heterogeneity see online supplement B for details; ➔higher hospital volume	very low ⊕○○○
-receipt of curative treatment	1 OBS (1,591 pts.)	L: 1 (1,591 pts.); ➔higher hospital volume	low ⊕⊕○○
subgroup 2: All lung cancer, all stages, better hospital specialization in surgical resections (vs. less hospital specialization)			
-overall survival	8 OBS (95,099 pts.)	L: 4 (53,563 pts.); M: 3 (39,945 pts.); T: 1 (1,591 pts.); ➔better hospital specialization	very low ⊕○○○
-in-house mortality	3 OBS (185,454 pts.)	S; 2 (122,826 pts.); T: 1 (62,628 pts.); ➔better hospital specialization	very low ⊕○○○
-30-day mortality	11 OBS (431489 pts.)	L: 6 (364,796 pts.); M: 3 (49,686 pts.); T: 2 (17,007 pts.); ➔better hospital specialization	very low ⊕○○○
-90-day mortality	3 OBS (349,685 pts.)	L: 3 (349,685 pts.); ➔better hospital specialization	very low ⊕○○○
-morbidity	1 OBS (13,735 pts.)	L: 1 (13,735 pts.); ➔better hospital specialization	low ⊕⊕○○
-accuracy of staging	1 OBB (40,090 pts.)	L: 1 (40,090 pts.); ➔better hospital specialization	very low ⊕○○○
-receipt of curative treatment	1 OBB (1,591 pts.)	L: 1 (1,591 pts.); OR 1.72, 95% CI 1.06-2.80,➔better hospital specialization	very low ⊕○○○
subgroup 3: All lung cancer, all stages, higher surgeon volume of of surgical resections (vs. lower surgeon volume)			
-overall survival	2 OBS (2,950 pts.)	L: 2 (2,950 pts.); ➔higher surgeon volume	low ⊕⊕○○
-in-house mortality	2 OBS (8,869 pts.)	L: 1 (4,841 pts.); T: 1 (4,028 pts.); ➔higher surgeon volume	very low ⊕○○○
-30-day mortality	4 OBS (53,981 pts.)	L: 2 (9,249 pts.); M: 1 (24,092 pts.); T: 1 (20,640 pts.); ➔higher surgeon volume	very low ⊕○○○
-morbidity	1 OBS (2,295 pts.)	due to heterogeneity see online supplement B for details; ➔higher surgeon volume	very low ⊕○○○
subgroup 4: All lung cancer, all stages, better surgeon specialization in surgical resections (vs. less surgeon specialization)			
-overall survival	3 OBS (21,576 pts.)	L: 1 (19,745 pts.); T: 2 (1,831 pts.); ➔better surgeon specialization	very low ⊕○○○
-in-house mortality	3 OBS (224,056 pts.)	L: 3 (224,056 pts.); ➔better surgeon specialization	very low ⊕○○○
-30-day mortality	4 OBS (266,488 pts.)	L: 2 (45,290 pts.); M: 1 (9,579 pts.); S: 1 (211,619 pts.); ➔better surgeon specialization	very low ⊕○○○
-accuracy of staging	1 OBS (222,233 pts.)	L: 1 (222,233 pts.); ➔better surgeon specialization	low ⊕⊕○○
-receipt of curative treatment	2 OBS (4,482 pts.)	L: 1 (2,891 pts.); T: 1 (1,591 pts.); ➔better surgeon specialization	very low ⊕○○○
subgroups 5a-5i: Hospital volume of care, procedures other than surgical resection			
5a) All lung cancer, all stages, higher hospital volume of diagnostic bronchoscopies including EBUS (vs. lower hospital volume)			
-7-day mortality	1 OBS (77,755 pts.)	L: 1 (77,755 pts.); ➔higher hospital volume	very low ⊕○○○
-15-day mortality	1 OBS (77,755 pts.)	L: 1 (77,755 pts.); ➔higher hospital volume	low ⊕⊕○○
-30-day mortality	1 OBS (77,755 pts.)	L: 1 (77,755 pts.); ➔higher hospital volume	low ⊕⊕○○
-morbidity	1 OBS (77,755 pts.)	T: 1 (77,755 pts.); ➔higher hospital volume	very low ⊕○○○
- pathological confirmation	1 OBS (891 pts.)	T: 1 (891 pts.); ➔higher hospital volume	very low ⊕○○○
5b) All lung cancer, all stages, higher hospital volume of pathological lung cancer diagnostics (vs. lower hospital volume)			
- pathological confirmation	1 OBS (89,409 pts.)	L: 1 (89,409 pts.); ➔higher hospital volume	low ⊕⊕○○
5c) NSCLC, stage II/IIIA, higher hospital volume of chemoradiotherapy (vs. lower volume)			
-overall survival	2 OBS (734 pts.)	L: 2 (734 pts.); ➔higher hospital volume	very low ⊕○○○
-progression-free survival	1 OBS (495 pts.)	M: 1 (495 pts.); HR 0.85, 95% CI 0.68-1.06➔higher hospital volume	very low ⊕○○○
5d) NSCLC, stage IIIA, higher hospital volume of different tumour-specific therapies (vs. lower volume)			
-overall survival	1 OBS (83,673 pts.)	L: 1 (83,673 pts.); ➔higher hospital volume	low ⊕⊕○○
-receipt of curative	1 OBS (83,673 pts.)	L: 1 (83,673 pts.); ➔higher hospital volume	low ⊕⊕○○

treatment			
5e) All lung cancer, stage III/IV, higher hospital volumes of systemic therapies (vs. lower volume)			
-30-day mortality	1 OBS (26,277 pts.)	T: 1 (26,277 pts.); ➔higher hospital volume	very low ⊕○○○
5f) NSCLC, stage IV, higher hospital volume of different tumour-specific therapies (vs. lower volume)			
-overall survival	1 OBS (338,445 pts.)	L: 1 (338,445 pts.); ➔higher hospital volume	low ⊕⊕○○
-receipt of any tumour-specific treatment	1 OBS (338,445 pts.)	L: 1 (338,445 pts.); ➔higher hospital volume	low ⊕⊕○○
5g) NSCLC, all stages, higher hospital volume of different tumour-specific therapies (vs. lower volume)			
-receipt of curative treatment	1 OBS (43,544 pts.)	L: 1 (43,544); ➔higher hospital volume	low ⊕⊕○○
5h) All lung cancer, all stages, higher hospital volume of different tumour-specific therapies (vs. lower volume)			
-overall survival	1 OBS (9,235 pts.)	L: 1 (9,235 pts.):➔ higher hospital volume	low ⊕⊕○○
5i) All lung cancer, all stages, higher hospital volume of ICU-treated lung cancer patients (vs. lower volume)			
-30-day mortality	1 OBS (449 pts.)	L: 1 (449 pts.); ➔higher hospital volume	very low ⊕○○○
-180-day mortality -	1 OBS (449 pts.)	L: 1 (449 pts.); ➔higher hospital volume	very low ⊕○○○
subgroups 6a-6b: Hospital specialization, procedures other than surgical resection			
6a) All lung cancer, all stages, better hospital specialization in pathological lung cancer diagnostics (vs. less specialization)			
-pathological confirmation	1 OBS (89,409 pts.)	T: 1 (89,409 pts.); ➔better hospital specialization	very low ⊕○○○
6b) NSCLC, all stages, better hospital specialization in different tumour-specific therapies (vs. less specialization			
-receipt of curative treatment	1 OBS (43,544 pts.)	L: 1 (43,544 pts.); ➔better hospital specialization	low ⊕⊕○○
PICO 5: Should patients with lung cancer (or those suspected of having lung cancer) receive pathological confirmation of tumours or subtyping of lung cancers rather than no pathological confirmation of tumours or subtyping of lung cancers?			
PICO 5a: Should pathological confirmation of tumours be obtained in lung cancer patients?			
subgroup 1: All lung cancer, all stages, all treatment modalities, pathological confirmation (vs. no pathological confirmation)			
-overall survival	3 OBS (143,410 pts.)	L: 2 (6,417 pts.); L, M, S, T: 1 depending on subgroup (143,410 pts.); ➔pathological confirmation	very low ⊕○○○
-receipt of any tumour-specific treatment	1 OBS (5,906 pts.)	L: 1 (5,906); ➔pathological confirmation	low ⊕⊕○○
subgroup 2: NSCLC, stage I/II, stereotactic body radiation, pathological confirmation (vs. no pathological confirmation)			
-overall survival	4 OBS (481 pts.)	Meta: 1 (481 pts.); HR 1.28, 95% CI 0.59-1.85 ➔no pathological confirmation	very low ⊕○○○
-progression-free survival	1 OBS (165 pts.)	1 (165 pts.); HR 1.39, 95% CI 0.80-2.42 ➔no pathological confirmation	very low ⊕○○○
PICO 5b: Should histological subtyping of lung cancers be obtained in lung cancer patients?			
No systematic review performed due to limited direct evidence			
PICO 5c: Should molecular characterisation of lung cancers for actionable targets or response to treatment be performed in lung cancer patients?			
No systematic review performed due to limited direct evidence			
PICO 6: In patients with lung cancer (or those suspected of having lung cancer), should palliative care or its delivery by specialists be integrated into lung cancer care already early during the course of the disease rather than no integration of palliative care or no palliative care delivery by specialists?			
All lung cancer, all stages, early palliative care integration (vs. no early palliative care integration)			
-overall survival	2 RCT (642 pts.)	Meta: 2 (642 pts.); HR 0.72, 95% CI 0.55-0.96; ➔early palliative care integration	very low ⊕○○○
-receipt of any tumour-specific treatment	1 OBS based on RCT (151 pts.)	1 (151 pts.); 1st line CT: OR 0.68, 95% CI 0.34-1.36; 2nd line CT: OR 0.92, 95% CI 0.45-1.87; ➔no early palliative care integration 3rd line CT: OR 1.19, 95% CI 0.51-2.78, 4th line CT: OR 1.38, 95% CI 0.54-3.51; ➔early palliative care integration	very low ⊕○○○
-quality of life	20 RCT, 2 nRCT (1,747 pts.)	M: 1 (150 pts.); S: 3 (359 pts.); T: 18 (1,238 pts.); ➔early palliative care integration	very low ⊕○○○
-patient satisfaction	4 RCT (>101 pts.)	T: 4 (>101 pts.); ➔early palliative care integration	very low ⊕○○○
PICO 7: In patients with lung cancer (or those suspected of having lung cancer), should quality improvement measures be applied for lung cancer patients rather than no application of these methods in lung cancer care?			
subgroup 1: All lung cancer, all stages, application of cancer registries and quality indicators (vs. no application)			
-overall survival	4 OBS (191,693 pts.)	L: 2 (52,435 pts.); T: 2 (139,258 pts.) ; ➔application of cancer registries and quality indicators	very low ⊕○○○
-30-day-mortality	1 OBS (52,435 pts.)	L: 1 (52,435 pts.) ; ➔application of cancer registries and quality indicators	very low ⊕○○○
-accuracy of staging	2 OBS (50,910 pts.)	L: 2 (50,910 pts.) ; ➔application of cancer registries and quality indicators	very low ⊕○○○
-pathological confirmation	1 OBS (>140,000 pts.)	M: 1 (>140,000 pts.) ; ➔application of cancer registries and quality indicators	very low ⊕○○○
-receipt of curative treatment	3 OBS (>231,096 pts.)	S: 3 (>231,096 pts.) ; ➔application of cancer registries and quality indicators	very low ⊕○○○
-receipt of any tumour-specific treatment	3 OBS (>178,661 pts.)	L: 3 (>178,661 pts.) ; ➔application of cancer registries and quality indicators	very low ⊕○○○
subgroup 2: All lung cancer, all stages, application of specialized lung cancer services (vs. no application)			
-overall survival	3 OBS (296,548 pts.)	L: 3 (296,548 pts.) ; ➔application of specialized lung cancer services	very low ⊕○○○
-receipt of curative treatment	1 OBS (33,312 pts.)	L: 1 (33,312 pts.) ; ➔application of specialized lung cancer services	low ⊕⊕○○
subgroup 3: All lung cancer, all stages, application of individual quality improvement measures (vs. no application)			
-overall survival	1 OBS (1,898 pts.)	1 (1,898 pts.); HR 0.80, 95% CI 0.70-0.90; ➔application of individual quality improvement measures	very low ⊕○○○
-30-day mortality	1 OBS (2,566 pts.)	1 (2,566 pts.); OR 0.85, 95% CI 0.58-1.23; ➔application of individual quality improvement measures	very low ⊕○○○
-60-day mortality	1 OBS (2,566 pts.)	1 (2,566 pts.); OR 0.74, 95% CI 0.54-1.01; ➔application of individual quality improvement measures	very low ⊕○○○
-90-day mortality	1 OBS (2,566 pts.)	1 (2,566 pts.); OR 0.82, 95% CI 0.62-1.09; ➔application of individual quality	very low ⊕○○○

		improvement measures	
-accuracy of staging	2 OBS (4,477 pts.)	Meta: 2 (4,477 pts.); OR 1.47, 95% CI 1.10-1.96; ➔application of individual quality improvement measures	very low ⊕○○○
-pathological confirmation	1 OBS (1,896 pts.)	1 (1,911 pts.); OR 1.19, 95% CI 0.97-1.47; ➔application of individual quality improvement measures	very low ⊕○○○
-receipt of curative treatment	1 OBS (1,898 pts.)	1 (1,911 pts.); OR 1.04, 95% CI 0.77-1.40; ➔application of individual quality improvement measures	very low ⊕○○○
-receipt of any tumour-specific treatment	1 OBS (1,898 pts.)	1 (1,911 pts.); OR 1.31, 95% CI 1.05-1.63; ➔application of individual quality improvement measures	very low ⊕○○○
subgroup 4: All lung cancer, all stages, application of audits/quality indicator systems (no application)			
-30-day mortality	3 OBS (4,739pts.)	L: 1 (202 pts.); S: 2 (4,537pts.); ➔application of audit/quality indicator systems	very low ⊕○○○
-morbidity	2 OBS (20,335 pts.)	L: 1 (778 pts.); T: 1 (19,557 pts.); ➔application of audit/quality indicator systems	very low ⊕○○○
PICO 8: In patients with lung cancer (or those suspected of having lung cancer), should patient decision tools be involved in the decision-making and -sharing process rather than not involving them?			
All lung cancer, all stages, involvement of patient decision tools (vs. no involvement of patient decision tools)			
-patient satisfaction	5 RCT (233 pts.)	S: 1 (109 pts.); T: 4 (124 pts.); ➔involvement of patient decision tool	very low ⊕○○○

Table 1: Summary of the underlying available evidence and the GRADE-based evidence rating per outcomes sorted according to the eight PICO questions and their respective subgroups (***study types***: OBS – observational study, RCT – randomized controlled trial; ***effect strength***: Meta – meta-analysis, L/M/S/T – large, moderate, small, trivial effect based on own individual four-stage evaluation scheme in studies ineligible for meta-analysis (online supplement A for details); ***effect direction***: ➔ arrow indicates whether the observed effect favours the implementation of a specific quality improved measure or no implementation of a specific quality improvement measure; all PICO questions were developed a priori)

Quality improvement measure (vs. control)	**Recommendation**	**Strength**	**Overall quality of evidence**	**Specific implementation considerations and research needs**
PICO 1: In patients with lung cancer (or those suspected of having lung cancer), should shorter rather than longer cancer care time intervals be used (e.g. time from diagnosis to treatment)?				
Shorter treatment interval (vs. longer treatment interval)	1. In patients with lung cancer, we suggest minimizing delay in initiation of first treatment. Remark: Evaluation should be complete before proceeding to any definitive treatment. Minimizing delay in initial evaluation of the patient and specialist referral may also help to improve outcomes in lung cancer patients.	Conditional	Very low	*International/national/regional level:* a) Creation of a comprehensive data basis on waiting times • acquisition of waiting time threshold benchmarks: prospective multicentric observational studies among specialized lung cancer service networks assessing waiting times and perceived factors for delay • depiction of general care situation: retro-/prospective population-based observational studies among clinical lung cancer registries assessing waiting times • survey-based assessment of patient preferences/behavioural patterns b) Definition and consensus-building of standardized waiting time thresholds • preferably pan-European consensus meeting of dedicated European societies and national representatives c) Monitoring and optimization initiatives • periodical monitoring of waiting times and – if needed – adaption of waiting time thresholds • coordinated optimization initiatives with mutual knowledge exchange • thorough exploration of the putative effect of longer waiting times resulting in better survival

				in advancer lung cancer
PICO 2: In patients with lung cancer (or those suspected of having lung cancer), should a multi-disciplinary team (MDT) or certain disciplines be involved during lung cancer care rather than no involvement of an MDT or certain disciplines?				
Involvement of MDT (no involvement of MDT)	2. We suggest the integration of multidisciplinary teams and/or multidisciplinary consultation in the management of patients with (suspected) lung cancer. Remark: We acknowledge that MDT is already implemented broadly in lung cancer care, yet to achieve good integration, we see the need for better implementation of multidisciplinary teamwork throughout the lung cancer pathway as well as for frequent surveillance and optimisation of MDT meetings and processes.	Conditional	Very low	*International/national/regional level:* a) Definition and consensus-building to harmonize and improve MDT-practices • preferably pan-European consensus meeting of dedicated European societies and national representatives • creation of standardized self-assessment and/or peer-to-peer benchmark tools on MDT practices b) Coordinated quality improvement initiatives to optimize MDT infrastructure and processes • multi-centric surveys and/or peer-to-peer visits for gap analyses on current MDT practices • quality improvement studies on various aspects of MDT care, i.e. essential standards of documentation and case presentations as well as time management
PICO 3: In patients with lung cancer (or those suspected of having lung cancer), should guidelines or standard operating procedures (SOP) for lung cancer care be implemented or adhered to rather than non-implementation of or non-adherence to these guidelines or standard operating procedures?				
Guideline implementations and adherence (vs. no guideline implementation and adherence)	3. In patients with lung cancer, we suggest that methodologically robust, evidence-based guidelines and standard operating procedures should be implemented and adhered to (based on informed consent by the patient). Remark: We acknowledge that clinical practice guidelines are generally perceived as highest level of evidence-based medicine and have been created frequently in lung cancer care. Yet, even if	Conditional	Very low	*International/national/regional level:* a) Establishing active guideline cycles in a collaborative approach • linkage of guideline groups (guideline development), lung cancer services (guideline implementation/adherence) and clinical lung cancer registries (quality assurance) • frequent updates of evidence searches as well as short-handed appraisal of newly available evidence and adaption of guideline

	guidelines are issued in good metholodogical and contentual quality, their overall impact strongly depends on the recognition and adherence by the target audience. Stakeholder need assessments, measures to improve implementation and applicability as well as regular updates of guidelines may facilitate user acceptation. At the same time guidelines are not mandates but do need unsolicitous approval by competent patients after provision of understandable information on recommended practices by physicians and time for discussion on their benefits and risks as well as alternatives.			recommendations, preferably jointly among guideline groups to reduce duplication of work b) Monitoring and optimization initiatives • acquisition of guideline adherence benchmarks: prospective multicentric observational studies among specialized lung cancer service networks assessing guideline adherence on various key recommendations and factors for non-adherence • depiction of general care situation: retro-/prospective population-based observational studies among clinical lung cancer registries assessing various key recommendations • coordinated quality improvement studies on guideline implementation/adherence with mutual knowledge exchange c) Creation of new guideline models based on evidence from randomized-controlled trials and real-world data with inclusion of artificial intelligence tools for complex diagnostic/treatment decisions and to extrapolate/adapt recommendations to patient populations not covered by randomized controlled trials
PICO 4: Should patients with lung cancer (or those suspected of having lung cancer) receive lung cancer-specific diagnostic or therapeutic procedures in hospitals/from professionals with higher volumes of activity/with a higher grade of specialization for these procedures rather than receiving them in hospitals/from professionals with lower volumes of activity/with lower grade of specialization for these procedures?				
Higher hospital volume of care (vs. lower hospital volume of care) Higher volume of care by surgeons or	4. In lung cancer patients, we recommend performing lung cancer surgery a) in lung cancer services specialised in thoracic surgery with high institutional volumes of pulmonary resections and b) by surgeons specialised in thoracic surgery with high	Strong (paradigmatic situation)	Very low	*International/national/regional level:* a) Quality of care research relating to better hospital and individual procedural performance quality • broadening of scope beyond thoracic surgical procedures • identification of underlying causal factors • survey-based assessment of national

other professionals (vs. lower volume of care by surgeons or other professionals) Better hospital specialization (vs. less hospitals specialization) Better specialization of surgeons and other professionals (vs. less specialization of surgeons and other professionals)	individual volumes of pulmonary resections. 5. In lung cancer patients, we suggest performing procedures other than lung cancer surgery (*) a) in lung cancer services specialised in these procedures with high institutional volumes of these procedures and b) by professionals specialised in these procedures with high individual volumes of these procedures. (*) evidence available for diagnostic bronchoscopy including EBUS, quality of pathological diagnostics, different tumour-specific treatments in stage II-IV lung cancer, and ICU therapy in lung cancer patients	Conditional	Very low	requirements • process optimization methods to improve or remodel operating parts within lung cancer services • survey-based assessment of patient characteristics and preferences when re-organisation of lung cancer care is envisaged b) Definition and consensus-building of volume of care thresholds as well as specialization levels for hospitals and individuals • preferably pan-European consensus meeting of dedicated European societies and national representatives
PICO 5: Should patients with lung cancer (or those suspected of having lung cancer) obtain pathological confirmation of tumours or subtyping of lung cancers rather than no pathological confirmation of tumours or subtyping of lung cancers?				
Pathological confirmation of suspected lung cancers (vs. no pathological confirmation Subtyping of confirmed lung cancers (vs. no subtyping of confirmed tumours)	6. In patients with suspected lung cancer, we recommend seeking pathological confirmation where it determines management. 7. In patients with confirmed lung cancer, further subtyping of lung cancers through application of the WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart as well as molecular characterisation for actionable	Strong (paradigmatic situation) Good practice statement	Very low	*International/national/regional level:* a) Quality of care research relating to pathological confirmation and subtyping of lung cancers • acquisition of benchmarks for pathological confirmation, histological subtyping and molecular alterations: prospective multicentric observational studies among specialized lung cancer service networks • depiction of general care situation: retro-/prospective population-based observational studies among clinical lung cancer registries b) Translational/clinical research on non- or less

	targets or response to treatment should be performed.			invasive diagnostics for lung cancer confirmation and molecular subtyping: • liquid biopsies, breath exhalate analyses, imaging techniques, or combination of these
PICO 6: In patients with lung cancer (or those suspected of having lung cancer), should palliative care or its delivery by specialists be integrated into lung cancer care already early during the course of the disease rather than no integration of palliative care or no palliative care delivery by specialists?				
Early integration of palliative care (vs. no early integration of palliative care)	8. We suggest integrating palliative care already at an early stage into lung cancer care pathways based on patient symptom load and well-linked to routine tumour-specific management Remark: Delivery of palliative care may be by palliative care specialists or palliative care teams.	Conditional	Very low	*International/national/regional level:* a) Quality of care research relating to early integration of palliative care • creation and assessment of graduated models to better deliver flexible needs-based palliative care alongside tumour-specific care throughout the lung cancer pathway • survey-based assessment of patient preferences b) Translational/clinical research relating to early integration of palliative care • identification of causes and mechanisms of the assumed temporary life-prolonging effect of early palliative care integration • definition/standardization of core elements of early integration of palliative care • definition/standardization of quality assurance measures
PICO 7: In patients with lung cancer (or those suspected of having lung cancer), should quality improvement measures be applied in lung cancer care rather than no application of these methods in lung cancer care?				
Application of quality improvement measures (no application of	9. We suggest utilizing national clinical lung cancer registries involving quality indicators to provide feedback for future lung cancer guidelines and to inform lung cancer services.	Conditional	Very low	*International/national/regional level:* a) Quality improvement research in a collaborative approach • multicentric quality improvement studies for piloting and evaluating certain measures

quality improvement measures)	10. We suggest referring lung cancer patients to services with ready access (*) to multiple lung cancer specialist facilities (**). (*) ready access: reasonable proximity and timeliness (**) lung cancer specialist facilities include functional diagnostics, imaging, endoscopy, pathology/molecular biology, thoracic surgery, radiotherapy, systemic treatments, and palliative care, clinical trials as well as multidisciplinary teams	Conditional	Very low	• creation of open-access depositories for quality improvement measures b) Definition and consensus-building of quality-relevant structural and processual elements as well as outcomes within lung cancer services • preferably pan-European consensus meeting of dedicated European societies and national representatives • definition of an essential quality parameter catalogue for peer-to-peer visits, audits or benchmarking initiatives
	11. We suggest developing and implementing specific quality improvement measures (***) to improve quality of lung cancer care where required and when superordinate guidance is missing (***) i.e. clinical pathways	Conditional	Very low	c) set-up and prospective utilization of high-quality multi-centric lung cancer service-based registries as well as population-based registries to better facilitate future quality of care-research in lung cancer (i.e., ERS Clinical Research Collaboration PERSPECTIVE [16], EU IMI Consortium OPTIMA [17])
	12. We suggest the implementation of an internal and/or external evaluation system (****) for lung cancer services. (****) different terms are used beside evaluation system: i.e. internal/external audit system, certification system, quality indicator systems	Conditional	Very low	

PICO 8: In patients with lung cancer (or those suspected of having lung cancer), should patient decision tools be involved in the decision-making and -sharing process rather than not involving them?				
Involvement of patient decision tools (vs. no involvement of patient decision tools)	13. In patients with lung cancer, we suggest using patient decision tools as a measure to improve patient involvement in decision making. Remark: While current evidence does not suggest benefits from patient decision tools in lung cancer patients, we as a committee considered that the perceived positive impact on shared decision-making and informed consent processes outweighs barriers for certain patient subgroups.	Conditional	Very low	*International/national/regional level:* a) Behavioural and communications research relating to patient decision tools • qualitative analyses on patient and professional preferences and behavioural/learning patterns • creation and evaluation of different patient decision tool formats tailored to user preferences and capabilities b) Creation of patient decision tools in a collaborative approach • creation and evaluation of different patient decision tool formats tailored to user preferences and capabilities • preferably definition of essential information contents and quality standards facilitating active patient share in decision-making by dedicated European/national societies and patient organisation • creation of open access depositories for patient decision tool contents

Table 2: Summary of recommendations in this guideline as well as specific implementation considerations and research needs

PICO question 1: ***In patients with lung cancer (or those suspected of having lung cancer), should shorter rather than longer cancer care time intervals be used (e.g. time from diagnosis to treatment)?***

ERS recommendation

In patients with lung cancer, we suggest minimizing delay in initiation of first treatment. [conditional recommendation for the intervention; very low quality of evidence].

Remark: Evaluation should be complete before proceeding to any definitive treatment. Minimizing delay in initial evaluation of the patient and specialist referral may also help to improve outcomes in lung cancer patients.

Problem

Early diagnosis and treatment of lung cancer is central to improve outcomes. Yet, lung cancer mortality is still high due to lack or late onset of symptoms as well as delayed presentation of patients to primary and secondary care. Delays may be contributed to by patients, primary and/or secondary care professionals as well as other factors [18].

Summary of evidence and overall quality of evidence

Due to substantial heterogeneity of the body of evidence relating to applied time intervals, we included only studies investigating treatment interval (time from date of diagnosis to date of treatment start) as intervention and selected 65 observational studies and two RCTs out of the 1,791 initially identified abstracts accordingly [19-85]. We formed six subgroups (1. NSCLC, stage I/II, surgery; 2. NSCLC, stage I/II, all treatment modalities; 3. NSCLC, stage I-III, all treatment modalities; 4. NSCLC, stage I-IV, all treatment modalities; 5) ALK-positive NSCLC, stage IIIB/IV, ALK-TKI; 6. SCLC, stage I-IV, all treatment modalities) which allowed clinically meaningful pooling of data. From our predefined critical or important outcomes of interest, the following were addressed in the included studies: *overall survival*, *30-day and 90-day mortality* as well as *accuracy of staging*. The overall quality of evidence was rated as very low.

Desirable effects

Benefits of achieving shorter treatment intervals differed among the predefined subgroups. Patients with lung cancer subtypes stage I/II NSCLC with surgical resection (HR 0.893; 95% CI 0.847-0.943) and any tumour-specific treatment (HR 0.734; 95% CI 0.642-0.893) as well as ALK-positive stage IIIB/IV NSCLC (HR 0.49; 95% CI 0.27-0.88) who did not delay care had an increase in overall survival. With increasing stage or histological aggressiveness of tumours, analyses no longer detected any definite impact (i.e. stage III, NSCLC). *30-day mortality* as a short-term outcome was improved in the shorter treatment interval cohorts. While there may be an effect on *90-day mortality* and *accuracy of staging*, the evidence was very uncertain.

Undesirable effects

In SCLC-and stage IV NSCLC patients, shorter waiting times may not improve overall survival, however, the evidence is uncertain. Despite adjustments for stage in these studies, we assume other factors contributed to this effect which were unaccounted for in the study designs (i.e. imminent local tumour complications with worse prognostic impact) and which may have forced clinicians to act immediately (i.e. salvage therapies) and by that shorten the treatment interval. Likewise, this may explain similar effects in more advanced NSCLC with higher risk for

short-term tumour-related complications, both corresponding to a Will Rodgers phenomenon [86].

No further harms were identified in the included 67 studies.

Other considerations

We determined very low certainty due to concerns about risk of bias, indirectness, inconsistency, and imprecision. Applied treatment interval thresholds ranged between 7 and 90 days across studies. In addition, we considered the growing negative prognostic impact of local tumour growth as well as risk of locoregional and distant metastatic spread over time. We were aware of the substantial psychological impact on patients with suspected lung cancer and their caregivers, both warranting clinicians to ensure short waiting times from tumour detection to treatment initiation. However, we anticipate potential risks if treatment is initiated before completion of essential diagnostics that may affect management, namely access times to advanced imaging techniques and processing times of modern molecular diagnostics. Furthermore, fitness for therapy may need to be accounted for in certain patients (i.e. prehabilitation in comorbid patients) [87]. All are prerequisites for state-of-the-art lung cancer care. Improved overall survival through higher curative rates or at least tumour-specific treatment allocation is indeed feasible by improvement of timeliness. While local amelioration measures appear actionable with low use of resources, fundamental pathway optimization will generate costs for healthcare systems. Yet in the long run, a significant reduction of the large economic lung cancer burden in Europe is conceivable by coordinated measures for earlier detection and treatment [4]. In addition, there is a realistic potential for improving health equity in deprived populations or underserved regions. Thus, full acceptance by patients, medical professionals and healthcare authorities is deemed very probable.

Justifications of recommendation

Most lung cancer patients present in advanced, no longer curatively treatable stages [2]. Given the life-threatening potential of lung cancer treated too late after diagnosis, every measure on the side of primary and secondary care professionals needs to be taken to achieve timely diagnostic and treatment pathways for patients willing to be treated. Thus, we suggest minimizing delay. Our recommendation is conditional due to the very low certainty of evidence and potential harms if treatment is started before completion of diagnostics or optimisation of patient fitness.

Time points and intervals from first symptom to treatment start have been well-defined in the Aarhus statement paper [88]. A recent review summarized varying arbitrary national timeliness requirements, none of which were evidence-based or internationally consented [18]. At this stage, we have therefore deliberately refrained from naming specific requirements from an international perspective.

Conclusions, implementation considerations and research needs

Despite lack of evidence on many of our predefined outcomes, we are confident that optimizing waiting times is an important measure to improve outcomes in lung cancer care. With the implementation of population-based lung cancer screening programmes on the horizon, individuals at-risk will benefit from effective information campaigns encouraging them to seek prompt medical attention when experiencing alarm symptoms. In contrast, treatment intervals in modern systemic therapies based on molecular lung cancer profiling have still not been systematically explored yet.

PICO question 2: ***In patients with lung cancer (or those suspected of having lung cancer), should a multi-disciplinary team (MDT) or certain disciplines be involved rather than no involvement of an MDT or certain disciplines during lung cancer care?***

ERS recommendation

We suggest the integration of multidisciplinary teams and/or multidisciplinary consultation in the management of patients with (suspected) lung cancer [conditional recommendation for the intervention; very low overall quality of evidence].

Remark: We acknowledge that MDT is already implemented broadly in lung cancer care, yet to achieve good integration, we see the need for better implementation of multidisciplinary teamwork throughout the lung cancer pathway as well as for frequent surveillance and optimisation of MDT meetings and processes.

Problem

Multidisciplinary approaches facilitate interprofessional collaboration leading to joint discussion and consensus on personalized diagnostic and therapeutic strategies for patients, yet also provide challenges to lung cancer services [89]. Thus, we considered it important to systematically assess the benefits and potential downsides of lung cancer MDT.

Summary of evidence and overall quality of evidence

We identified 25 observational studies and one RCT out of the 874 initial abstracts [19, 76, 90-113]. We formed four subgroups (1. all lung cancer types, all stages, all treatment modalities; 2. NSCLC, all stages, all treatment modalities; 3. NSCLC, all stages, surgical resection; 4. NSCLC, stage III/IV, all treatment modalities) enabling clinically meaningful pooling of data. From our predefined outcomes of interest, the following were reported in the included studies: *overall survival*, *30-day mortality*, *morbidity*, *accuracy of staging*, *pathological confirmation*, *receipt of curative treatment*, *receipt of any tumour-specific treatment*, *quality of life* and *patient satisfaction*. All outcomes were considered either critical or important. The overall quality of evidence was rated as very low.

Desirable effects

Benefits of implementing MDT measures differed among the predefined subgroups. However, MDT measures resulted in improved overall survival according to the meta-analyses in NSCLC in stage III/IV (HR 0.750, 95% CI 0.623-0.903) and in all stages (all treatments: HR 0.759, 95% CI 0.614-0.939; surgical resection: HR 0.765, 95% CI 0.496-1.145) as well as cohorts incorporating all lung cancer types (HR 0,618, 95% CI 0,578-0,662), lower 30-day mortality in resected NSCLC, better accuracy of staging in the subgroup analyses for early and advanced NSCLC, higher pathological confirmation rates for all lung cancer types and resected NSCLC, higher rates of receipt of curative treatment in subgroup assessments of all lung cancer types and resected NSCLC, and higher rates of receipt of any tumour-specific treatment in all 4 subgroups.

Undesirable effects

No clinically meaningful harms were seen resulting of MDT interventions.

Other considerations

We determined very low certainty due to concerns about risk of bias, indirectness, inconsistency, and imprecision. The limited evidence basis may be partially explained since MDT meetings have been commonly established for many years worldwide in routine cancer care impeding related quality of care research due to lack of patients treated outside from multidisciplinary structures. We see major benefits in MDTs including interprofessional collaboration and consensus-finding on personalized management strategies. For us, resulting desirable effects are reduction in clinical practice variability, shortened and standardized decision processes balancing patient preferences and guideline-recommended care.

At the same time, patients value and benefit from multidisciplinary teamwork which has already become an obligation by health authorities in many countries. Despite the progress already made, multidisciplinary consultation and set-up of corresponding elements of care still need to be broadened across the lung cancer continuum. We see potential needs for improvement of MDT meetings and processes based upon periodic monitoring. Implementation seems feasible to us as the provision of needed resources may be compensated by saved expenditures for avoided under-, over- and mistreatment.

Justifications of recommendation

Multidisciplinary structures and processes seem necessary to ensure best personalized diagnostic and therapeutic strategies for patients. There were no evident substantial harms related to implementation of MDT measures. Thus, we suggest the implementation of MDT measures, even if the survival benefit is not always clear. The recommendation is conditional due to the very low certainty of evidence which is additionally limited to few of our predefined outcomes.

Conclusions, implementation considerations and research needs

Multidisciplinary care represents a holistic approach to ensure good clinical and patient-centred lung cancer care. It has become medico-legally mandatory in various countries. Comprehensive essential and advanced MDT standards were first issued by an ERS task force [7] which were later further developed by another European initiative [114]. Yet in practice, MDTs need to be committed to broaden their actions throughout the lung cancer continuum and optimize them based on self-assessment at regular intervals [115].

PICO question 3: ***In patients with lung cancer (or those suspected of having lung cancer), should guidelines or standard operating procedures (SOP) for lung cancer care be implemented or adhered to rather than non-implementation of or non-adherence to these guidelines or standard operating procedures?***

ERS recommendation

In patients with lung cancer, we suggest that methodologically robust, evidence-based guidelines and standard operating procedures should be implemented and adhered to (based on informed consent by the patient) [conditional recommendation for the intervention; very low overall quality of evidence].

Remark: We acknowledge that clinical practice guidelines are generally perceived as highest level of evidence-based medicine and have been created frequently in lung cancer care. Yet, even if guidelines are issued in good metholodogical and contentual quality, their overall impact strongly depends on the recognition and adherence by the target audience. Stakeholder need assessments, measures to improve implementation and applicability as well as regular updates of guidelines may facilitate user acceptance. Guidelines are not mandates but do need unsolicitous approval by competent patients after provision of understandable information on recommended practices by physicians and time for discussion on their benefits and risks as well as alternatives.

Problem

Large numbers of international and national lung cancer guidelines exist with significantly varying methodological quality and partially outdated recommendations. Higher national financial resources correlated with enhanced guideline quality [6, 116]. Dissemination, implementation, adherence and updates are the essential next steps within the guideline cycle introduced by the EU commission in 2004 ensuring a value-added utilization of well-developed guidelines [117]. Yet, in real life, difficulties in guideline implementation and adherence among professionals [118, 119] and stakeholders [120, 121] were identified, while some evidence indicated limited impact and substantial variation of assisting tools for guideline implementation [122].

Summary of evidence and overall quality of evidence

15 observational studies were finally selected out of the 754 initially identified abstracts [123-137]. To allow clinically meaningful rating of evidence, we defined six subgroups (guideline implementation: 1. all lung cancer types, all stages, all therapies; guideline adherence: 2. NSCLC, all stages, surgical resection plus neoadjuvant/adjuvant therapies; 3. all lung cancer, all stages, all treatment modalities; 4. NSCLC, unresectable stage III, chemo- and/or radiotherapy; 5. NSCLC, all stages, chemotherapy; 6. SCLC, all stages, all treatment modalities). The included studies addressed the following outcomes that were a priori assessed as important or critical: *overall survival*, *30-day mortality*, *morbidity*, *accuracy of staging*, *receipt of curative treatment* and *receipt of any tumour-specific treatment*. The overall quality of evidence was rated as very low.

Desirable effects

Improved *overall survival*, *postsurgical 30-day mortality*, *accuracy of staging*, *receipt of curative treatment* and *receipt of any tumour-specific treatment* were seen in the Danish national *guideline implementation* initiative linked to the re-organisation of lung cancer services and the set-up of a national clinical lung cancer registry [128, 129], whereas a comparable earlier study

from the United Kingdom showed positive effects on *overall survival* relating to some organisational standards [130].

Guideline adherence to single or combined recommendation-derived quality measures improved overall survival in the context of NSCLC thoracic surgery [134-136], chemo-/radiotherapy in NSCLC stage III [123] and various SCLC treatment modalities [127].

Undesirable effects

None of the evaluated studies indicated any substantial harms regarding guideline implementation or adherence. The calculated opposite negative effect on *overall survival* in the work by *Odell et al.* suggesting non-adherence to the evidence-based recommendation to initiate neo-adjuvant therapy before surgery in clinical stage IIIA NSCLC-patients was invalidated by the authors due to a disproportionate, potentially non-representative control arm [134].

Other considerations

We determined very low certainty due to concerns about risk of bias, indirectness, inconsistency, and imprecision. Meta-analyses were not meaningful in any of the predefined groups. Nevertheless, we value methodologically robust guidelines (currently best measured by the AGREE II-tool [138]) as the most valid sources in evidence-based medicine facilitating good standardized care.

We see certain risks deriving from outdated guideline recommendations and the surplus of available guidelines on certain topics with sometimes contradicting recommendations. In addition, we note that guideline recommendations cannot be transferred into patient management in all cases due to potential contraindications, but also opportunities for individualized treatment concepts. Funding of guidelines by health care authorities or industry may be accompanied by certain limitations, namely the constraint to national available resources or less transparent, objective conclusions, respectively [139].

Ensuring equity among patients receiving guideline-concordant care should be an unquestionable goal. Based on Surveillance, Epidemiology, and End Results Medicare (SEER) US data, *Fang et al.* detected that black patients compared to white patients were less likely to receive stereotactic radiation or surgery in stage I NSCLC (14,605 patients; 61% vs. 75%, $p<0.0001$) as well as chemotherapy in addition to radiotherapy or surgery in stage III NSCLC (15,609 patients; 36% vs. 41%, $p<0.0001$) [140].

No increased costs after guideline implementation were detected by *Casebeer et al.* after multivariate analysis [126]. *Neubauer et al.* could even demonstrate lower costs for guideline-concordant care within a period of 1 year after initiation of 1st line chemotherapy in NSCLC patients in a regional outpatient US-oncology network (1,409 patients; average 12-month on/off pathway costs: $18,042 v $27,737; on/off cost ratio 0.71, 95% CI 0.64-0.80) [132].

Justifications of recommendation

While there is very low level of certainty in the effect estimates, we recognize the above-mentioned benefits of guidelines and the limited potential for harms when evidence-based recommendations are properly implemented and used to inform practice (e.g., supporting appropriate clinical decision-making with the patient).

Conclusions, implementation considerations and research needs

The above-mentioned potential problems of creation, dissemination and implementation as well as maintaining up-to-date guidelines should be considered and actively addressed in respective national, regional, and local settings. Systematic surveillance of guideline implementation and adherence is desirable, but currently often fails due to insufficient data sources as well as width, quality and completeness of data. Valuable financial and human resources for guideline development may be saved by multidisciplinary collaborations across societies and governmental bodies within and between countries as well as on the international level avoiding unnecessary duplication of work within the evidence synthesis. However, evidence-based guideline recommendations are usually adapted according to different national health care system organization and resources (amongst many others, a positive example is the conjoint development and implementation of the Belgian Lung Cancer Guideline led by the Belgian Health Care Knowledge Centre KCE [141]).

PICO question 4. ***Should patients with lung cancer (or those suspected of having lung cancer) receive lung cancer-specific diagnostic or therapeutic procedures in hospitals/from professionals with higher volumes of activity/with a higher grade of specialization for these procedures rather than receiving them in hospitals/from professionals with lower volumes of activity/with lower grade of specialization for these procedures?***

ERS recommendation

In lung cancer patients, we recommend performing lung cancer surgery a) in lung cancer services specialised in thoracic surgery with high institutional volumes of pulmonary resections and b) by surgeons specialised in thoracic surgery with high individual volumes of pulmonary resections [strong recommendation, paradigmatic situation in very low overall quality of evidence].

In lung cancer patients, we suggest performing procedures other than lung cancer surgery (*) a) in lung cancer services specialised in these procedures with high institutional volumes of these procedures and b) by professionals specialised in these procedures with high individual volumes of these procedures [conditional recommendation very low overall quality of evidence].

(*) evidence available for diagnostic bronchoscopy including EBUS, quality of pathological diagnostics, different tumour-specific treatments in stage II-IV lung cancer, and ICU therapy in lung cancer patients

Problem

Over the last three decades, numerous studies reported that higher procedural volumes or better specialization of care delivered by hospitals and clinicians lead to improved outcomes in lung cancer patients. Yet, the knowledge of this positive correlation has still not been fully translated into routine care [142].

Summary of evidence and overall quality of evidence

76 observational studies were finally selected out of the 440 initially identified abstracts [85, 103, 143-216]. To allow clinically meaningful rating of evidence, we defined six subgroups (1. hospital volume of care, surgical resection; 2. hospital specialization, surgical resection; 3. surgeon volume of care, surgical resection; 4. surgeon specialization, surgical resection; 5. hospital volume of care, procedures other than surgical resection; 6. hospital specialization, procedures other than surgical resection). The included studies addressed the following outcomes that were a priori assessed as important or critical: *overall survival*, *progression-free survival, mortality*, *morbidity*, *accuracy of staging*, *pathological confirmation*, and *receipt of curative treatment*. The overall quality of evidence was rated as very low.

Desirable effects

Regarding *surgical resections*, the following desirable effects were seen: improved overall survival, reduced mortality rates (studies applied in-hospital, 30-day, 60-day or 90-day mortality), and reduced rates of certain types of morbidity in 1) hospitals with higher volumes, 2) better specialized hospitals, 3) surgeons with higher individual volumes, and 4) better specialized surgeons. More accurate staging was detected in better specialized hospitals and

surgeons, likewise higher surgical resection rates in these two subgroups as well as in hospitals with higher volumes.

Due to substantial heterogeneity in terms of patient populations, extent of pulmonary resections as well as number and thresholds of volume strata or categorisation of specialization across studies resulting in very low or low certainty in the evidence, we did not conduct any meta-analyses in all four subgroups. Nevertheless, based on our self-selected evaluation scheme to estimate the effect sizes of single studies, for all addressed outcomes in the four subgroups, the number and pooled patient figures of studies with large effects outnumbered those of studies with trivial effects when comparing highest versus lower volumes or best versus least defined grade of specialization. Additionally, we detected several studies with moderate and small effects (see PICO 4 evidence tables, subgroups 1-4 for detailed effect sizes).

The evidence basis on *procedures other than surgical resections* was limited and focussed on hospital volumes and specialization only. Here we detected in 1) *diagnostic bronchoscopies including EBUS* improved 7-day, 15-day and 30-day mortality rates in hospitals with higher volumes (1 study, large effect, 77,755 patients), 2) *quality of pathological lung cancer diagnostics* more accurate pathological diagnoses in hospitals with higher volumes and better specialized hospitals (both in 1 study, large effect, 89,409 lung cancer specimens), 3) *chemoradiotherapy in stage II and IIIA/B NSCLC* improved overall survival (2 studies large effects, 734 patients) and progression-free survival (1 study, moderate effect, 495 patients) in hospitals with higher volumes, 4) *different tumour-specific therapies in stage IIIA NSCLC* improved overall survival and receipt of curative treatment in hospitals with higher volumes (both in 1 study, large effects, 83,673 patients), 5) *different tumour-specific therapies in stage IV NSCLC* improved overall survival and receipt of curative treatment in hospitals with higher volumes (both in 1 study, large effects, 338,445 patients), 6) *different tumour-specific therapies in all-stage NSCLC* improved receipt of curative treatment in hospitals with higher volumes and better specialized hospitals (both in 1 study, large effect, 43,544 patients), 7) *different tumour-specific therapies in all-stage lung cancers* improved overall survival in hospitals with higher volumes (1 study, large effect, 9,235 patients), and 8) *ICU therapy in lung cancer patients* improved 30-day and 180-day mortality rates in hospitals with higher volumes (both in 1 study, large effects, 499 patients).

Undesirable effects

None of the evaluated studies indicated any substantial harms regarding higher volumes of care or better specialization.

Other considerations

The implementation of medico-legal requirements concerning volumes and specialization of hospitals and surgeons related to lung cancer surgery and the potential consequence of the need for re-organisation of lung cancer services seems feasible on the national levels across Europe and has already taken place. The Danish health care system successfully pursued this implementation through reduction and subsequent regional centralisation of thoracic surgery services with adjacent satellite centres for local diagnostics and systemic therapies, all in close collaboration with lung cancer-related societies and professionals [217].

Regionalisation of care to achieve higher volumes and better specialization may reduce proximity to suitable lung cancer services and by that impose burden to some patients.

Justifications of recommendations

We have acknowledged that differing individual, institutional and healthcare system factors as well as patient preferences could not be fully accounted for in the retrospective observational studies and few randomized controlled trials. Yet, regarding *lung cancer surgery*, the body of evidence contained a considerable number of studies from different countries and many with large patient figures or even population-based observational designs. Most studies justified the recommendation, none showed a converse correlation. Despite the varying level of confidence from moderate to low and very low in the respective effect estimates for hospital as well as surgeon volume and specialization, a strong recommendation for the above-mentioned lung cancer surgery performance is warranted given the life-threatening potential of lung cancer, especially when operated improperly (very low quality evidence suggesting benefit in a life-threatening situation as paradigmatic scenario in accordance to GRADE methodology) [15]. No substantial harms were evident or foreseen by us. Patient preferences need to be addressed and acknowledged in joint decision making.

Given the limited body of evidence for the *other named diagnostic and therapeutic procedures*, only conditional recommendations were consented.

Purposely, no lower thresholds narrowing the best volume of activity were defined at this stage for any of the appraised procedures since these would need in addition consensus by relevant stakeholders on the national level. Thresholds for institutional and surgeon high volumes utilized in the analysed studies ranged between 10-468 and 6-132 surgical resections per year, respectively. Likewise, no upper thresholds were defined by us despite bearing in mind that resources are limited and that excessive volumes of care may lead to potentially harmful resource depletion within all procedures.

Conclusions, implementation considerations and research needs

Further patient-centred quality of care research is needed to better identify and describe underlying factors leading to better quality of hospitals and individual professionals as well as to define lower and upper thresholds for volumes of care in lung cancer-related procedures.

PICO question 5: ***Should patients with lung cancer (or those suspected of having lung cancer) obtain pathological confirmation of tumours or subtyping of lung cancers rather than no pathological confirmation of tumours or subtyping of lung cancers?***

ERS recommendation

In patients with suspected lung cancer, we recommend seeking pathological confirmation where it determines management [strong recommendation for the intervention; paradigmatic situation in very low overall quality of evidence].

In patients with confirmed lung cancer, further subtyping of lung cancers through application of the WHO Classification of Tumours: Thoracic Tumours, 5th edition [218] (*) as well as molecular characterisation for actionable targets or response to treatment should be performed [good practice statement].

(*) the WHO Classification represents the internationally accepted standard

Problem

Due to the considerable expansion of therapeutic options over the last decade, diligent tumour biological profiling of lung cancers is considered as an essential prerequisite to tailor personalized treatments. However, its availability seems very heterogeneous within and across countries [6].

Summary of evidence and overall quality of evidence

7 observational studies were finally selected out of the 759 initially identified abstracts which reported on *overall survival*, *progression-free survival* and *receipt of any tumour-specific treatment* [219-225]. All outcomes were considered critical. All studies related to pathological confirmation of lesions suspicious for lung cancer. We formed two subgroups (1. All lung cancer types, all stages, all treatment modalities; 2. NSCLC, stage I/II, stereotactic radiotherapy) for clinically meaningful rating of evidence. No evidence was retrieved for histological subtyping as well as molecular characterisation of confirmed lung cancers directly applicable to this search question. The overall quality assessment of evidence was rated as very low.

Desirable effects

Regarding pathological confirmation, improved overall survival was shown in the two studies with unselected patients for all lung cancers and NSCLC, respectively.

Undesirable effects

The subgroup analysis by *Khakwani et al.* indicated that elderly patients as well as those with poor performance status did not benefit from pathological confirmation of suspicious lesions which may be due to lack of therapeutical benefit as well as higher diagnostic procedural risk and/or reduced fitness for subsequent therapy [221].

Only trivial effects were seen suggesting lower overall and progressions-free survival in the clinically suspected stage I/II patients receiving stereotactic radiotherapy without prior pathological confirmation. Yet, a bias seemed likely here due to the unavoidable inclusion of individuals with non-malignant solitary pulmonary nodules (with better prognosis) in the cohort with no pathological confirmation.

Otherwise, none of the evaluated studies of both subgroups indicated any substantial peri-procedural harms resulting from pathological confirmation.

Other considerations

The direct evidence in view of pathological confirmation was very limited and graded as very low due to concerns about risk of bias, indirectness, and imprecision. However, the panel felt that a substantial body of indirect evidence demonstrated the added value of pathological confirmation as a prerequisite for more effective and less harmful personalized treatment decisions. While no direct evidence was retrieved with reference to histological subtyping and molecular profiling of lung cancers compared to their non-execution, both are generally accepted mainstays for personalized therapy planning in lung cancer following several therapeutic randomized-controlled trials [226]. Additionally, the approval of several systemic drugs by the European Medicines Agency is based on this indirect, high-level evidence most often with the mandatory prerequisite to determine the respective molecular targets or predictive markers before prescription of any of these drugs [227]. The panel acknowledged the need to avoid performance of invasive diagnostics in unfit patients.

Justifications of recommendations

Improvements in pathological confirmation rates and thorough profiling of lung cancers by light microscopy, immunohistochemistry and molecular techniques have been one of the major advances in lung cancer care with substantial predictive and prognostic impact [226]. While the limited direct evidence basis of very low overall quality suggests equivalence of pathological confirmation vs. non-confirmation, the above-mentioned indirect evidence of high quality showed less harm in treating patients with pathologically confirmed lung cancers as tumour material is the fundamental requirement for subsequent tumour profiling. Thus, we consented a strong recommendation for pathological confirmation of suspected lung cancer since this constellation constitutes a paradigmatic situation according to GRADE methodology [15].

To underline the need and net benefit of performing histological subtyping and molecular profiling in confirmed lung cancers, we formulated a clear and actionable good practice statement given that direct evidence was missing as well as to avoid time-consuming efforts to formally accumulate and review the already well-established and supportive indirect evidence of high quality [228].

Conclusions, implementation considerations and research needs

Whilst pathological confirmation (whenever feasible), WHO lung cancer classification-compliant subtyping and characterization of treatable or predictive molecular targets are deemed as good clinical practice, valid evidence on their implementation in routine lung cancer diagnostics still lacks for the most part. Substantial advances in imaging validity as well as endoscopic procedures, transthoracic CT-/ultrasound-guided, minimally invasive thoracic surgery and the multi-disciplinary interplay of professionals have led to a reduction of peri-procedural risks of invasive sampling techniques.

PICO question 6: ***In patients with lung cancer (or those suspected of having lung cancer), should palliative care or its delivery by specialists be integrated into lung cancer care already early during the course of the disease rather than no integration of palliative care or no palliative care delivery by specialists?***

ERS recommendation

We suggest integrating palliative care already at an early stage into lung cancer care pathways based on patient symptom load and well-linked to routine tumour-specific management [conditional recommendation for the intervention; very low overall quality of evidence].

Remark: Delivery of palliative care may be by palliative care specialists or palliative care teams.

Problem

There is a growing body of evidence for early integration of palliative care into standard care in lung cancer but also other tumour entities which may positively influence quality of life, patient satisfaction and prognosis. This potentially beneficial practice is still not regularly implemented into routine processes though [229].

Summary of evidence and overall quality of evidence

We included 23 RCTs, two non-randomized clinical trials with a prospective sequential control-intervention-group design and five observational studies out of the 269 primarily identified abstracts [230-259]. Out of the predefined outcomes of interest, *overall survival*, *receipt of any tumour-specific therapy*, *quality of life* and *patient satisfaction* were explored in the 30 studies. All outcomes were considered critical. The overall quality of evidence was rated as very low.

Desirable effects

Improved *overall survival* was seen in the meta-analysis of one RCT and one non-randomized clinical trial providing lung cancer-specific findings for patients receiving palliative care alongside standard care (HR 1.383, 95% CI 1.047-1.824). The *receipt of any tumour-specific treatment* was not influenced by early integration in one RCT. *Quality of life* improved in four (509 patients) compared to 18 RCTs with trivial effects (1,238 patients). Four studies revealed only trivial effects regarding *patient satisfaction* (101 patients; no lung cancer-specific figures in 3 studies). The heterogeneity of quality of life and patient satisfaction tools across studies impeded meta-analyses.

Undesirable effects

None of the evaluated studies indicated any definite harms by early integration of palliative care.

Other considerations

We determined very low certainty due to concerns about risk of bias, indirectness, inconsistency, and imprecision. Standards for palliative care were previously defined by the

European Association for Palliative Care in 2009/2010 [260, 261] and similarly for the USA by the National Consensus Project for Quality Palliative Care in 2013 [262]. Yet, the modes of palliative care differed substantially in the appraised studies related to composition of palliative care teams as well as to content and extent of applied palliative care measures. Although not evident, in our perception, integrating palliative care early into standard lung cancer care has improved over time, but there still seem to subsist co-existence instead of joint patient care bearing the risk of contradictory treatment recommendations to patients by lung cancer and palliative care specialists. Likewise, we may not ignore the need to overcome the still existing stigma of palliative care as terminal care-only measure to reduce prevalent reservations among patients and professionals.

At least moderate increase of costs is assumed by us regarding comprehensive programs for implementation of palliative care into standard lung cancer care, yet sufficient cost-effectiveness models have not been introduced so far.

Justifications of recommendation

Due to the high symptom burden in lung cancer patients, we consider early integration of palliative care into standard lung cancer care as an effective measure to address the complex patient needs already at the beginning of the lung cancer continuum. The recommendation is conditional due to the very low certainty of evidence.

Conclusions, implementation considerations and research needs

The implementation of palliative care elements seems feasible when sufficient funding is provided. Joint strategies by governments and scientific societies are favoured including standardisation of palliative care measures and related quality indicators to assess outcomes. Professionals not specialized in palliative care would benefit from respective training to support coping unmet needs [229].

PICO question 7: ***In patients with lung cancer (or those suspected of having lung cancer), should quality improvement measures be applied in lung cancer care rather than no application of these methods in lung cancer care?***

ERS recommendations

We suggest utilizing national clinical lung cancer registries involving quality indicators to provide feedback for future lung cancer guidelines and to inform lung cancer services [conditional recommendation for the intervention; very low overall quality of evidence].

We suggest referring lung cancer patients to services with ready access (*) to multiple lung cancer specialist facilities (**) [conditional recommendation for the intervention; very low overall quality of evidence].

(*) ready access: reasonable proximity and timeliness

(**) lung cancer specialist facilities include functional diagnostics, imaging, endoscopy, pathology/molecular biology, thoracic surgery, radiotherapy, systemic treatments, and palliative care as well as multidisciplinary teams

We suggest developing and implementing specific quality improvement measures (***) to improve quality of lung cancer care where required and when superordinate guidance is missing [conditional recommendation, very low overall quality of evidence].

(***) i.e. clinical pathways

We suggest the implementation of an internal and/or external evaluation system (****) for lung cancer services [conditional recommendation; very low overall quality of evidence].

(****) different terms are used beside evaluation system: i.e. internal/external audit system, certification system, quality indicator systems

Problem

Quality improvement measures for lung cancer care aim to improve infrastructure, processes and patient outcomes at the same time. Rarely, their specific impact has been systematically assessed though.

Summary of evidence and overall quality of evidence

We selected thirteen observational studies out of the 1,037 initially identified abstracts which we divided into four groups to ensure clinically meaningful assessments and separate recommendations (1. cancer registries and quality indicators; 2. specialized lung cancer services; 3. quality improvement measures; 4. audits/quality indicator systems) [128, 217, 263-273]. From the predefined outcomes of interest, *overall survival*, *mortality*, *accuracy of staging*, *pathological confirmation*, *receipt of curative treatment*, and *receipt of any tumour-specific treatment* were addressed in these study groups. All outcomes were considered critical. The overall quality of evidence was rated as very low.

Desirable effects

The implementation of cancer registries and quality indicators resulted in improvement of *overall survival*, *mortality*, *accuracy of staging*, *pathological confirmation*, *receipt of curative therapy, and receipt of any tumour-specific treatment*. While exploring the impact of specialized lung cancer services, three studies demonstrated improved *overall survival* compared to less

specialized lung cancer services. Likewise, one study also proved higher *rates of receipt of any tumour-specific treatment*.

Specific quality improvement measures positively affected *overall survival*, *accuracy of staging,* and *receipt of any tumour-specific treatment*.

Three studies demonstrated better *30-day mortality* resulting from the application of audits/quality indicator systems. One study additionally detected lower *morbidity rates*.

Undesirable effects

We did not identify any harms in the four predefined groups.

Other considerations

The very low certainty resulted from noted risk of bias, indirectness, inconsistency, and imprecision. We considered higher satisfaction of patients and staff as additional benefit but were concerned about the lack of standardization and validation.

Quality improvement measures may be resource-intensive and impose costs to local healthcare providers as well as national health care systems which may be outweighed by avoided costs for non-conformity to lung cancer care standards.

Justifications of recommendations

We are confident that all four types of quality improvement measures bear the potential to optimize lung cancer processes and to improve patient-relevant outcomes. The limited and heterogeneous body of evidence with a very low level of confidence in the effect estimates led to conditional recommendations.

Conclusions, implementation considerations and research needs

Quality improvement initiatives based on the explored measures seem essential for achieving and maintaining an adequate, state-of-the-art management of lung cancer patients. Yet these measures need to be adapted according to future research and evidence-based developments.

PICO question 8: ***In patients with lung cancer (or those suspected of having lung cancer), should patient decision tools be involved in the decision-making and -sharing process rather than not involving them?***

ERS recommendation

In patients with lung cancer, we suggest using patient decision tools as a measure to improve patient involvement in decision making [conditional recommendation for the intervention; very low overall quality of evidence].

Remark: While current evidence does not suggest benefits from patient decision tools in lung cancer patients, we as a committee considered that the perceived positive impact on shared decision-making and informed consent processes outweighs barriers for certain patient subgroups.

Problem

Provision of patient information and obtainment of patient consent are fundamental ethical and legal requirements within the medical profession. However, the knowledge gap in the physician-patient relationship may impose a barrier in communication and decision-making.

Summary of evidence and overall quality of evidence

The initially phrased PICO question focussed on patient involvement as a whole. Yet, due to the scarce body of evidence retrieved by the corresponding literature search, we could only focus on patient decision tools as an intervention to facilitate better patient involvement in the shared decision-making process. Accordingly, we narrowed the scope of this PICO question. 5 RCTs were finally selected out of the 357 initially identified abstracts [274-278]. From the predefined outcomes of interest, the identified studies assessed solely *patient satisfaction.* This outcome was considered critical. The overall quality of evidence was rated as very low.

Desirable effects

Patient satisfaction was the sole outcome of interest reported in all five RCTs. None reported lung cancer-specific results. One study resulted in improved patient satisfaction when applying patient decision tools (629 patients) [278], while four studies had trivial findings (726 patients) [274-277].

Undesirable effects

None of the evaluated studies indicated any definite harms.

Other considerations

We concluded a very low certainty in the limited evidence due to concerns about risk of bias, indirectness, inconsistency, and imprecision. From our point of view, patient decision tools may additionally facilitate better disease understanding and more structured patient-professional communication. Consequently, shared decision-making, informed consent processes and patient satisfaction may result. We regard factors such as age, language barriers, educational and cultural background as well as the readiness to receive and recognise bad news as potential limitations.

Justifications of recommendation

Patient decision tools – if well-designed and implemented - may improve patient satisfaction and facilitate disease understanding. However, as our graded certainty in the limited body of evidence was very low level and only one of our outcomes of interest was addressed, we made a conditional recommendation.

Conclusions, implementation considerations and research needs

Need assessments among lung cancer patients and patient organizations as well as setting up essential standards may help to develop better patient-tailored decision tools at a sufficient quality level. In addition, modern learning theory approaches should be considered.

Summary

Based on a thorough systematic literature search, this task force compiled a comprehensive evidence basis relating to eight relevant PICO questions in quality of lung cancer care. In accordance with GRADE methodology, the systematic review revealed in several instances only sparse available evidence and for all eight PICO questions only a very low overall quality of evidence. While the certainty of effect directions suggested that implementation of quality improvement measures resulted in at least some ameliorations in 107 of all 113 assessed outcomes in the eight PICO questions, the interpretation of effect strengths was sometimes difficult due to inconsistency and imprecision among studies. Likewise, the body of evidence did not address several outcomes of interest in some PICO questions. Nevertheless, after careful considerations among our multidisciplinary panel including patient representatives, we are convinced that the deliberate implementation of our recommendations can sustainably improve quality and outcomes of lung cancer patient care. In addition, we are confident that this work will set a basis for future quality of care research and specific qualitive improvement initiatives in patient-centred lung cancer care.

Two strong recommendations were made regarding volume and specialization of care related to hospitals and individuals in surgical resections as well as pathological confirmation of suspected lung cancers. The panel felt that strong recommendations were warranted based on eligible paradigmatic scenarios with very low-quality evidence suggesting benefit in a life-threatening situation as well as very low-quality evidence suggesting equivalence of both alternatives but high-quality evidence of less harm in the intervention, respectively [15].

Ten conditional recommendations were made regarding timeliness of care, implementation of multidisciplinary teams and/or multidisciplinary consultation, guideline and SOP implementation/adherence, volume and specialization of care in procedures other than surgical resections, early integration of palliative care, implementation of quality improvement measures, and the application of patient decision tools in patient decision making.

Finally, one good practice statement was formulated on subtyping of confirmed lung cancers justified by the pre-defined GRADE-criteria [228].

The present recommendations should be reconsidered as new evidence becomes available.

Acknowledgements

We are very grateful to the European Respiratory Society for their generous support of this task force as well as to the foundation Stiftung Oskar Helene Heim (Berlin, Germany) for their unrestricted research grant to T. Blum by which the work of this task force through assistance staff was supported. In addition, we would like to thank Jessica Denning from the European Lung Foundation, Sheffield, United Kingdom for creating the plain language summary accompanying this task force report document as well as Françoise Pasleau, Université de Liège, Liège, Belgium for her contribution as librarian to the initial evidence searches.

References

1. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, Trama A, Visser O, Brenner H, Ardanaz E, Bielska-Lasota M, Engholm G, Nennecke A, Siesling S, Berrino F, Capocaccia R, Group E-W. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study. *Lancet Oncol* 2014: 15(1): 23-34.
2. International Agency for Research on Cancer, World Health Organization. Lung cancer fact sheet 2020. 2020 [cited 10.07.2022]; Available from: http://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf
3. Statistical office of the European Union. Eurostat. Cancer statistics - specific cancers. 2020 [cited 10.07.2020]; Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Cancer_statistics_-_specific_cancers#Lung_cancer
4. Luengo-Fernandez R, Leal J, Gray A, Sullivan R. Economic burden of cancer across the European Union: a population-based cost analysis. *Lancet Oncol* 2013: 14(12): 1165-1174.
5. Ellis J. The impact of lung cancer on patients and carers. *Chron Respir Dis* 2012: 9(1): 39-47.
6. Blum TG, Rich A, Baldwin D, Beckett P, De Ruysscher D, Faivre-Finn C, Gaga M, Gamarra F, Grigoriu B, Hansen NC, Hubbard R, Huber RM, Jakobsen E, Jovanovic D, Konsoulova A, Kollmeier J, Massard G, McPhelim J, Meert AP, Milroy R, Paesmans M, Peake M, Putora PM, Scherpereel A, Schonfeld N, Sitter H, Skaug K, Spiro S, Strand TE, Taright S, Thomas M, van Schil PE, Vansteenkiste JF, Wiewrodt R, Sculier JP. The European initiative for quality management in lung cancer care. *Eur Respir J* 2014: 43(5): 1254-1277.
7. Rich AL, Baldwin DR, Beckett P, Berghmans T, Boyd J, Faivre-Finn C, Galateau-Salle F, Gamarra F, Grigoriu B, Hansen N-CG, Hardavella G, Jakobsen E, Jovanovic D, Konsoulova A, Massard G, McPhelim J, Meert A-P, Milroy R, Mutti L, Paesmans M, Peake MD, Putora PM, De Ruysscher DKM, Sculier J-P, Schepereel A, Subotic DR, Van Schil P, Torsten. ERS statement on harmonised standards for lung cancer registration and lung cancer services in Europe. *European Respiratory Journal* 2018: 52(6): 1800610.
8. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, Debeer H. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011: 64(4): 383-394.
9. Alonso-Coello P, Schunemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, Treweek S, Mustafa RA, Rada G, Rosenbaum S, Morelli A, Guyatt GH, Oxman AD, Group GW. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ* 2016: 353: i2016.
10. Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, Treweek S, Mustafa RA, Vandvik PO, Meerpohl J, Guyatt GH, Schunemann HJ, Group GW. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ* 2016: 353: i2089.
11. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA, Cochrane Bias Methods G, Cochrane Statistical Methods G. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011: 343: d5928.
12. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, Montori V, Akl EA, Djulbegovic B, Falck-Ytter Y, Norris SL, Williams JW, Jr., Atkins D, Meerpohl J, Schunemann HJ. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *J Clin Epidemiol* 2011: 64(4): 407-415.
13. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, Alderson P, Glasziou P, Falck-Ytter Y, Schünemann HJ. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol* 2011: 64(4): 395-400.
14. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J,

O'Connell D, Oxman AD, Phillips B, Schunemann HJ, Edejer T, Varonen H, Vist GE, Williams JW, Jr., Zaza S, Group GW. Grading quality of evidence and strength of recommendations. *BMJ* 2004: 328(7454): 1490.
15. Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, Rind D, Montori VM, Brito JP, Norris S, Elbarbary M, Post P, Nasser M, Shukla V, Jaeschke R, Brozek J, Djulbegovic B, Guyatt G. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013: 66(7): 726-735.
16. European Respiratory Society. ERS Clinical Research Collaboration PERSPECTIVE 2021 [cited 10.07.2022]; Available from: https://www.ersnet.org/science-and-research/clinical-research-collaboration-application-programme/perspective/
17. EU IMI Grant Consortium OPTIMA. OPTIMA. 2022 [cited 10.07.2022]; Available from: https://www.optima-oncology.eu/
18. Malalasekera A, Nahm S, Blinman PL, Kao SC, Dhillon HM, Vardy JL. How long is too long? A scoping review of health system delays in lung cancer. *European Respiratory Review* 2018: 27(149): 180045.
19. Murray PV, O'Brien ME, Sayer R, Cooke N, Knowles G, Miller AC, Varney V, Rowell NP, Padhani AR, MacVicar D, Norton A, Ashley S, Smith IE. The pathway study: results of a pilot feasibility study in patients suspected of having lung carcinoma investigated in a conventional chest clinic setting compared to a centralised two-stop pathway. *Lung Cancer* 2003: 42(3): 283-290.
20. Abdel-Rahman O. Impact of Timeliness of Surgical Treatment on the Outcomes of Patients with Non-metastatic Non-small Cell Lung Cancer: Findings From the PLCO Trial. *World J Surg* 2019: 43(11): 2927-2933.
21. Porta M, Gallen M, Malats N, Planas J. Influence of "diagnostic delay" upon cancer survival: an analysis of five tumour sites. *J Epidemiol Community Health* 1991: 45(3): 225-230.
22. Robinson E, Mohilever J, Zidan J, Sapir D. Delay in diagnosis of cancer. Possible effects on the stage of disease and survival. *Cancer* 1984: 54(7): 1454-1460.
23. Yang KY, Chen YM, Huang MH, Perng RP. Revisit of primary malignant neoplasms of the trachea: clinical characteristics and survival analysis. *Jpn J Clin Oncol* 1997: 27(5): 305-309.
24. Abrao FC, de Abreu I, Rocha RO, Munhoz FD, Rodrigues JHG, Batista BN. Interaction between treatment delivery delay and stage on the mortality from non-small cell lung cancer. *J* 2018: 10(5): 2813-2819.
25. Alanen V, Koivunen JP. Association of diagnostic delays to survival in lung cancer: single center experience. *Acta Oncol* 2019: 1-6.
26. Annakkaya AN, Arbak P, Balbay O, Bilgin C, Erbas M, Bulut I. Effect of symptom-to-treatment interval on prognosis in lung cancer. *Tumori* 2007: 93(1): 61-67.
27. Bhandari S, Pham D, Pinkston C, Oechsli M, Kloecker G. Timing of treatment in small-cell lung cancer. *Med Oncol* 2019: 36(6): 47.
28. Bozcuk H, Martin C. Does treatment delay affect survival in non-small cell lung cancer? A retrospective analysis from a single UK centre. *Lung Cancer* 2001: 34(2): 243-252.
29. Bryant AS, Cerfolio RJ. Differences in outcomes between younger and older patients with non-small cell lung cancer. *Ann Thorac Surg* 2008: 85(5): 1735-1739; discussion 1739.
30. Buccheri G, Ferrigno D. Lung cancer: clinical presentation and specialist referral time. *European Respiratory Journal* 2004: 24(6): 898-904.
31. Canizares Carretero MA, Rivo Vazquez JE, Blanco Ramos M, Toscano Novella A, Garcia Fontan EM, Purrinos Hermida MJ. [Influence of delay of surgery on the survival of patients with bronchogenic carcinoma]. *Arch Bronconeumol* 2007: 43(3): 165-170.
32. Coughlin S, Plourde M, Guidolin K, Fortin D, Frechette E, Malthaner R, Inculet R. Is it safe to wait? The effect of surgical wait time on survival in patients with non-small cell lung cancer. *Can J Surg* 2015: 58(6): 414-418.
33. Di Girolamo C, Walters S, Gildea C, Benitez Majano S, Rachet B, Morris M. Can we assess Cancer Waiting Time targets with cancer survival? A population-based study of individually linked

data from the National Cancer Waiting Times monitoring dataset in England, 2009-2013. *PLoS ONE* 2018: 13(8): e0201288.
34. Diaconescu R, Lafond C, Whittom R. Treatment delays in non-small cell lung cancer and their prognostic implications. *J Thorac Oncol* 2011: 6(7): 1254-1259.
35. Forrest LF, Adams J, Rubin G, White M. The role of receipt and timeliness of treatment in socioeconomic inequalities in lung cancer survival: population-based, data-linkage study. *Thorax* 2015: 70(2): 138-145.
36. Gomez DR, Liao KP, Swisher SG, Blumenschein GR, Erasmus JJ, Jr., Buchholz TA, Giordano SH, Smith BD. Time to treatment as a quality metric in lung cancer: Staging studies, time to treatment, and patient survival. *Radiother Oncol* 2015: 115(2): 257-263.
37. Gonzalez-Barcala FJ, Falagan JA, Garcia-Prim JM, Valdes L, Carreira JM, Puga A, Martin-Lancharro P, Garcia-Sanz MT, Anton-Sanmartin D, Canive-Gomez JC, Pose-Reino A, Lopez-Lopez R. Timeliness of care and prognosis in patients with lung cancer. *Ir J Med Sci* 2014: 183(3): 383-390.
38. Gonzalez-Barcala FJ, Garcia-Prim JM, Alvarez-Dobano JM, Moldes-Rodriguez M, Garcia-Sanz MT, Pose-Reino A, Valdes-Cuadrado L. Effect of delays on survival in patients with lung cancer. *Clin Transl Oncol* 2010: 12(12): 836-842.
39. Gould MK, Ghaus SJ, Olsson JK, Schultz EM. Timeliness of care in veterans with non-small cell lung cancer. *Chest* 2008: 133(5): 1167-1173.
40. Hansen HC, Janssen S, Thieme C, Perlov A, Schild SE, Rades D. Potential Impact of the Interval Between Imaging and Whole-brain Radiotherapy in Patients With Relatively Favorable Survival Prognoses. *Anticancer Res* 2019: 39(3): 1343-1346.
41. Kanarek NF, Hooker CM, Mathieu L, Tsai HL, Rudin CM, Herman JG, Brock MV. Survival after community diagnosis of early-stage non-small cell lung cancer. *Am J Med* 2014: 127(5): 443-449.
42. Kashiwabara K, Koshi S, Itonaga K, Nakahara O, Tanaka M, Toyonaga M. Outcome in patients with lung cancer found on lung cancer mass screening roentgenograms, but who did not subsequently consult a doctor. *Lung Cancer* 2003: 40(1): 67-72.
43. Kasymjanova G, Small D, Cohen V, Jagoe RT, Batist G, Sateren W, Ernst P, Pepe C, Sakr L, Agulnik J. Lung cancer care trajectory at a Canadian centre: an evaluation of how wait times affect clinical outcomes. *Curr* 2017: 24(5): 302-309.
44. Labbe C, Anderson M, Simard S, Tremblay L, Laberge F, Vaillancourt R, Lacasse Y. Wait times for diagnosis and treatment of lung cancer: a single-centre experience. *Curr* 2017: 24(6): 367-373.
45. Montero C, Rosales M, Otero I, Blanco M, Rodriguez G, Peterga S, Pita S, Verea H. [Lung cancer in the health care area of A Coruna (Spain): incidence, clinical approach and survival]. *Arch Bronconeumol* 2003: 39(5): 209-216.
46. Myrdal G, Lambe M, Hillerdal G, Lamberg K, Agustsson T, Stahle E. Effect of delays on prognosis in patients with non-small cell lung cancer. *Thorax* 2004: 59(1): 45-49.
47. Neal RD, Allgar VL, Ali N, Leese B, Heywood P, Proctor G, Evans J. Stage, survival and delays in lung, colorectal, prostate and ovarian cancer: comparison between diagnostic routes. *Br J Gen Pract* 2007: 57(536): 212-219.
48. Pita-Fernandez S, Montero-Martinez C, Pertega-Diaz S, Verea-Hernando H. Relationship between delayed diagnosis and the degree of invasion and survival in lung cancer. *J Clin Epidemiol* 2003: 56(9): 820-825.
49. Radzikowska E, Roszkowski-Sliz K, Chabowski M, Glaz P. Influence of delays in diagnosis and treatment on survival in small cell lung cancer patients. *Adv Exp Med Biol* 2013: 788: 355-362.
50. Radzikowska E, Roszkowski-Sliz K, Glaz P. The impact of timeliness of care on survival in non-small cell lung cancer patients. *Pneumonol Alergol Pol* 2012: 80(5): 422-429.
51. Salomaa ER, Sallinen S, Hiekkanen H, Liippo K. Delays in the diagnosis and treatment of lung cancer. *Chest* 2005: 128(4): 2282-2288.
52. Shin DW, Cho J, Kim SY, Guallar E, Hwang SS, Cho B, Oh JH, Jung KW, Seo HG, Park JH. Delay to curative surgery greater than 12 weeks is associated with increased mortality in patients with colorectal and breast cancer but not lung or thyroid cancer. *Ann Surg Oncol* 2013: 20(8): 2468-2476.

53. Vinod SK, Chandra A, Berthelsen A, Descallar J. Does timeliness of care in Non-Small Cell Lung Cancer impact on survival? *Lung Cancer* 2017: 112: 16-24.
54. Yorio JT, Xie Y, Yan J, Gerber DE. Lung cancer diagnostic and treatment intervals in the United States: a health care disparity? *J Thorac Oncol* 2009: 4(11): 1322-1330.
55. Zivkovic D. Effect of delays on survival in patients with lung carcinoma in Montenegro. *Acta Clin* 2014: 53(4): 390-398.
56. Samson P, Patel A, Garrett T, Crabtree T, Kreisel D, Krupnick AS, Patterson GA, Broderick S, Meyers BF, Puri V. Effects of Delayed Surgical Resection on Short-Term and Long-Term Outcomes in Clinical Stage I Non-Small Cell Lung Cancer. *Ann Thorac Surg* 2015: 99(6): 1906-1912; discussion 1913.
57. Nadpara P, Madhavan SS, Tworek C. Guideline-concordant timely lung cancer care and prognosis among elderly patients in the United States: A population-based study. *Cancer epidemiol* 2015: 39(6): 1136-1144.
58. Redaniel MT, Martin RM, Ridd MJ, Wade J, Jeffreys M. Diagnostic intervals and its association with breast, prostate, lung and colorectal cancer survival in England: historical cohort study using the Clinical Practice Research Datalink. *PLoS ONE* 2015: 10(5): e0126608.
59. Anggondowati T, Ganti AK, Islam KMM. Impact of time-to-treatment on overall survival of non-small cell lung cancer patients-an analysis of the national cancer database. *Transl* 2020: 9(4): 1202-1211.
60. Arici S, Sakin A, Cekin R, Secmeler S, Yasar N, Cihan S. Does the Waiting Period for Genetic Tests Affect the Prognosis in Chemotherapy-Treated de novo Metastatic Non-Small Cell Lung Cancer Patients without a Driver Mutation? *Oncol Res Treat* 2020: 1-7.
61. Booth CM, Shepherd FA, Peng Y, Darling G, Li G, Kong W, Biagi JJ, Mackillop WJ. Time to adjuvant chemotherapy and survival in non-small cell lung cancer: a population-based study. *Cancer* 2013: 119(6): 1243-1250.
62. Bullard JT, Eberth JM, Arrington AK, Adams SA, Cheng X, Salloum RG. Timeliness of Treatment Initiation and Associated Survival Following Diagnosis of Non-Small-Cell Lung Cancer in South Carolina. *South Med J* 2017: 110(2): 107-113.
63. Bütof R, Kirchner K, Appold S, Löck S, Rolle A, Höffken G, Krause M, Baumann M. Potential clinical predictors of outcome after postoperative radiotherapy of non-small cell lung cancer. *Strahlenther Onkol* 2014: 190(3): 263-269.
64. Huang CS, Hsu PK, Chen CK, Yeh YC, Shih CC, Huang BS. Delayed surgery after histologic or radiologic-diagnosed clinical stage I lung adenocarcinoma. *J* 2020: 12(3): 615-625.
65. Sheinson D, Wong WB, Wu N, Mansfield AS. Impact of delaying initiation of anaplastic lymphoma kinase inhibitor treatment on survival in patients with advanced non-small-cell lung cancer. *Lung Cancer* 2020: 143: 86-92.
66. Tsai CH, Kung PT, Kuo WY, Tsai WC. Effect of time interval from diagnosis to treatment for non-small cell lung cancer on survival: a national cohort study in Taiwan. *BMJ Open* 2020: 10(4): e034351.
67. Cone EB, Marchese M, Paciotti M, Nguyen DD, Nabi J, Cole AP, Molina G, Molina RL, Minami CA, Mucci LA, Kibel AS, Trinh QD. Assessment of Time-to-Treatment Initiation and Survival in a Cohort of Patients With Common Cancers. *JAMA netw* 2020: 3(12): e2030072.
68. Aragoneses FG, Moreno N, Leon P, Fontan EG, Folque E, Bronchogenic Carcinoma Cooperative Group of the Spanish Society of P, Thoracic S. Influence of delays on survival in the surgical treatment of bronchogenic carcinoma. *Lung Cancer* 2002: 36(1): 59-63.
69. Cushman TR, Jones B, Akhavan D, Rusthoven CG, Verma V, Salgia R, Sedrak M, Massarelli E, Welsh JW, Amini A. The Effects of Time to Treatment Initiation for Patients With Non-small-cell Lung Cancer in the United States. *Clin Lung Cancer* 2020: 18.
70. Gao SJ, Corso CD, Wang EH, Blasberg JD, Detterbeck FC, Boffa DJ, Decker RH, Kim AW. Timing of Surgery after Neoadjuvant Chemoradiation in Locally Advanced Non-Small Cell Lung Cancer. *J Thorac Oncol* 2017: 12(2): 314-322.
71. Khorana AA, Tullio K, Elson P, Pennell NA, Grobmyer SR, Kalady MF, Raymond D, Abraham J, Klein EA, Walsh RM, Monteleone EE, Wei W, Hobbs B, Bolwell BJ. Time to initial cancer treatment in

the United States and association with survival over time: An observational study. *PLoS ONE* 2019: 14(3): e0213209.
72. Liu Y, Zhai X, Li J, Li Z, Ma D, Wang Z. Is there an optimal time to initiate adjuvant chemotherapy to predict benefit of survival in non-small cell lung cancer? *Chin* 2017: 29(3): 263-271.
73. Ramsden K, Laskin J, Ho C. Adjuvant Chemotherapy in Resected Stage II Non-small Cell Lung Cancer: Evaluating the Impact of Dose Intensity and Time to Treatment. *Clinical Oncology (Royal College of Radiologists)* 2015: 27(7): 394-400.
74. Salazar MC, Rosen JE, Wang Z, Arnold BN, Thomas DC, Herbst RS, Kim AW, Detterbeck FC, Blasberg JD, Boffa DJ. Association of Delayed Adjuvant Chemotherapy With Survival After Lung Cancer Surgery. *JAMA Oncol* 2017: 3(5): 610-619.
75. Samson P, Crabtree TD, Robinson CG, Morgensztern D, Broderick S, Krupnick AS, Kreisel D, Patterson GA, Meyers B, Puri V. Defining the Ideal Time Interval Between Planned Induction Therapy and Surgery for Stage IIIA Non-Small Cell Lung Cancer. *Ann Thorac Surg* 2017: 103(4): 1070-1075.
76. Wah W, Stirling RG, Ahern S, Earnest A. Influence of timeliness and receipt of first treatment on geographic variation in non-small cell lung cancer mortality. *Int J Cancer* 2020: 12.
77. Würschmidt F, Bünemann H, Ehnert M, Heilmann HP. Is the time interval between surgery and radiotherapy important in operable nonsmall cell lung cancer? A retrospective analysis of 340 cases. *Int J Radiat Oncol Biol Phys* 1997: 39(3): 553-559.
78. Yang CJ, Wang H, Kumar A, Wang X, Hartwig MG, D'Amico TA, Berry MF. Impact of Timing of Lobectomy on Survival for Clinical Stage IA Lung Squamous Cell Carcinoma. *Chest* 2017: 152(6): 1239-1250.
79. Bhandari S, Kumar R, Pham D, Gaskins J, Kloecker G. Treatment Timing in Small Cell Lung Cancer, a National Cancer Database Analysis. *Am J Clin Oncol* 2020: 43(5): 362-365.
80. Loh LC, Chan LY, Tan RY, Govindaraju S, Ratnavelu K, Kumar S, Raman S, Vijayasingham P, Thayaparan T. Effect of time delay on survival in patients with non-small cell lung cancer--a Malaysian study. *Asia Pac J Public Health* 2006: 18(1): 69-71.
81. Quarterman RL, McMillan A, Ratcliffe MB, Block MI. Effect of preoperative delay on prognosis for patients with early stage non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2003: 125(1): 108-113; discussion 113-104.
82. Torring ML, Frydenberg M, Hansen RP, Olesen F, Vedsted P. Evidence of increasing mortality with longer diagnostic intervals for five common cancers: a cohort study in primary care. *Eur J Cancer* 2013: 49(9): 2187-2198.
83. Wang L, Correa CR, Hayman JA, Zhao L, Cease K, Brenner D, Arenberg D, Curtis J, Kalemkerian GP, Kong FM. Time to treatment in patients with stage III non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2009: 74(3): 790-795.
84. Comber H, Cronin DP, Deady S, Lorcain PO, Riordan P. Delays in treatment in the cancer services: impact on cancer stage and survival. *Ir Med J* 2005: 98(8): 238-239.
85. Yun YH, Kim YA, Min YH, Park S, Won YJ, Kim DY, Choi IJ, Kim YW, Park SJ, Kim JH, Lee DH, Yoon SJ, Jeong SY, Noh DY, Heo DS. The influence of hospital volume and surgical treatment delay on long-term survival after cancer surgery. *Ann Oncol* 2012: 23(10): 2731-2737.
86. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 1985: 312(25): 1604-1608.
87. Gravier FE, Smondack P, Prieur G, Medrinal C, Combret Y, Muir JF, Baste JM, Cuvelier A, Boujibar F, Bonnevie T. Effects of exercise training in people with non-small cell lung cancer before lung resection: a systematic review and meta-analysis. *Thorax* 2022: 77(5): 486-496.
88. Weller D, Vedsted P, Rubin G, Walter FM, Emery J, Scott S, Campbell C, Andersen RS, Hamilton W, Olesen F, Rose P, Nafees S, Van Rijswijk E, Hiom S, Muth C, Beyer M, Neal RD. The Aarhus statement: improving design and reporting of studies on early cancer diagnosis. *Br J Cancer* 2012: 106(7): 1262-1267.
89. Powell HA, Baldwin DR. Multidisciplinary team management in thoracic oncology: more than just a concept? *Eur Respir J* 2014: 43(6): 1776-1786.

90. Bilfinger TV, Albano D, Perwaiz M, Keresztes R, Nemesure B. Survival Outcomes Among Lung Cancer Patients Treated Using a Multidisciplinary Team Approach. *Clin Lung Cancer* 2018: 19(4): 346-351.
91. Bowen EF, Anderson JR, Roddie ME. Improving surgical resection rates in lung cancer without a two stop service. *Thorax* 2003: 58(4): 368.
92. Boxer MM, Vinod SK, Shafiq J, Duggan KJ. Do multidisciplinary team meetings make a difference in the management of lung cancer? *Cancer* 2011: 117(22): 5112-5120.
93. Bydder S, Nowak A, Marion K, Phillips M, Atun R. The impact of case discussion at a multidisciplinary team meeting on the treatment and survival of patients with inoperable non-small cell lung cancer. *Intern Med J* 2009: 39(12): 838-841.
94. Dillman RO, Chico SD. Cancer patient survival improvement is correlated with the opening of a community cancer center: comparisons with intramural and extramural benchmarks. *J Oncol Pract* 2005: 1(3): 84-92.
95. Fergusson RJ, Thomson CS, Brewster DH, Brown PH, Milroy R, Scottish Cancer Trials Lung G, Scottish Cancer Therapy N. Lung cancer: the importance of seeing a respiratory physician. *European Respiratory Journal* 2003: 21(4): 606-610.
96. Forrest LM, McMillan DC, McArdle CS, Dunlop DJ. An evaluation of the impact of a multidisciplinary team, in a single centre, on treatment and survival in patients with inoperable non-small-cell lung cancer. *Br J Cancer* 2005: 93(9): 977-978.
97. Freeman RK, Van Woerkom JM, Vyverberg A, Ascioti AJ. The effect of a multidisciplinary thoracic malignancy conference on the treatment of patients with lung cancer. *European Journal of Cardio-Thoracic Surgery* 2010: 38(1): 1-5.
98. Friedman EL, Kruklitis RJ, Patson BJ, Sopka DM, Weiss MJ. Effectiveness of a thoracic multidisciplinary clinic in the treatment of stage III non-small-cell lung cancer. *J Multidiscip Healthc* 2016: 9: 267-274.
99. Hung HY, Tseng YH, Chao HS, Chiu CH, Hsu WH, Hsu HS, Wu YC, Chou TY, Chen CK, Lan KL, Chen YW, Wu YH, Chen YM. Multidisciplinary team discussion results in survival benefit for patients with stage III non-small-cell lung cancer. *PLoS ONE* 2020: 15(10): e0236503.
100. Keating NL, Landrum MB, Lamont EB, Bozeman SR, Shulman LN, McNeil BJ. Tumor boards and the quality of cancer care. *J Natl Cancer Inst* 2013: 105(2): 113-121.
101. Kehl KL, Landrum MB, Kahn KL, Gray SW, Chen AB, Keating NL. Tumor board participation among physicians caring for patients with lung or colorectal cancer. *J Oncol Pract* 2015: 11(3): e267-278.
102. Lau KK, Rathinam S, Waller DA, Peake MD. The effects of increased provision of thoracic surgical specialists on the variation in lung cancer resection rate in England. *J Thorac Oncol* 2013: 8(1): 68-72.
103. Martin-Ucar AE, Waller DA, Atkins JL, Swinson D, O'Byrne KJ, Peake MD. The beneficial effects of specialist thoracic surgery on the resection rate for non-small-cell lung cancer. *Lung Cancer* 2004: 46(2): 227-232.
104. Mitchell PL, Thursfield VJ, Ball DL, Richardson GE, Irving LB, Torn-Broers Y, Giles GG, Wright GM. Lung cancer in Victoria: are we making progress? *Med J Aust* 2013: 199(10): 674-679.
105. Nemesure B, Albano D, Bilfinger T. Lung cancer recurrence and mortality outcomes over a 10-year period using a multidisciplinary team approach. *Cancer epidemiol* 2020: 68: 101804.
106. Nwaejike N, Elbur E, Malagon I, Dodman N, Hewitt K, Fontaine E, Krysiak P, Jones M, Shah R, Rammohan KS. Is there a role for the high-risk multidisciplinary team meeting in thoracic surgery? *Interact Cardiovasc Thorac Surg* 2016: 22(4): 397-400.
107. Pan CC, Kung PT, Wang YH, Chang YC, Wang ST, Tsai WC. Effects of multidisciplinary team care on the survival of patients with different stages of non-small cell lung cancer: a national cohort study. *PLoS ONE* 2015: 10(5): e0126547.
108. Riedel RF, Wang X, McCormack M, Toloza E, Montana GS, Schreiber G, Kelley MJ. Impact of a multidisciplinary thoracic oncology clinic on the timeliness of care. *J Thorac Oncol* 2006: 1(7): 692-696.

109. Rogers MJ, Matheson L, Garrard B, Maher B, Cowdery S, Luo W, Reed M, Riches S, Pitson G, Ashley DM. Comparison of outcomes for cancer patients discussed and not discussed at a multidisciplinary meeting. *Public Health* 2017: 149: 74-80.
110. Stevens W, Stevens G, Kolbe J, Cox B. Management of stages I and II non-small-cell lung cancer in a New Zealand study: divergence from international practice and recommendations. *Intern Med J* 2008: 38(10): 758-768.
111. Stewart I, Leary A, Khakwani A, Borthwick D, Tod A, Hubbard R, Beckett P, Tata LJ. Do working practices of cancer nurse specialists improve clinical outcomes? Retrospective cohort analysis from the English National Lung Cancer Audit. *Int J Nurs Stud* 2020: 103718.
112. Stone E, Rankin N, Kerr S, Fong K, Currow DC, Phillips J, Connon T, Zhang L, Shaw T. Does presentation at multidisciplinary team meetings improve lung cancer survival? Findings from a consecutive cohort study. *Lung Cancer* 2018: 124: 199-204.
113. Tamburini N, Maniscalco P, Mazzara S, Maietti E, Santini A, Calia N, Stefanelli A, Frassoldati A, Santi I, Rinaldi R, Nigim F, Righi R, Pedrazzi S, Cavallesco G. Multidisciplinary management improves survival at 1 year after surgical treatment for non-small-cell lung cancer: a propensity score-matched study. *European Journal of Cardio-Thoracic Surgery* 2018: 53(6): 1199-1204.
114. Berghmans T, Lievens Y, Aapro M, Baird AM, Beishon M, Calabrese F, Degi C, Delgado Bolton RC, Gaga M, Lovey J, Luciani A, Pereira P, Prosch H, Saar M, Shackcloth M, Tabak-Houwaard G, Costa A, Poortmans P. European Cancer Organisation Essential Requirements for Quality Cancer Care (ERQCC): Lung cancer. *Lung Cancer* 2020: 150: 221-239.
115. Russell GK, Jimenez S, Martin L, Stanley R, Peake MD, Woolhouse I. A multicentre randomised controlled trial of reciprocal lung cancer peer review and supported quality improvement: results from the improving lung cancer outcomes project. *Br J Cancer* 2014: 110(8): 1936-1942.
116. Fervers B, Burgers JS, Haugh MC, Brouwers M, Browman G, Cluzeau F, Philip T. Predictors of high quality clinical practice guidelines: examples in oncology. *Int J Qual Health Care* 2005: 17(2): 123-132.
117. Commission; E. Aid Delivery Methods. Volume 1. Project Cycle Management Guidelines. European Commission, Brussels, 2004.
118. Nuckols TK, Lim Y-W, Wynn BO, Mattke S, Maclean CH, Harber P, Brook RH, Wallace P, Garland RH, Asch S. Rigorous Development does not Ensure that Guidelines are Acceptable to a Panel of Knowledgeable Providers. *Journal of General Internal Medicine* 2008: 23(1): 37-44.
119. Shaneyfelt TM, Mayo-Smith MF, Rothwangl J. Are Guidelines Following Guidelines? *Jama* 1999: 281(20): 1900.
120. Perrier L, Mrklas K, Lavis JN, Straus SE. Interventions encouraging the use of systematic reviews by health policymakers and managers: A systematic review. *Implementation Science* 2011: 6(1): 43.
121. Murthy L, Shepperd S, Clarke MJ, Garner SE, Lavis JN, Perrier L, Roberts NW, Straus SE. Interventions to improve the use of systematic reviews in decision-making by health system managers, policy makers and clinicians. *Cochrane Database Syst Rev* 2012(9): CD009401.
122. Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, Whitty P, Eccles MP, Matowe L, Shirran L, Wensing M, Dijkstra R, Donaldson C. Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health Technol Assess* 2004: 8(6): iii-iv, 1-72.
123. Ahmed HZ, Liu Y, O'Connell K, Ahmed MZ, Cassidy RJ, Gillespie TW, Patel P, Pillai RN, Behera M, Steuer CE, Owonikoko TK, Ramalingam SS, Curran WJ, Higgins KA. Guideline-concordant Care Improves Overall Survival for Locally Advanced Non-Small-cell Lung Carcinoma Patients: A National Cancer Database Analysis. *Clin Lung Cancer* 2017: 18(6): 706-718.
124. Allen JW, Farooq A, O'Brien TF, Osarogiagbon RU. Quality of surgical resection for nonsmall cell lung cancer in a US metropolitan area. *Cancer* 2011: 117(1): 134-142.
125. Boxer MM, Duggan KJ, Descallar J, Vinod SK. Do patients discussed at a lung cancer multidisciplinary team meeting receive guideline-recommended treatment? *Asia Pac J Clin Oncol* 2016: 12(1): 52-60.

126. Casebeer A, Antol DD, DeClue RW, Hopson S, Li Y, Khoury R, Michael T, Sehman M, Parikh A, Stemkowski S, Bunce M. The Relationship Between Guideline-Recommended Initiation of Therapy, Outcomes, and Cost for Patients with Metastatic Non-Small Cell Lung Cancer. *J Manag Care Spec Pharm* 2018: 24(6): 554-564.
127. Elegbede AA, Gibson AJ, Fu H, Dean ML, Ezeife DA, Lau H, Cheung WY, Bebb DG. Real-World Adherence to Guideline-Recommended Treatment for Small Cell Lung Cancer. *American Journal of Clinical Oncology* 2020: 43(4): 236-242.
128. Jakobsen E, Green A, Oesterlind K, Rasmussen TR, Iachina M, Palshof T. Nationwide quality improvement in lung cancer care: the role of the Danish Lung Cancer Group and Registry. *J Thorac Oncol* 2013: 8(10): 1238-1247.
129. Mainz J, Hansen AM, Palshof T, Bartels PD. National quality measurement using clinical indicators: the Danish National Indicator Project. *J Surg Oncol* 2009: 99(8): 500-504.
130. McCarthy M, Datta P, Khachatryan A, Coleman MP, Rachet B. eWould compliance with cancer care standards improve survival for breast, colorectal and lung cancers? *J Epidemiol Community Health* 2008: 62(7): 650-654.
131. Nadpara PA, Madhavan SS, Tworek C, Sambamoorthi U, Hendryx M, Almubarak M. Guideline-concordant lung cancer care and associated health outcomes among elderly patients in the United States. *J Geriatr Oncol* 2015: 6(2): 101-110.
132. Neubauer MA, Hoverman JR, Kolodziej M, Reisman L, Gruschkus SK, Hoang S, Alva AA, McArthur M, Forsyth M, Rothermel T, Beveridge RA. Cost effectiveness of evidence-based treatment guidelines for the treatment of non-small-cell lung cancer in the community setting. *Journal of oncology practice/American Society of Clinical Oncology* 2010: 6(1): 12-18.
133. Novoa N, Jimenez MF, Aranda JL, Rodriguez M, Ramos J, Gomez Hernandez MT, Varela G. Effect of implementing the European guidelines for functional evaluation before lung resection on cardiorespiratory morbidity and 30-day mortality in lung cancer patients: a case-control study on a matched series of patients. *European Journal of Cardio-Thoracic Surgery* 2014: 45(4): e89-93; discussion e93.
134. Odell DD, Feinglass J, Engelhardt K, Papastefan S, Meyerson SL, Bharat A, DeCamp MM, Bilimoria KY. Evaluation of adherence to the Commission on Cancer lung cancer quality measures. *J Thorac Cardiovasc Surg* 2019: 157(3): 1219-1235.
135. Osarogiagbon RU, Ray MA, Faris NR, Smeltzer MP, Fehnel C, Houston-Harris C, Signore RS, McHugh LM, Levy P, Wiggins L, Sachdev V, Robbins ET. Prognostic Value of National Comprehensive Cancer Network Lung Cancer Resection Quality Criteria. *Ann Thorac Surg* 2017: 103(5): 1557-1565.
136. Samson P, Crabtree T, Broderick S, Kreisel D, Krupnick AS, Patterson GA, Meyers B, Puri V. Quality Measures in Clinical Stage I Non-Small Cell Lung Cancer: Improved Performance Is Associated With Improved Survival. *Ann Thorac Surg* 2017: 103(1): 303-311.
137. Yue D, Gong L, You J, Su Y, Zhang Z, Zhang Z, Gu F, Wang M, Wang C. Survival analysis of patients with non-small cell lung cancer who underwent surgical resection following 4 lung cancer resection guidelines. *BMC Cancer* 2014: 14: 422.
138. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, Fervers B, Graham ID, Grimshaw J, Hanna SE, Littlejohns P, Makarski J, Zitzelsberger L. AGREE II: advancing guideline development, reporting and evaluation in health care. *Cmaj* 2010: 182(18): E839-842.
139. Jørgensen AW, Hilden J, Gøtzsche PC. Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review. *Bmj* 2006: 333(7572): 782.
140. Fang P, He W, Gomez D, Hoffman KE, Smith BD, Giordano SH, Jagsi R, Smith GL. Racial disparities in guideline-concordant cancer care and mortality in the United States. *Adv Radiat Oncol* 2018: 3(3): 221-229.
141. Wauters I, Robays J, Verleye L, Holdt Henningsen K, Hulstaert F, Berghmans T, De Wever W, Y.; L, Pauwels P, Stroobants S, Van Houtte P, Van Meerbeeck J, Van Schil P, Weynand B, De Grève J. Cancer du poumon à petites cellules et non à petites cellules: diagnostic, traitement et suivi -

Synthèse. Good Clinical Practice (GCP). KCE Reports 206Bs. D/2013/10.273/54. Brussels: Centre Fédéral d'Expertise des Soins de Santé (KCE); 2013.
142. von Meyenfeldt EM, Gooiker GA, van Gijn W, Post PN, van de Velde CJ, Tollenaar RA, Klomp HM, Wouters MW. The relationship between volume or surgeon specialty and outcome in the surgical treatment of lung cancer: a systematic review and meta-analysis. *J Thorac Oncol* 2012: 7(7): 1170-1178.
143. Bach PB, Cramer LD, Schrag D, Downey RJ, Gelfand SE, Begg CB. The influence of hospital volume on survival after resection for lung cancer. *N Engl J Med* 2001: 345(3): 181-188.
144. Baum P, Diers J, Haag J, Klotz L, Eichhorn F, Eichhorn M, Wiegering A, Winter H. Nationwide effect of high procedure volume in lung cancer surgery on in-house mortality in Germany. *Lung Cancer* 2020: 149: 78-83.
145. Begg CB, Cramer LD, Hoskins WJ, Brennan MF. Impact of hospital volume on operative mortality for major cancer surgery. *Jama* 1998: 280(20): 1747-1751.
146. Bernard A, Cottenet J, Mariet AS, Quantin C, Pages PB. Is an activity volume threshold really realistic for lung cancer resection? *J* 2018: 10(10): 5685-5694.
147. Bernard A, Pages PB, Mariet AS, Pforr A, Cottenet J, Quantin C. [Evaluation of surgical practice in the treatment of lung cancer in France from the PMSI national database]. *Rev Mal Respir* 2019: 36(1): 31-38.
148. Bilimoria KY, Bentrem DJ, Feinglass JM, Stewart AK, Winchester DP, Talamonti MS, Ko CY. Directing surgical quality improvement initiatives: comparison of perioperative mortality and long-term survival for cancer surgery. *Journal of Clinical Oncology* 2008: 26(28): 4626-4633.
149. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. *N Engl J Med* 2003: 349(22): 2117-2127.
150. Birkmeyer JD, Sun Y, Goldfaden A, Birkmeyer NJ, Stukel TA. Volume and process of care in high-risk cancer surgery. *Cancer* 2006: 106(11): 2476-2481.
151. Birkmeyer JD, Sun Y, Wong SL, Stukel TA. Hospital volume and late survival after cancer surgery. *Ann Surg* 2007: 245(5): 777-783.
152. Burgers JA, Damhuis RA. 30-day mortality after the start of systemic anticancer therapy for lung cancer: is it really a useful performance indicator? *ERJ open res* 2018: 4(4).
153. Chang CM, Huang KY, Hsu TW, Su YC, Yang WZ, Chen TC, Chou P, Lee CC. Multivariate analyses to assess the effects of surgeon and hospital volume on cancer survival rates: a nationwide population-based study in Taiwan. *PLoS ONE* 2012: 7(7): e40590.
154. Cheung MC, Hamilton K, Sherman R, Byrne MM, Nguyen DM, Franceschi D, Koniaris LG. Impact of teaching facility status and high-volume centers on outcomes for lung cancer resection: an examination of 13,469 surgical patients. *Ann Surg Oncol* 2009: 16(1): 3-13.
155. Committee for Scientific A, Kazui T, Osada H, Fujita H. An attempt to analyze the relation between hospital surgical volume and clinical outcome. *Gen Thorac Cardiovasc Surg* 2007: 55(12): 483-492.
156. Damhuis RA, Maat AP, Plaisier PW. Performance indicators for lung cancer surgery in the Netherlands. *European Journal of Cardio-Thoracic Surgery* 2015: 47(5): 897-903; discussion 903-894.
157. Eaton BR, Pugh SL, Bradley JD, Masters G, Kavadi VS, Narayan S, Nedzi L, Robinson C, Wynn RB, Koprowski C, Johnson DW, Meng J, Curran WJ, Jr. Institutional Enrollment and Survival Among NSCLC Patients Receiving Chemoradiation: NRG Oncology Radiation Therapy Oncology Group (RTOG) 0617. *J Natl Cancer Inst* 2016: 108(9).
158. Falcoz PE, Puyraveau M, Rivera C, Bernard A, Massard G, Mauny F, Dahan M, Thomas PA, Epithor G. The impact of hospital and surgeon volume on the 30-day mortality of lung cancer surgery: A nation-based reappraisal. *J Thorac Cardiovasc Surg* 2014: 148(3): 841-848; discussion 848.
159. Finlayson EV, Goodney PP, Birkmeyer JD. Hospital volume and operative mortality in cancer surgery: a national study. *Arch Surg* 2003: 138(7): 721-725; discussion 726.
160. Freixinet JL, Julia-Serda G, Rodriguez PM, Santana NB, de Castro FR, Fiuza MD, Lopez-Encuentra A, Bronchogenic Carcinoma Cooperative Group of the Spanish Society of P, Thoracic Surgery G-S. Hospital volume: operative morbidity, mortality and survival in thoracotomy for lung

cancer. A Spanish multicenter study of 2994 cases. *European Journal of Cardio-Thoracic Surgery* 2006: 29(1): 20-25.
161. Gansler T, Fedewa SA, Flanders D, Virgo KS, Ward EM. "Lumping" vs "splitting" in oncologic pathology: association with cancer center type and case volume. *J Registry Manag* 2012: 39(2): 43-52.
162. Goyal G, Kommalapati A, Bartley AC, Gunderson TM, Adjei AA, Go RS. Association between hospital volume and mortality of patients with metastatic non-small cell lung cancer. *Lung Cancer* 2018: 122: 214-219.
163. Hadaya J, Dobaria V, Aguayo E, Mandelbaum A, Sanaiha Y, Revels SL, Benharash P. Impact of Hospital Volume on Outcomes of Elective Pneumonectomy in the United States. *Ann Thorac Surg* 2020: 110(6): 1874-1881.
164. Hannan EL, Radzyner M, Rubin D, Dougherty J, Brennan MF. The influence of hospital and surgeon volume on in-hospital mortality for colectomy, gastrectomy, and lung lobectomy in patients with cancer. *Surgery* 2002: 131(1): 6-15.
165. Harrison S, Tangel V, Wu X, Christos P, Gaber-Baylis L, Turnbull Z, Port J, Altorki N, Stiles B. Are minimum volume standards appropriate for lung and esophageal surgery? *J Thorac Cardiovasc Surg* 2018: 155(6): 2683-2694.e2681.
166. Hiraishi Y, Jo T, Michihata N, Hasegawa W, Sakamoto Y, Urushiyama H, Matsui H, Fushimi K, Nagase T, Yasunaga H, Yamauchi Y. Hospital Volume and Mortality following Diagnostic Bronchoscopy in Lung Cancer Patients: Data from a National Inpatient Database in Japan. *Respiration* 2019: 97(3): 264-272.
167. Hoffmann H, Passlick B, Ukena D, Wesselmann S. [Surgical Therapy for Lung Cancer: Why it Should be Performed in High Volume Centres]. *Zentralbl Chir* 2019: 144(1): 62-70.
168. Hollenbeck BK, Hong J, Zaojun Y, Birkmeyer JD. Misclassification of hospital volume with Surveillance, Epidemiology, and End Results Medicare data. *Surg Innov* 2007: 14(3): 192-198.
169. Ioka A, Tsukuma H, Ajiki W, Oshima A. Hospital procedure volume and survival of cancer patients in Osaka, Japan: a population-based study with latest cases. *Jpn J Clin Oncol* 2007: 37(7): 544-553.
170. Kim SY, Park JH, Kim SG, Woo HK, Park JH, Kim Y, Park EC. Disparities in utilization of high-volume hospitals for cancer surgery: results of a Korean population-based study. *Ann Surg Oncol* 2010: 17(11): 2806-2815.
171. Kozower BD, Stukenborg GJ. The relationship between hospital lung cancer resection volume and patient mortality risk. *Ann Surg* 2011: 254(6): 1032-1037.
172. Learn PA, Bach PB. A decade of mortality reductions in major oncologic surgery: the impact of centralization and quality improvement. *Med Care* 2010: 48(12): 1041-1049.
173. Lee JS, Scott CB, Komaki R, Ettinger DS, Sause WT. Impact of institutional experience on survival outcome of patients undergoing combined chemoradiation therapy for inoperable non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2002: 52(2): 362-370.
174. Li WW, Visser O, Ubbink DT, Klomp HM, Kloek JJ, de Mol BA. The influence of provider characteristics on resection rates and survival in patients with localized non-small cell lung cancer. *Lung Cancer* 2008: 60(3): 441-451.
175. Lien YC, Huang MT, Lin HC. Association between surgeon and hospital volume and in-hospital fatalities after lung cancer resections: the experience of an Asian country. *Ann Thorac Surg* 2007: 83(5): 1837-1843.
176. Little AG, Rusch VW, Bonner JA, Gaspar LE, Green MR, Webb WR, Stewart AK. Patterns of surgical care of lung cancer patients. *Ann Thorac Surg* 2005: 80(6): 2051-2056; discussion 2056.
177. Luchtenborg M, Riaz SP, Coupland VH, Lim E, Jakobsen E, Krasnik M, Page R, Lind MJ, Peake MD, Moller H. High procedure volume is strongly associated with improved survival after lung cancer surgery. *Journal of Clinical Oncology* 2013: 31(25): 3141-3146.
178. Moller H, Riaz SP, Holmberg L, Jakobsen E, Lagergren J, Page R, Peake MD, Pearce N, Purushotham A, Sullivan R, Vedsted P, Luchtenborg M. High lung cancer surgical procedure volume is

associated with shorter length of stay and lower risks of re-admission and death: National cohort analysis in England. *Eur J Cancer* 2016: 64: 32-43.
179. Moore CB, Cox ML, Mulvihill MS, Klapper J, D'Amico TA, Hartwig MG. Challenging 30-day mortality as a site-specific quality metric in non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2019: 28.
180. Mulvihill MS, Cox ML, Becerra DC, Watson JA, Voigt SL, Yerokun BA, Speicher PJ, D'Amico TA, Tong B, Hartwig MG. Higher Utilization of Surgery Confers Superior Survival in Stage I Non-Small Cell Lung Cancer. *Ann Thorac Surg* 2018: 27.
181. Khuri SF, Daley J, Henderson W, Hur K, Hossain M, Soybel D, Kizer KW, Aust JB, Bell RH, Jr., Chong V, Demakis J, Fabri PJ, Gibbs JO, Grover F, Hammermeister K, McDonald G, Passaro E, Jr., Phillips L, Scamman F, Spencer J, Stremple JF. Relation of surgical volume to outcome in eight common operations: results from the VA National Surgical Quality Improvement Program. *Ann Surg* 1999: 230(3): 414-429; discussion 429-432.
182. Kommalapati A, Tella SH, Appiah AK, Smith L, Ganti AK. Association Between Treatment Facility Volume, Therapy Types, and Overall Survival in Patients With Stage IIIA Non-Small Cell Lung Cancer. *Journal of the National Comprehensive Cancer Network* 2019: 17(3): 229-236.
183. Kunisawa S, Yamashita K, Ikai H, Otsubo T, Imanaka Y. Survival analyses of postoperative lung cancer patients: an investigation using Japanese administrative data. *Springerplus* 2014: 3: 217.
184. Nagayasu T, Sato S, Yamamoto H, Yamasaki N, Tsuchiya T, Matsumoto K, Miyazaki T, Endo S, Tanaka F, Yokomise H, Okumura M. The impact of certification of general thoracic surgeons on lung cancer mortality: a survey by The Japanese Association for Thoracic Surgery. *European Journal of Cardio-Thoracic Surgery* 2016: 49(5): e134-140.
185. Nathan H, Atoria CL, Bach PB, Elkin EB. Hospital volume, complications, and cost of cancer surgery in the elderly. *Journal of Clinical Oncology* 2015: 33(1): 107-114.
186. Okawa S, Tabuchi T, Morishima T, Koyama S, Taniyama Y, Miyashiro I. Hospital volume and postoperative 5-year survival for five different cancer sites: A population-based study in Japan. *Cancer Sci* 2020: 111(3): 985-993.
187. Osada H, Yamakoshi E. Hospital volume and surgical outcomes of lung cancer in Japan. *Gen Thorac Cardiovasc Surg* 2007: 55(9): 360-365.
188. Ost DE, Ernst A, Lei X, Feller-Kopman D, Eapen GA, Kovitz KL, Herth FJ, Simoff M, Registry AQB. Diagnostic yield of endobronchial ultrasound-guided transbronchial needle aspiration: results of the AQuIRE Bronchoscopy Registry. *Chest* 2011: 140(6): 1557-1566.
189. Otake H, Yasunaga H, Horiguchi H, Matsutani N, Matsuda S, Ohe K. Impact of hospital volume on chest tube duration, length of stay, and mortality after lobectomy. *Ann Thorac Surg* 2011: 92(3): 1069-1074.
190. Pages PB, Cottenet J, Mariet AS, Bernard A, Quantin C. In-hospital mortality following lung cancer resection: nationwide administrative database. *European Respiratory Journal* 2016: 47(6): 1809-1817.
191. Pezzi CM, Mallin K, Mendez AS, Greer Gay E, Putnam JB, Jr. Ninety-day mortality after resection for lung cancer is nearly double 30-day mortality. *J Thorac Cardiovasc Surg* 2014: 148(5): 2269-2277.
192. Romano PS, Mark DH. Patient and hospital characteristics related to in-hospital mortality after lung cancer resection. *Chest* 1992: 101(5): 1332-1337.
193. Sakata R, Kuwano H, Yokomise H. Hospital volume and outcomes of cardiothoracic surgery in Japan: 2005-2009 national survey. *Gen Thorac Cardiovasc Surg* 2012: 60(10): 625-638.
194. Schillemans V, Vrijens F, De Gendt C, Robays J, Silversmit G, Verleye L, Camberlin C, Dubois C, Stordeur S, Wauters I, Van Meerbeeck JP, Van Eycken E, De Leyn P. Association between surgical volume and post-operative mortality and survival after surgical resection in lung cancer in Belgium: A population-based study. *Eur J Surg Oncol* 2019: 16.
195. Sheetz KH, Chhabra KR, Smith ME, Dimick JB, Nathan H. Association of Discretionary Hospital Volume Standards for High-risk Cancer Surgery With Patient Outcomes and Access, 2005-2016. *JAMA Surg* 2019: 14.

196. Simunovic M, Rempel E, Theriault ME, Coates A, Whelan T, Holowaty E, Langer B, Levine M. Influence of hospital characteristics on operative death and survival of patients after major cancer surgery in Ontario. *Can J Surg* 2006: 49(4): 251-258.
197. Sioris T, Sihvo E, Sankila R, Salo J. Effect of surgical volume and hospital type on outcome in non-small cell lung cancer surgery: a Finnish population-based study. *Lung Cancer* 2008: 59(1): 119-125.
198. Soares M, Toffart AC, Timsit JF, Burghi G, Irrazabal C, Pattison N, Tobar E, Almeida BF, Silva UV, Azevedo LC, Rabbat A, Lamer C, Parrot A, Souza-Dantas VC, Wallet F, Blot F, Bourdin G, Piras C, Delemazure J, Durand M, Tejera D, Salluh JI, Azoulay E, Lung Cancer in Critical Care Study I. Intensive care in patients with lung cancer: a multinational study. *Ann Oncol* 2014: 25(9): 1829-1835.
199. Strand TE, Rostad H, Damhuis RA, Norstein J. Risk factors for 30-day mortality after resection of lung cancer and prediction of their magnitude. *Thorax* 2007: 62(11): 991-997.
200. Thai AA, Stuart E, Te Marvelde L, Milne RL, Knight S, Whitfield K, Mitchell P. Hospital lung surgery volume and patient outcomes. *Lung Cancer* 2019: 129: 22-27.
201. Tchouta LN, Park HS, Boffa DJ, Blasberg JD, Detterbeck FC, Kim AW. Hospital Volume and Outcomes of Robot-Assisted Lobectomies. *Chest* 2017: 151(2): 329-339.
202. Urbach DR, Bell CM, Austin PC. Differences in operative mortality between high- and low-volume hospitals in Ontario for 5 major surgical procedures: estimating the number of lives potentially saved through regionalization. *Cmaj* 2003: 168(11): 1409-1414.
203. Urbach DR, Baxter NN. Does it matter what a hospital is "high volume" for? Specificity of hospital volume-outcome associations for surgical procedures: analysis of administrative data. *Qual Saf Health Care* 2004: 13(5): 379-383.
204. von Itzstein MS, Lu R, Kernstine KH, Halm EA, Wang S, Xie Y, Gerber DE. Closing the gap: Contribution of surgical best practices to outcome differences between high- and low-volume centers for lung cancer resection. *Cancer Med* 2020: 21.
205. Wouters MW, Siesling S, Jansen-Landheer ML, Elferink MA, Belderbos J, Coebergh JW, Schramel FM. Variation in treatment and outcome in patients with non-small cell lung cancer by region, hospital type and volume in the Netherlands. *Eur J Surg Oncol* 2010: 36 Suppl 1: S83-92.
206. Bendzsak AM, Baxter NN, Darling GE, Austin PC, Urbach DR. Regionalization and Outcomes of Lung Cancer Surgery in Ontario, Canada. *Journal of Clinical Oncology* 2017: 35(24): 2772-2780.
207. Birkmeyer NJ, Goodney PP, Stukel TA, Hillner BE, Birkmeyer JD. Do cancer centers designated by the National Cancer Institute have better surgical outcomes? *Cancer* 2005: 103(3): 435-441.
208. Boffa DJ, Mallin K, Herrin J, Resio B, Salazar MC, Palis B, Facktor M, McCabe R, Nelson H, Shulman LN. Survival After Cancer Treatment at Top-Ranked US Cancer Hospitals vs Affiliates of Top-Ranked Cancer Hospitals. *JAMA netw* 2020: 3(5): e203942.
209. Ellis MC, Diggs BS, Vetto JT, Schipper PH. Intraoperative oncologic staging and outcomes for lung cancer resection vary by surgeon specialty. *Ann Thorac Surg* 2011: 92(6): 1958-1963; discussion 1963-1954.
210. Farjah F, Flum DR, Varghese TK, Jr., Symons RG, Wood DE. Surgeon specialty and long-term survival after pulmonary resection for lung cancer. *Ann Thorac Surg* 2009: 87(4): 995-1004; discussion 1005-1006.
211. Goodney PP, Lucas FL, Stukel TA, Birkmeyer JD. Surgeon specialty and operative mortality with lung resection. *Ann Surg* 2005: 241(1): 179-184.
212. Meguid RA, Brooke BS, Chang DC, Sherwood JT, Brock MV, Yang SC. Are surgical outcomes for lung cancer resections improved at teaching hospitals? *Ann Thorac Surg* 2008: 85(3): 1015-1024; discussion 1024-1015.
213. Samson P, Patel A, Crabtree TD, Morgensztern D, Robinson CG, Colditz GA, Waqar S, Kreisel D, Krupnick AS, Patterson GA, Broderick S, Meyers BF, Puri V. Multidisciplinary Treatment for Stage IIIA Non-Small Cell Lung Cancer: Does Institution Type Matter? *Ann Thorac Surg* 2015: 100(5): 1773-1779.
214. Silvestri GA, Handy J, Lackland D, Corley E, Reed CE. Specialists achieve better outcomes than generalists for lung cancer surgery. *Chest* 1998: 114(3): 675-680.

215. Smith CB, Wolf A, Mhango G, Wisnivesky JP. Impact of Surgeon Volume on Outcomes of Older Stage I Lung Cancer Patients Treated via Video-assisted Thoracoscopic Surgery. *Semin Thorac Cardiovasc Surg* 2017: 29(2): 223-230.
216. Treasure T, Utley M, Bailey A. Assessment of whether in-hospital mortality for lobectomy is a useful standard for the quality of lung cancer surgery: retrospective study. *BMJ* 2003: 327(7406): 73.
217. Jakobsen E, Rasmussen TR, Green A. Mortality and survival of lung cancer in Denmark: Results from the Danish Lung Cancer Group 2000-2012. *Acta Oncol* 2016: 55 Suppl 2: 2-9.
218. WHO Classification of Tumours Editorial Board. Thoracic Tumours. 5th ed. International Agency for Research on Cancer, Lyon, France, 2021.
219. Erridge SC, Murray B, Williams L, Brewster D, Black R, Price A, Murray N, Sheehan F. Improved survival from lung cancer in British Columbia compared to Scotland-are different treatment rates the whole story? *Lung Cancer* 2009: 64(3): 358-366.
220. Imperatori A, Harrison RN, Leitch DN, Rovera F, Lepore G, Dionigi G, Sutton P, Dominioni L. Lung cancer in Teesside (UK) and Varese (Italy): a comparison of management and survival. *Thorax* 2006: 61(3): 232-239.
221. Khakwani A, Rich AL, Tata LJ, Powell HA, Stanley RA, Baldwin DR, Hubbard RB. The pathological confirmation rate of lung cancer in England using the NLCA database. *Lung Cancer* 2013: 79(2): 125-131.
222. Fischer-Valuck BW, Boggs H, Katz S, Durci M, Acharya S, Rosen LR. Comparison of stereotactic body radiation therapy for biopsy-proven versus radiographically diagnosed early-stage non-small lung cancer: a single-institution experience. *Tumori* 2015: 101(3): 287-293.
223. Fujii O, Demizu Y, Hashimoto N, Takagi M, Terashima K, Mima M, Jin D, Nagano F, Katsui K, Okimoto T, Iwata H, Niwa Y, Yamashita T, Akagi T, Daimon T, Sasaki R, Hishikawa Y, Abe M, Murakami M, Fuwa N. Particle therapy for clinically diagnosed stage I lung cancer: comparison with pathologically proven non-small cell lung cancer. *Acta Oncol* 2015: 54(3): 315-321.
224. Haidar YM, Rahn DA, 3rd, Nath S, Song W, Bazhenova L, Makani S, Fuster MM, Sandhu AP. Comparison of outcomes following stereotactic body radiotherapy for non-small cell lung cancer in patients with and without pathological confirmation. *Therap* 2014: 8(1): 3-12.
225. Takeda A, Kunieda E, Sanuki N, Aoki Y, Oku Y, Handa H. Stereotactic body radiotherapy (SBRT) for solitary pulmonary nodules clinically diagnosed as lung cancer with no pathological confirmation: comparison with non-small-cell lung cancer. *Lung Cancer* 2012: 77(1): 77-82.
226. Reck M, Rabe KF. Precision Diagnosis and Treatment for Advanced Non-Small-Cell Lung Cancer. *N Engl J Med* 2017: 377(9): 849-861.
227. European Medicines Agency. Medicines. 2019 [cited 10.07.2022]; Available from: https://www.ema.europa.eu/en/medicines
228. Guyatt GH, Alonso-Coello P, Schunemann HJ, Djulbegovic B, Nothacker M, Lange S, Murad MH, Akl EA. Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. *J Clin Epidemiol* 2016: 80: 3-7.
229. Blum T, Schonfeld N. The lung cancer patient, the pneumologist and palliative care: a developing alliance. *Eur Respir J* 2015: 45(1): 211-226.
230. Badr H, Smith CB, Goldstein NE, Gomez JE, Redd WH. Dyadic psychosocial intervention for advanced lung cancer patients and their family caregivers: results of a randomized pilot trial. *Cancer* 2015: 121(1): 150-158.
231. Bakitas M, Lyons KD, Hegel MT, Balan S, Brokaw FC, Seville J, Hull JG, Li Z, Tosteson TD, Byock IR, Ahles TA. Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. *Jama* 2009: 302(7): 741-749.
232. Bakitas MA, Tosteson TD, Li Z, Lyons KD, Hull JG, Li Z, Dionne-Odom JN, Frost J, Dragnev KH, Hegel MT, Azuero A, Ahles TA. Early Versus Delayed Initiation of Concurrent Palliative Oncology Care: Patient Outcomes in the ENABLE III Randomized Controlled Trial. *J Clin Oncol* 2015: 33(13): 1438-1445.

233. Brumley R, Enguidanos S, Jamison P, Seitz R, Morgenstern N, Saito S, McIlwane J, Hillary K, Gonzalez J. Increased satisfaction with care and lower costs: results of a randomized trial of in-home palliative care. *J Am Geriatr Soc* 2007: 55(7): 993-1000.
234. Cheville AL, Kollasch J, Vandenberg J, Shen T, Grothey A, Gamble G, Basford JR. A home-based exercise program to improve function, fatigue, and sleep quality in patients with Stage IV lung and colorectal cancer: a randomized controlled trial. *J Pain Symptom Manage* 2013: 45(5): 811-821.
235. Franciosi V, Maglietta G, Degli Esposti C, Caruso G, Cavanna L, Berte R, Bacchini G, Bocchi L, Piva E, Monfredo M, Scafuri V, Di Cesare P, Melotti B, Sequino M, Rimanti A, Binovi C, Ghisoni F, Caminiti C. Early palliative care and quality of life of advanced cancer patients-a multicenter randomized clinical trial. *Ann* 2019: 14.
236. Gade G, Venohr I, Conner D, McGrady K, Beane J, Richardson RH, Williams MP, Liberson M, Blum M, Della Penna R. Impact of an inpatient palliative care team: a randomized control trial. *J Palliat Med* 2008: 11(2): 180-190.
237. Greer JA, Pirl WF, Jackson VA, Muzikansky A, Lennes IT, Heist RS, Gallagher ER, Temel JS. Effect of early palliative care on chemotherapy use and end-of-life care in patients with metastatic non-small-cell lung cancer. *J Clin Oncol* 2012: 30(4): 394-400.
238. Groenvold M, Petersen MA, Damkier A, Neergaard MA, Nielsen JB, Pedersen L, Sjogren P, Stromgren AS, Vejlgaard TB, Gluud C, Lindschou J, Fayers P, Higginson IJ, Johnsen AT. Randomised clinical trial of early specialist palliative care plus standard care versus standard care alone in patients with advanced cancer: The Danish Palliative Care Trial. *Palliat Med* 2017: 31(9): 814-824.
239. Higginson IJ, Bausewein C, Reilly CC, Gao W, Gysels M, Dzingina M, McCrone P, Booth S, Jolley CJ, Moxham J. An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. *Lancet Respir Med* 2014: 2(12): 979-987.
240. McCorkle R, Jeon S, Ercolano E, Lazenby M, Reid A, Davies M, Viveiros D, Gettinger S. An Advanced Practice Nurse Coordinated Multidisciplinary Intervention for Patients with Late-Stage Cancer: A Cluster Randomized Trial. *Journal of Palliative Medicine* 2015: 18(11): 962-969.
241. Meyers FJ, Carducci M, Loscalzo MJ, Linder J, Greasby T, Beckett LA. Effects of a problem-solving intervention (COPE) on quality of life for patients with advanced cancer on clinical trials and their caregivers: simultaneous care educational intervention (SCEI): linking palliation and clinical trials. *J Palliat Med* 2011: 14(4): 465-473.
242. Nipp RD, Temel B, Fuh CX, Kay P, Landay S, Lage D, Franco-Garcia E, Scott E, Stevens E, O'Malley T, Mohile S, Dale W, Traeger L, Jackson V, Greer JA, El-Jawahri A, Temel JS. Pilot Randomized Trial of a Transdisciplinary Geriatric and Palliative Care Intervention for Older Adults With Cancer. *Journal of the National Comprehensive Cancer Network* 2020: 18(5): 591-598.
243. Pantilat SZ, O'Riordan DL, Dibble SL, Landefeld CS. Hospital-based palliative medicine consultation: a randomized controlled trial. *Arch Intern Med* 2010: 170(22): 2038-2040.
244. Rabow MW, Dibble SL, Pantilat SZ, McPhee SJ. The comprehensive care team: a controlled trial of outpatient palliative medicine consultation. *Arch Intern Med* 2004: 164(1): 83-91.
245. Steinhauser KE, Alexander SC, Byock IR, George LK, Olsen MK, Tulsky JA. Do preparation and life completion discussions improve functioning and quality of life in seriously ill patients? Pilot randomized control trial. *Journal of Palliative Medicine* 2008: 11(9): 1234-1240.
246. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, Dahlin CM, Blinderman CD, Jacobsen J, Pirl WF, Billings JA, Lynch TJ. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010: 363(8): 733-742.
247. Temel JS, Greer JA, El-Jawahri A, Pirl WF, Park ER, Jackson VA, Back AL, Kamdar M, Jacobsen J, Chittenden EH, Rinaldi SP, Gallagher ER, Eusebio JR, Li Z, Muzikansky A, Ryan DP. Effects of Early Integrated Palliative Care in Patients With Lung and GI Cancer: A Randomized Clinical Trial. *Journal of Clinical Oncology* 2017: 35(8): 834-841.
248. Temel JS, Sloan J, Zemla T, Greer JA, Jackson VA, El-Jawahri A, Kamdar M, Kamal A, Blinderman CD, Strand J, Zylla D, Daugherty C, Furqan M, Obel J, Razaq M, Roeland EJ, Loprinzi C. Multisite, Randomized Trial of Early Integrated Palliative and Oncology Care in Patients with

Advanced Lung and Gastrointestinal Cancer: Alliance A221303. *Journal of Palliative Medicine* 2020: 07.
249. Vanbutsele G, Pardon K, Van Belle S, Surmont V, De Laat M, Colman R, Eecloo K, Cocquyt V, Geboes K, Deliens L. Effect of early and systematic integration of palliative care in patients with advanced cancer: a randomised controlled trial. *Lancet Oncol* 2018: 19(3): 394-404.
250. Wagner EH, Ludman EJ, Aiello Bowles EJ, Penfold R, Reid RJ, Rutter CM, Chubak J, McCorkle R. Nurse navigators in early cancer care: a randomized, controlled trial. *J Clin Oncol* 2014: 32(1): 12-18.
251. Zhuang H, Ma Y, Wang L, Zhang H. Effect of early palliative care on quality of life in patients with non-small-cell lung cancer. *Curr* 2018: 25(1): e54-e58.
252. Zimmermann C, Swami N, Krzyzanowska M, Hannon B, Leighl N, Oza A, Moore M, Rydall A, Rodin G, Tannock I, Donner A, Lo C. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *Lancet* 2014: 383(9930): 1721-1730.
253. Ferrell B, Sun V, Hurria A, Cristea M, Raz DJ, Kim JY, Reckamp K, Williams AC, Borneman T, Uman G, Koczywas M. Interdisciplinary Palliative Care for Patients With Lung Cancer. *J Pain Symptom Manage* 2015: 50(6): 758-767.
254. Nguyen HQ, Ruel N, Macias M, Borneman T, Alian M, Becher M, Lee K, Ferrell B. Translation and Evaluation of a Lung Cancer, Palliative Care Intervention for Community Practice. *J Pain Symptom Manage* 2018: 02.
255. King JD, Eickhoff J, Traynor A, Campbell TC. Integrated Onco-Palliative Care Associated With Prolonged Survival Compared to Standard Care for Patients With Advanced Lung Cancer: A Retrospective Review. *J Pain Symptom Manage* 2016: 51(6): 1027-1032.
256. Lafitte C, Etienne-Mastroianni B, Fournel C, Natoli L, Foucaut AM, Girard N. Implementation of optimized supportive care and hospital needs along the management of patients with advanced lung cancer. *Lung Cancer* 2018: 124: 143-147.
257. Lammers A, Slatore CG, Fromme EK, Vranas KC, Sullivan DR. Association of Early Palliative Care With Chemotherapy Intensity in Patients With Advanced Stage Lung Cancer: A National Cohort Study. *J Thorac Oncol* 2019: 14(2): 176-183.
258. Nieder C, Tollali T, Haukland E, Reigstad A, Flatoy LR, Engljahringer K. Impact of early palliative interventions on the outcomes of care for patients with non-small cell lung cancer. *Support Care Cancer* 2016: 24(10): 4385-4391.
259. Sullivan DR, Chan B, Lapidus JA, Ganzini L, Hansen L, Carney PA, Fromme EK, Marino M, Golden SE, Vranas KC, Slatore CG. Association of Early Palliative Care Use With Survival and Place of Death Among Patients With Advanced Lung Cancer Receiving Care in the Veterans Health Administration. *JAMA Oncol* 2019: 19.
260. Radbruch L, Payne S. White Paper on standards and norms for hospice and palliative care in Europe: part 2. *Eur J Palliat Care* 2010: 17: 22–33.
261. Radbruch L, Payne S. White Paper on standards and norms for hospice and palliative care in Europe: part 1. *Eur J Palliat Care* 2009: 16: 278–289.
262. Edn CPGfQPCr. Pittsburgh, National Consensus Project for Quality Palliative Care,. 2013 [cited 10.07.2022]; Available from: www.nationalconsensusproject.org/Guidelines_Download2.aspx
263. Beckett P, Woolhouse I, Stanley R, Peake MD. Exploring variations in lung cancer care across the UK--the 'story so far' for the National Lung Cancer Audit. *Clin Med* 2012: 12(1): 14-18.
264. Khakwani A, Rich AL, Powell HA, Tata LJ, Stanley RA, Baldwin DR, Duffy JP, Hubbard RB. Lung cancer survival in England: trends in non-small-cell lung cancer survival over the duration of the National Lung Cancer Audit. *Br J Cancer* 2013: 109(8): 2058-2065.
265. Khakwani A, Rich AL, Tata LJ, Powell HA, Stanley RA, Baldwin DR, Hubbard RB. Small-cell lung cancer in England: trends in survival and chemotherapy using the National Lung Cancer Audit. *PLoS ONE* 2014: 9(2): e89426.
266. Adizie JB, Khakwani A, Beckett P, Hubbard R, Navani N, Harden SV, Woolhouse I. Impact of organisation and specialist service delivery on lung cancer outcomes. *Thorax* 2019: 74(6): 546-550.

267. Cerfolio RJ, Bryant AS. Optimal care of patients with non-small cell lung cancer reduces perioperative morbidity. *J Thorac Cardiovasc Surg* 2011: 141(1): 22-33.
268. Erridge SC, Murray B, Price A, Ironside J, Little F, Mackean M, Walker W, Brewster DH, Black R, Fergusson RJ, South-East Scotland Cancer Network Lung Cancer T. Improved treatment and survival for lung cancer patients in South-East Scotland. *J Thorac Oncol* 2008: 3(5): 491-498.
269. Faris NR, Smeltzer MP, Lu F, Fehnel CL, Chakraborty N, Houston-Harris CL, Robbins ET, Signore RS, McHugh LM, Wolf BA, Wiggins L, Levy P, Sachdev V, Osarogiagbon RU. Evolution in the Surgical Care of Patients With Non-Small Cell Lung Cancer in the Mid-South Quality of Surgical Resection Cohort. *Semin Thorac Cardiovasc Surg* 2017: 29(1): 91-101.
270. Hagan ME, Williams ST, Socci L, Malik M, Internullo E, Martin-Ucar AE. Completing the audit cycle improves surgical standards in lung cancer. Why do some patients still not receive the best care? *J Thorac Oncol* 2013: 8(6): 779-782.
271. Shulman LN, Palis BE, McCabe R, Mallin K, Loomis A, Winchester D, McKellar D. Survival As a Quality Metric of Cancer Care: Use of the National Cancer Data Base to Assess Hospital Performance. *Journal of oncology practice/American Society of Clinical Oncology* 2018: 14(1): e59-e72.
272. Ten Berge M, Beck N, Heineman DJ, Damhuis R, Steup WH, van Huijstee PJ, Eerenberg JP, Veen E, Maat A, Versteegh M, van Brakel T, Schreurs WH, Wouters MW. Dutch Lung Surgery Audit: A National Audit Comprising Lung and Thoracic Surgery Patients. *Ann Thorac Surg* 2018: 106(2): 390-397.
273. Wolfson JA, Sun CL, Wyatt LP, Hurria A, Bhatia S. Impact of care at comprehensive cancer centers on outcome: Results from a population-based study. *Cancer* 2015: 121(21): 3885-3893.
274. De Lorenzo F, Ballatori E, Di Costanzo F, Giacalone A, Ruggeri B, Tirelli U. Improving information to Italian cancer patients: results of a randomized study. *Ann Oncol* 2004: 15(5): 721-725.
275. Clayton JM, Butow PN, Tattersall MH, Devine RJ, Simpson JM, Aggarwal G, Clark KJ, Currow DC, Elliott LM, Lacey J, Lee PG, Noel MA. Randomized controlled trial of a prompt list to help advanced cancer patients and their caregivers to ask questions about prognosis and end-of-life care. *J Clin Oncol* 2007: 25(6): 715-723.
276. Butow P, Devine R, Boyer M, Pendlebury S, Jackson M, Tattersall MH. Cancer consultation preparation package: changing patients but not physicians is not enough. *J Clin Oncol* 2004: 22(21): 4401-4409.
277. Brown R, Butow PN, Boyer MJ, Tattersall MH. Promoting patient participation in the cancer consultation: evaluation of a prompt sheet and coaching in question-asking. *Br J Cancer* 1999: 80(1-2): 242-248.
278. Meropol NJ, Egleston BL, Buzaglo JS, Balshem A, Benson AB, 3rd, Cegala DJ, Cohen RB, Collins M, Diefenbach MA, Miller SM, Fleisher L, Millard JL, Ross EA, Schulman KA, Silver A, Slater E, Solarino N, Sulmasy DP, Trinastic J, Weinfurt KP. A Web-based communication aid for patients with cancer: the CONNECT Study. *Cancer* 2013: 119(7): 1437-1445.

Conflict of Interest:

Torsten Gerriet Blum reports an unrestricted grant of less than €1000 from Stiftung Oskar Helene Heim (Berlin, Germany), through which staff support for the work of the current Task Force was provided.

Rebecca L. Morgan declares no competing interests.

Valérie Durieux declares no competing interests.

Joanna Chorostowska-Wynimko declares grants to the National Institute of Tuberculosis and Lung Diseases from Pfizer and to the Polish Respiratory Society from AstraZeneca; consulting fees from AstraZeneca, Pfizer, Amgen, Takeda, Merck Sharp & Dohme, Roche and Roche Diagnostica; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca, Pfizer, CelonPharma, Amgen, Takeda, Novartis, Bristol Myers Squibb, Merck Sharp & Dohme, Roche, Roche Diagnostica and Amoy; support for attending meetings and/or travel from Bristol Myers Squibb, AstraZeneca, Merck Sharp & Dohme, Pfizer and Amgen; participation on a Data Safety Monitoring Board or Advisory Board for AstraZeneca, Pfizer, Takeda, Merck Sharp & Dohme, Roche and Roche Diagnostica, all in the 36 months prior to manuscript submission; and that they are Secretary General of the European Respiratory Society and a member of the Executive Committees of the Polish Respiratory Society and the Polish Coalition for Personalized Medicine.

David R Baldwin declares payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Bristol Myers Squibb, AstraZeneca, Roche and Merck Sharp & Dohme, in the 36 months prior to manuiscript submission.

Jeanette Boyd is an employee of the European Lung Foundation

Corinne Faivre-Finn reports research grants from AstraZeneca and Elekta; payment or honoraria for presentations from AstraZeneca; support for attending meetings and/or travel from Elekta and AstraZeneca; and participation on a Data Safety Monitoring Board or Advisory Board for AstraZeneca and Merck Sharp & Dohme, all in the 36 months prior to manuscript submission.

Françoise Galateau-Salle declares no competing interests.

Fernando Gamarra declares no competing interests.

Bogdan Grigoriu declares support for attending meetings and/or travel from Roche and AstraZeneca; and participation on a Data Safety Monitoring Board or Advisory Board for AstraZeneca, all in the 36 months prior to manuscript submission.

Georgia Hardavella declares no competing interests.

Michael Hauptmann declares no competing interests.

Erik Jakobsen declares no competing interests.

Dragana Jovanovic declares payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Merck Sharp & Dohme, Roche, Boehringer Ingelheim, WCBIP 2020 and AstraZeneca; payment for expert testimony relating to the health effects of air pollution from SO₂ released by Serbia Zijin Copper mining and smelting complex and the two biggest Serbian power plants, all in the 36 months prior to manuscript submission; and that they are a member of the editorial boards of the Journal of Thoracic Disease and the AME Surgical Journal, and a Committee member of The National Ecological Association (NEA), Serbia.

Paul Knaut declares no competing interests.

Gilbert Massard declares a speaker's fee from Pneumo Update Europe, in the 36 months prior to manuscript submission.

John McPhelim declares advisory board payments from AstraZeneca, Janssen-Cilag and Bristol Myers Squibb, in the 36 months prior to manuscript submission.

Anne-Pascale Meert declares no competing interests.

Robert Milroy declares no competing interests.

Riccardo Muhr declares no competing interests.

Luciano Mutti declares no competing interests.

Marianne Paesmans declares no competing interests.

Pippa Powell is an employee of the European Lung Foundation.

Paul Martin Putora declares research grants to their institution from AstraZeneca, Takeda and Bayer; and a speaker's fee from Janssen-Cilag, all in the 36 months prior to manuscript submission.

Janette Rawlinson declares travel/accommodation support from BTOG to attend annual meeting in Dublin as patient advocate/steering committee member Jan 2019; travel/accommodation support from ERS to attend screening meeting in Barcelona Dec 2018 (patient representative) and ELF patient event at ERS Congress Madrid 2019; travel/accommodation support from NCRI to attend conference in Glasgow 2019 (consumer member); Travel/accommodation support from EORTC to attend Patient Days event as a speaker and patient panel member Feb 2020; and that they have been a Non Executive Director (lay member) at Sandwell and West Birmingham Clinical Commissioning Group, UK (until April 2021).

Anna L Rich declares no competing interests.

David Rigau is a methodologist of the European Respiratory Society.

Dirk de Ruysscher declares grants to their institution from AstraZeneca and BeiGene; payment to their institution for lectures, presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca; and payment to their institution for participation on an Advisory Board from AstraZeneca, all in the 36 months prior to manuscript submission.

Jean-Paul Sculier declares no competing interests.

Arnaud Schepereel declares a research grant to their institution from Bristol Myers Squibb; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca, Bristol Myers Squibb and Leo Pharma; support for attending meetings and/or travel from AstraZeneca, Bristol Myers Squibb, Merck Sharp & Dohme and Roche; and payment for Participation on a Data Safety Monitoring Board or Advisory Board from AstraZeneca, Bristol Myers Squibb and Merck Sharp & Dohme, all in the 36 months prior to manuscript submission.

Dragan Subotic declares no competing interests.

Paul Van Schil declares consulting fees paid to their institution by AstraZeneca and Merck Sharp & Dohme; payment to their institution for lectures, presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca; and travel expenses related to participation in Data

Safety Monitoring or Advisory Boards for the LungART Trial and the Pearls Trial, all in the 36 months prior to manuscript submission; and that they are the President-elect of the International Association for the Study of Lung Cancer and the Treasurer of the Belgian Association for Cardio-Thoracic Surgery.

Clare Williams is an employee of the European Lung Foundation

Thomy Tonia is a methodologist of the European Respiratory Society.

Thierry Berghmans declares consulting fees from InhaTarget; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Janssen; and participation on a Data Safety Monitoring Board or Advisory Board for Janssen and Roche, all in the 36 months prior to manuscript submission.

ERS Guideline on various aspects of quality in lung cancer care – *Online Supplement A*

Table of Contents

Details on methodology

Determining topics of interest, formulation of PICO questions and outcomes, rating the importance of outcome parameters

During the initial task force meeting, eight topics of interest within the scope of this task force on various aspects of quality in lung cancer care were developed and consented based on an unanimous decision by the task force members. Subsequently, well-framed questions were formulated for each topic of interest by the co-chairs and the lead methodologist using the PICO (Population, Intervention, Comparator and Outcomes) format [1]. Equally, outcome parameters for the questions were defined and consented by the Task Force group (see ***online supplement section B*** for detailed PICO questions including outcome parameters).

For each question, all outcome parameters were rated individually regarding their importance for clinical decision making for the respective question by the accountable task force members applying a rating scale from 1 to 9 (of limited importance: 1-3, important: 4-6, critical: 7-9). Rounded means of the scorings rates were calculated and further discussed, leading to final importance score for each outcome (not important, important, critical) (see ***online supplement section C*** for results of the outcome parameter scoring).

Literature searches

The literature search was designed by V. Durieux and T. Berghmans and reviewed by T. Blum. Searches were performed in April 2016 and updated in September 2017, September 2018, May 2019, December 2019, May 2020 and January 2021 in the Medline database by one medical librarian (V. Durieux), experienced in searching for medical and scientific publications, and supervised by the two co-chairs (T. Berghmans, T. Blum).

Ovid Medline was searched using the OvidSP interface (Online supplement 3. Search strategies). Unless otherwise stated, search terms were MeSH terms (medical subject headings). MeSH terms were also combined with relevant free-text terms that were searched for in titles and abstracts.

The corresponding PICO search criteria were translated into MeSH terms and free-text keywords which were usable as search equations by the OvidSP interface. Completed search strategies included P and I criteria, further limited by O criteria only when the number of retrieved citations for the P and I criteria combinations exceeded 5,000 citations. This cut-off was chosen arbitrary to ensure a meaningful, but manageable basic set of studies per PICO for the selection process by avoiding excessive noise around the evidence of interest. Although a possible risk of study selection bias could not be completely ruled out, initial validity controls of the search equations demonstrated that this differentiated approach recorded all the reference articles known to the authors in advance in the context of all the PICO questions. Subsequently, topic-related review articles and systematic reviews which were identified during the periodic literature searches served as external validity controls for the completeness of search results. The Ovid Medline search strategies are provided in the ***online supplement section D***.

For each of the PICO searches, citations were separately exported from Medline into reference management software (Endnote®) to allow the removal of duplicates and to facilitate the selection process performed by reviewers (V. Durieux).

Study selection

Studies were eligible for selection if fulfilling pre-defined inclusion criteria relating to study type (randomized controlled trials, non-randomized controlled trials as well as observational studies with cohort and case-control studies), publication language (English, French, Dutch, German, and Spanish) and according to the PICO-questions themselves. Detailed eligibility criteria are listed in ***online supplement table 4***.

In a first step, exported references were screened for relevance. Articles were selected or rejected on initial screening by two independent reviewers depending on whether titles and abstracts met or did not meet the inclusion criteria, respectively (PICO 1: B. Grigoriu, T. Berghmans; PICO 2: A.-P. Meert, T. Berghmans; PICO 3: J.-P. Sculier, T. Berghmans; PICO 4: P. Knaut, T. Blum; PICO 5: D. Subotic, T. Blum; PICO 6: D. Jovanovic, T. Blum; PICO 7: R. Muhr, T. Blum; PICO 8: P. Knaut, T. Blum). In case of discrepancy of the evidence synthesis results for one PICO question, consensus was sought by the two reviewers. Full paper publications were requested if at least one reviewer selected the reference.

Full paper publications for all articles selected in step 1 were collected and linked to the reference management databases (T. Blum, P. Knaut, R. Muhr, V. Durieux). In a second step, for each question, the remaining articles were then evaluated based on the full paper publications for final inclusion in the current systematic reviews. Final selections were done in agreement of the two allocated reviewers for the respective PICO questions, again discrepancies being resolved by consensus. The same methodology was applied by the two co-chairs for the literature update searches (T. Berghmans, T. Blum).

These selections were supplemented by the above-mentioned update searches as well as additional full paper publications derived from screening the references of the selected articles as well as other related literature known to the task force group. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagrams were utilized to report the search results for each of the eight questions (V. Durieux, T. Blum) [2].

All results were provided to the task force members to check for missing evidence.

Data extraction and risk of bias assessment

Two task force members were allocated to collaboratively perform the data extraction from the studies and the evidence assessment per search question (PICO 1: B. Grigoriu, T. Berghmans; PICO 2: A.-P. Meert, T. Berghmans; PICO 3: J.-P. Sculier, T. Berghmans; PICO 4: P. Knaut, T. Blum; PICO 5: D. Subotic, T. Blum; PICO 6: D. Jovanovic, T. Blum; PICO 7: R. Muhr, T. Blum; PICO 8: P. Knaut, T. Blum). The two task force co-chairs T. Berghmans and T. Blum took the lead in performing the subsequent tasks for PICO-question 1-3 and 4-8, respectively, supported by the named other task force member for each PICO. First, the respective pairs per PICO extracted study characteristics, types of participants, interventions, outcomes measured, and results from each of the selected studies. Second, they assessed the risk of bias for the individual outcomes within every selected study. Randomized controlled trials were analysed for specific study limitations according to *the Cochrane risk of bias tool for assessing risk of bias in randomized trials* consisting of five discrete items: 1. lack of randomization (selection bias), 2. lack of allocation concealment (selection bias), 3. lack of blinding (performance bias), 4. incomplete accounting of patients and outcome events (attrition bias), and 5. selective outcome reporting (reporting bias) [3]. In addition to these domains, observational studies were also assessed based on four distinct items: 1. failure to develop and apply appropriate eligibility criteria, 2. flawed measurement of both exposure and outcome, 3. failure to adequately control confounding, and 4. incomplete follow-up in observational studies [4].

Specific data collection forms were designed for a standardised handling of the extracted data and the risk of bias assessment for the individual outcomes within the studies (T. Berghmans, D. Rigau, T. Tonia). In case of discrepancy of the extraction or assessment results, consensus was sought by the two task force members allocated to each PICO.

All results were provided to the task force members for validation.

Data synthesis, meta-analyses, own individual four-stage effect strength evaluation scheme as well as assessing the effect direction, effect size and certainty of the evidence

Just like in the narrative review by the preceding task force [5], substantial heterogeneity of evidence regarding study designs and methodologies was detected for all PICO questions. To ensure meaningful evidence synthesis and conclusion of guideline recommendations, the three task force chairs together with one co-lead methodologist (R. Morgan) thoroughly discussed and agreed upon the formation of representative subgroups (based on type of cancer and cancer staging) out of the selected full publications to ensure the most direct evidence to answer the PICO questions. These were selected posteriori to the risk of bias assessment of individual studies.

Whenever clinically meaningful, the available evidence per outcome was synthesized quantitatively with the calculation of aggregated effects using a meta-analytic technique and personal programming for calculating these combined effects. For binary outcomes, the individual effect of the covariate of interest was reported as odds ratio with a 95% confidence interval (CI) and for continuous outcomes, it was reported as a mean difference with a 95% CI. Heterogeneity between individual effects was assessed using the I^2 statistic. Heterogeneity was suspected and explored when I^2 was greater than 60%. For survival outcomes, individual effects were

summarized with hazard ratios (HR) and 95% CI. Fixed-effects model was used when fewer than 3 studies were pooled, otherwise, random effects models were used. Findings from the meta-analysis were presented in a forest plot using the Metaplot®-software. If needed data to allow a quantitative synthesis were not stated or incalculable out of the publications, results were summarized narratively.

In situations in which statistically pooling the results of studies was inappropriate, i. e. studies were too different to reasonable synthesize in a meta-analysis, the evidence were presented narratively [6]. For each outcome of interest, the two task force co-chairs predefined an individual four-stage evaluation scheme to discriminate the effect size into trivial, small, moderate and large which contains self-selected thresholds. In view of a lack of evidence-based recommendations, the absolute and relative threshold values for each outcome were chosen based on clinical experience providing a clinical meaningful distinction between a trivial and small effect as well as between small, moderate, and large effects. The evaluation scheme which was agreed upon by all task force members is depicted in **Table 1**. To assess the effect direction and effect size of the evidence per outcome, first, all single studies were rated according to this evaluation scheme. Second (if meta-analysis was not feasible), individual studies were grouped according to their estimated effect sizes and respective included patient figures per study were summed up for each of the four effect size categories. Finally, the effect direction for each outcome was determined depending on whether the total number of patients predominated in the group of studies with small to large effects for the intervention or the group with trivial effects or those even opposite to the intervention. Likewise, the overall effect size per outcome was selected based on the effect size category with the largest number of included patients.

Outcome	**Absolute difference**	**Relative difference (if absolute difference incalculable/not stated)**
1. Overall survival	5-year overall survival rate benefit:	HR point estimate benefit:
-large	- >5%	- >10%
-moderate	- >2.5-5%	- >5-10%
-small	- >1-2.5%	- >1-5%
-trivial	- ≤1%	- ≤1%
2. Disease-free survival (DSF)	DFS benefit:	HR point estimate benefit:
-large	- >12 months	- >10%
-moderate	- >6-12 months	- >5-10%
-small	- >1-6 months	- >1-5%
-trivial	- ≤1%	- ≤1%
3. Progression-free survival (PFS)	PFS benefit:	HR point estimate benefit:
-large	- >6 months	- >10%
-moderate	- >3-6 months	- >5-10%
-small	- >1-3 months	- >1-5%
-trivial	- ≤1 month	- ≤1%
4. Mortality	Mortality rate benefit:	OR point estimate benefit:
-large	- >1.5%	- >30%
-moderate	- >1.0-1.5%	- >20-30%
-small	- >0.5-1.0%	- >10-20%
-trivial	- ≤0.5%	- ≤10%
5. Morbidity	Morbidity rate benefit:	OR point estimate benefit:
-large	- >5%	- >40%
-moderate	- >2.5-5%	- >20-40%
-small	- >1-2.5%	- >10-20%
-trivial	- ≤1%	- ≤10%
6. Accuracy of staging	Accuracy of staging rate benefit:	OR point estimate benefit:
-large	- >10%	- >20%
-moderate	- >5-10%	- >10-20%
-small	- >1-5%	- >1-10%
-trivial	- ≤1%	- ≤1%
7. Pathological confirmation	Pathological confirmation rate benefit:	OR point estimate benefit:
-large	- >10%	- >20%
-moderate	- >5-10%	- >10-20%
-small	- >1-5%	- >5-10%
-trivial	- ≤1%	- ≤5%
8. Receipt of curative treatment	Curative treatment rate benefit:	OR point estimate benefit:
-large	- >10%	- >20%
-moderate	- >5-10%	- >10-20%
-small	- >1-5%	- >5-10%
-trivial	- ≤1%	- ≤5%

9. Receipt of any tumour-specific treatment -large -moderate -small -trivial	Any tumour-specific treatment rate benefit: - >10% - >5-10% - >1-5% - ≤1%	OR point estimate benefit: - >20% - >10-20% - >5-10% - ≤5%
10. Quality of Life -large -moderate -small -trivial	Quality of Life improvement: a) Center for Epidemiological Study-Depression Scale (score: 0-60 points) - >12 points - >6-12 points - >3-6 points - ≤3 points b) Chronic Respiratory Disease Questionnaire Health-related Quality of Life (20-140 points) - >28 points - >14-28 points - >7-14 points - ≤7 points c) City of Hope Quality of Life Instruments (score: 0-100 points) - >20 points - >10-20 points - >5-10 points - ≤5 points d) Edmonton Symptom Assessment Scale (0-900 points) - >180 points - >90-180 points - >45-90 points - ≤45 points e) EORTC QLQ-C30 (0-100 points) - >20 points - >10-20 points - >5-10 points - ≤5 points f) EQ-5D (0-100 points) - >20 points - >10-20 points - >5-10 points - ≤5 points g) FACIT-Pal (0-184 points) - >36 points - >18-36 points - >9-18 points - ≤9 points h) FACIT-Spiritual Well-Being (score: 0-156 points) - >32 points - >16-32 points - >8-16 points - ≤8 points i) FACT-G (0-108 points) - >22 points - >11-22 points - >6-11 points - ≤6 points j) FACT-L (0-140 points) - >28 points - >14-28 points - >7-14 points	OR point estimate benefit: a)-m) All - >20% - >10-20% - >5-10% - ≤5%

	- ≤7 points k) Multidimensional Quality of Life Scale-Cancer Version (score: 0-100 points) 100 points) - >20 points - >10-20 points - >5-10 points - ≤5 points l) Quality of Life at End of Life (4-20 points) - >4 points - >2-4 points - >1-2 points - ≤1 points m) Reid-Gundlach Satisfaction with Services instrument (0-48 points) - >10 points - >5-10 points - >3-5 points - ≤3 points	
11. Patient satisfaction -large -moderate -small -trivial	Patient satisfaction improvement: a) FAMCARE-P16 scale (score 16-80) - >16 points - >8-16 points - >4-8 points - ≤4 points b) Group Health Association of America Consumer Satisfaction Survey (score:20-100) - >20 points - >10-20 points - >5-10 points - ≤5 points	OR point estimate benefit: a)-b) All - >20% - >10-20% - >5-10% - ≤5%
12. Performance status -large -moderate -small -trivial	Depending on specific performance status-measure	

Table 1: Self-selected evaluation to estimate the effect sizes of single studies per outcome.

The level of certainty of evidence was then assessed per outcome across studies as per GRADE approach [7-9], which grades the certainty of the evidence across 8 domains. Evidence may be rated down for 1) risk of bias [4], 2) imprecision [10], 3) inconsistency [11], 4) indirectness [12], 5) publication bias [13]. If there are no concerns for rating down, the body of evidence informed by observational studies may be rated up due to 1) Large or very large magnitude of effect, 2) dose-response, or 3) opposing residual confounding. The two task force co-chairs T. Berghmans and T. Blum collaboratively conducted the evidence assessment for all PICO questions.

GRADEpro Guideline Development Tool evidence profile forms (available online: www.gradepro.org) were used to present the quality of evidence per outcome across studies for each PICO question (T. Blum, R. Morgan) [8].

All results were discussed with the task force members.

Determining strength and direction of guideline recommendations

The GRADE approach for evidence to decision-making was used to determine the strength and direction of the recommendations collaboratively by the three task force co-chairs for each search question [14]. Accordance was found among the three co-chairs if their initial recommendation proposals related to one search

question differed. Utilizing GRADE Evidence to Decision (EtD) frameworks (available online: www.gradepro.org) [8, 9], in addition to the results of the evidence assessment, the task force members considered the balance of benefits and harms, values and preferences, resource use, health equity, acceptability and feasibility when making recommendations. The task force group members discussed and formulated the guideline recommendations for each of the PICO questions during five virtual task force meetings in March/April 2021 which were used to collect individual feedback on the revised guideline manuscript as well as to formulate and consent the recommendations. The framework for the interpretation of strong and conditional recommendations is depicted in

Table 2.

Target group	Strong recommendations (*)	Conditional recommendations
Patients	All or almost all informed people would choose the recommended choice for or against an intervention.	Most informed people would choose the recommended course of action, but a substantial number would not.
Clinicians	Most patients should receive the recommended course of action.	Recognise that different choices will be appropriate for different patients. Clinicians and other healthcare providers need to devote more time to the process of shared decision-making, by which they ensure that the informed choice reflects individual values and preferences; decision aids and shared decision-making are particularly useful.
Policymakers	The recommendation can be adopted as a policy in most situations.	Policy making will require substantial debate and involvement of many stakeholders.

Table 2: Framework for interpretation of recommendations

(*) strong recommendations based on high or moderate quality evidence will apply to most patients for whom these recommendations are made, but they may not apply to all patients in all conditions; no recommendation can take into account all of the unique features of individual patients and clinical circumstances. [15, 16].

Paradigmatic situations according to GRADE

In accordance with GRADE methodology, the task force group considered strong recommendations despite low or very low quality of evidence in the following five phrased constellations, so-called ***paradigmatic situations*** [16]:

1. "When low quality evidence suggests benefit in a life-threatening situation (evidence regarding harms can be low or high)"

2. "When low quality evidence suggests benefit and high quality evidence suggests harm or a very high cost"

3. "When low quality evidence suggests equivalence of two alternatives, but high quality evidence of less harm for one of the competing alternatives"

4. "When high quality evidence suggests equivalence of two alternatives and low quality evidence suggests harm in one alternative"

5. "When high quality evidence suggests modest benefits and low/ very low quality evidence suggests

possibility of catastrophic harm"

Exceptionally, the task force group also considered good practice statements as an alternative for GRADE-derived recommendations for individual search questions in presence of high-certainty indirect evidence that would be onerous and time-consuming to formally accumulate and review yet supporting the recommendation [16, 17].

Manuscript preparation

The initial draft of the manuscript and the online supplements were prepared by the three co-chairs (T. Berghmans, T. Blum, J. Chorostowska-Wynimko) and two methodologists (R. Morgan, T. Tonia). Both the manuscript and the online supplement were reviewed, edited and approved by all panel members prior to submission.

Detailed description of search questions based on PICO format

1. Do waiting times have an impact on outcome in lung cancer?

PICO question 1: *In patients with lung cancer (or those suspected of having lung cancer), should shorter rather than longer cancer care time intervals be used (e.g., time from diagnosis to treatment)?*

Population: Adult patients with suspected or clinically confirmed lung cancer (e.g., NSCLC, SCLC)

Intervention:

- ***patient interval:*** time from first symptom to first presentation/clinical appearance [regular if ≤ 7-14 days]
- ***doctor interval:*** time from first presentation/clinical appearance to first investigation, primary care responsible for the patient [regular if ≤ 7-14 days]
- ***system interval:*** time from first investigation, primary care responsible for the patient to treatment start [regular if ≤ 28-42 days]
- ***primary care interval:*** time from first presentation/clinical appearance to first referral to secondary care/refer responsibility [regular if ≤ 14-21 days]
- ***secondary care interval:*** time from first referral to secondary care/refer responsibility to treatment start [regular if ≤ 21-35 days]
- ***diagnostic interval:*** time from first presentation/clinical appearance to diagnosis [regular if ≤ 14-28 days]
- ***treatment interval:*** time from diagnosis to treatment start [regular if ≤ 14-28 days]
- ***total interval:*** time from first symptom to treatment start [regular if ≤ 56-84 days]

Remarks: All listed time points and waiting time intervals within the lung cancer care continuum from first symptom to treatment start were adopted from the internationally well-accepted Aarhus statement paper1. So far, several varying timelines of lung cancer care have been introduced, yet all by national bodies only. At this stage, no evidence-based recommendations regarding waiting time cut-off-values can be made from an international perspective. Thus, we arbitrarily defined one individual upper time limit interval for each of the defined waiting time intervals related to lung cancer care in regular patients.
Yet, we were aware that special treatment situations (not considered as regular lung cancer care) might require different waiting time limits (i. e. urgent admissions during standard working times; emergency admissions anytime 24/7).

Comparison: Longer time of diagnosis to treatment (e.g. exceeding the time period specified by Aarhus staging

Outcomes considered important or critical for decision-making and included in the GRADE evidence profile: overall survival, progression-free survival, disease-free survival, mortality, morbidity, accuracy of staging, pathological confirmation, receipt of curative treatment, receipt of any active tumour-specific treatment, quality of life, patient satisfaction, performance status

Setting: Health care systems

2. Does the involvement of MDT or certain discipline in lung cancer care have an impact on the outcome in lung cancer?

PICO question 2: *In patients with lung cancer (or those suspected of having lung cancer), should a multi-disciplinary team (MDT) or certain disciplines be involved during lung cancer care rather than no involvement of an MDT or certain disciplines during lung cancer care?*

Population: adult lung cancer patients or those suspected of having lung cancer

Intervention: involvement of an MDT or oncology nurses during lung cancer care

Remarks: We have defined multi-disciplinary team (MDT) care according to the statement paper of the Metropolitan Health and Aged Care Services Division (Melbourne, Victoria, Australia) broadly as 'an integrated team approach to health care in which medical and allied health care professionals consider all relevant treatment options and develop an individual treatment plan for each patient collaboratively'. Specifically, the Task Force members opted for the following disciplines as essential constituents of an MDT in lung cancer care:

- respiratory medicine
- pathology
- radiology
- thoracic surgery
- radiotherapy
- oncology
- oncology nurse

The Task Force panel has adopted the definition of the National Cancer Institute (USA) for an Oncology Nurse: 'nurse who specializes in treating and caring for people who have cancer.'

Comparison: non-involvement of an MDT or oncology nurses during lung cancer care

Outcomes considered important or critical for decision-making and included in the GRADE evidence profile: overall survival, progression-free survival, disease-free survival, mortality, morbidity, accuracy of staging, pathological confirmation, receipt of curative treatment, receipt of any active tumour-specific treatment, quality of life, patient satisfaction, performance status

Setting: Health care system

3. Should guidelines or standard operating procedures (SOP) be used in lung cancer care?

PICO question 3: *In patients with lung cancer (or those suspected of having lung cancer), should guidelines or standard operating procedures (SOP) for lung cancer care be implemented or adhered to rather than non-implementation of or non-adherence to these guidelines or standard operating procedures?*

Population: adult lung cancer patients or those suspected of having lung cancer

Intervention: implementation of or adherence to guidelines or standard operating procedures (SOP) for lung cancer care

Comparison: non-implementation of or non-adherence to guidelines or standard operating procedures (SOP) for lung cancer care

Outcomes considered important or critical for decision-making and included in the GRADE evidence profile: overall survival, progression-free survival, disease-free survival, mortality, morbidity, accuracy of staging, pathological confirmation, receipt of curative treatment, receipt of any active tumour-specific treatment, quality of life, patient satisfaction, performance status

Setting: Health care system

4. Does hospital/professional volume of care/specialization have an impact in lung cancer diagnostics or therapy?

PICO question 4: *Should patients with lung cancer patients (or those suspected of having lung cancer) receive lung cancer-specific diagnostic or therapeutic procedures in hospitals/from professionals with higher volumes of activity/with a higher grade of specialization for these procedures rather than (compared to receiving them in hospitals/from professionals with lower volumes of activity/with lower grade of specialization for these procedures)?*

4a) Does hospital volume of activity have an impact in lung cancer diagnostics or therapy?

PICO question 4a: *Should patients with lung cancer (or those suspected of having lung cancer) receive lung cancer-specific diagnostic or therapeutic procedures in hospitals with higher volumes of activity for these procedures rather than receiving them in hospitals with lower volumes of activity for these procedures?*

Population: adult lung cancer patients or those suspected of having lung cancer
Subgroups*:* according to diagnostic or therapeutic procedures
- surgical resection of lung cancer
- other diagnostic and therapeutic modalities

Intervention: lung cancer-specific diagnostic or therapeutic procedure received in hospitals with higher volumes of activity for this procedure

Comparison: lung cancer-specific diagnostic or therapeutic procedure received in hospitals with lower volumes of activity for this procedure

Outcomes considered important or critical for decision-making and included in the GRADE evidence profile: overall survival, progression-free survival, disease-free survival, mortality, morbidity, accuracy of staging, pathological confirmation, receipt of curative treatment, receipt of any active tumour-specific treatment, quality of life, patient satisfaction, performance status

Setting: Health care system

4b) Does hospital specialization have an impact in lung cancer diagnostics or therapy?

PICO question 4b: *Should patients with lung cancer (or those suspected of having lung cancer) receive lung cancer-specific diagnostic or therapeutic procedures in hospitals with a higher grade of specialization for these procedures rather than receiving them hospitals with lower grade of specialization for these procedures?*

Population: adult lung cancer patients or those suspected of having lung cancer
Subgroups: according to diagnostic or therapeutic procedures
- surgical resection of lung cancer
- other diagnostic and therapeutic modalities

Intervention: lung cancer-specific diagnostic or therapeutic procedure received in hospitals with a higher grade of specialization for this procedure

Comparison: lung cancer-specific diagnostic or therapeutic procedure received in hospitals with a lower grade of specialization for this procedure

Outcomes considered important or critical for decision-making and included in the GRADE evidence profile: overall survival, progression-free survival, disease-free survival, mortality, morbidity, accuracy of staging, pathological confirmation, receipt of curative treatment, receipt of any active tumour-specific treatment, quality of life, patient satisfaction, performance status

Setting: Health care system

4c) Does surgeon and other professional volume of activity have an impact in lung cancer diagnostics or therapy?

PICO question 4c: *Should patients with lung cancer (or those suspected of having lung cancer) receive lung cancer-specific diagnostic or therapeutic procedures from surgeons and other professionals with higher volumes of activity for these procedures rather than receiving them from surgeons and other professionals with lower volumes of activity for these procedures?*

Population: adult lung cancer patients or those suspected of having lung cancer
Subgroups: according to diagnostic or therapeutic procedures

- surgical resection of lung cancer
- other diagnostic and therapeutic modalities

Intervention: lung cancer-specific diagnostic or therapeutic procedure received from surgeons and other professionals with higher volumes of activity for this procedure

Comparison: lung cancer-specific diagnostic or therapeutic procedure received from surgeons and other professionals with higher volumes of activity for this procedure

Outcomes considered important or critical for decision-making and included in the GRADE evidence profile: overall survival, progression-free survival, disease-free survival, mortality, morbidity, accuracy of staging, pathological confirmation, receipt of curative treatment, receipt of any active tumour-specific treatment, quality of life, patient satisfaction, performance status

Setting: Health care system

4d) Does surgeon and other professional specialization have an impact in lung cancer diagnostics or therapy?

PICO question 4d: *Should patients with lung cancer (or those suspected of having lung cancer) receive lung cancer-specific diagnostic or therapeutic procedures from surgeons and other professionals with a higher grade of specialization for these procedures rather than receiving them from surgeons and other professionals with a lower grade of specialization for these procedures?*

Population: adult lung cancer patients or those suspected of having lung cancer
Subgroups: according to diagnostic or therapeutic procedures

- surgical resection of lung cancer
- other diagnostic and therapeutic modalities

Intervention: lung cancer-specific diagnostic or therapeutic procedure received from surgeons with a higher grade of specialization for these procedures

Comparison: lung cancer-specific diagnostic or therapeutic procedure received from surgeons with a higher grade of specialization for these procedures

Outcomes considered important or critical for decision-making and included in the GRADE evidence profile: overall survival, progression-free survival, disease-free survival, mortality, morbidity, accuracy of staging, pathological confirmation, receipt of curative treatment, receipt of any active tumour-specific treatment, quality of life, patient satisfaction, performance status

Setting: Health care system

5. Should pathological confirmation of tumours or subtyping of lung cancers be obtained in lung cancer patients?

PICO question 5: *In lung cancer patients (or those suspected of having lung cancer), should pathological confirmation of tumours or subtyping of lung cancers be obtained rather than (compared to no attempted pathological confirmation of tumours or subtyping of lung cancers?*

Population: adult lung cancer patients or those suspected of having lung cancer

Intervention: pathological confirmation of tumours or subtyping of lung cancers
Subgroups: according to kind of lung cancer subtyping

- SCLC vs. NSCLC
- Subtyping of NSCLC
- Application of new WHO lung cancer classification for adenocarcinoma

Comparison: no attempted pathological confirmation tumours or subtyping of lung cancers

Outcomes considered important or critical for decision-making and included in the GRADE evidence profile: overall survival, progression-free survival, disease-free survival, mortality, morbidity, accuracy of staging, pathological confirmation, receipt of curative treatment, receipt of any active tumour-specific treatment, quality of life, patient satisfaction, performance status

Setting: Health care system

6. Should palliative care or palliative care specialists be included early in lung cancer care?

Search question: *In patients with lung cancer(or those suspected of having lung cancer), should palliative care or its delivery by specialists be integrated into lung cancer care already early during the course of the disease rather than no integration of palliative care or no palliative care delivery by specialists?*

Population: adult lung cancer patients

Intervention: integration of palliative care or its deliverance by specialists into lung cancer care early during the disease course

Comparison: no integration of palliative care or no palliative care delivery by specialists early during the disease course

Outcomes considered important or critical for decision-making and included in the GRADE evidence profile: overall survival, progression-free survival, disease-free survival, mortality, morbidity, accuracy of staging, pathological confirmation, receipt of curative treatment, receipt of any active tumour-specific treatment, quality of life, patient satisfaction, performance status

Setting: Health care system

7. Should quality improvement measures be applied in lung cancer care?

Search question: *In patients with lung cancer (or those suspected of having lung cancer), should quality improvement measures be applied in lung cancer care rather than no application of these methods in lung cancer care?*

Population: adult lung cancer patients

Intervention: application of quality assurance methods in lung cancer care
Subgroups: according to specification of quality improvement measures

- cancer registries and quality indicators
- specialized lung cancer services
- individual quality improvement measures
- audits/quality indicator systems

Comparison: no application of quality assurance methods in lung cancer care

Outcomes considered important or critical for decision-making and included in the GRADE evidence profile: overall survival, progression-free survival, disease-free survival, mortality, morbidity, accuracy of staging, pathological confirmation, receipt of curative treatment, receipt of any active tumour-specific treatment, quality of life, patient satisfaction, performance status

Setting: Health care system

8. Should patient decision tools be involved in the decision making in lung cancer?

Search question: *In patients with lung cancer (or those suspected of having lung cancer), should patient decision tools be involved in the decision-making and -sharing process rather than not involving them?*

Population: adult lung cancer patients

Intervention: involving patients in the decision-making process

Comparison: not involving patients in the decision-making process

Outcomes considered important or critical for decision-making and included in the GRADE evidence profile: overall survival, progression-free survival, disease-free survival, mortality, morbidity, accuracy of staging, pathological confirmation, receipt of curative treatment, receipt of any active tumour-specific treatment, quality of life, patient satisfaction, performance status

Setting: Health care system

Rating of outcomes for PICO questions 1-8

For the rating of outcomes by the task force members the following rating scale was used to assess the importance for clinical decision making of outcome parameters:
1-3 points: limited importance
4-6 points: important
7-9 points: critical

The rating results for each of the eight PICO questions are listed in **Table 3**.

	Outcome parameters	**PICO 1**	**PICO 2**	**PICO 3**	**PICO 4**	**PICO 5**	**PICO 6**	**PICO 7**	**PICO 8**
1	Overall survival	**9***	**9***	**9***	**8***	**9***	**7***	**8***	**7**
2	Progression-free survival	**8**	**5**	**6**	**7**	**8***	**5**	**6**	**7**
3	Disease-free survival	**8**	**5**	**6**	**7**	**8**	**5**	**7**	**7**
4	Mortality	**9***	**9***	**9***	**8***	**9**	**7**	**8***	**6**
5	Morbidity	**6**	**8**	**8**	**8**	**7**	**6**	**5**	**6**
6	Accuracy of staging	**5***	**6***	**8**	**7***	**7**	**6**	**7***	**5**
7	Pathological confirmation	**6**	**7***	**6**	**6***	**7**	**6**	**8***	**5**
8	Receipt of curative treatment	**8**	**8***	**8**	**7***	**7***	**6**	**9***	**7**
9	Receipt of any active tumour-specific treatment	**7**	**4***	**7**	**5**	**7**	**7***	**8***	**8**
10	Quality of Life	**6**	**5***	**7**	**6**	**7**	**9***	**7**	**9**
11	Patient satisfaction	**6**	**7***	**6**	**7**	**7**	**9***	**7**	**9***
12	Performance status	**7**	**8**	**8**	**7**	**6**	**9**	**5**	**8**

Table 3: Results of rating of outcomes for each PICO question (rating scale: 1-3 points - limited importance; 4-6 points – important; 7-9 points – critical; *outcomes that were actually selected for respective PICOs based on appropriate evidence)

Search strategy Medline for PICO questions 1-8

Database : Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to January 5th, 2021

Search for P [lung neoplasms]

lung neoplasms/ or bronchial neoplasms/ or carcinoma, bronchogenic/ or carcinoma, non-small-cell lung/ or small cell lung carcinoma/ or pancoast syndrome/ or pulmonary blastoma/ or lung neoplasm*.ti,ab. or lung cancer*.ti,ab. or lung carcinoma*.ti,ab. or lung tumour*.ti,ab. or lung tumor*.ti,ab. or pulmonary neoplasm*.ti,ab. or pulmonary cancer*.ti,ab. or pulmonary carcinoma*.ti,ab. or pulmonary tumour*.ti,ab. or pulmonary tumor*.ti,ab. or bronchial neoplasm*.ti,ab. or bronchial cancer*.ti,ab. or bronchial carcinoma*.ti,ab. or bronchial tumour*.ti,ab. or bronchial tumor*.ti,ab. or bronchogenic neoplasm*.ti,ab. or bronchogenic cancer*.ti,ab. or bronchogenic carcinoma*.ti,ab. or bronchogenic tumour*.ti,ab. or bronchogenic tumor*.ti,ab. or pancoast* syndrome*.ti,ab. or pancoast* tumor*.ti,ab. or pancoast* tumour*.ti,ab. or ((lung.ti,ab or pulmonary.ti,ab) and (cancer*.ti,ab OR neoplasms/))

1. Do waiting times have an impact on outcome in lung cancer?

I

time factor*.ti,ab OR diagnosis delay*.ti,ab OR diagnostic delay*.ti,ab OR care delay*.ti,ab OR referral delay*.ti,ab OR treatment delay*.ti,ab OR therapeutic delay*.ti,ab OR delay* in diagnos*.ti,ab OR delay* of diagnosis.ti,ab OR wait time*.ti,ab OR time to diagnosis.ti,ab OR delayed initiation*.ti,ab OR consultation delay*.ti,ab OR travel time*.ti,ab OR delay* of treatment.ti,ab OR delay* to surgery.ti,ab OR delay* diagnosis.ti,ab OR doctor* delay*.ti,ab OR timeliness of diagnosis.ti,ab OR delay* in the diagnosis.ti,ab OR timing of referral.ti,ab OR waiting.ti,ab OR delay* in the referral.ti,ab OR timely care.ti,ab OR delay* cancer treatment*.ti,ab OR timeliness of care.ti,ab OR time before consulting.ti,ab OR delay* in assessment.ti,ab

O

Hospital mortality/ OR Mortality/ OR Survival/ OR Survival rate/ OR Disease-Free Survival/ OR "Quality of Life"/ OR Patient Satisfaction/ OR exp Intraoperative Complications/ OR exp Postoperative Complications/ OR complication*.ti,ab OR survival.ti,ab OR mortality.ti,ab OR quality of life.ti,ab OR patient* satisfaction.ti,ab OR morbidit*.ti,ab OR Treatment Outcome/ OR treatment outcome*.ti,ab

2. Does the involvement of MDT or certain discipline in lung cancer care have an impact on the outcome in lung cancer?

I

interdisciplinary communication/ OR multidisciplinary lung cancer team*.ti,ab OR multidisciplinary participation*.ti,ab OR multidisciplinary team*.ti,ab OR interdisciplinary team*.ti,ab OR interdisciplinary perspective*.ti,ab OR multidisciplinary perspective*.ti,ab OR interdisciplinary care.ti,ab OR multidisciplinary care.ti,ab OR multidisciplinary approach*.ti,ab OR interdisciplinary approach*.ti,ab OR multidisciplinary management.ti,ab OR interdisciplinary management.ti,ab OR multidisciplinary meeting*.ti,ab OR multidisciplinary clinic*.ti,ab OR interdisciplinary end of life care*.ti,ab OR multidisciplinary conference*.ti,ab OR multisciplinary oncology.ti,ab OR interdisciplinary collaboration*.ti,ab OR multidisciplinary lung cancer clinic*.ti,ab OR integrative practice*.ti,ab OR integrative medicine.ti,ab OR nursing-led intervention*.ti,ab OR nurse led follow up.ti,ab OR educational intervention*.ti,ab OR educational session*.ti,ab OR Nurse role/ OR Nurse-Patient Relations/ OR psycho-oncological.ti,ab OR Nutritionists/ OR nutritionist*.ti,ab OR dietician*.ti,ab OR psychologist*.ti,ab OR social workers/ OR social worker*.ti,ab OR Pastoral care/ OR Spirituality/ OR spiritual care worker*.ti,ab

O

Hospital mortality/ OR Mortality/ OR Survival/ OR Survival rate/ OR Disease-Free Survival/ OR "Quality of Life"/ OR Patient Satisfaction/ OR exp Intraoperative Complications/ OR exp Postoperative Complications/ OR complication*.ti,ab OR survival.ti,ab OR mortality.ti,ab OR quality of life.ti,ab OR patient* satisfaction.ti,ab OR morbidit*.ti,ab OR accuracy of staging.ti,ab OR accurate staging.ti,ab OR histological confirmation*.ti,ab OR histology confirmation*.ti,ab OR Treatment Outcome/ OR treatment outcome*.ti,ab

3. Should guidelines or standard operating procedures (SOP) be used in lung cancer care?
I
Practice guidelines as topic/ OR standard operating procedure*.ti,ab OR clinical recommendations.ti,ab OR practice guideline*.ti,ab OR management guideline*.ti,ab OR care guideline*.ti,ab OR treatment guideline*.ti,ab
O
Hospital mortality/ OR Mortality/ OR Survival/ OR Survival rate/ OR Disease-Free Survival/ OR "Quality of Life"/ OR Patient Satisfaction/ OR exp Intraoperative Complications/ OR exp Postoperative Complications/ OR complication*.ti,ab OR survival.ti,ab OR mortality.ti,ab OR quality of life.ti,ab OR patient* satisfaction.ti,ab OR morbidit*.ti,ab OR accuracy of staging.ti,ab OR accurate staging.ti,ab OR histological confirmation*.ti,ab OR histology confirmation*.ti,ab OR Treatment Outcome/ OR treatment outcome*.ti,ab

4. Does hospital/individual volume of activity/specialization have an impact in lung cancer diagnostics or therapy?
I
hospital volume*.ti,ab or high* volume hospital*.ti,ab or low volume hospital*.ti,ab or hospital procedure volume*.ti,ab or surgeon volume*.ti,ab or volume-outcome relationship*.ti,ab or operative volume.ti,ab or high* volume center*.ti,ab or low volume center*.ti,ab or surgical volume*.ti,ab or number of procedures performed.ti,ab or institutional experience.ti,ab

5. Should pathological confirmation of tumours or subtyping of lung cancers be obtained in lung cancer patients?
I
(histological confirmation.ti,ab OR histology confirmation.ti,ab OR histological classification.ti,ab OR histology diagnosis.ti,ab OR pathological confirmation.ti,ab OR diagnosed histologically.ti,ab) OR ((EGFR OR epidermal growth factor receptor OR EGF receptor* OR erbB 1).ti,ab. AND (Mutation/ OR mutation*.ti,ab.) AND (guideline* or documentation* or recommendation*).ti,ab) OR (ALK Translocation*.ti,ab OR ALK rearrangement*.ti,ab OR ALK fusion*.ti,ab OR ALK testing.ti,ab)
O
Hospital mortality/ or Mortality/ or Survival/ or Survival rate/ or Disease-Free Survival/ or survival.ti,ab. or mortality.ti,ab. or "Quality of Life"/ or quality of life.ti,ab

6. Should palliative care or palliative care specialists be included early in lung cancer care?
I
(Palliative care/ OR palliative care.ti,ab OR Terminal care/) AND (integration.ti,ab OR integrating.ti,ab OR integrated.ti,ab OR introducing.ti,ab OR general ward*.ti,ab OR early palliative care.ti,ab OR interdisciplinary palliative care.ti,ab OR palliative care intervention.ti,ab)

7. Should quality improvement measures be applied for lung cancer patients?
I
"Quality of Health Care"/ OR Quality Assurance, Health Care/ OR Quality Indicators, Health Care/ OR Patient Care Management/ OR Benchmarking/ OR Clinical audit/ OR Medical audit/ OR Certification/ OR "Outcome and Process Assessment (Health Care)"/ OR Peer Review, Health Care/ OR "Organization and administration"/ OR logistics.ti,ab OR supervision.ti,ab OR

administrative technics.ti,ab OR administrative technique*.ti,ab OR quality of healthcare.ti,ab OR quality of health care.ti,ab OR healthcare quality.ti,ab OR health care quality.ti,ab OR assessment* of quality.ti,ab OR quality assurance*.ti,ab OR quality assessment*.ti,ab OR quality measure*.ti,ab OR quality evaluation*.ti,ab OR quality apprais*.ti,ab OR performance measure*.ti,ab. OR quality indicator*.ti,ab OR certification program*.ti,ab OR benchmarking.ti,ab OR audits.ti,ab OR audit.ti,ab

O

Hospital mortality/ OR Mortality/ OR Survival/ OR Survival rate/ OR Disease-Free Survival/ OR "Quality of Life"/ OR Patient Satisfaction/ OR exp Intraoperative Complications/ OR exp Postoperative Complications/ OR complication*.ti,ab OR survival.ti,ab OR mortality.ti,ab OR quality of life.ti,ab OR patient* satisfaction.ti,ab OR morbidit*.ti,ab OR Treatment Outcome/ OR treatment outcome*.ti,ab

8. Should patient decision tools be involved in the decision making in lung cancer?

I

patient decision making.ti,ab OR shared decision making.ti,ab OR ((Patient participation/ OR patient* participation.ti,ab OR patient* involvement.ti,ab OR patient* engagement.ti,ab OR patient* empowerment.ti,ab OR engaging patient*.ti,ab OR involving patient*.ti,ab) AND (decision*.ti,ab OR choice*.ti,ab))

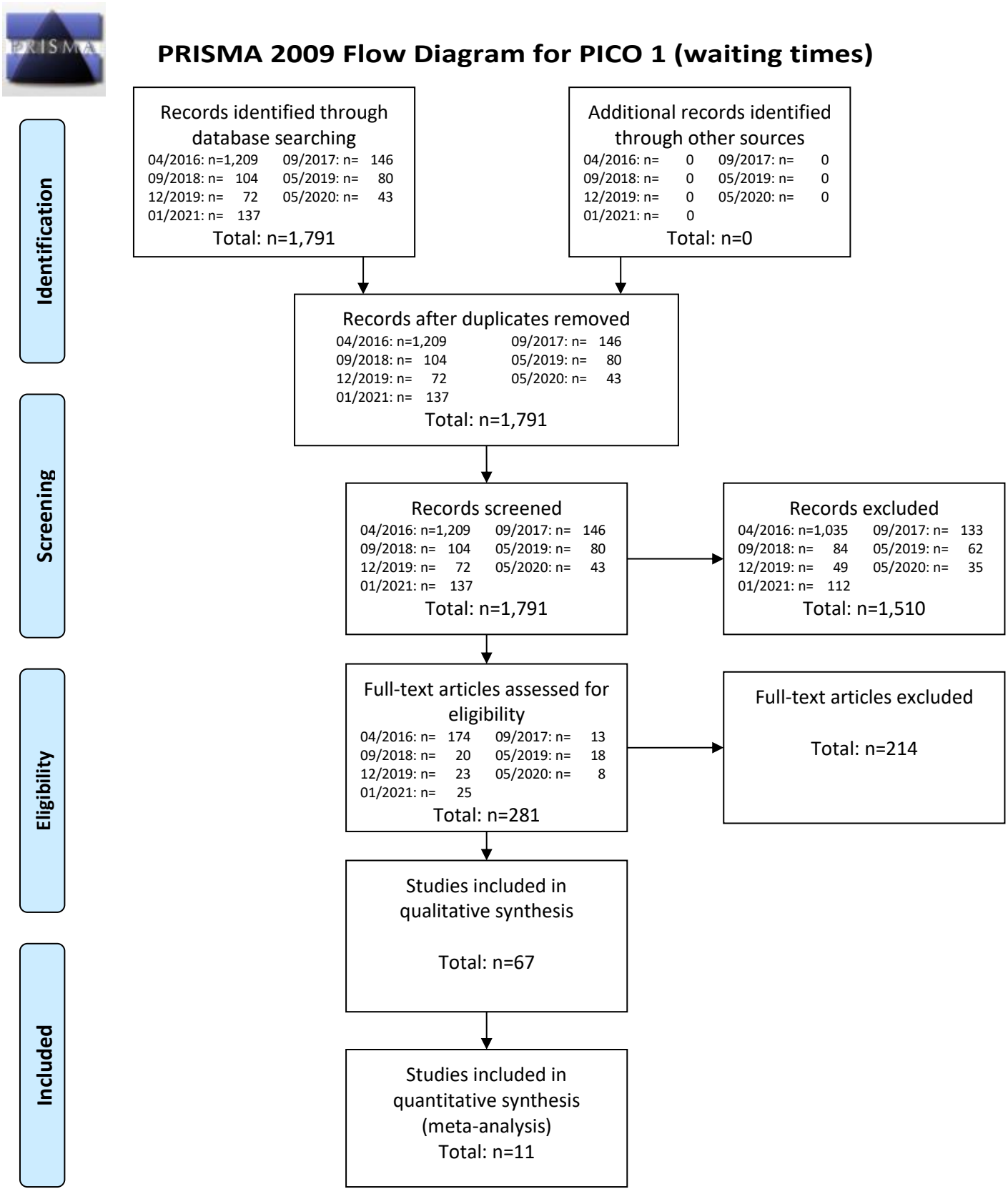
Eligibility criteria for included studies to inform PICO questions 1-8

Eligibility criteria for inclusion of studies to inform PICOs 1-8:

- study design: randomized controlled trials and comparative non-randomized studies including trials, observational cohort, and case-control studies
- study population: within the scope of the respective PICO question, yet mixed study populations are allowed if the pre-defined population of interest is included and separate data for lung cancer patients are available
- study interventions/controls: within the scope of the respective search question, yet additional study interventions/controls are allowed if the pre-defined interventions/controls of interest are included and separate data are available for the latter
- publication language: only languages fluently spoken by Task Force members which are English, French, Dutch, German, and Spanish
- publication period: no restrictions by Task Force panel, yet technically limited from 1946 (due to accessibility through the OvidSP interface) to January 5th, 2021 (latest search date)

PRISMA flow charts for PICO questions 1-8

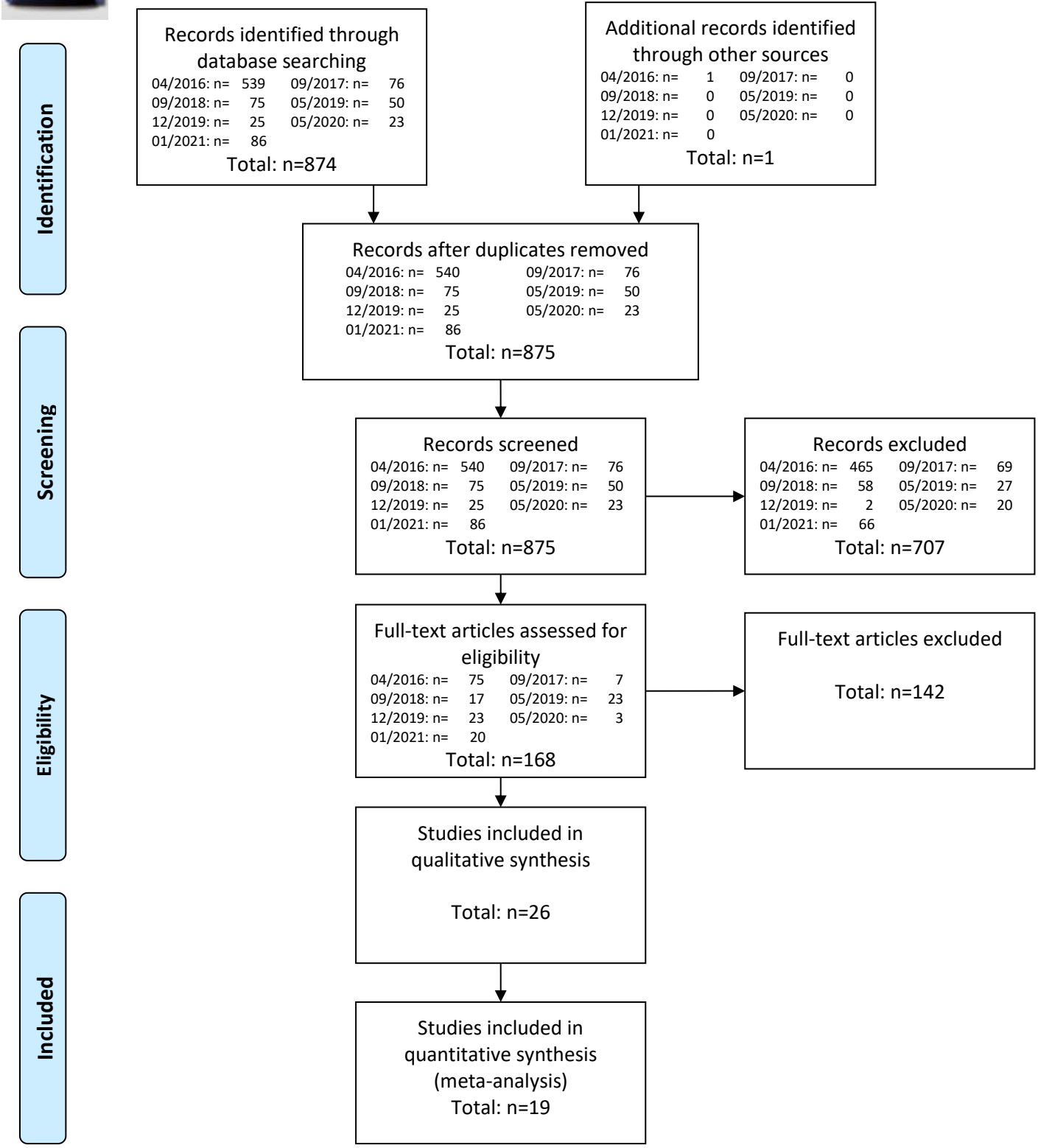
This sections includes the PRISMA flow diagrams for each of the eight PICO question



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

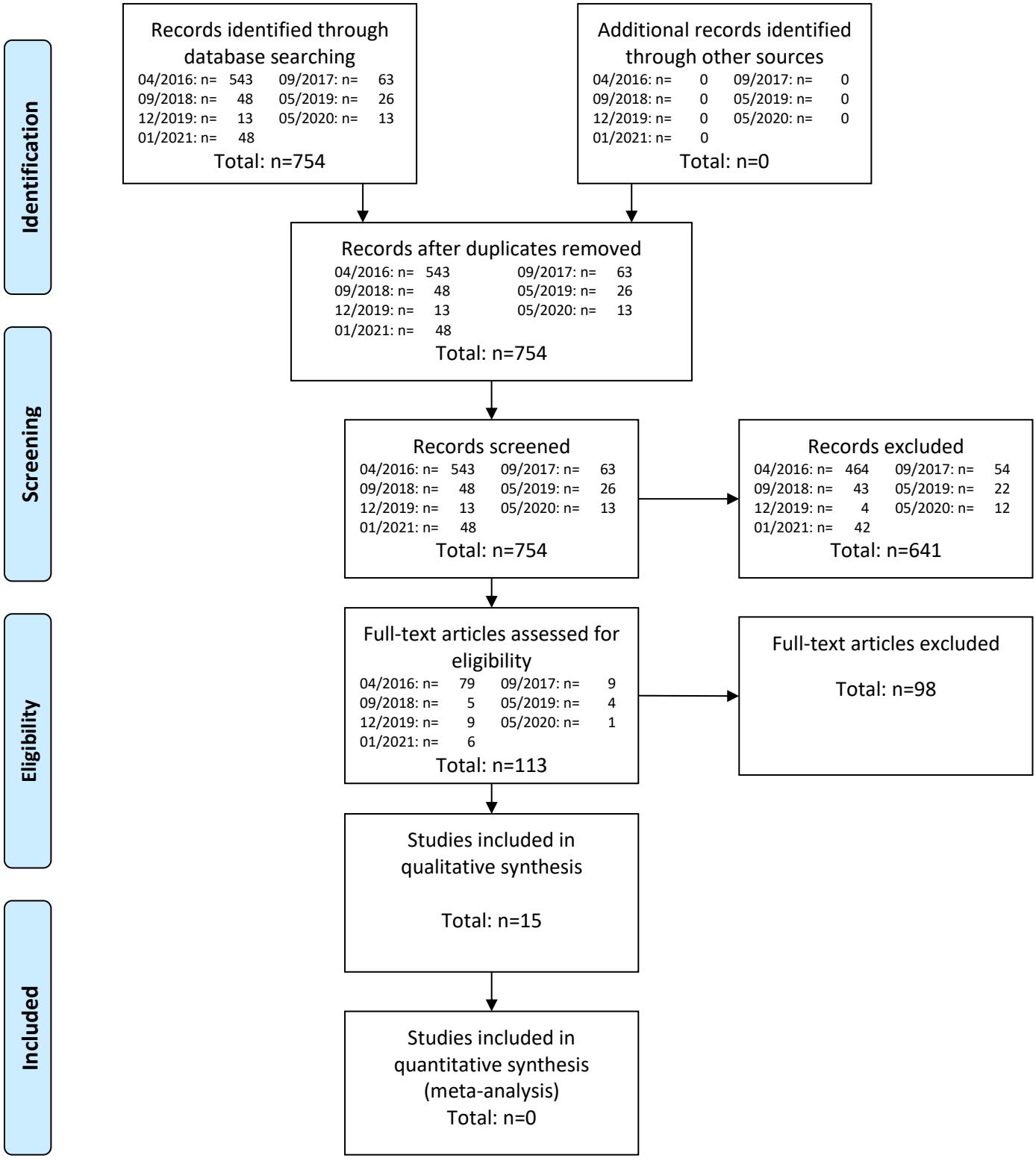
PRISMA 2009 Flow Diagram for PICO 2 (MDT)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

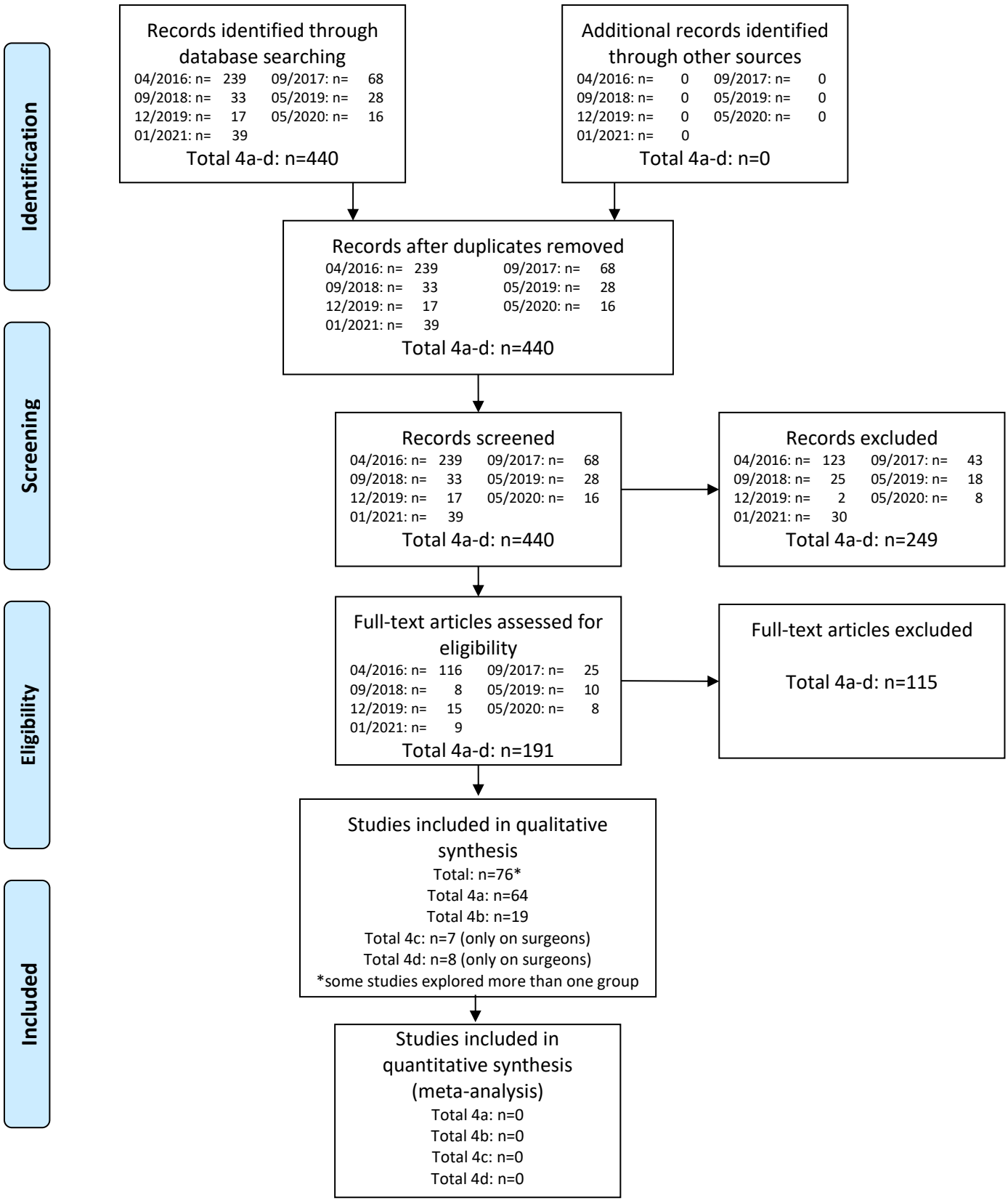
For more information, visit www.prisma-statement.org.

PRISMA 2009 Flow Diagram for PICO 3 (guideline implementation/adherence)



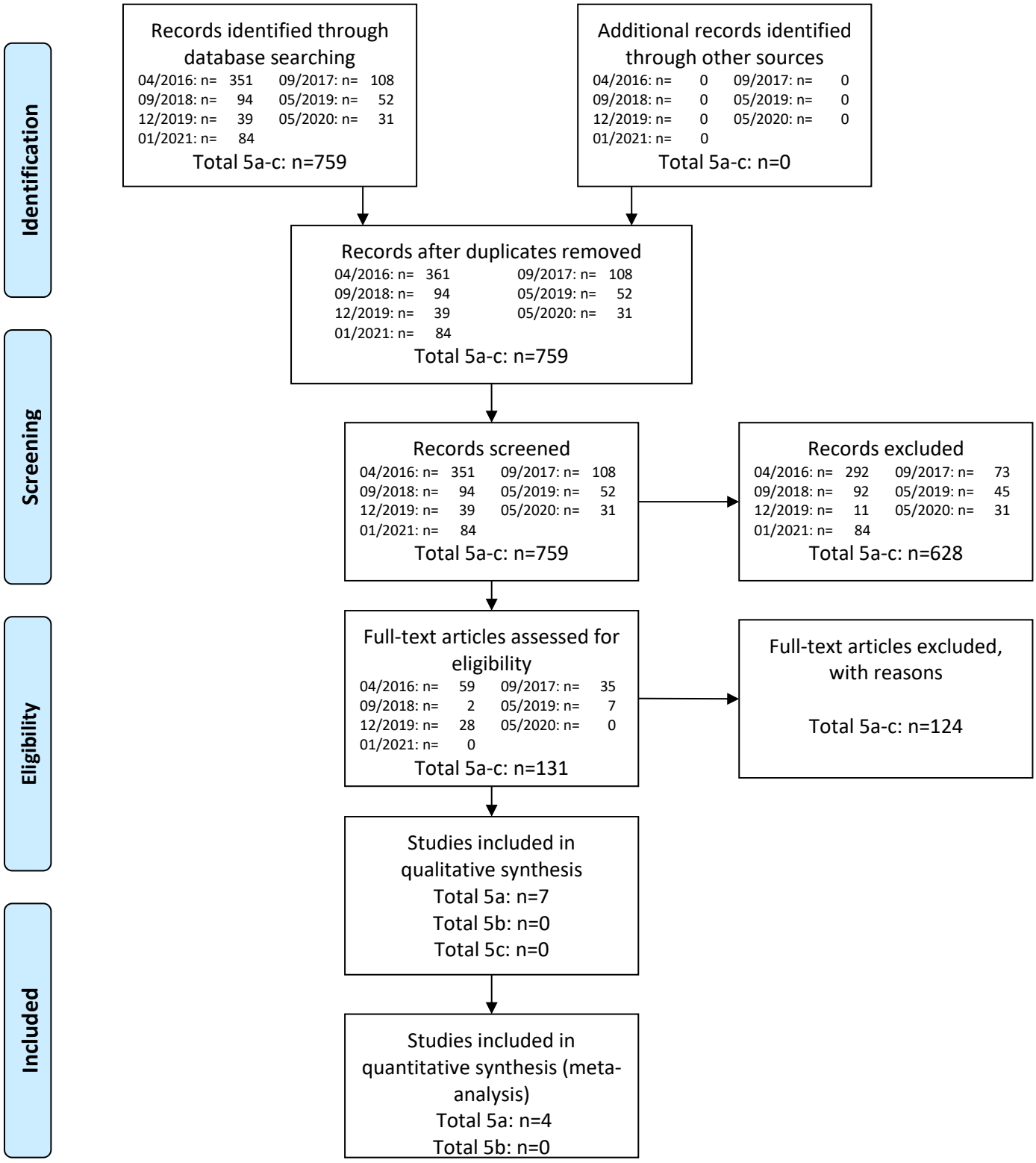
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Flow Diagram for PICO 4a-d
(hospital/professional volume of care [4a+c] and specialization [4b+d])



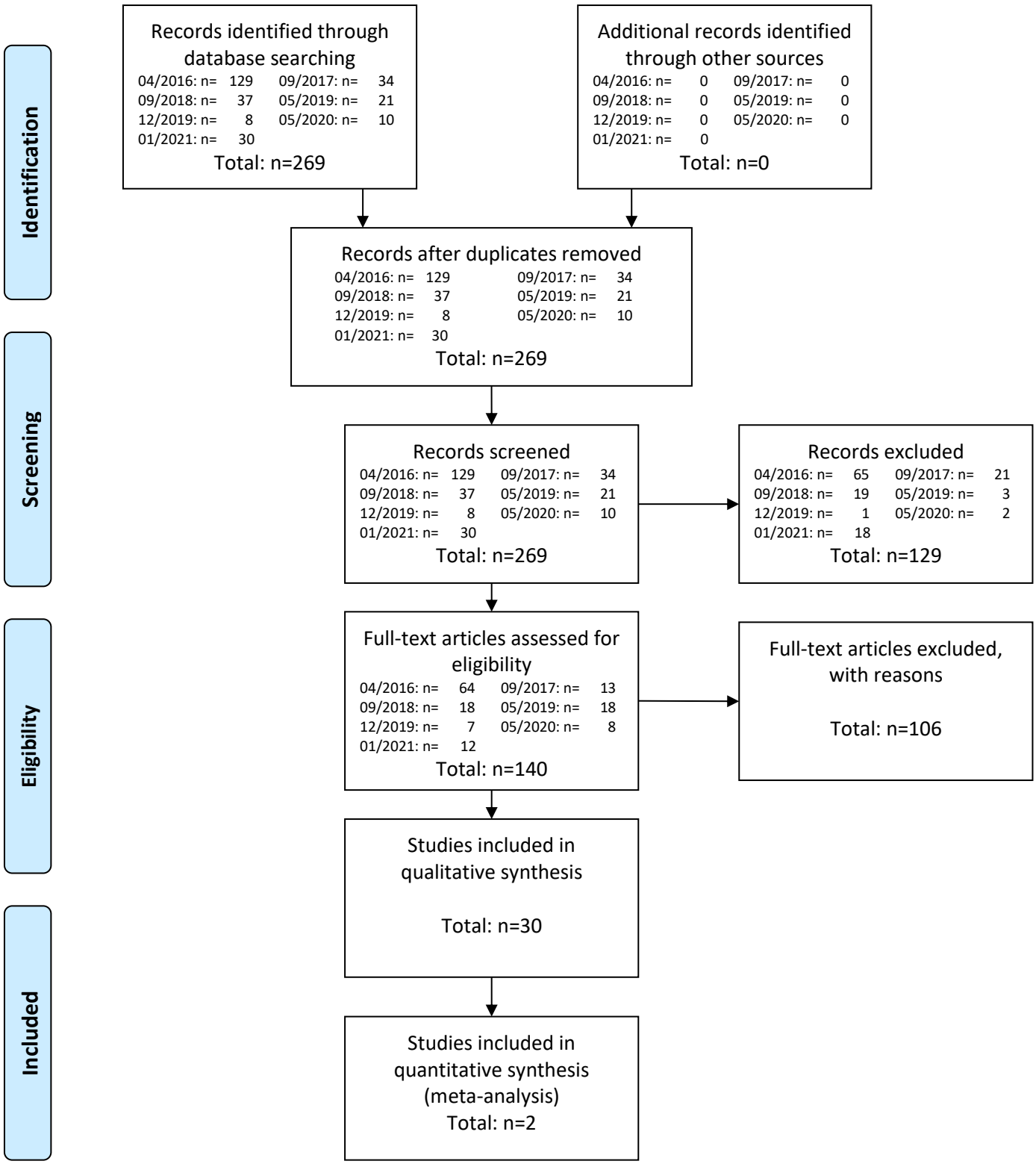
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Flow Diagram for PICO 5a-c (pathological confirmation of tumours [5a] and subtyping of lung cancers [5b+c])



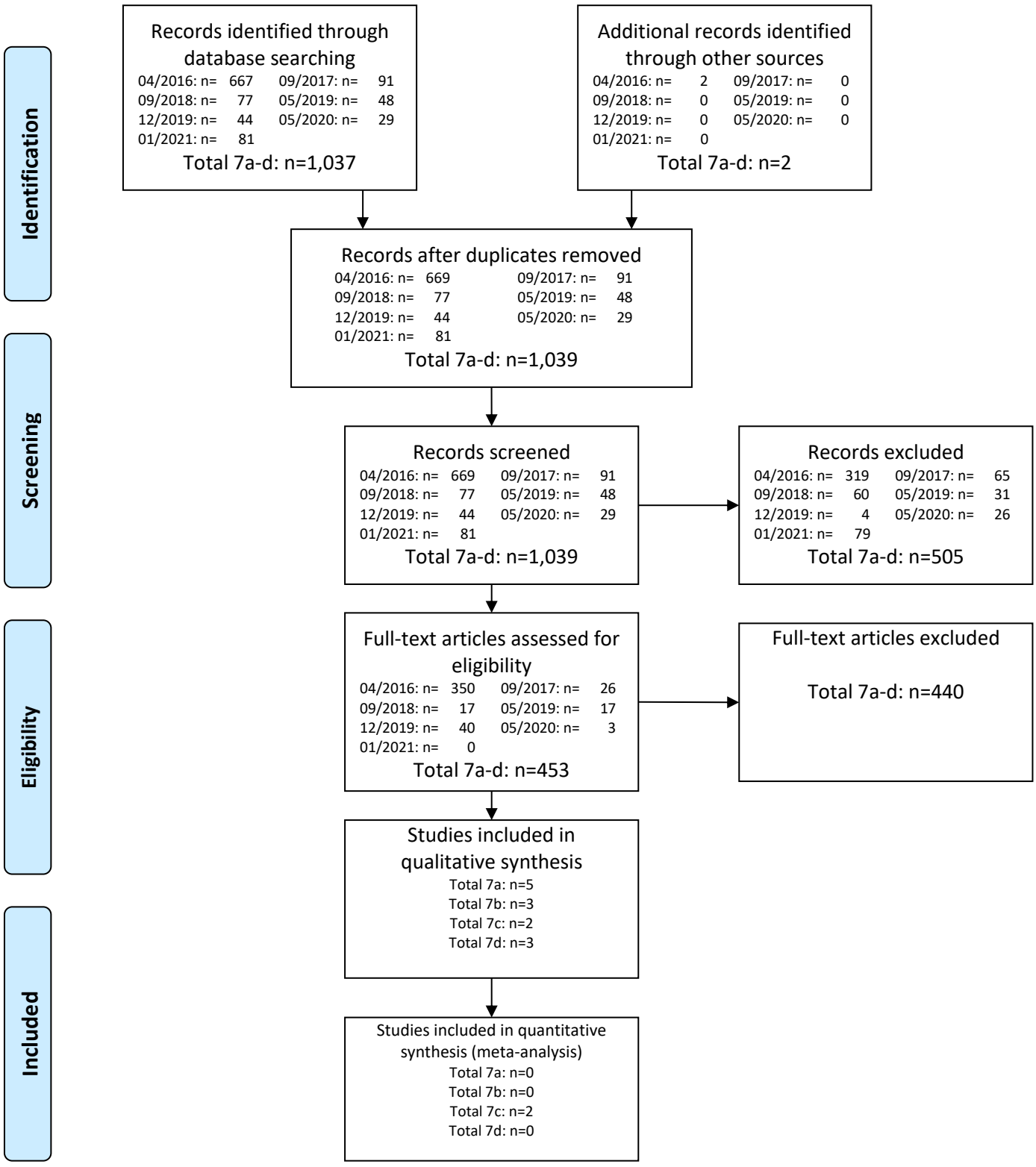
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Flow Diagram for PICO 6 (early integration of palliative care)



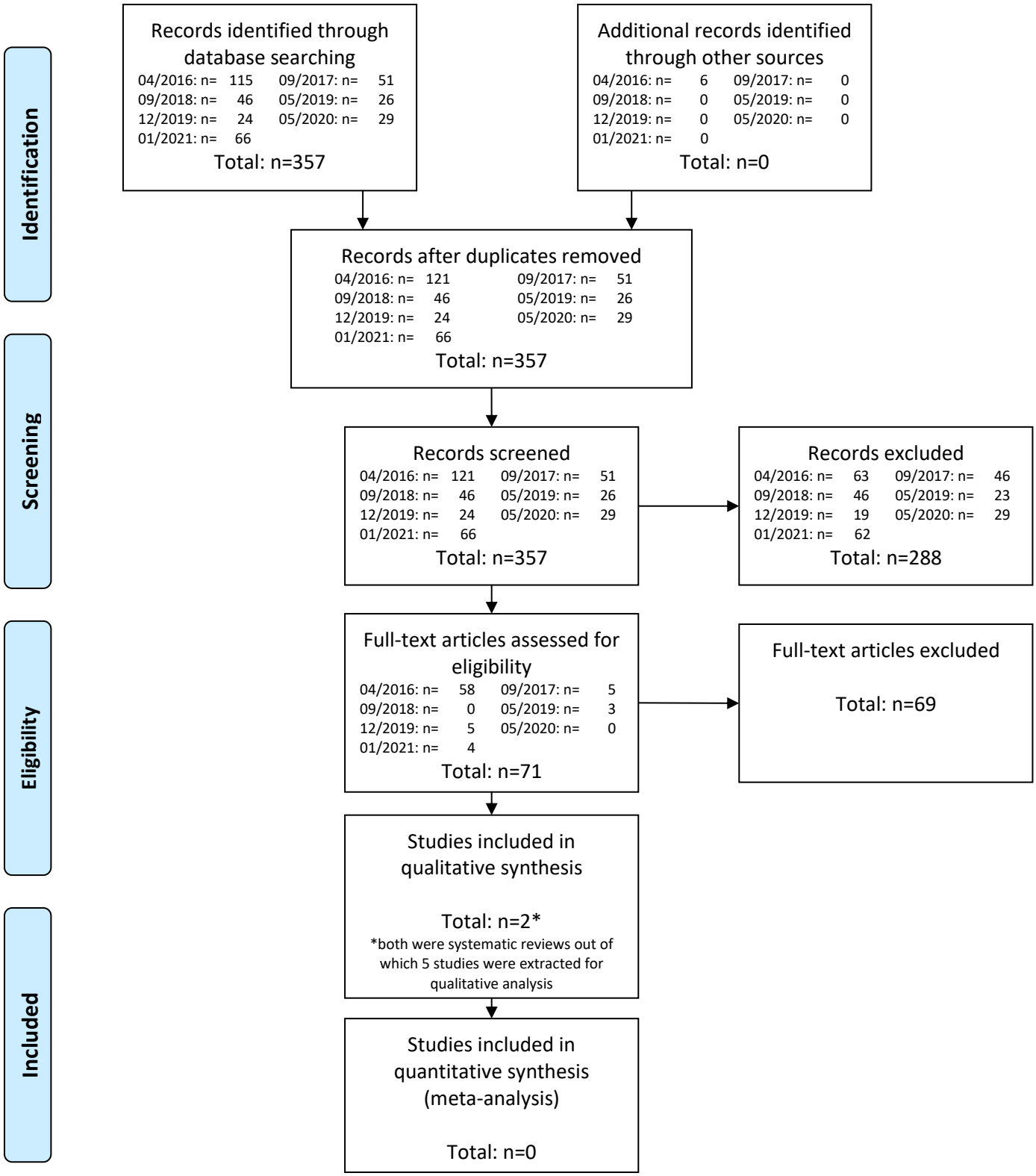
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Flow Diagram for PICO 7a-d (cancer registries and quality indicators [7a], specialized lung cancer services [7b], individual quality improvement measures [7c], audits/quality indicator systems [7d])



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Flow Diagram for PICO 8 (patient decision tools)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

References

1. Asking Answerable Clinical Questions. *In:* Sackett D L SSE, Richardson W S, Rosenberg W, Haynes R B, ed. Evidence-Based Medicine How to Practice and Teach EBM, 2nd ed. Churchill Livingstone, Edinburgh, 2000; pp. 13–27.
2. Oxford ORHIUo. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). 2015 [cited 27.11.2017]; Available from: http://www.prisma-statement.org/
3. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA, Cochrane Bias Methods G, Cochrane Statistical Methods G. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011: 343: d5928.
4. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, Montori V, Akl EA, Djulbegovic B, Falck-Ytter Y, Norris SL, Williams JW, Jr., Atkins D, Meerpohl J, Schunemann HJ. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *J Clin Epidemiol* 2011: 64(4): 407-415.
5. Blum TG, Rich A, Baldwin D, Beckett P, De Ruysscher D, Faivre-Finn C, Gaga M, Gamarra F, Grigoriu B, Hansen NC, Hubbard R, Huber RM, Jakobsen E, Jovanovic D, Konsoulova A, Kollmeier J, Massard G, McPhelim J, Meert AP, Milroy R, Paesmans M, Peake M, Putora PM, Scherpereel A, Schonfeld N, Sitter H, Skaug K, Spiro S, Strand TE, Taright S, Thomas M, van Schil PE, Vansteenkiste JF, Wiewrodt R, Sculier JP. The European initiative for quality management in lung cancer care. *Eur Respir J* 2014: 43(5): 1254-1277.
6. Santesso N, Glenton C, Dahm P, Garner P, Akl EA, Alper B, Brignardello-Petersen R, Carrasco-Labra A, De Beer H, Hultcrantz M, Kuijpers T, Meerpohl J, Morgan R, Mustafa R, Skoetz N, Sultan S, Wiysonge C, Guyatt G, Schünemann HJ. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. *J Clin Epidemiol* 2020: 119: 126-135.
7. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, Debeer H. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011: 64(4): 383-394.
8. Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, Treweek S, Mustafa RA, Vandvik PO, Meerpohl J, Guyatt GH, Schunemann HJ, Group GW. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ* 2016: 353: i2089.
9. Alonso-Coello P, Schunemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, Treweek S, Mustafa RA, Rada G, Rosenbaum S, Morelli A, Guyatt GH, Oxman AD, Group GW. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ* 2016: 353: i2016.
10. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, Devereaux PJ, Montori VM, Freyschuss B, Vist G, Jaeschke R, Williams JW, Jr., Murad MH, Sinclair D, Falck-Ytter Y, Meerpohl J, Whittington C, Thorlund K, Andrews J, Schunemann HJ. GRADE guidelines 6. Rating the quality of evidence--imprecision. *J Clin Epidemiol* 2011: 64(12): 1283-1293.
11. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Glasziou P, Jaeschke R, Akl EA, Norris S, Vist G, Dahm P, Shukla VK, Higgins J, Falck-Ytter Y, Schunemann HJ, Group GW. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. *J Clin Epidemiol* 2011: 64(12): 1294-1302.

12. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Falck-Ytter Y, Jaeschke R, Vist G, Akl EA, Post PN, Norris S, Meerpohl J, Shukla VK, Nasser M, Schunemann HJ, Group GW. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *J Clin Epidemiol* 2011: 64(12): 1303-1310.
13. Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, Alonso-Coello P, Djulbegovic B, Atkins D, Falck-Ytter Y, Williams JW, Jr., Meerpohl J, Norris SL, Akl EA, Schunemann HJ. GRADE guidelines: 5. Rating the quality of evidence--publication bias. *J Clin Epidemiol* 2011: 64(12): 1277-1282.
14. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schunemann HJ, Edejer T, Varonen H, Vist GE, Williams JW, Jr., Zaza S, Group GW. Grading quality of evidence and strength of recommendations. *BMJ* 2004: 328(7454): 1490.
15. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, Nasser M, Meerpohl J, Post PN, Kunz R, Brozek J, Vist G, Rind D, Akl EA, Schünemann HJ. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol* 2013: 66(7): 719-725.
16. Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, Rind D, Montori VM, Brito JP, Norris S, Elbarbary M, Post P, Nasser M, Shukla V, Jaeschke R, Brozek J, Djulbegovic B, Guyatt G. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013: 66(7): 726-735.
17. Guyatt GH, Alonso-Coello P, Schunemann HJ, Djulbegovic B, Nothacker M, Lange S, Murad MH, Akl EA. Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. *J Clin Epidemiol* 2016: 80: 3-7.

Table of Contents

PICO question 1. In patients with lung cancer (or those suspected of having lung cancer), should shorter rather than longer cancer care time intervals be used (e.g. time from diagnosis to treatment)?

A. PICO 1: General summary of the evidence

A total of 67 publications were selected out of the 1,791 initially identified abstracts (PRISMA flow diagram: ***online supplement A***) concerning various outcome items [1-67] including 65 observational studies [3-67]. In addition, there was one prospective randomized controlled trial published in 2003 [1] and one post-hoc analysis of another prospective randomized controlled trial [2], the former one addressing overall survival, receipt of performance of curative therapy, and patient satisfaction as outcome parameters, the latter one only overall survival. A total of 1,748,596 patients were assessed in 65 studies (two studies without patient figures [66, 67]) with a median of 466 patients per study.

However, due to the low patient numbers in the randomized controlled trial by *Murray et al.* (interventional arm 45 patients; control arm 43 patients) and the post-hoc analysis design in the other randomized controlled trial by *Abdel-Rahman et al.* [2], we decided to primarily focus and base our evidence tables on the 65 observational studies.

64 of the observational studies were retrospective investigations, only one was based on a prospective cohort-study design [8]. The publication period ranged from 1984 to 2020. There were 31 population-based data collections at the national and regional level, fifteen from the United States [9, 18, 38, 39, 41, 44, 47, 49, 51-53, 56, 60, 61, 68], four from the United Kingdom [15, 17, 29, 40] , two each from Australia [35, 58], Canada [43, 55], Poland [31, 32] and South Korea [34, 67] as well as single studies from Denmark, Ireland, Spain and Taiwan [48, 50, 64, 66]. The remainder is composed of 34 centre-based studies from various countries (Brazil: 1 study [6], Canada: 4 studies [14, 16, 25, 26], China: 1 study [54], Finland: 2 study [7, 33], Germany: 3 study [22, 45, 59], Israel: 1 study [4, 22, 45, 59], Italy: 1 study [12], Japan: 1 study [24], Malaysia: 1 study [62], Montenegro: 1 study [37], Spain: 6 studies [3, 13, 19, 20, 27, 30], Sweden: 1 study [28], Taiwan: 2 studies [5, 46], Turkey: 2 studies [5, 8, 42, 46], UK: 1 study [10], and USA: 6 studies [11, 21, 23, 36, 63, 65]).

Thirteen observational studies included mixed cancer types [3, 4, 15, 22, 29, 34, 40, 45, 49, 52, 53, 64, 66, 67], while 52 studies were based on lung cancer patients only.

36 studies focussed on NSCLC cohorts in stage I/II (11 studies) [14, 23, 38, 45, 46, 49, 50, 53, 55, 60, 63], stage I-III (4 studies) [36, 51, 54, 56], stage III (4 studies) [52, 57, 59, 65], stage IIIB/IV (1 study with ALK-positive patients only) [47], stage IV (2 studies) [42, 58], and all stages (14 studies) [10, 11, 15, 16, 18, 21, 28, 32, 35, 41, 43, 44, 48, 62], respectively. Correspondingly, NSCLC treatment concepts observed were surgery (8 studies) [11, 14, 23, 38, 46, 50, 60, 63], surgery combined with neoadjuvant or adjuvant modalities (9 studies) [36, 43, 45, 52, 54-57, 59], chemoradiotherapy (1 study) [65], systemic therapies (2 studies) [42, 47] or any of those (15 studies) [10, 15, 16, 18, 21, 28, 32, 35, 41, 44, 48, 49, 51, 53, 58]. One study did not state specific treatment modalities [62].

Three observational studies explored SCLC populations each of which encompassing all stages and SCLC-specific treatment options [9, 31, 61]. One study investigated tracheal cancer patients [5]. Thirteen studies did not specify lung cancer histology compiling mainly stage I-IV patient populations (stage I-III: 1 study, no information on stage: 4 studies) [3, 4, 6, 12, 13, 26, 27, 29, 34, 40, 64, 66, 67].

Waiting time intervals were grouped according to the internationally accepted definitions of the Aarhus statement following the chronological order of the patient pathway from first symptoms to start of treatment [69]. Among the 65 included studies, 15 different waiting time intervals were investigated with ten studies assessing more than one interval. Subsequently, the number of studies as well as the respective definitions and ranges of applied thresholds are given for each waiting time interval (the latter two in brackets): 1) *patient interval* in 2 studies (time from first symptom to first presentation/clinical appearance; 30 days)

[31, 32], 2) *patient interval plus primary care interval* in 5 studies (time from first symptom to first referral to secondary care/refer responsibility; 30-90 days) [7, 8, 19, 20, 62], 3) *patient interval plus diagnostic interval* in 6 studies (time from first symptom to diagnosis; 56-130 days) [3, 5, 12, 27, 30, 37], 4) *total interval* in 5 studies (time from first symptom to treatment start; 60-130.5 days) [4, 7, 8, 20, 28], 5) *primary care interval plus secondary care interval* in 3 studies (time from first presentation/clinical appearance to treatment start; 42-84 days) [21, 31, 32], 6) *diagnostic interval* in 2 studies (time from first presentation/clinical appearance to diagnosis; 30 days) [40, 64], 7) *diagnostic interval plus treatment interval* in 1 study (time from first presentation/clinical appearance to treatment start; 30 days) [28], 8) *system interval* in 3 studies (time from first investigation, primary care responsible for the patient to treatment start; 30-60 days) [16, 36, 65], 9) *first referral to secondary care to first specialist visit* in 3 studies (14 days) [15, 17, 24], 10) *first referral to secondary care to diagnosis* in 1 study (33 days) [7]. 11) *first specialist visit to diagnosis* in 1 study (30 days) [19], 12) *secondary care interval* in 9 studies (time from first referral to secondary care/refer responsibility to treatment start; 14-62 days) [10, 15, 19, 20, 26, 29, 33, 62, 66], 13) *neoadjuvant treatment interval* in 2 studies (time from neoadjuvant treatment to date of surgery; 21-90 days) [52, 57], 14) *treatment interval* in 32 studies (time from diagnosis to date of surgery; 7-90 days) [6, 7, 9, 11, 13-15, 17-19, 22, 23, 25, 34, 35, 38, 41, 42, 46-51, 53, 58, 60, 61, 63, 67, 70, 71], 15) and *adjuvant treatment interval* in 6 studies (time from date of surgery to start of adjuvant treatment; 35-70 days) [43, 45, 54-56, 59].

Regarding outcome parameters, all 65 observational studies assessed *overall survival* except two studies [54, 56]. Two studies each recorded *DFS* [26, 54] and *PFS* [26, 42]. Likewise, *mortality*, *accuracy of staging* (concordance of clinical and pathological staging) and *receipt of curative treatments* were reported in three [38, 56, 60], ten studies [12-14, 24, 29, 30, 38, 46, 50, 60] and two studies [13, 24], respectively. *Patient satisfaction* was only addressed in the randomized controlled trial by *Murray et al.* [1]. No evidence was found relating to *morbidity, pathological confirmation, other treatment outcome, receipt of any active tumour-specific treatments (versus palliative care only), quality of life,* and *performance status*.

B. PICO 1: Summary, rating of the quality of evidence and GRADE evidence profiles in specific subgroups

Individual studies, their main characteristics, and assessments of respective limitations per outcome are depicted in ***online supplement C***. Due to the substantial heterogeneity across the body of evidence relating to varying lung cancer populations as well as different temporal comparison measures, distinct subgroups were composed out of the 65 observational studies matching pieces of evidence according to underlying waiting time intervals, histologies, tumour stages and treatment modalities.

The assessments of individual studies across the groupings allowed only a meaningful quality assessment for *treatment interval* for the following subgroups: 1) NSCLC, stage I/II, surgery, treatment interval; 2) NSCLC, stage I/II, all treatment modalities, treatment interval; 3) NSCLC, stage I-III, all treatment modalities, treatment interval; 4) NSCLC, stage I/II/III/IV, all treatment modalities, treatment interval; 5) ALK-positive NSCLC, stage IIIB/IV, ALK-TKI, treatment interval; 6) SCLC, all stages, all treatment modalities, treatment interval.

A priori, all outcomes were considered either critical or important related to this PICO (***online supplement A***). Effectively, only *overall survival*, *mortality*, and *accuracy of staging* were addressed in the selected study groups.

1) PICO 1, subgroup1: NSCLC, stage I/II, surgical resection, treatment interval with shorter waiting times (vs. longer waiting times)

Overall survival was assessed in eight observational studies (341,915 patients, range 174-277,245 patients) exploring thresholds of 21-90 days to discriminate shorter vs. longer treatment intervals [14, 23, 38, 41, 46, 49, 50, 53, 60, 63]. A total of 244,924 patients out of seven eligible studies were included into a meta-analysis [23, 38, 41, 46, 50, 60, 63]. Yet, all patients were omitted from the meta-analysis who were not propensity-matched in *Samson et al.* (28,631 patients) [38] as well as those who received surgical resection as primary invasive diagnostics (=treatment interval 0 days) in *Anggondowati et al.* (68,138 patients) [41]. One study was excluded from the meta-analysis due to insufficient attribution of confounding factors (222 patients) [14].

The meta-analysis revealed an overall survival benefit for a shorter treatment interval (HR 0.893, 95% CI 0.847-0.943); however, there were concerns with inconsistency (I^2 75%) partially explained by the also detected indirectness (different treatment time intervals) across studies. The forest plot is shown in ***Figure 1***.

[quality of evidence for overall survival: very low ⊕○○○; downgraded because of serious indirectness and inconsistency across studies]

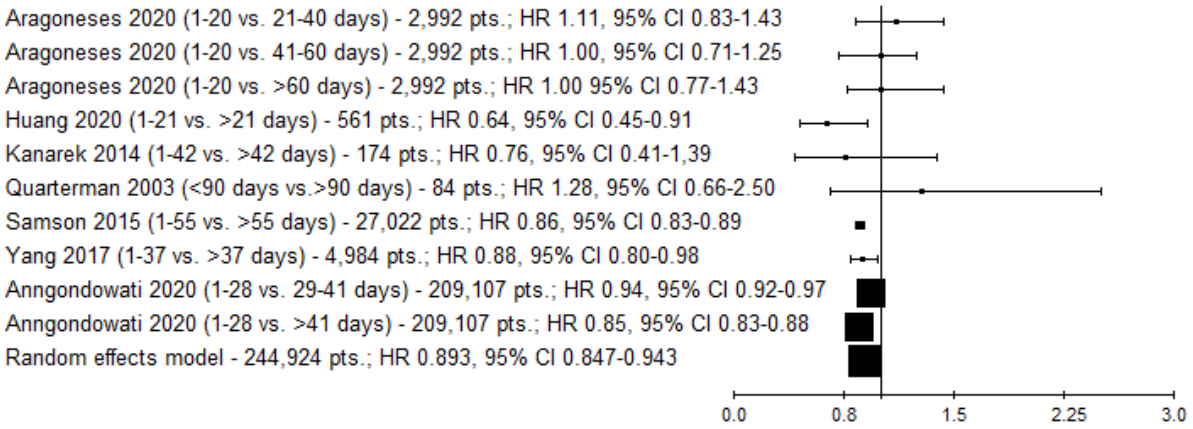


Figure 1: Forest plot with HR and 95% CI for effect of shorter treatment interval vs. longer treatment interval (thresholds per studies in brackets) in PICO 1, subgroup1 (NSCLC, stage I/II, surgical resection, treatment interval) on overall survival based on meta-analysis in seven eligible observational studies (740,254 patients; I^2 75%; HR<1.0: shorter treatment interval correlating with higher overall survival) [23, 38, 41, 46, 50, 60, 63]

30-day mortality was explored in two studies (32,006 patients; treatment interval thresholds 37 and 56 days) [38, 60]. The *30-day mortality* was calculated to be 19% lower when shorter waiting times were applied (OR 0.81; 95% CI 0.71-0.93). *Yang et al.* investigated also *90-day mortality* (4,984 patients; treatment interval threshold 37 days) indicating the same effect direction (OR 0.80; 95% CI 0.62-1.03) [60].

[quality of evidence for 30-day: very low ⊕○○○; downgraded because of serious indirectness and imprecision]

[quality of evidence for 90-day mortality: very low ⊕○○○; downgraded because of serious imprecision]

Accuracy of staging was analysed in four studies (33,649 patients; treatment interval thresholds of 37 and 56 days) [38, 46, 50, 60]. The largest study by *Samson et al.* (27,022 patients; treatment interval threshold 56 days) demonstrated a small effect with more favourable stage distribution compared to initial clinical staging for the shorter treatment interval cohort (OR 1.12, 95% CI 1.05-1.19) [38] while effects were trivial in the other three studies (6,627 patients). A pooled effect across studies was not estimable.

[quality of evidence for accuracy of staging: very low ⊕◯◯◯; downgraded because of serious indirectness across studies].

The GRADE evidence profile relating to the subgroup 1 in PICO 1 (NSCLC, stage I/II, surgical resection, treatment interval) is presented in ***Table 1***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	shorter waiting times	longer waiting times	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
7 [23, 38, 41, 46, 50, 60, 63]	observational studies	not serious	serious [a]	serious [b]	not serious	none	-/88953 [c,d]	-/152979 [c,d]	**HR 0.89** (0.85 to 0.94)	**-- per 1.000** (from -- to --) [c]	⊕◯◯◯ VERY LOW	CRITICAL
Mortality (follow up: 30 days)												
2 [38, 60]	observational studies	not serious	not serious	serious [e]	serious [f]	none	389/15951 (2.4%)	480/16055 (3.0%)	**OR 0.81** (0.71 to 0.93)	**5 fewer per 1.000** (from 8 fewer to 2 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality (follow up: 90 days)												
1 [60]	observational studies	not serious	not serious	not serious	serious [f]	none	116/2440 (4.8%)	150/2544 (5.9%)	**OR 0.80** (0.62 to 1.03)	**11 fewer per 1.000** (from 21 fewer to 1 more)	⊕◯◯◯ VERY LOW	CRITICAL
Accuracy of clinical staging												
4 [38, 46, 50, 60]	observational studies	not serious	not serious	serious [b]	serious [g]	none	The effects were small in the largest study by *Samson et al.* (27,022 patients) in which shorter waiting times correlated with more favourable pathological stage distribution compared to initial clinical staging (OR 1.12, 95% CI 1.05-1.19) while effects were trivial in the other three studies (6,627 patients; no ORs calculable). Thus, shorter treatment interval may improve accuracy of staging but the evidence is very uncertain.				⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations:

a. High heterogeneity (I^2= 75%) among studies suspected, beside different time intervals used, other factors may contribute as well.

b. Different time intervals were compared within and across studies with thresholds from as low as 21 days (Aragoneses 2020, Huang 2020) to up to 56 days (Samson 2015).
c. None of the studies provided number of events.
d. Aragoneses, 2020 did not provide total number of patients.
e. Different time intervals were compared in both study with thresholds of 37 (Yang 2017) and 56 days (Samson 2015).
f. The 95% CI in Yang, 2019 includes the potential for benefit; however, we cannot exclude the possibility of no benefit.
g. A pooled effect across studies was not estimable.

Table 1: GRADE evidence profile for PICO 1, subgroup 1 (NSCLC, stage I/II, surgical resection, treatment interval)

2) PICO 1, subgroup 2: NSCLC, stage I/II, all treatment modalities, treatment interval with shorter waiting times (vs. longer waiting times)

Overall survival for stage I/II was specifically addressed in eight observational studies (670,006 patients, treatment interval thresholds 7-60 days) [6, 18, 35, 44, 48, 49, 51, 53]. Out of these, four studies were eligible for meta-analysis (132,673 patients) [6, 18, 48, 51]. 42,313 patients from *Cushman et al.* were excluded since lacking survival data for the 45-day threshold [51]. The meta-analysis associated a shorter treatment interval with improved overall survival within the pooled studies (HR 0.734; 95% CI 0.642-0.839) while again both serious inconsistency (I^2 96%) and indirection (different time intervals) were present. The forest plot is shown in ***Figure 2***.

Two studies were excluded from meta-analysis since assessing mixed cancer cohorts with specific information on a total of 494,460 lung cancer patients using 60 days and 42 days as treatment interval thresholds, respectively [49, 53]. *Cone et al.* highlighted significantly better 5- and 10-year overall survival for the shorter treatment interval group in stage I NSCLC (105,266 patients; $p<0.05$) in contrast to an indeterminate effect in stage II NSCLC (25,331 patients) [49]. *Khorana et al.* proved positive correlations for both stage I (HR 0,969, 95% CI 0,967-0,970) and stage II NSCLC (HR 0,984; 0,982-0,986), respectively [53]. Two studies were excluded due to missing information on confidence intervals (185 patients) [44] and analysis of waiting time as a continuous variable (375 patients) [35].

[quality of evidence for overall survival: very low ⊕◯◯◯; downgraded because of serious indirectness, inconsistency and imprecision across studies].

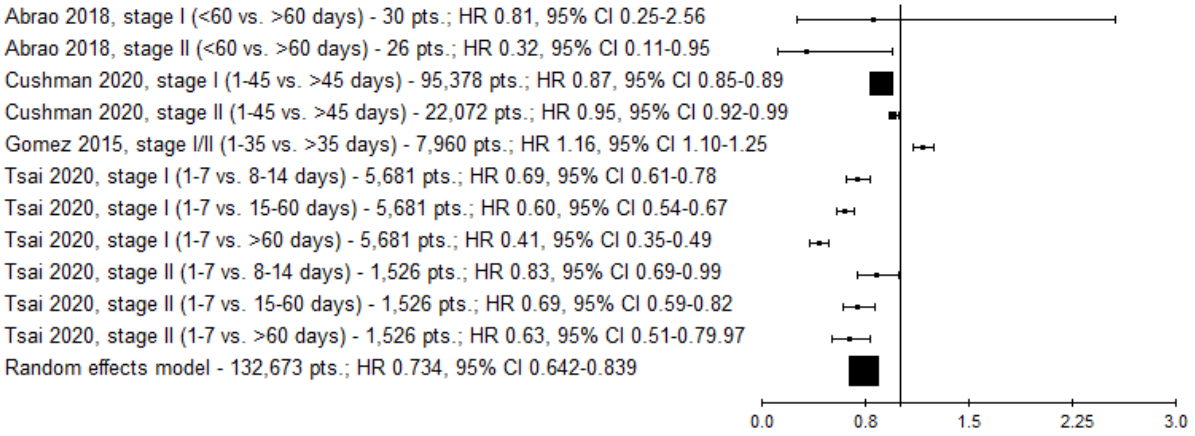


Figure 2: Forest plot with HR and 95% CI for effect of shorter treatment interval vs. longer treatment interval (thresholds per studies in brackets) in PICO 1, subgroup 2 (NSCLC, stage I/II, all treatment modalities, treatment interval) on overall survival based on meta-analysis in four eligible observational studies (132,673 patients; I^2 96%; HR<1.0: shorter treatment interval correlating with higher overall survival) [6, 18, 48, 51]

The GRADE evidence profile relating to the subgroup 2 in PICO 1 (NSCLC, stage I/II, all treatment modalities, treatment interval) is presented in ***Table* 2**.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	shorter treatment interval	longer treatment interval	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
4 [6, 18, 48, 51]	observational studies	not serious	not serious [a]	serious [b]	not serious [c]	none	-/76377 [d,e]	-/48280 [d,e]	**HR 0,73** (0,64 to 0,84)	**-- per 1.000** (from -- to --)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio

Explanations:

a. High heterogeneity (I^2= 75%) among studies suspected, beside different time intervals used, other factors may contribute as well.

b. Different time intervals were compared in each study with thresholds from as low as 7 days (Tsai 2020) to up to 60 days (Abrao 2018).

c. The pooled 95% CI includes the potential for benefit; however, we cannot exclude the possibility of no benefit since 4 studies were excluded: Cone 2020 revealed a benefit in stage I NSCLC (105,266), but no effect in the subgroup of stage II NSCLC (25,331 patients). Another 2 excluded studies (560 patients) did show no effect (no suitable HRs provided). Yet, as the largest study by Khorana 2019 (363,863) favoured shorter treatment interval (stage I HR 1.032; 95% CI 1.031-1.034, stage II HR 1.016; 1.014-1.018), imprecision seems insignificant.

d. None of the studies provided data on events.

e. Abrao, 2018 and Gomez, 2015 did not provide total number of patients.

Table 2: GRADE evidence profile for PICO 1, subgroup 2 (NSCLC, stage I/II, all treatment modalities, treatment interval)

3) PICO 1, subgroup 3: NSCLC, stage III, all treatment modalities, treatment interval with shorter waiting times (vs. longer waiting times)

Overall survival was assessed in six observational studies (48,693 patients; treatment interval thresholds 7-60 days) [6, 18, 35, 44, 48, 51]. Four studies were suitable for meta-analysis (44,163 patients; treatment interval thresholds 7-60 days; 3,876 patients from *Cushman et al.* excluded due to missing survival data for 45-day threshold) [6, 18, 48, 51], the already cited two studies had to be omitted again for the above-mentioned reasons (654 patients) [35, 44].

Length of treatment may not have a difference in overall survival (HR 0.999; 95% CI 0.844-1.182); however, the certainty of the evidence is low based on concerns with indirectness and imprecision. The forest plot is shown in

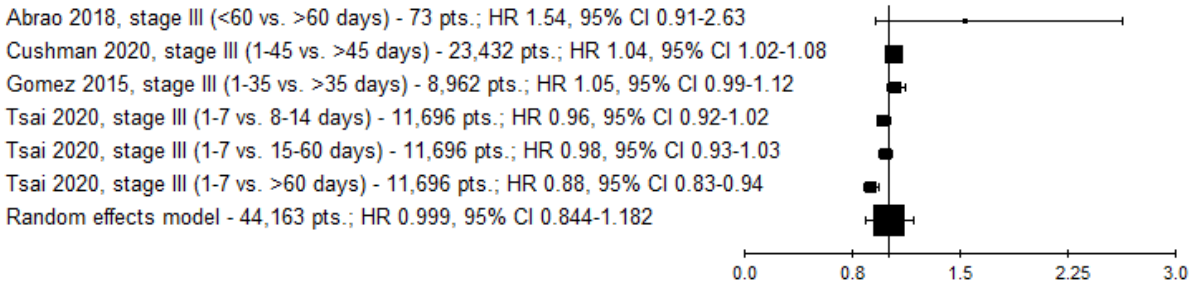


***Figure* 3**.

[quality of evidence for overall survival: very low ⊕◯◯◯; downgraded because of serious indirectness, inconsistency and imprecision across studies]

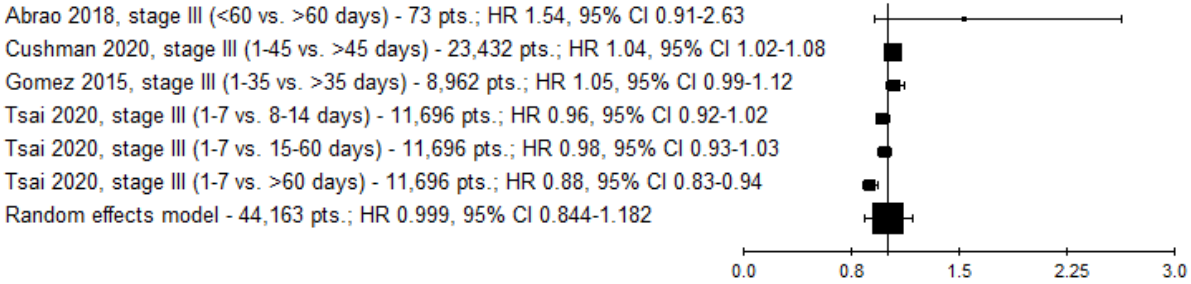


Figure 3: Forest plot with HR and 95% CI for effect of shorter treatment interval vs. longer treatment interval (thresholds per studies in brackets) in PICO 1, subgroup 3 (NSCLC, stage III, all treatment modalities, treatment interval) on overall survival based on meta-analysis in four eligible observational studies (44,163 patients; I^2 84%; HR<1.0: shorter treatment interval correlating with higher overall survival) [6, 18, 48, 51]

The GRADE evidence profile relating to the subgroup 3 in PICO 1 (NSCLC, stage III, all treatment modalities, treatment interval) is presented in ***Table 3***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	shorter waiting times	longer	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
4 [6, 18, 48, 51]	observational studies	not serious	serious [a]	serious [b]	serious [c]	none	-/19659 [d,e]	-/15469 [d,e]	**HR 1.00** (0.84 to 1.18)	**-- per 1.000** (from -- to --) [d,e]	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio

Explanations:

a. High heterogeneity (I^2= 84%) among studies suspected, beside different time intervals used, other factors may contribute as well.
b. Different time intervals were compared in each study with thresholds from as low as 7 days (Tsai 2020) to up to 60 days (Abrao 2018).
c. The 95% CIs include the potential for benefit as well no benefit.
d. None of the studies provided number of events.
e. Abrao 2018 and Gomez 2015 did not provide total number of patients.

Table 3: GRADE evidence profile for PICO 1, subgroup 3 (NSCLC, stage III, all treatment modalities, treatment interval)

4) PICO 1, subgroup 4: NSCLC, stage IV, all treatment modalities, treatment interval with shorter waiting times (vs. longer waiting times)

Overall survival was analysed in five studies (37,306 patients; treatment interval thresholds 7-60 days) [6, 18, 35, 44, 48] enabling a meta-analysis in two studies (24,289 patients; treatment interval thresholds 7-60 days) [6, 48].

As for the locally advanced NSCLC stages, the length of treatment intervals may not influence overall survival based on aggregated results (HR 1.138; 95% CI 0.928-1.395). The forest plot is shown in

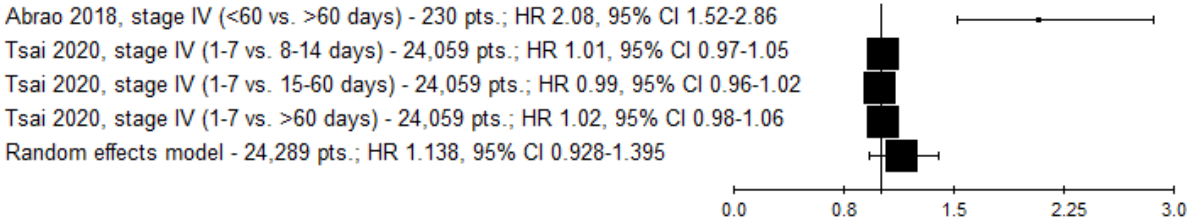


Figure 4. The stage IV NSCLC sub-cohort from *Gomez et al.* (11,810 patients) could not be included as the proportional hazard assumption was not fulfilled. Interestingly, in patients with a survival of more than a year, shorter waiting times correlated with improved overall survival (HR 0.86, 95% CI 0.74-0.99) contrasted by the opposite effect in patients dying within a year (HR 1.35, 95% CI 1.28-1.41) [18]. The two studies by *Vinod et al.* and *Bullard et al.* were again ineligible (1,207 patients) [35, 44].

[quality of evidence for overall survival: very low ⊕◯◯◯; downgraded because of serious indirectness and imprecision across studies].

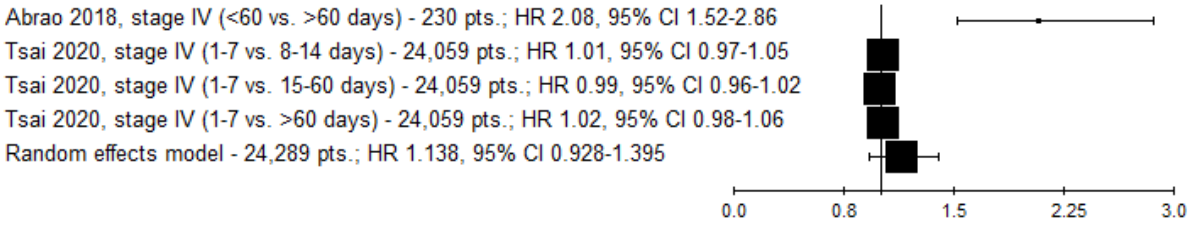


Figure 4: Forest plot with HR and 95% CI for effect of shorter treatment interval vs. longer treatment interval (thresholds per studies in brackets) in PICO 1, subgroup 4 (NSCLC, stage III, all treatment modalities, treatment interval) on overall survival based on meta-analysis in two eligible observational studies (24,289 patients; I^2 86%; HR<1.0: shorter treatment interval correlating with higher overall survival) [6, 48]

The GRADE evidence profile relating to the subgroup 4 in PICO 1 (NSCLC, stage IV, all treatment modalities, treatment interval) is presented in ***Table 4***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	shorter waiting times	longer waiting times	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
2 [6, 48]	observational studies	not serious	serious [a]	serious [b]	serious [c]	none	-/7924 [d,e]	-/16135 [d,e]	**HR 1.14** (0.93 to 1.40)	**1 fewer per 1.000** (from 1 fewer to 1 fewer) [d,f]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio

Explanations:

a. High heterogeneity (I^2= 86%) among studies suspected, beside different time intervals used, other factors may contribute as well.
b. Different time intervals were compared in each study with thresholds from as low as 7 days (Tsai 2020) to up to 60 days (Abrao 2018).
c. The 95% Cis include the potential for benefit as well no benefit.
d. None of the studies provided number of events.
e. Abrao 2018 and Gomez 2015 did not provide total number of patients.
f. Abrao did not provide total number of patients.

Table 4: GRADE evidence profile for PICO 1, subgroup 4 (NSCLC, stage IV, all treatment modalities, treatment interval)

5) PICO 1, subgroup 5: ALK-positive NSCLC, stage IIIB/IV, ALK-TKI, treatment interval with shorter waiting times (vs. longer waiting times)

Overall survival was investigated in one population-based observational study (442 patients) [47]. According to the adjusted HR, a shorter treatment interval correlated with better prognosis, yet due to small sample size and no given event numbers, there is a risk for imprecision (HR 0.49; 95% CI 0.27-0.88) [47].

[quality of evidence for overall survival: very low ⊕○○○].

The GRADE evidence profile relating to the subgroup 5 in PICO 1 (ALK-positive NSCLC, stage IIIB/IV, ALK-TKI, treatment interval) is presented in ***Table 5***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	shorter waiting times	longer waiting times	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
1 [47]	observational studies	not serious	not serious	not serious	serious [a]	none	-/257 [b]	-/185 [b]	**HR 0.49** (0.27 to 0.88)	**-- per 1.000** (from -- to --) [b]	⊕○○○ VERY LOW	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio

Explanations:

a. Sheinson 2020 with small sample size (415 patients) and no provision of numbers of events, thus, there is a concern of potential imprecision

b. Study did not provide numbers of events.

Table 5: GRADE evidence profile for PICO 1, subgroup 5 (ALK-positive NSCLC, stage IIIB/IV, ALK-TKI, treatment interval)

6) PICO 1, subgroup 6: SCLC, all stages, all treatment modalities, treatment interval with shorter waiting times (vs. longer waiting times)

Bhandari et al. analysed ***overall survival*** in general SCLC cohorts both on a regional and a national level [9, 61]. In their study based on Kentucky cancer registry data (2,992 patients) a large effect was seen with a treatment interval shorter than 28 days relating to a poorer survival compared to a longer treatment interval even after adjustment for potential confounders (1-year overall survival: HR 1.43; 95% CI 1.2-1.6; 2-year overall survival: HR 1.45; 95% CI 1.3-1.6) [9]. Similarly, their evaluation of National Cancer Database (64,941 patients) revealed a significant reverse correlation of waiting times (treatment time threshold 7 days) and overall survival times. Adjusted hazard ratio point estimates of treatment interval subgroups (0-7 days as reference vs. 8-14 days, 15-28 days and >28 days) indicated a large effect on improved overall survival with longer intervals [61].

[quality of evidence for overall survival: very low ⊕○○○; downgraded because of serious risk of bias and indirectness]

The GRADE evidence profile relating to the subgroup 6 in PICO 1 (SCLC, all stages, all treatment modalities, treatment interval) is presented in ***Table 6***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	shorter waiting times	longer waiting times	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
2 [9, 61]	observational studies	serious [a]	not serious	serious [b]	serious [c]	none	We detected 2 studies both with large reverse effects (67,933 patients): Bhandari et al. 2019: treatment interval shorter than 28 days related to a poorer survival (1-year overall survival: HR 1.43; 95% CI 1.2-1.6; p<0.01; 2-year overall survival: HR 1.45; 95% CI 1.3-1.6) Bhandari et al. 2020: treatment interval shorter than 7 days related to a poorer survival (adjusted HRs estimates of treatment interval subgroups indicated increasingly improved overall survival with longer intervals).				⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations:

a. Despite adjusting for several potential confounders, other factors unassessed or unaccounted for may explain the inferior overall survival in shorter treatment interval (i.e. high rate of imminent tumour complications with poor prognosis in SCLC prompting clinicians to act immediately).

b. The 2 studies use different thresholds of 7 days and 28 days, respectively. The latter threshold appears too long for SCLC.

c. No pooled estimate to assess given.

Table 6: GRADE evidence profile for PICO 1, subgroup 6 (SCLC, all stages, all treatment modalities, treatment interval)

C. PICO 1: GRADE evidence to decision framework

Table 7 depicts the GRADE evidence to decision framework relating to PICO 1based upon on the GRADE evidence profiles as well as additional considerations by the task force panel.

PICO 1: In patients with lung cancer (or those suspected of having lung cancer), should shorter rather than longer cancer care time intervals be used (e.g. time from diagnosis to treatment)?	
POPULATION:	people diagnosed with lung cancer
INTERVENTION:	shorter treatment intervals
COMPARISON:	longer treatment intervals
MAIN OUTCOMES:	overall survival, 30-day mortality,90-day mortality, accuracy of staging
SETTING:	Both outpatient and inpatient
PERSPECTIVE:	Clinical recommendations – population perspective
BACKGROUND:	Early diagnosis and treatment of lung cancer is central to improve outcomes. Yet, lung cancer mortality is still high due to lack or late onset of symptoms as well as delayed presentation of patients to primary and secondary care for diagnostics and treatment. Delays may be contributed to by patients, primary and/or secondary care professionals as well as other factors.
CONFLICT OF INTERESTS:	N/A

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Early diagnosis and treatment of lung cancer is considered to be central to improve outcomes. Yet, lung cancer mortality is still high due to lack or late onset of symptoms as well as delayed presentation of patients to primary, secondary care diagnostics and treatment which may be caused by patients, primary and/or secondary care professionals as well as other factors. The natural course of untreated lung cancer will most often lead to accelerated premature death [72].	The improvement of waiting times is considered as an essential topic in lung cancer care by us, Likewise, it is a key priority topic for ERS as well as ELF and the Patient Advisory Group

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Our systematic review revealed the following desirable effects of shorter treatment intervals (see related PICO 1 evidence tables, subgroups 1-6 for details): -improved overall survival in early stage NSCLC and ALK+NSCLC with ALK-targeted therapies while no certain effects could be seen in locally advanced and metastasized NSCLC. -reduced mortality in stage I/II NSCLC-patients with surgery (as the only subgroup assessed) -higher accuracy of staging in stage I/II NSCLC-patients (small effect in 1 study with 27,022 patients; 3 studies with trivial effect, 6,627 patients)	From clinical experience, the TF members consider the following additional desirable effects of shorter treatment intervals to be likely: -higher rates of treatments with curative intent, especially in more advanced stages -higher rates of treatments with palliative intent in more advanced stages -higher satisfaction of patients and medical professionals -reduction of psychological burden of patients

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Our systematic review revealed the following undesirable effects of shorter treatment intervals: -poorer overall survival in SCLC and stage IV NSCLC patients No other harms were detected by our systematic review (see related PICO 1 evidence tables, subgroups 1-6 for details).	From clinical experience, the TF members are concerned about the following additional undesirable effects of shorter treatment intervals: -striving for shorter treatment intervals may prompt medical professionals to initiate treatment before therapy-deciding diagnostics have been completed (i.e. molecular testing results) or chances for short-term improvement of fitness for therapy were not used (i.e. prehabilitation in patients at-risk) [73]. Regarding the reported poorer overall survival in SCLC patients, we assume other factors contributed to this effect which were unassessed or unaccounted for in the 2 available studies (i.e. imminent local tumour complications with worse prognostic impact) and which may have forced clinicians to act immediately (i.e. salvage therapies) and by that shorten the treatment interval. This may correspond to a Will Rogers phenomenon which may also explain the uncertain effects in more advanced NSCLC (with higher risk for short-term tumour-related complications) [74].

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the evidence was graded as very low (see related PICO 1 evidence tables, subgroups 1-6 for details)	None

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	We did not perform a systematic literature search specifically on patient values relating to treatment intervals. Our systematic review did not retrieve any related pieces of evidence.	Timely diagnostics and initiation of treatment are a key priority of patients as confirmed by patient and ELF representatives in our task force panel: Minimum delays are aspired as the psychological burden varies relating to time until first receipt of treatment. National waiting time targets are often not met in practice. Patient concerns about long waiting times have been a key finding of a pan-European survey project run by ELF in 2015 which addressed patients, caretakers and national patient organisations. https://europeanlunginfo.org/lung-cancer/research-and-news/report-on-consultation-lung-cancer-patient-priorities-report

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Our systematic evidence assessment resulted in moderate desirable effects and no undesirable effects.	Weighing desirable and undesirable effects based on our systematic evidence assessment, our task force panel discussions and clinical experience, we see benefits in reduction of treatment intervals in lung cancer care in principle, unless there is a risk of incomplete diagnostics and suboptimal fitness of patients when commencing treatment prematurely.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	We did not perform a systematic literature search specifically on required resources relating to treatment intervals. Our systematic review did not retrieve any related pieces of evidence.	We estimate at least moderate costs to optimize treatment intervals as well as other waiting time intervals in lung cancer care. In particular, we do see a need for additional coordinating staff as well as more advanced IT to better link and synchronize cross-departmental processes.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● No included studies	not applicable	Required resources are depending on multiple factors, especially already existing infrastructure, staff and network setting. A substantial variation across European countries is suspected impeding general cost estimates.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	We did not perform a systematic literature search specifically on cost effectiveness relating to treatment intervals. Our systematic review did not retrieve any related pieces of evidence.	Despite increased short-term costs for lung cancer pathway and service network optimisation, we assume mid- and long-term savings due to more efficient utilization of diagnostic and therapeutic capacities.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced	We did not perform a systematic literature search specifically on equity relating to treatment intervals.	Achieving shorter and reliable treatment intervals may facilitate patient adherence to treatments. Well-coordinated lung cancer

○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Our systematic review did not retrieve any related pieces of evidence.	services bear the potential to overcome inequalities through providing better access to instantaneous treatment initiation. Conversely, appropriate implementation is not expected to create inequality.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not perform a systematic literature search specifically on acceptability to key stakeholders relating to treatment intervals. Our systematic review did not retrieve any related pieces of evidence.	We assume that shorter treatment intervals will be accepted very well by patients, medical professionals and healthcare providers alike.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not perform a systematic literature search specifically on feasibility of implementing quality improvement measure to optimize treatment intervals. Our systematic review did not retrieve any related pieces of evidence.	If sufficient resources are made available, we assume these pathway optimization measures to be implemented and maintained well.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know

	JUDGEMENT						
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

In patients with lung cancer, we suggest minimizing delay in initiation of first treatment (conditional recommendation; very low certainty of evidence).

Remark: Evaluation should be complete before proceeding to any definitive treatment. Minimizing delay in initial evaluation of the patient and specialist referral may also help to improve outcomes in lung cancer patients.

Justification

Given the life-threatening potential of lung cancer treated too late after diagnosis and the fact that there were no substantial harms evident of foreseen related to optimisation of waiting times, we suggest delay avoidance, even if we have not found data showing improved survival in all subgroups. The recommendation is conditional due to the very low certainty of evidence.

Time points and intervals from first symptom to treatment start have been well-defined in the Aarhus statement paper [3]. So far, several varying timelines of lung cancer care have been introduced, yet all by national bodies only [1]. At this stage, no evidence-based recommendations regarding timelines can be made from an international perspective.

Subgroup considerations

None

Implementation considerations

We are confident that optimizing waiting times is an eminently suitable measure to improve outcomes in lung cancer care, namely rates of curative therapy and overall survival as well as quality of life and satisfaction with care in lung cancer patients.

Monitoring and evaluation

Lung cancer services are highly encouraged to periodically review their timelines on a cross-sectional basis and to strive for optimization accordingly.

Research priorities

Beyond that, larger initiatives on regional, national, or even international scales are needed, also addressing the level of necessary resources and satisfying so far unmet research needs. Population-based clinical cancer registries may serve as valid prospective observational data sources, likewise centre-based prospective observational data collection in high level lung cancer service networks as benchmarks, both setting the basis for definition and broader consensus-building of standardized waiting time thresholds.

In addition, cost-effectiveness analyses seem necessary to us taking into account variation on the local and national care level as well as among different health care systems.

Table 7: GRADE evidence to decision framework relating to PICO 1

PICO question 2: In patients with lung cancer (or those suspected of having lung cancer), should a multi-disciplinary team (MDT) or certain disciplines be involved during lung cancer care rather than no involvement of an MDT or certain disciplines?

A. PICO 2: General summary of the evidence

Out of the 874 studies identified by the literature search, 26 eligible publications were retrieved [1, 58, 75-98] among which there was only one randomized controlled trial [1] besides the remaining observational studies (PRISMA flow diagram: ***online supplement A***). The years of publication ranged from 2003 to 2020 with included patient numbers between 88 patients and 108,115 patients summing up to a total of 238,583 patients. Twelve studies had a single-centre [75, 76, 78, 79, 81, 82, 84, 88, 91, 93, 97, 98] and fourteen studies a multi-centre design either on a regional or national level [1, 58, 77, 80, 83, 85-87, 89, 90, 92, 94-96], respectively. Eight studies each were performed in the United Kingdom [1, 76, 80, 81, 87, 88, 91, 96] and in the United States of America [75, 79, 82, 83, 85, 86, 90, 93], six studies in Australia [58, 77, 78, 89, 94, 97], two in Taiwan [84, 92] and one study each in Italy [98] and New Zealand [95].

Regarding patient populations, twelve studies included all lung cancer types [1, 75, 77, 79, 80, 85, 86, 89, 90, 93, 94, 97] and 14 studies only NSCLC patients [58, 76, 78, 81-84, 87, 88, 91, 92, 95, 96, 98]. 21 studies explored patients in all stages [1, 58, 75-77, 79, 80, 82, 85-94, 96-98], the remaining studies were limited to stage I [95], stage III [83, 84], and inoperable stage III/IV [78, 81], respectively. All treatment modalities were eligible in 21 studies [1, 58, 75-80, 82-86, 89, 90, 92-97, 99], while the remainder assessed only patients with surgical resections [87, 88, 91, 98] as well as chemotherapy, radiotherapy or palliative care [81].

Although multi-disciplinary team (MDT) care and MDT meetings are usually more or less indivisible in routine care, the methodological scope of the 26 studies was differing with thirteen studies focussing solely on the effect of MDT meetings [58, 76-78, 82, 84, 85, 89, 91, 94, 95, 97, 98], five studies on the effect of MDT care alone [75, 79, 81, 83, 90], and another study on the effect of a combination of MDT care and MDT meetings [92]. Five studies reported on the impact of involving distinct disciplines in MDT lung cancer care, namely a thoracic surgeon in two studies [87, 88], a thoracic surgeon and/or an oncologist in one study [86], a respiratory physician in one study [80] and a lung cancer nurse [96], respectively. The remaining three studies investigated the effect of more complex MDT interrelationships: a daily MDT clinic without direct access to a surgeon vs. weekly MDT meetings with an integrated surgeon [93] and in a randomized controlled trial by *Murray et al.* a MDT meeting integrated into a fast-track lung cancer care pathway vs. a routine care pathway without a MDT meeting [1].

Overall survival was assessed in 22 studies [1, 58, 75, 77-81, 83-86, 88-94, 96-98]. *Mortality*, *morbidity*, *accuracy of staging* and *pathological confirmation* were reported in three [82, 88, 91], one [91], eight [77, 80-83, 85, 94, 98], and three studies [77, 80, 88], respectively. Thirteen studies investigated *receipt of curative treatment* [1, 76-78, 80, 82, 85-89, 94, 95], likewise eight studies analysed *receipt of any tumour-specific treatment* [77, 78, 80, 81, 85, 89, 94, 95]. One study explored *quality of life* (measured with EORTC questionnaire) and *patient satisfaction* [1]. *Progression-free survival (PFS)*, *disease-free survival (DFS)*, *other treatment outcome*, *performance status* and *other PROMs* were not reported as outcome parameters in any of the 26 studies.

B. PICO 2: Summary, rating of the quality of evidence and GRADE evidence profiles in specific subgroups

Individual studies, their main characteristics, and assessments of respective limitations per outcome are depicted in ***online supplement C***. The GRADE assessment for this search question was based on the 25 observational studies, because the randomized controlled trial by *Murray et al.* was conducted in single centres with low patient numbers (88 patients) – with the exception of *quality of life (measured with EORTC questionnaire)* and *patient satisfaction* as outcome parameters in which the randomized controlled trial was respectively used in the absence of any observational trials [1]. Since the observational studies revealed

substantial heterogeneity due to varying lung cancer populations, distinct subgroups were composed out of the 25 observational studies according to lung cancer types, stages, and treatment modalities.

The following subgroups were assessed: 1) All lung cancer types, all stages, all treatment modalities; 2) NSCLC, all stages, all treatment modalities; 3) NSCLC, all stages, surgical resection; 4) NSCLC, stage III/IV, all treatment modalities.

A priori, all outcomes were considered either critical or important related to this PICO (***online supplement A***). However, overall survival, mortality, morbidity, accuracy of staging, pathological confirmation, receipt of curative treatment and receipt of any tumour-specific treatment were the outcomes addressed in the retrieved studies.

1) PICO 2, subgroup 1: All lung cancer types, all stages, all treatment modalities, MDT involvement (vs. no MDT involvement)

Eleven observational studies [75, 77, 79, 80, 85, 86, 89, 90, 93, 94, 97] as well as the randomized controlled trial by Murray et al. [1] included patient data on all lung cancer types, stages and treatment modalities.

Overall survival was addressed in all eleven observational studies (43,118 patients) [75, 77, 79, 80, 85, 86, 89, 90, 93, 94, 97]. Four studies were eligible for meta-analysis (9,916 patients) [75, 80, 94, 97], while seven studies had to be excluded due to missing or incalculable hazard ratios (33,202 patients) [77, 79, 85, 86, 89, 90, 93]. The meta-analysis demonstrated a clear benefit of MDT-measures on overall survival (random effects model HR 0,618, 95% CI 0,578-0,662, I^2 14%) (forest plot in ***Figure 5***). Out of the studies ineligible for meta-analysis, one study each demonstrated a moderate (814 patients) [89] and small effect (2,263 patients) [79] of MDT on better overall survival, while four studies reported only trivial effects (27,933 patients) [77, 85, 90, 93] . Kehl et al. showed varying effects according to subgroups (2,132 patients) [86] (effect results in ***Table 8***).

[quality of evidence for *overall survival*: very low ⊕◯◯◯; downgraded because of indirectness across studies]

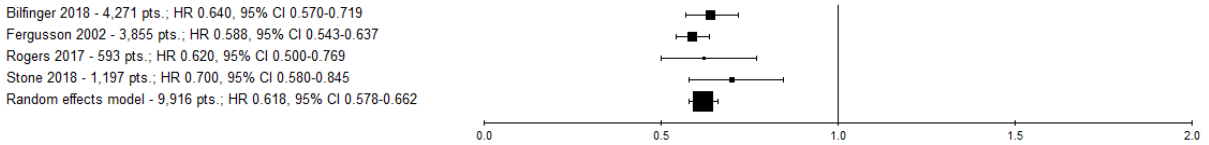


Figure 5: Forest plot with HR and 95% CI for effect of MDT measures in PICO 2, subgroup 1 (all lung cancer types, all stages, all treatment modalities, MDT involvement) on overall survival based on meta-analysis in four eligible observational studies (9,916 patients; I^2 14%; HR<1.0: MDT involvement correlating with higher overall survival) [75, 80, 94, 97]

Accuracy of staging was investigated in four observational studies (30,052 patients) [77, 80, 85, 94]. A meta-analysis was not feasible due to incalculable odds ratios in three studies [77, 85, 94]. As depicted in ***Table 8***, one study each demonstrated a large (988 patients) [77], a moderate (3,855 patients) [80] and a small effect (593 patients) [94]for more accurate staging when MDT measures were applied, while *Keating et al.* showed only a trivial effect, however with a more favourable trend for lung cancer-specific MDT against general MDT and no MDT (24,616 patients) [85].

[quality of evidence for *accuracy of staging*: very low ⊕◯◯◯; downgraded because of serious risk of bias, indirectness, inconsistency and imprecision across studies]

Pathological confirmation was explored in two studies (4,043 patients). The meta-analysis revealed higher pathological confirmation rates as a result of MDT application (fixed effects model OR 2.419, 95%, CI 1.748-3.350, I^2 64%) (forest plot in ***Figure 6***) [77, 80].

[quality of evidence for *pathological confirmation*: very low ⊕○○○; downgraded because of serious risk of bias across studies]

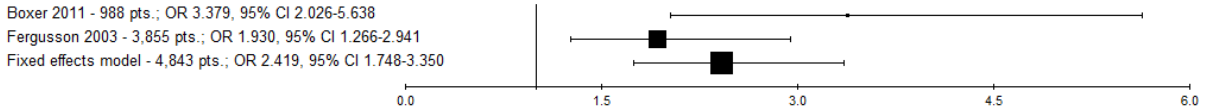


Figure 6: Forest plot with OR and 95% CI for effect of MDT measures in PICO 2, subgroup 1 (all lung cancer types, all stages, all treatment modalities, MDT involvement) on pathological confirmation based on meta-analysis in two eligible observational studies (4,043 patients; I^2 64%; OR>1.0: MDT involvement correlating with higher pathological confirmation rates) [77, 80]

Receipt of curative treatment was investigated in six studies (32,998 patients) [77, 80, 85, 86, 89, 94]. The meta-analysis in the eligible four studies proved higher rates of curative treatment as an effect of MDT implementation (7,789 patients; random effects model OR 1.875, 95% CI 1.151-3.054, I^2 84%) (forest plot in ***Figure 7***) [77, 80, 86, 89]. Among the other two studies, *Rogers et al.* resulted in a small effect (593 patients) [94]. Likewise, *Keating et al.* showed a small effect, yet with a large effect for lung cancer-specific MDT compared to general/no MDT (effect results in ***Table 8***) [85].

[quality of evidence for: very low ⊕○○○; downgraded because of serious risk of bias, indirectness and inconsistency across studies]

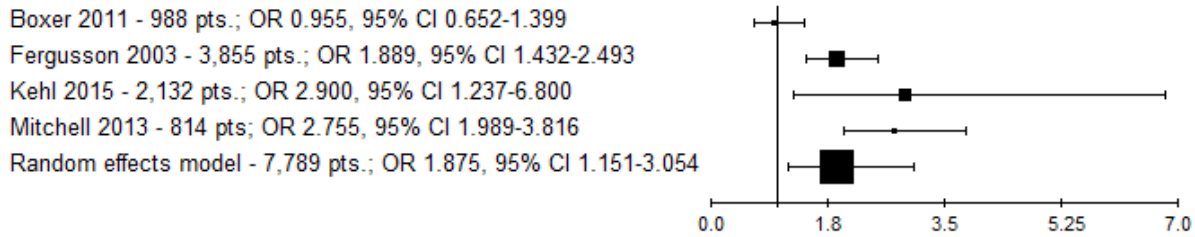


Figure 7: Forest plot with OR and 95% CI for effect of MDT measures in PICO 2, subgroup 1 (all lung cancer types, all stages, all treatment modalities, MDT involvement) on receipt of curative treatment based on meta-analysis in four eligible observational studies (7,789 patients; I^2 84%; OR>1.0: MDT involvement correlating with higher rates of curative treatment) [77, 80, 86, 89]

Receipt of any tumour-specific treatment was addressed in five studies [77, 80, 85, 89, 94]. The meta-analysis of the two suitable studies yielded higher rates of any tumour-specific treatment through MDT measures (4,669 patients; fixed effects model OR 2.707, 95% CI 2.352-3.115, I^2 78%) (forest plot in ***Figure 8***) [80, 89]. The remaining three studies highlighted small to large effects (26,197 patients; effect results in ***Table 8***) [77, 85, 94].

[quality of evidence for: very low ⊕○○○; downgraded because of serious risk of bias and indirectness across studies].

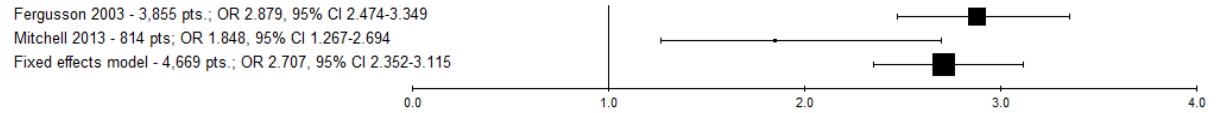


Figure 8: Forest plot with OR and 95% CI for effect of MDT measures in PICO 2, subgroup 1 (all lung cancer types, all stages and all treatment modalities, MDT involvement) on receipt of any tumour-specific treatment based on meta-analysis in two eligible observational studies (4,669 patients; I^2 78%; OR>1.0: MDT measures correlating with higher rates of any tumour-specific treatment) [80, 89]

Quality of life measured with the EORTC quality of life questionnaire (QLQ-C30) as reported in the randomized controlled trial by *Murray et al.* demonstrated a trivial effect with no meaningful change between the interventional and conventional arms (88 patients) (effect results in ***Table 8***) [1].

[quality of evidence for: moderate ⊕⊕⊕◯; downgraded because of serious risk of bias]

Patient satisfaction was increased among patients receiving fast-track pathway with MDT meeting more convenient (p=0.01) and faster (p=0.01), while the overall effect was trivial, based on the randomized controlled trial by *Murray et al.*, the only study addressing this outcome parameter (88 patients) (effect results in ***Table 8***) [1].

[quality of evidence for: moderate ⊕⊕⊕◯; downgraded because of serious risk of bias]

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 2, subgroup 1: All lung cancer types, all stages, all treatment modalities, MDT involvement		
***Overall survival (OS)* – 7 observational studies (36,219 patients)**		
Boxer, 2011**[77]**	988	*Overall survival – MDT involvement with trivial effect* (OR<1.0: MDT involvement correlating with higher OS)*:* 1) MDT: OR 1.0; 95% CI 0.86-1.17 2) no MDT: OR 1.0 (reference)
Dillman, 2005 **[79]**	2,263	Overall survival – *MDT involvement with small effect:* -5-year OS: 1) MDT: 19% 2) no MDT: 16%; p=0.012

Keating, 2013 **[85]**	24,616	*Overall survival – MDT involvement with trivial effect:* -1-year OS NSCLC: 1) lung cancer-specific MDT: 41.0% 2) general MDT: 39.0% 3) no MDT: 41.3%; p=0.22 -1-year OS SCLC: 1) lung cancer-specific MDT: 26.6% 2) general MDT: 26.2% 3) no MDT: 25.2%; p=0.88
Kehl, 2015 **[86]**	2,132	*Overall survival – MDT involvement with large effect* (HR<1.0: MDT involvement correlating with higher OS)*:* -stage I NSCLC: 1) MDT: HR 0.8, 95% CI 0.6-1.0 2) no MDT: HR 1.0 (reference); p=0.058 -stage III NSCLC: 1) MDT: HR 0.9, 95% CI 0.7-1.1 2) no MDT: HR 1.0 (reference); p=0.42 -ED SCLC: 1) MDT: HR 0.6, 95% CI 0.3-1.0 2) no MDT: HR 1.0 (reference); p=0.04 *Overall survival – MDT involvement with trivial effect* (HR<1.0: MDT involvement correlating with higher OS)*:* -stage II NSCLC: 1) MDT: HR 1.0, 95% CI 0.5-1.7 2) no MDT: HR 1.0 (reference); p=0.86 -stage IV NSCLC: 1) MDT: HR 1.0, 95% CI 0.9-1.3 2) no MDT: HR 1.0 (reference); p=0.69 *Overall survival – no MDT involvement with large effect* (HR<1.0: MDT involvement correlating with higher OS)*:* -LD SCLC: 1) MDT: HR 1.4, 95% CI 0.8-2.7 2) no MDT: HR 1.0 (reference); p=0.26

Mitchell, 2013 **[89]**	814	*Overall survival – MDT involvement with moderate effect:* -median OS: 1) MDT: 10.8 months 2) no MDT: 5.5 months; p<0.001
Nemesure, 2020 **[90]**	2,044	*Overall survival – MDT involvement with trivial effect:* -1-year mortality: lower in MDT group (p<0.001) -3-year mortality: lower in MDT group (p<0.001)
Riedel, 2006 **[93]**	345	*Overall survival – MDT involvement with trivial effect:* -median OS: 1) MDT: 1.0 years (95% CI 0.81-1.33 years) 2) no MDT: 1.2 years (95% CI 0.91-2.12 years); p=0.39
Accuracy of staging **– 4 observational studies (30,052 patients)**		
Boxer, 2011**[77]**	988	*Accuracy of staging – MDT involvement with large effect:* -rate of unknown stages: 1) MDT: 0/504 pts. (0%) 2) no MDT: 80/484 pts. (16.5%); p<0.01
Fergusson, 2009 **[80]**	3,855	*Accuracy of staging – MDT involvement with moderate effect:* -rate of unknown stages: 1) MDT: 260/2,901 pts. (9.0%) 2) no MDT: 163/954 pts. (17.1%); p<0.001
Keating, 2013 **[85]**	24,616	*Accuracy of staging – MDT involvement with trivial effect:* -adjusted rate of mediastinal evaluation for stage I/II NSCLC: 1) lung cancer-specific MDT: 89.3% 2) general MDT: 85.6% 3) no MDT: 85.7%; p=0.37
Rogers, 2017 **[94]**	593	*Accuracy of staging – MDT involvement with small effect:* -rate of unknown stages: less in MDT; p<0593.01
Receipt of curative treatment **– 2 observational studies (25,209 patients)**		
Keating, 2013 **[85]**	24,616	*Receipt of curative treatment – MDT involvement with small effect:* -adjusted rate of stage I/II NSCLC with curative surgery: 1) lung cancer-specific MDT: 61.9% 2) general MDT: 56.5% 3) no MDT: 53.2%; p=0.14
Rogers, 2017	593	*Receipt of curative treatment – MDT involvement with small effect:* -receipt of curative treatment: higher in MDT; p<0.01

***Receipt of any tumour-specific treatment* – 3 observational studies (26,197 patients)**		
Boxer, 2011**[77]**	988	*Receipt of any tumour-specific treatment – MDT involvement with large effect:* -receipt of chemotherapy: 1) MDT: 224/504 pts. (44.4%) 2) no MDT: 136/484 pts. (28.1%); p<0.001 -receipt of radiotherapy: 1) MDT: 325/504 pts. (64.5%) 2) no MDT: 157/484 pts. (32.4%); p<0.001
Keating, 2013 **[85]**	24,616	*Receipt of any tumour-specific treatment – MDT involvement with moderate-large effect:* -adjusted rate of chemoradiotherapy in unresectable stage IIIA NSCLC: 1) lung cancer-specific MDT: 35.6% 2) general MDT: 39.5% 3) no MDT: 23.9%; p=0.02 -adjusted rate of doublet chemotherapy stage IV NSCLC: 1) lung cancer-specific MDT: 42.8% 2) general MDT: 42.7% 3) no MDT: 37.3%; p=0.15 -adjusted rate of chemoradiotherapy in LD SCLC: 1) lung cancer-specific MDT: 62.9% 2) general MDT: 61.8% 3) no MDT: 28.4%; p<0.001
Rogers, 2017 **[94]**	593	*Receipt of any tumour-specific treatment – MDT involvement with small effect:* -receipt of any treatment: higher in MDT; p<0.01
***Quality of life* – 1 randomized controlled trial (88 patients)**		
Murray, 2003 **[1]**	88	*Quality of life – MDT involvement with trivial effect:* Difference and significance of difference between the central arm (MDT) and conventional arm (no MDT) (changes after 6 weeks compared to baseline) -physical functioning 0.1 and 0.8; p=0.2 -role functioning 0.02 and 0.6; p=0.3 -emotional functioning 0.8 and 0.8; p=0.9 -cognitive functioning 0.1 and 0.8; p=0.4 -social functioning 0.03 and 0.3; p=0.4 -financial functioning 0.03 and 0.06; p=1.0 -global health 1.0 and 0.6; p=0.6

***Patient satisfaction* – 1 randomized controlled trial (88 patients)**

Murray, 2003 **[1]**	88	*Patient satisfaction – MDT involvement with trivial effect:* Patients received - faster treatment in central arm (MDT) (p=0.02) -better understanding for what patient were going through by medical team in central arm (MDT) (p=0.01) -better consideration of patient views of illness in central arm (MDT) (p=0.03) compared to the conventional arm (no MDT)

Table 8: Effect results of studies ineligible for meta-analyses sorted by outcomes for PICO 2, subgroup 1 (all lung cancer types, all stages, all treatment modalities, MDT involvement)

The GRADE evidence profile relating to the subgroup 1 in PICO 2 (All lung cancer types, all stages, all treatment modalities, MDT involvement) is presented in ***Table 9***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDT	no MDT	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
4 [75, 80, 94, 97]	observational studies	not serious	not serious	serious [a]	not serious	none	-/5507 [b]	-/4409 [b]	**HR 0.62** (0.58 to 0.66) [c]	**-- per 1.000** (from -- to --) [b]	⊕◯◯◯ VERY LOW	CRITICAL
Accuracy of staging												
4 [77, 80, 85, 94]	observational studies	serious [d]	serious [e]	serious [a]	not serious [f]	none	We detected 1 study with a large effect (988 patients), 1 study with a moderate effect (3,855 patients), and 1 study with a small effect (593 patients). 1 study showed a trivial effect, however with a more favourable trend for lung cancer-specific MDT against general MDT and no MDT (24,616 patients).				⊕◯◯◯ VERY LOW	IMPORTANT
Pathological confirmation												
2 [77, 80]	observational studies	serious [d]	not serious	serious [a]	serious [g]	none	95/2811 (3.4%)	95/1033 (9.2%)	**OR 2.42** (1.75 to 3.35)	**105 more per 1.000** (from 58 more to 161 more)	⊕◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDT	no MDT	Relative (95% CI)	Absolute (95% CI)		
Receipt of curative treatment												
4 [77, 80, 86, 89]	observational studies	serious [d]	serious [h]	serious [a]	not serious	none	510/3639 (14.0%) [i]	249/2001 (12.4%) [i]	**OR 1.88** (1.15 to 3.05)	**86 more per 1.000** (from 16 more to 178 more)	⊕◯◯◯ VERY LOW	CRITICAL
Receipt of any tumour-specific treatment												
2 [80, 89]	observational studies	serious [d]	not serious	serious [a]	not serious	none	2022/3134 (64.5%)	753/1517 (49.6%)	**OR 2.71** (2.35 to 3.12)	**231 more per 1.000** (from 202 more to 258 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Quality of life												
1 [1]	randomised trials	serious [d]	not serious	not serious	serious [j]	none	Murray, 2003 (88 pts.) with trivial effect:(EORTC QLQ-30 without overall statistical difference between MDT and no MDT)				⊕⊕◯◯ LOW	IMPORTANT
Patient satisfaction												
1 [1]	randomised trials	serious [d]	not serious	not serious	serious [j]	none	Murray, 2003 (88 pts.) with trivial effect (higher patient satisfaction in MDT relating to timeliness (p=0.02), better understanding for patient experiences (p=0.01) and consideration of patient views of illness, p=0.03)				⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **HR:** Hazard Ratio; **OR:** Odds ratio

Explanations:

a. Applied MDT measures were different across studies.
b. None of the studies provided number of events.
c. Seven studies ineligible for meta-analysis may reduce the effect estimate as these demonstrated inconsistent effects.
d. Failure to adequately control confounding in some studies
e. 3 studies favour MDT, the largest study with uncertain effect
f. Pooled effect was incalculable, yet 3 studies favoured the intervention. The largest study showing a trivial effect did not control against no MDT.
g. few events raise concerns with fragility
h. Statistical heterogeneity raises concerns with inconsistency.
i. Kehl 2015 did not state patient figures
j. Due to small sample size one cannot exclude no meaningful difference between both groups.

Table 9: GRADE evidence profile for PICO 2, subgroup 1 (All lung cancer types, all stages, all treatment modalities, MDT involvement)

2) PICO 2, subgroup 2: NSCLC, all stages, all treatment modalities, MDT involvement (vs. no MDT involvement)

Five observational studies focussed on NSCLC including all stages and treatment modalities (145,370 patients) [58, 76, 82, 92, 96].

Overall survival was the primary outcome in three observational studies (144,014 patients) [58, 92, 96]. The meta-analysis of these studies illustrated as an aggregated effect enhanced overall survival in the MDT-setting (random effects model HR 0.759, 95% CI 0.614-0.939, I^2 92%) albeit missing certainty in the subgroups for surgery and chemotherapy with implementation of a lung cancer nurse as MDT measure in *Stewart et al.* (forest plot in ***Figure 9***) [96].

[quality of evidence for *overall survival*: very low ⊕◯◯◯; downgraded because of serious risk of bias and inconsistency across studies]

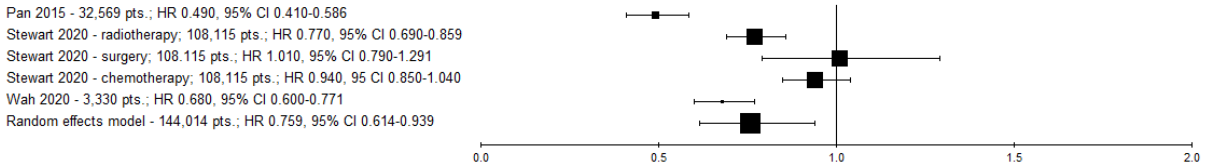


Figure 9: Forest plot with HR and 95% CI for effect of MDT measures in PICO 2, subgroup 2 (NSCLC, all stages, all treatment modalities, MDT involvement) on overall survival based on meta-analysis in three eligible observational studies (144,014 patients; I^2 92%; HR<1.0: MDT involvement correlating with higher overall survival) [58, 92, 96]

Mortality and ***accuracy of staging*** were only assessed by *Freeman et al.* (1,222 patients) resulting in a trivial effect on post-operative 30-day mortality and a moderate effect with more accurate staging by MDT measures with odds ratios of 1.23 (95% CI 0.47-3.2) and 3.56 (95% CI 2.49-5.10), respectively [82].

[quality of evidence for *mortality*: very low ⊕◯◯◯; downgraded because of serious risk of bias and imprecision]

[quality of evidence for *accuracy of staging*: very low ⊕◯◯◯; downgraded because of serious risk of bias]

Receipt of curative treatment was investigated in two observational studies (1,356 patients). Due to inconsistency, only a trend towards higher curative treatment rates in the MDT cohort was seen in the meta-analysis (fixed effects model OR 1.261, 95% CI 1.001-1.589, I^2 87%) (forest plot in ***Figure 10***) [76, 82].

[quality of evidence for *receipt of curative treatment*: very low ⊕◯◯◯; downgraded because of serious risk of bias and inconsistency]

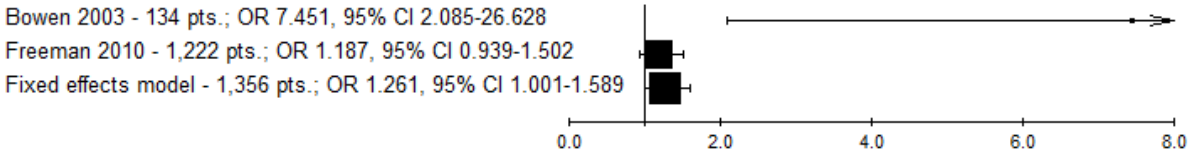


Figure 10: Forest plot with OR and 95% CI for effect of MDT measures in PICO 2, subgroup 2 (NSCLC, all stages, all treatment modalities, MDT involvement) on receipt of curative treatment based on meta-analysis in two eligible observational studies (1,356 patients; I^2 87%; OR>1.0: MDT involvement correlating with higher rates of curative treatment) [76, 82]

The GRADE evidence profile relating to the subgroup 2 in PICO 2 (NSCLC, all stages, all treatment modalities, MDT involvement) is presented in ***Table 10***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDT	no MDT	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
3 [58, 92, 96]	observational studies	serious [a]	serious [b]	serious [c]	not serious	none	-/57516 [d]	-/31364 [d]	**HR 0.76** (0.61 to 0.94)	**-- per 1.000** (from -- to --) [d]	⊕◯◯◯ VERY LOW	CRITICAL
Mortality												
1 [82]	observational studies	serious [a]	not serious	not serious	very serious [e]	none	11/451 (2.4%)	7/330 (2.1%)	**OR 1.23** (0.47 to 3.20)	**5 more per 1.000** (from 11 fewer to 44 more)	⊕◯◯◯ VERY LOW	CRITICAL
Accuracy of staging												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDT	no MDT	Relative (95% CI)	Absolute (95% CI)		
1 [82]	observational studies	serious [a]	not serious	not serious	not serious	none	489/687 (71.2%)	179/535 (33.5%)	**OR 3.56** (2.49 to 5.10)	**307 more per 1.000** (from 221 more to 385 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Receipt of curative treatment												
2 [76, 82]	observational studies	serious [a]	not serious	serious [c]	serious [f]	none	2022/3134 (64.5%)	753/1517 (49.6%)	**OR 1.26** (1.00 to 1.59)	**58 more per 1.000** (from 0 fewer to 114 more)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio; **OR:** Odds ratio

Explanations:

a. Failure to adequately control confounding in some studies
b. 2 subgroups (surgery, chemotherapy) in Stewart 2020 without certain effect
c. Applied MDT measures were different across studies.
d. The numbers of events were not provided in the studies.
e. In addition to the few events, the 95% CI includes the potential for benefit; however, cannot exclude the possibility of no benefit.
f. The 95% CI includes the potential for benefit; however, cannot exclude the possibility of no benefit.

Table 10: GRADE evidence profile for PICO 2, subgroup 2 (NSCLC, all stages, all treatment modalities, MDT involvement)

3) PICO 2, subgroup 3: NSCLC, all stages, surgical resection, MDT involvement (vs. no MDT involvement)

Five studies dealt specifically with surgical resected NSCLC patients (49,130 patients) [87, 88, 91, 95, 98].

Overall survival was captured in three observational studies [88, 91, 98]. The meta-analysis of two eligible studies highlighted inconsistency and a trivial effect (1,555 patients; HR 0.754, 95% CI 0.496-1.145, I^2 68%) (forest plot in ***Figure 11***) [88, 98]. *Nwaejike et al.* detected similar overall survival when comparing a MDT for patients with high perioperative risk against a regular MDT (820 patients; p=0.24) (effect results in

***Table* 11**) [91].

[quality of evidence for *overall survival*: very low ⊕○○○; downgraded because of indirectness, inconsistency and imprecision across studies]

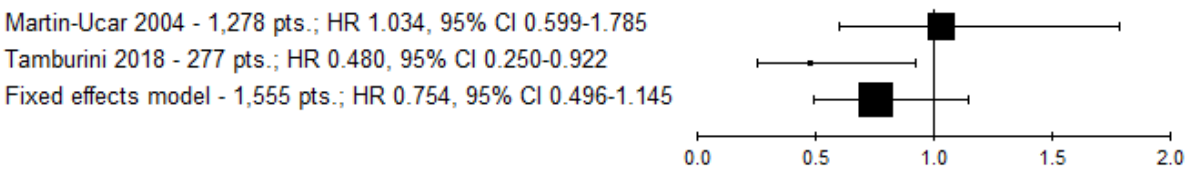


Figure 11: Forest plot with HR and 95% CI for effect of MDT measures in PICO 2, subgroup 3 (NSCLC, all stages, surgical resection, MDT involvement) on overall survival based on meta-analysis in three eligible observational studies (1,555 patients; I^2 68%; HR<1.0: MDT involvement correlating with higher overall survival) [88, 98]

Mortality was explored in two studies (1,060 patients), both not suitable for meta-analysis. *Martin-Ucar et al.* indicated a large effect (240 resected patients) relating to 30-day mortality. *Nwaejike et al.* showed a trivial effect (820 patients) yet comparing high-risk patient MDT against non-high-risk patient MDT (effect results in

***Table* 11**) [88, 91].

[quality of evidence for *mortality*: very low ⊕○○○; downgraded because of indirectness across studies]

Morbidity was measured by *Nwaejike et al.* (820 patients), again comparing MDT in high-risk and non-high-risk patients. Only trivial effects were detectable for any type of complication (OR 1.0, 95% CI 0.57-1.77) as well as for cardiac, cardiovascular artery, gastrointestinal, pulmonary, and renal complications in particular [91].

[quality of evidence for *morbidity*: very low ⊕○○○; downgraded because of serious indirectness and imprecision]

Accuracy of staging analysis by *Tamburini et al.* (277 patients) documented better staging in the MDT group (OR 8.09, 95% CI 4.07-16.08) [98].

[quality of evidence for *accuracy of staging*: very low ⊕○○○; downgraded because of serious risk of bias]

Pathological confirmation was achieved more often in MDT care as spotted by *Martin-Ucar et al.* (1,278 patients; OR 1.8, 95% CI 1.55-2.09) [88].

[quality of evidence for *pathological confirmation*: very low ⊕○○○; downgraded because of serious risk of bias]

Receipt of curative treatment proved to be higher in MDT cohorts according to the meta-analysis of two observational studies (1,418 patients; fixed effects model OR 2.551, 95% CI 1.917-3.394, I^2 84%) (forest plot in ***Figure 12***) [88, 95]. as well as with a small effect in *Lau et al.* (46,615 patients; p=0.028) (effect results in

***Table* 11**) [87].

[quality of evidence for *receipt of curative treatment*: very low ⊕○○○; downgraded because of serious risk of bias across studies]

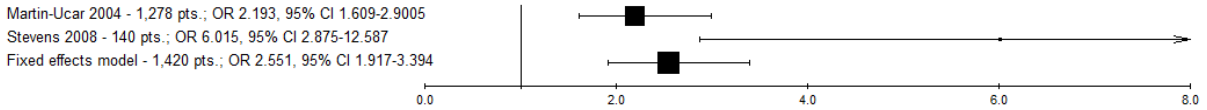


Figure 12: Forest plot with OR and 95% CI for effect of MDT measures in PICO 2, subgroup 3 (NSCLC, all stages, surgical resection, MDT involvement) on receipt of curative treatment based on meta-analysis in two eligible observational studies (1,420 patients; I^2 84%; OR>1.0: MDT involvement correlating with higher rates of curative treatment) [88, 95]

Receipt of any tumour-specific treatment was reported on in one small study in which a large effect of MDT measures was detected (140 patients; OR 8.86, 95% CI 3.75-20.96) [95].

[quality of evidence for *receipt of any tumour-specific treatment*: very low ⊕○○○; downgraded because of serious risk of bias and imprecision]

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 2, subgroup 3: NSCLC, all stages, surgical resection, MDT involvement		
***Overall survival (OS)* – 1 observational study (820 patients)**		
Nwaejike, 2016 **[91]**	820	*Overall survival – trivial effect in high-risk pts. compared with MDT in non-high-risk pts.:* -overall survival: p=0.24
***Mortality* – 2 observational studies (2,098 patients)**		
Martin-Ucar, 2004 **[88]**	240 pts.	*30-day mortality - MDT involvement with large effect:* 1) no MDT care (no specialist thoracic surgeon): 5/65 (7.7%) 2) MDT care (specialist thoracic surgeon): 9/175 (5.5%) p=n.s.
Nwaejike, 2016 **[91]**	820	*30-day mortality – trivial effect for MDT in high-risk pts. compared with MDT in non-high-risk pts.* (OR<1.0: MDT involvement correlating with lower 30-day mortality)*:* 1) no high-risk MDT meeting: OR 1.0 (reference) 2) high-risk MDT meeting: OR 2.15, 95% CI 0.58-7.95
***Receipt of curative treatment* – 1 observational study (46,615 patients)**		

Lau, 2013 **[87]**		46,615	*Receipt of curative treatment – MDT involvement with small effect:* -receipt of curative treatment: 1) MDT: 14.7% 2) no MDT: 12.7%; p=0.028

Table 11: Effect results of studies ineligible for meta-analyses sorted by outcomes for PICO 2, subgroup 3 (NSCLC, all stages, surgical resection, MDT involvement)

The GRADE evidence profile relating to the subgroup 3 in PICO 2 (NSCLC, all stages, surgical resection, MDT involvement) is presented in **Table 12**.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDT	no MDT	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
2 [88, 98]	observational studies	not serious	serious [a]	serious [b]	serious [c]	none	-/917 [d]	-/701 [d]	**HR 0.75** (0.50 to 1.15)	**-- per 1.000** (from -- to --)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality												
2 [88, 91]	observational studies	not serious	not serious	serious [b,e]	serious [f]	none	We detected 1 study with a large effect (240 pts.). One study (820 pts.) showed a trivial effect yet comparing MDT in high-risk pts. with MDT in non-high-risk pts.				⊕◯◯◯ VERY LOW	CRITICAL
Morbidity												
1 [91]	observational studies	not serious	not serious	serious [e]	very serious [c]	none	16/102 (15.7%)	113/718 (15.7%)	**OR 1.00** (0.57 to 1.77)	**110 more per 1.000** (from 61 fewer to 91 more)	⊕◯◯◯ VERY LOW	CRITICAL
Accuracy of staging												
1 [98]	observational studies	serious [g]	not serious	not serious	not serious	none	159/170 (93.5%)	109/170 (64.1%)	**OR 8.09** (4.07 to 16.08)	**294 more per 1.000** (from 238 more to 325 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Pathological confirmation												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDT	no MDT	Relative (95% CI)	Absolute (95% CI)		
1 [88]	observational studies	serious [g]	not serious	not serious	not serious	none	747/1455 (51.3%)	531/1436 (37.0%)	**OR 1.80** (1.55 to 2.09)	**144 more per 1.000** (from 107 more to 181 more)	⊕◯◯◯ VERY LOW	CRITICAL
Receipt of curative treatment												
2 [88, 95]	observational studies	serious [g]	not serious	serious [b]	not serious	none	235/828 (28.4%)	84/590 (14.2%)	**OR 2.55** (1.92 to 3.39)	**155 more per 1.000** (from 99 more to 218 more)	⊕◯◯◯ VERY LOW	CRITICAL
Receipt of any tumour-specific treatment												
1 [95]	observational studies	serious [g]	not serious	not serious	serious [h]	none	72/100 (72.0%)	9/40 (22.5%)	**OR 8.86** (3.75 to 20.96)	**495 more per 1.000** (from 296 more to 634 more)	⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **HR:** Hazard Ratio; **OR:** Odds ratio

Explanations:

a. 1 study favours MDT, 1 study without certain effect
b. Applied MDT measures were different across studies.
c. The 95% CI includes the potential for benefit; however, cannot exclude the possibility of no benefit.
d. no event figures stated
e. Nwaejike 2016 compared only MDTs in high-risk pts. against non-high-risk pts.
f. Pooled effect was incalculable; in addition, the estimates of both studies cannot exclude no meaningful differences between groups.
g. Failure to adequately control confounding in one/some studies
h. Small sample size of study raises concerns about potential imprecision.

Table 12: GRADE evidence profile for PICO 2, subgroup 3 (NSCLC, all stages, surgical resection, MDT involvement)

4) PICO 2, subgroup 4: NSCLC, stage III/IV, all treatment modalities, MDT involvement (vs. no MDT involvement

Four observational studies were retrieved scoping on stage III/IV NSCLC and all treatment modalities (965 patients) [78, 81, 83, 84].

Overall survival was the focus in all four studies [78, 81, 83, 84]. Three studies qualified for meta-analysis which underlined enhanced overall survival in MDT treated patients as pooled effect (722 patients; random effects model HR 0.750, 95% CI 0.623-0.903) (forest plot in ***Figure 13***) [78, 83, 84]. *Forrest et al.* demonstrated a large effect (p<0.001) (effect results in ***Table 13***) [81].

[quality of evidence for *overall survival*: very low ⊕◯◯◯; downgraded because of serious risk of bias, indirectness and inconsistency across studies]

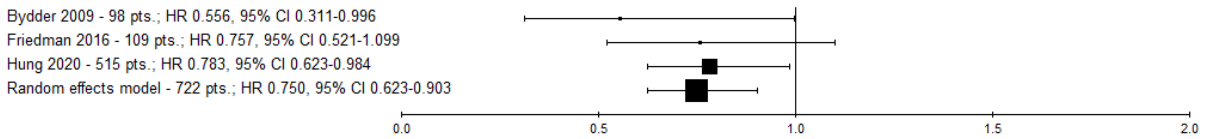


Figure 13: Forest plot with HR and 95% CI for effect of MDT measures in PICO 2, subgroup 4 (NSCLC, stage III/IV, all treatment modalities, MDT involvement) on overall survival based on meta-analysis in three eligible observational studies (722 patients; HR<1.0: MDT involvement correlating with higher overall survival) [78, 83, 84]

Accuracy of staging was improved in MDT-driven care based on the meta-analysis in two studies (352 patients; fixed effects model OR 2.060, 95% CI 1.371-3.096) (forest plot in ***Figure 14***) [81, 83].

[quality of evidence for *accuracy of staging*: very low ⊕◯◯◯; downgraded because of serious risk of bias, indirectness and inconsistency across studies]

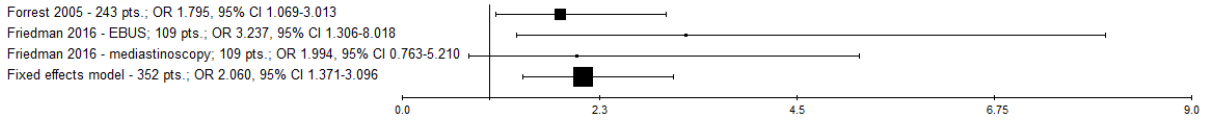


Figure 14: Forest plot with OR and 95% CI for effect of MDT measures in PICO 2, subgroup 4 (NSCLC, stage III/IV, all treatment modalities, MDT involvement) on accuracy of staging based on meta-analysis in two eligible observational studies (352 patients; OR>1.0: MDT involvement correlating with more accurate staging) [81, 83]

Receipt of curative treatment was positively impacted by MDT care according to the small effect described in Bydder et al. (98 patients; OR 1.68, 95% CI 0.2-14.33) [78].

[quality of evidence for *receipt of curative treatment*: very low ⊕◯◯◯; downgraded because of serious risk of bias and imprecision]

Receipt of any tumour-specific treatment was investigated in two observational studies (341 patients). The meta-analysis of both indicated higher treatment rates in the MDT group (fixed effects model OR 1.668, 95% CI 1.047-2.658) (forest plot in ***Figure 15***) [78, 81].

[quality of evidence for *receipt of any tumour-specific treatment*: very low ⊕◯◯◯; downgraded because of serious risk of bias, indirectness and inconsistency across studies]

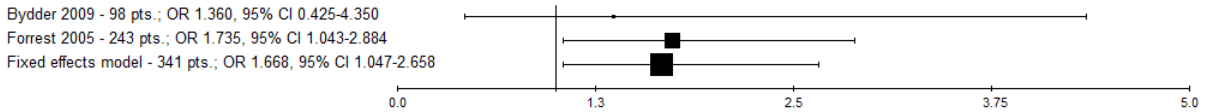


Figure 15: Forest plot with OR and 95% CI for effect of MDT measures in PICO 2, subgroup 4 (NSCLC, stage III/IV and all treatment modalities, MDT involvement) on receipt of curative treatment based on meta-analysis in two eligible observational studies (341 patients; OR>1.0: MDT involvement correlating with higher rates of curative treatment) [78, 81]

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 2, subgroup 4: NSCLC, stage III/IV, all treatment modalities, MDT involvement		
***Overall survival (OS)* – 1 observational study (243 patients)**		
Forrest, 2005 **[81]**	243	*Overall survival – MDT involvement with large effect:* -median OS: 1) MDT: 6.6 months 2) no MDT: 3.2 months, p<0.001

Table 13: Effect results of studies ineligible for meta-analyses on overall survival for PICO 2, subgroup 4 (NSCLC, stage III/IV, all treatment modalities, MDT involvement)

The GRADE evidence profile relating to the subgroup 4 in PICO 2 (NSCLC, stage III/IV, all treatment modalities, MDT involvement) is presented in ***Table 14***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDT	no MDT	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
3 [78, 83, 84]	observational studies	serious [a]	not serious	serious [b]	serious [c]	none	0/368 (0.0%) [d]	0/354 (0.0%) [d]	**HR 0.75** (0.62 to 0.90)	**-- per 1.000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Accuracy of staging												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDT	no MDT	Relative (95% CI)	Absolute (95% CI)		
2 [81, 83]	observational studies	serious [a]	not serious	serious [b]	serious [c]	none	161/257 (62.6%)	134/276 (48.6%)	**OR 2.06** (1.37 to 3.10)	**175 more per 1.000** (from 79 more to 259 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Receipt of curative treatment												
1 [78]	observational studies	serious [a]	not serious	not serious	serious [e]	none	8/81 (9.9%)	1/17 (5.9%)	**OR 1.68** (0.20 to 14.33)	**36 more per 1.000** (from 46 fewer to 414 more)	⊕◯◯◯ VERY LOW	CRITICAL
Receipt of any tumour-specific treatment												
2 [78, 81]	observational studies	serious [a]	not serious	serious [b]	serious [c]	none	122/279 (43.7%)	67/160 (41.9%)	**OR 1.67** (1.05 to 2.66)	**127 more per 1.000** (from 11 more to 238 more)	⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **HR:** Hazard Ratio; **OR:** Odds ratio

Explanations:

a. Failure to adequately control confounding in one/some studies
b. Applied MDT measures were different across studies.
c. Due to small sample size one cannot exclude no meaningful difference between both groups
d. None of the studies provided number of events.
e. In addition to small sample size, the large 95% CI includes the potential for benefit; however, cannot exclude the possibility of no benefit.

Table 14: GRADE evidence profile for PICO 2, subgroup 4 (NSCLC, stage III/IV, all treatment modalities, MDT involvement)

C. PICO 2: GRADE evidence to decision framework

Table 15 depicts the GRADE evidence to decision framework relating to PICO 2 based upon on the GRADE evidence profiles as well as additional considerations by the task force panel.

PICO 2: In patients with lung cancer (or those suspected of having lung cancer), should a multi-disciplinary team (MDT) or certain disciplines be involved rather than no involvement of an MDT or certain disciplines during lung cancer care?	
POPULATION:	lung cancer patients in all stages and with all treatment modalities

INTERVENTION:	MDT
COMPARISON:	no MDT
MAIN OUTCOMES:	Overall survival; Mortality; Morbidity; Accuracy of staging; Pathological confirmation ; Receipt of curative treatment ; Receipt of any tumour-specific treatment ; Quality of life; Patient satisfaction;
SETTING:	Both outpatient and inpatient
PERSPECTIVE:	Clinical recommendations – population perspective
BACKGROUND:	Multidisciplinary approaches facilitate interprofessional collaboration leading to joint discussion and consensus on personalized diagnostic and therapeutic strategies for patients, yet also provide challenges to lung cancer services
CONFLICT OF INTERESTS:	N/A

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Multidisciplinary approaches facilitate interprofessional collaboration leading to joint discussion and consensus on personalized diagnostic and therapeutic strategies for patients, yet provide also challenges to lung cancer services [100]. Thus, it seemed important to us to systematically assess the benefits and potential harms of MDT specifically in lung cancer care.	The implementation of MDT measures is considered as an essential topic in lung cancer care by the guideline panel., Likewise, it is a key priority topic for ERS as well as ELF and the Patient Advisory Group

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Our systematic review revealed the following desirable effects of MDT implementation (see related PICO 2 evidence tables, subgroups 1-4 for details): -improved overall survival in the 4 subgroup meta-analyses for early and advanced NSCLC as well as all lung cancer types -lower mortality in resected NSCLC -better accuracy of staging in the subgroup analyses for all, early and advanced NSCLC -higher pathological confirmation rates for all lung cancer types and resected NSCLC -higher receipt of curative treatment in subgroup assessments of all lung cancer types and resected NSCLC	From clinical experience, the TF members consider the following additional desirable effects of MDT implementation to be likely: -higher satisfaction of patients and medical professionals -reduction of individual failure -higher guideline-concordant care and at the same time higher chances for individual treatment concepts outside of standard guideline recommendations

	-higher receipt of any tumour-specific treatments in all 4 subgroups Trivial effects were seen relating to: -mortality in all NSCLC -quality of life as well as patient satisfaction in the only RCT	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	no significant harms were detected by our systematic review (see related PICO 2 evidence tables, subgroups 1-4 for details). A slightly increased 30-day mortality in the MDT cohort (11/451 pts. [2.4%] vs. 7/330 pts [2.1%]) was noticed in the subgroup 2 (NSCLC, all stages, all treatment modalities) based on a single study, but the evidence is very uncertain.	From clinical experience, the TF members are concerned about the following additional undesirable effects of MDT implementation: -delay of diagnostics and/or initiation treatment due to over presentation of patients in MDT meetings or long MDT meeting intervals -flawed MDT decisions due to inadequate patient presentations -dominant characters may dominate MDT meeting decisions -some medical professionals may consider patient preferences inadequately tending to overexert or overprotect patients

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the evidence was graded as very low (see related PICO 2 evidence tables, subgroups 1-4 for details)	None

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	We did not perform a systematic literature search specifically on patient values relating to treatment intervals. Our present systematic review did not retrieve any related pieces of evidence. Patient desire for proper MDT implementation have been a key finding of a pan-European survey project run by ELF in 2015 which addressed patients, caretakers and national patient organisations. https://europeanlunginfo.org/lung-cancer/research-and-news/report-on-consultation-lung-cancer-patient-priorities-report	Comprehensive MDT implementation are a key priority of patients as confirmed by patient and ELF representatives in our task force panel.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Our systematic evidence assessment resulted in moderate desirable effects and no undesirable effects.	Weighing desirable and undesirable effects based on our systematic evidence assessment, our task force panel discussions and clinical experience, we see benefits in MDT implementation throughout the disease continuum in lung cancer care in principle. Yet, we are cautious about the named potential undesirable effects that may need MDT surveillance and streamlining initiatives.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	We did not perform a systematic literature search specifically on required resources relating to MDT implementation. Our systematic review did not retrieve any related pieces of evidence.	We estimate at least moderate costs to run frequent MDT meeting as well as to implement additional regular MDT measures alongside the lung cancer care continuum. In addition, more advanced IT may be needed to better link and facilitate MDT meetings within the network of a lung cancer service.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● No included studies	not applicable	Required resources are depending on multiple factors, especially staff and network coordination/linkage.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	We did not perform a systematic literature search specifically on cost effectiveness relating to MDT implementation. Our systematic review did not retrieve any related pieces of evidence. A systematic review from 2013 on costs in MDT meetings retrieved 15 studies (also on non-malignant diseases) and concluded an insufficient evidence basis regarding MDT cost-effectiveness [101]. De Ieso et al. assessed costs in oncological MDT meetings which may be reduced by optimization of MDT meeting efficiency [102].	Despite increased short-term costs to implement additional MDT measures as well as ongoing costs for maintaining established MDT measures, we assume mid- and long-term savings due to reduction of mis-, over- and undertreatment. Yet, cost-effectiveness analyses are missing taking into account variation on the local and national care level as well as among different health care systems.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	We did not perform a systematic literature search specifically on equity relating to MDT implementation. Our systematic review did not retrieve any related pieces of evidence.	Implementation of systematically applied MDT measures within a lung cancer services may help to reduce inequalities of care provision. Conversely, appropriate implementation is not expected to create inequality.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	We did not perform a systematic literature search specifically on acceptability to key stakeholders relating to MDT implementation. Our systematic review did not retrieve any related pieces of evidence.	The idea of MDT is already well-accepted by patients, medical professionals and healthcare providers alike. However, the above mentioned potential undesirable effects need to be regularly assessed and - if present - adequately addressed.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	We did not perform a systematic literature search specifically on feasibility of implementing MDT measures. Our systematic review did not retrieve any related pieces of evidence.	If sufficient resources are made available, we assume that already well-established, in some countries even mandatory MDT measures are maintained well, frequently surveyed and optimized or augmented if needed.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know

	JUDGEMENT						
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest the integration of multidisciplinary teams and/or multidisciplinary consultation in the management of patients with (suspected) lung cancer (conditional recommendation; very low certainty in the evidence)

Remark: We acknowledge that MDT is already implemented broadly in lung cancer care, yet to achieve good integration, we see the need for better implementation of multidisciplinary teamwork throughout the lung cancer pathway as well as for frequent surveillance and optimisation of MDT meetings and processes.

Justification

Given the life-threatening potential of lung cancer, multidisciplinary structures and processes seem necessary to reduce mis-, under- and overtreatment of lung cancer patients and instead ensuring best personalized diagnostic and therapeutic strategies for patients. There were no substantial harms evident of foreseen related to implementation of MDT measures. Thus, we suggest the implementation of MDT measures, even if the survival benefit is not always clear. The recommendation is conditional due to the very low certainty of evidence.

Subgroup considerations

None

Implementation considerations

Multidisciplinary care seems mandatory not only from a medico-legal perspective but particularly to ensure good clinical and patient-centred lung cancer care.

Monitoring and evaluation

Multidisciplinary teams need to be committed to broaden their actions throughout the lung cancer continuum and optimize them based on self-assessment at regular intervals. Peer-to-peer visits and application of benchmarking among lung cancer services are suitable collaborative quality improvement methods.

Research priorities

We see a need for linked and coordinated MDT quality improvement initiatives to optimize MDT infrastructure and processes including essential standards of documentation and case presentations. Cost-effectiveness analyses may assess the effects of these measures yet need to take into account variation on the local and national care level as well as among different health care systems.

Table 15: GRADE evidence to decision framework relating to PICO 2

PICO question 3: In patients with lung cancer (or those suspected of having lung cancer), should guidelines or standard operating procedures (SOP) for lung cancer care be implemented or adhered to rather than non-implementation of or non-adherence to these guidelines or standard operating procedures?

A. PICO 3: General summary of the evidence

Fifteen eligible publications [71, 103-116] were extracted out of the initially 754 literature search results (PRISMA flow diagram: ***online supplement A***). The evidence is based on retrospective observational data only originating from 1) national clinical lung cancer registries in seven studies (Denmark: *Jakobsen et al.*, Danish Lung Cancer Registry, 2000-2012, 38,661 patients [108]; *Mainz et al.*, Danish Lung Cancer Registry, 2003-2006, patient figures not stated [109]; overlapping Danish patient population in both studies; United Kingdom: *McCarthy et al.*, National Health Care Data, 1996-2001, patient figures not stated [110]; United States of America: *Nadpara et al.*, SEER, 2002-2007, 42,323 patients [71]; *Samson et al.*, National Cancer Database, 2004-2013, 133,366 patients [115]; *Ahmed et al.*, National Cancer Database, 2005-2013, 45,825 patients [103]; *Odell et al.*, National Cancer Database, 1998-2011, approx. 1.700.000 patients [113]), 2) five regional multi-centre studies (four from the United States of America: *Allen et al.*, 2004-2007, 746 patients [104]; *Neubauer et al.*, 07/2006-12/2007, 1,409 patients [111]; *Osarogiagbon et al.*, 2004-2013, 2,429 patients; *Casebeer et al.*, 2013-2014, 1,344 patients [106]), and one from Canada: *Elegbede et al.*, 2010-2016, 404 patients [107]), 3) one study in two sites from Australia (*Boxer et al.*, 12/2005-12/2010, 808 [105]), as well as 4) two single-centre studies, one Spanish study in 916 NSCLC patients with anatomical resections by *Novoa et al.* (09/2009-08/2012 vs. 12/2002-08/2009) [112] and one Chinese study on the number of mediastinal lymph nodes sampled after anatomical resections in 2,711 NSCLC patients (2001-2008) by *Yue et al.* [116].

The years of the publications span 2008 to 2020, the total number of patients summed up to 1.973.542 patients (absolute numbers not given in two studies) with individual patient cohorts ranging from 746 to approx. 1.700.000 patients.

Patient populations included all lung cancer types, NSCLC and SCLC in five (81,792 patients; no patient figures stated in *Mainz et al.* and *McCarthy et al.*) [71, 105, 108-110], nine (approx. 1,891,346 patients) [103, 104, 106, 111-116] and one (404 patients) [107] studies, respectively. Among these, Nadpara et al. focused on all lung cancer types in the elderly (≥65 years) [71].

The two studies from Denmark [108, 109] examined the impact of *guideline implementation* within the Danish comprehensive national quality improvement initiative (including the Danish national lung cancer guideline, the population-based Danish clinical lung cancer registry with high data quality and coverage rates as well as re-organization, centralisation, and regular optimization of Danish lung cancer services). The study objectives of the remaining trials were focused on rates of *adherence to guideline recommendations (vs. non-adherence)* in patient populations, which included guidelines issued by healthcare authorities (Alberta Health Service [107], Cancer Council Australia [105], National Health Service (NHS) [110]) and scientific societies (American College of Chest Physicians (ACCP) [71, 115], American College of Radiology (ACR) [103], American College of Surgeons (ACS) [104, 113, 115, 116], American Society for Clinical Oncology (ASCO) [103, 107], American Society for Radiation Oncology (ASTRO) [103], ERS/European Society of Thoracic Surgeons (ESTS) [112], International Association for the Study of Lung Cancer (IASLC) [116], National Comprehensive Cancer Network (NCCN) [104, 106, 114-116], Society of Thoracic Surgeons (STS) [115]) as well as an oncology network lung cancer guideline [111] and inclusion criteria from the single clinical trial RADIANT [104, 116].

Overall survival was the main outcome parameter in all [71, 103-111, 113-116] but one [112] of the fifteen observational studies (approx. 1,972,626 patients; no patient figures stated in *Mainz et al.* and *McCarthy et al.*). 30 day-*mortality* as the second outcome parameter in the reviewed evidence for this search question was utilized in four studies (40,323 patients; no patient figures stated in *Mainz et al.*) [104, 108, 109, 112]. *Morbidity* was explored in four studies (40,323 patients; no patient figures stated in *Mainz et al.*) [104, 108, 109, 112]. *Jakobsen et al.* were the only one to assess *accuracy of staging*, *receipt of curative treatment* and *any receipt*

of tumour-specific treatment as outcomes (38,661 patients each) [108]. No evidence was found relating to *progression-free survival, disease-free survival, pathological confirmation, other treatment outcome, quality of life, patient satisfaction, performance status* and *other patient reported outcome measures (PROMs).*

B. PICO 3: Summary, rating of the quality of evidence and GRADE evidence profiles in specific subgroups

Individual studies, their main characteristics, and assessments of respective limitations per outcome are depicted in ***online supplement C***. The following subgroups were formed to enable more meaningful quality assessments among the heterogenous body of evidence: 1) all lung cancer types, all stages, all therapies, guideline implementation [108-110], 2) NSCLC, all stages, surgical resection plus neoadjuvant/adjuvant therapies, guideline adherence [104, 112-116], 3) all lung cancer, all stages, all treatment modalities, guideline adherence, 4) NSCLC, unresectable stage III, chemo- and/or radiotherapy, guideline adherence [103], 5) NSCLC, all stages, chemotherapy, guideline adherence [106, 111], and 6) SCLC, all stages, all treatment modalities, guideline adherence [107].

A priori, all outcomes related to this PICO were considered either critical or important (***online supplement A***). Six outcome parameters were addressed in the body of evidence: *overall survival*, postoperative *mortality*, perioperative *morbidity, accuracy of staging, receipt of curative treatment* and *receipt of any active tumour-specific treatment.*

1) PICO 3, subgroup 1: All lung cancer types, all stages, all therapies, guideline implementation (vs. no guideline implementation)

The three studies by *Jakobsen et al.* and *Mainz et al.* from Denmark as well as by *McCarthy et al.* from the United Kingdom explored the effect of lung cancer guideline implementation accompanied by other nation-wide quality of care improvement measures in a population-based setting, all including patients with all types of lung cancer, all stages and all treatment modalities [108-110].

While the two Danish studies suggested an enhanced ***overall survival*** benefit over time (i. e. 5-year overall survival increase in all lung cancer patients from 9.8% in 2003 to 12.1%. in 2007 in the study by *Jakobsen et al.* 38,661 patients (moderate effect); *Mainz et al.* without exact patient figures; small effect) [108, 109], the older British study by *McCarthy et al.* (without exact patient figures) could demonstrate some significant overall survival improvements for implementation of organisational requirements, but only trivial effects for compliance with pathology and chemotherapy standards [110].

[quality of outcome: very low ⊕○○○, downgraded because of serious risk of bias, inconsistency and indirectness across studies].

The analysis of the large population-based Danish cohort (38,661 patients) by Jakobsen et al. manifested a large effect on postoperative ***30-day mortality*** improvement from 93.7% in 2003 to 99.0% in 2012 after the implementation of the above-mentioned quality management system including the Danish lung cancer guideline [108]. Previously, *Mainz et al.* could already observe a large effect in the same cohort for the 2003-2006 period [109].

[quality of outcome: very low ⊕○○○, downgraded because of serious risk of bias].

Within the observed decade, *Jakobsen et al.* (38,661 patients) reported in addition improved quality measures over time for ***accuracy of staging*** (accordance of cTNM and pTNM 68.2% in 2003 and 91.3% in 2012; large effect), ***receipt of curative treatment*** (NSCLC resection rate 18.7% in 2008 and 19.8% in 2012; trivial effect) and ***receipt of any active tumour-specific treatment*** (receipt of any treatment approx. 60% in 2000 and 85% in 2012; large effect) [108].

[quality of each outcome: very low ⊕○○○, downgraded because of serious risk of bias].

The GRADE evidence profile relating to the subgroup 1 in PICO 3 (All lung cancer types, all stages, all therapies, guideline implementation) is presented in ***Table 16***.

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Overall survival									
3 [108-110]	observational studies	serious [a]	serious [b]	serious [c]	serious [d]	none	We detected 1 study with a moderate effect (38,661 patients), 1 study with a small effect (no exact patient figures), and 1 study with a trivial effect (no exact patient figures).	⊕◯◯◯ VERY LOW	CRITICAL
30-day mortality									
2 [108, 109]	observational studies	serious [e]	not serious	not serious	serious [d]	none	We detected 2 studies with a large effect (38,661 patients), 1 study without exact patient figures).	⊕◯◯◯ VERY LOW	CRITICAL
Accuracy of staging									
1 [108]	observational studies	serious [f]	not serious	not serious	not serious	none	We detected 1 study with a large effect (38,661 patients).	⊕◯◯◯ VERY LOW	CRITICAL
Receipt of curative treatment									
1 [108]	observational studies	serious [f]	not serious	not serious	not serious	none	We detected 1 study with a trivial effect (38,661 patients).	⊕◯◯◯ VERY LOW	CRITICAL
Receipt of any active tumour-specific treatment									
1 [108]	observational studies	serious [f]	not serious	not serious	not serious	none	We detected 1 study with a large effect (38,661 patients).	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations:

a. Flawed measurement of both exposure and outcome in Mainz et al. and McCarthy et al, failure to adequately control confounding in all 3 studies
b. intervention with positive effect on overall survival in Jakobsen et al. and Mainz et al., but no certain effect on overall survival in McCarthy et al.
c. Jakobsen et al. and Mainz et al. assessed overall survival for all lung cancer patients, McCarthy et al. for pathology and chemotherapy standards
d. Pooled effect was incalculable and therefore barely estimable.
e. Flawed measurement of both exposure and outcome in Mainz et al., failure to adequately control confounding in both studies
f. Failure to adequately control confounding

Table 16: GRADE evidence profile for PICO 3, subgroup 1 (All lung cancer types, all stages, all therapies, guideline implementation)

2) PICO 3, subgroup 2: NSCLC, all stages, surgical resection with or without neoadjuvant/adjuvant therapies, guideline adherence (vs. no guideline adherence)

Six publications set their focus on guideline adherence related to thoracic surgery in approx. 1,840,168 NSCLC patients [104, 112-116].

Overall survival was reported in five studies (approx. 835,464 patients) evaluating the impact of attaining various surgical NSCLC guidelines recommendations by the American College of Chest Physicians (ACCP), the American College of Surgeons Oncology Group (ACOSOG), the American College of Surgeons (ACS), the International Association for the Study of Lung Cancer (IASLC), the National Comprehensive Cancer Network (NCCN), and the Society of Thoracic Surgeons (STS) [104, 113-116] as well as the inclusion criteria of the clinical trial RADIANT [104, 116]. Recommendation-derived quality measures included negative resection margins (ACCP, ACS, IASLC, NCCN, RADIANT) [104, 114-116], anatomic extent of resection (ACCP, ACS, IASLC, NCCN, RADIANT) [104, 114-116], hilar lymph node sampling (ACS, IASLC, NCCN) [104, 114, 116], and mediastinal lymph node sampling (ACS, IASLC, NCCN, RADIANT, STS) [104, 113-116], preference of non-surgical treatments in cN2M0-NSCLC (ACS) [113] as well as maximum periods from diagnosis to surgery [115], neoadjuvant therapy to surgery (ACS) [113] and surgery to adjuvant therapy (ACS) [113].

Odell et al. demonstrated improved ***overall survival*** for adherence to three single ACS-recommendations (sampling of ≥10 lymph nodes, time neoadjuvant therapy-surgery <120 days, time surgery-adjuvant therapy <180 days) whereas recommended preferring neoadjuvant therapy before surgery in cN2M0 resulted in the opposite effect. However, the latter statistical effect may not be representative for clinical stage IIIA NSCLC patients as 97.5% of patients received neoadjuvant therapy and the small remainder of 2.5% may bear more favourable characteristics unaccounted for in the underlying registry data [113]. The other four studies explored composite quality measures extracted from different guidelines. *Osarogiagbon et al.* and *Samson et al.* exhibited better overall survival when recommendations were followed [114, 115]. *Yue et al.* displayed similar overall benefits for compliance with three underlying guidelines and the RADIANT trial inclusion criteria in unadjusted analyses, yet after attribution to confounders significant improvement only for applying the IASLC-guideline. The different required extent of the lymph node resection per recommendation system could be a major factor contributing to this inconsistency (IASLC: systematic lymph node dissection vs. ACS, NCCN, RADIANT: selective lymph node sampling) [116]. Equally, *Allen et al.* showed a moderate and a small effect for adhering to NCCN-criteria (3-year overall survival 73% vs. 64%, p=0.50) and RADIANT-criteria (3-year overall survival 67% vs. 63%, p=0.71), respectively) [104]. ***Table 17*** depicts the corresponding effect results. Due to heterogeneity of underlying recommendations, a meta-analysis was purposely avoided.

[quality of evidence for overall survival: very low ⊕◯◯◯, downgraded because of serious indirectness and inconsistency across studies].

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 3, subgroup 2: NSCLC, all stages, surgical resection with or without neoadjuvant/adjuvant therapies, guideline adherence		
***Overall survival (OS)* – 5 observational studies (835,464 patients)**		
Allen, 2011 **[104]**	746	*Overall survival – guideline implementation/adherence with moderate-large effect* (HR<1.0: Guideline implementation/adherence correlating with higher OS)*:* -NCCN (3-year overall survival): 1) guideline adherence: 73% 2) no guideline adherence: 64%; p=0.50 -RADIANT (3-year overall survival): 1) guideline adherence: 67% 2) no guideline adherence: 63%; p=0.71

Odell, 2019 **[113]**		386,886 32,098 109,625 167,603	*Overall survival – guideline implementation/adherence with small-large effect* (HR<1.0: Guideline implementation/adherence correlating with higher OS)*:* -ACS (10 or more lymph nodes sampled): 1) guideline adherence: HR 0.85, 95% CI 0.83-0.86 2) no guideline adherence: HR 1.0 (reference) -ACS (time neoadjuvant therapy-surgery <120 days): 1) guideline adherence: HR 0.85, 95% CI 0.79-0.93 2) no guideline adherence: HR 1.0 (reference) -ACS (time surgery-adjuvant therapy <180 days): 1) guideline adherence: HR 0.71, 95% CI 0.69-0.73 2) no guideline adherence: HR 1.0 (reference) *Overall survival – no guideline implementation/adherence with large effect* (HR<1.0: guideline implementation/adherence correlating with higher OS)*:* -ACS (neoadjuvant therapy before surgery in cN2M0): 1) guideline adherence: HR 1.25, 95%CI 1.09-1.30 2) no guideline adherence: HR 1.0 (reference)
Osarogiagbon, 2017 **[114]**		2,429	*Overall survival – guideline implementation/adherence with large effect* (HR<1.0: guideline implementation/adherence correlating with higher OS)*:* -NCCN: 1) guideline adherence: HR 0.71, 95% CI 0.59-0.86 2) no guideline adherence: HR 1.0 (reference)
Samson, 2017 **[115]**	133,366		*Overall survival – guideline implementation/adherence with large effect* (HR<1.0: guideline implementation/adherence correlating with higher OS)*:* -ACCP, NCCN, STS, ACS: 1) guideline adherence: HR 0.39, 95% CI 0.31-0.48 2) no guideline adherence: HR 1.0 (reference)

Yue, 2014 **[116]**	2,711	*Overall survival –guideline implementation/adherence with large effect* (HR<1.0: guideline implementation/adherence correlating with higher OS)*:* -IASLC: 1) guideline adherence: HR 0.84, 95% CI 0.72-0.99 2) no guideline adherence: HR 1.0 (reference) *Overall survival –guideline implementation/adherence with trivial effect* (HR<1.0: guideline implementation/adherence correlating with higher OS)*::* -ACOSOG: 1) guideline adherence: HR 1.09, 95% CI 0.39-3.05 2) no guideline adherence: HR 1.0 (reference) -NCCN: HR 0.92, 95% CI 0.36-2.28 1) guideline adherence: HR 1.09, 95% CI 0.42-2.81 2) no guideline adherence: HR 1.0 (reference) -RADIANT: HR 1.12, 95% CI 0.93-1.35 1) guideline adherence: HR 0.89, 95% CI 0.74-1.07 2) no guideline adherence: HR 1.0 (reference)

Table 17: Effect results of studies ineligible for meta-analyses on overall survival for PICO 3, subgroup 2 (NSCLC, all stages, surgery plus neoadjuvant/adjuvant therapies and guideline adherence; ACCP: American College of Chest Physicians, ACOSOG: American College of Surgeons Oncology Group, ACS: American College of Surgeons, IASLC: International Association for the Study of Lung Cancer, NCCN: National Comprehensive Cancer Network, STS: Society of Thoracic Surgeons)

30 day-mortality and ***morbidity*** were assessed in the case-control-study by *Novoa et al.* relating to the ERS/ESTS guideline on fitness for radical therapy in lung cancer. The named outcomes showed a trivial (916 patients; 30-day mortality: 0.9% vs. 1.2%, OR 0.7, 95% CI 0.1-4.4) and small effect (cardiorespiratory morbidity: 8.1% vs. 9.8%, OR 0.8, 95% CI 0.4-1.4) by guideline adherence, respectively [112]. *Allen et al.* resulted in a trivial effect on *30-day mortality* by adherence to ACS/NCCN/RADIANT-originated quality measures (746 patients; 30-day mortality for guideline adherence and non-adherence: 5.7% vs 4.6%, p=0.55) [104].

[quality of outcome (30-day-mortality): very low ⊕◯◯◯, downgraded because of serious risk of bias and indirectness]

[quality of outcome (morbidity): low ⊕⊕◯◯].

The GRADE evidence profile relating to the subgroup 2 in PICO 3 (NSCLC, all stages, surgical resection with or without neoadjuvant/adjuvant therapies, guideline adherence) is presented in ***Table 18***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	guideline adherence	no guideline adherence	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
5 [104, 113-116]	observational studies	not serious	serious [a]	serious [b]	serious [c]	none	We detected 2 studies with large effects (135,795 patients), 1 study with a large effect for adherence to 1 guideline and a moderate effect for adherence to another guideline (746 patients), and 1 study with large effects for adherence to 1 guideline but trivial effects for adherence to another 3 guidelines (2,711 patients). Another study showed large effects for adherence to 3 recommendations but a reverse large effect in one subgroup favouring non-adherence (yet, in control arm only 2.5% of patients, thus potentially biased effect due to unknown patient factors) (approx. 1,700,000 patients).				⨁◯◯◯ VERY LOW	CRITICAL
30-day mortality												
2 [104, 112]	observational studies	serious [d]	not serious	serious [b]	serious [c]	none	We detected 2 studies with a trivial effect (1,662 patients).				⨁◯◯◯ VERY LOW	CRITICAL
Morbidity												
1 [112]	observational studies	not serious	not serious	not serious	very serious [e]	none	27/308 (8.8%)	33/335 (9.9%)	**OR 0.8** (0.4 to 1.4)	**18 fewer per 1.000** (from 57 fewer to 34 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

Explanations:

a. Effect of guideline adherence differs across studies
b. Studies use different guidelines to measure guideline adherence
c. Pooled effect was incalculable and therefore barely estimable.
d. Failure to adequately control confounding in Allen et al.
e. In addition to few events, the 95% CI includes the potential for benefit; however, cannot exclude the possibility of no benefit.

Table 18: GRADE evidence profile for PICO 3, subgroup 2 (NSCLC, all stages, surgical resection with or without neoadjuvant/adjuvant therapies, guideline adherence)

3) PICO 3, subgroup 3: All lung cancer, all stages, all treatment modalities, guideline adherence (vs. no guideline adherence)

Two studies on guideline adherence were conducted in patients with all lung cancer types, all stages and all treatment modalities [71, 105]. *Nadpara et al.*, demonstrated a large effect of guideline adherence on ***overall survival*** in a large but age-restricted study cohort of patients 65 years or older (42,323 patients; adjusted HR 0.52, 95% CI 0.50-0.55) [71]. Contrarily, *Boxer et al.* could prove a large effect in their much smaller but unrestricted cohort significance only for patients younger than 70 years but an opposite effect was seen in patients 70 years and older (808 patients; <60 years: adjusted HR 0.33, 95% CI 0.26-0.44; 60-69 years: adjusted HR 0.30, 95% CI 0.20-0.47; ≥70 years: adjusted HR 1.59, 95% CI 0.83-3.03) [105].

[quality of evidence for overall survival: very low ⊕◯◯◯, downgraded because of serious inconsistency and indirectness across studies]

The GRADE evidence profile relating to the subgroup 3 in PICO 3 (All lung cancer, all stages, all treatment modalities, guideline adherence) is presented in ***Table 19***.

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Overall survival									
2 [71, 105]	observational studies	not serious	serious [a]	serious [b]	serious [c]	none	We detected 2 studies (43,131 patients) with large effects yet focussing on different age-groups.	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval
Explanations:
a. age-dependent effects varied among both studies
b. Both studies focussed on different age groups
c. Due to different age groups in both studies, calculation of a pooled effect was not meaningful, the effect no estimable.

Table 19: GRADE evidence profile for PICO 3, subgroup 3 (All lung cancer, all stages, all treatment modalities, guideline adherence)

4) PICO 3, subgroup 4: NSCLC, unresectable stage III, chemo- and/or radiotherapy, guideline adherence (vs. no guideline adherence)

Ahmed et al. investigated 45,825 patients with unresectable stage III NSCLC and radiotherapy, chemotherapy or chemoradiotherapy. Guideline-concordant care associated with enhanced ***overall survival*** (adjusted HR 0.70, 95% 0.68-0.72) [103].

[quality of evidence for overall survival: low ⊕⊕◯◯]

The GRADE evidence profile relating to the subgroup 4 in PICO 3 (NSCLC, unresectable stage III, chemo- and/or radiotherapy, guideline adherence) is presented in **Table 20**.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	guideline adherence	no guideline adherence	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
1 [103]	observational studies	not serious	not serious	not serious	not serious	none	-/10476 [a]	-/35349 [a]	**HR 0.70** (0.68 to 0.72)	**-- per 1.000** (from -- to --) [a]	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio
Explanations:
a. Study did not provide numbers of events.

Table 20: GRADE evidence profile for PICO 3, subgroup 4 (NSCLC, unresectable stage III, chemo- and/or radiotherapy, guideline adherence)

5) PICO 3, subgroup 5: NSCLC, all stages, chemotherapy, guideline adherence (vs. no guideline adherence)

Casebeer et al. and *Neubauer et al.* collected data from NSCLC patients receiving chemotherapy (2,753 patients) [106, 111]. Both could show only trivial effects for guideline-adherence on ***overall survival*** (*Casebeer et al.*: 6-month mortality adjusted HR 0.987, 95% CI 0.723-1.347; *Neubauer et al.*: adjusted HR 0.95, 95% CI 0.77-1.16).

[quality of evidence for overall survival: very low ⨁◯◯◯, downgraded because of serious inconsistency and indirectness across studies].

The GRADE evidence profile relating to the subgroup 5 in PICO 3 (NSCLC, all stages, chemotherapy, guideline adherence) is presented in ***Table 21***.

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Overall survival									
2 [106, 111]	observational studies	not serious	not serious	serious [a]	serious [b]	none	We detected 2 studies (2,753 patients) with a trivial effect.	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval
Explanations:
a. Casebeer 2018 included only stage IV NSCLC, Neubauer included stage II-IV NSCLC
b. due to different included stages, calculating a pooled effect was not meaningful, likewise, the effect is barely estimable.

Table 21: GRADE evidence profile for PICO 3, subgroup 5 (NSCLC, all stages, chemotherapy, guideline adherence)

6) PICO 3, subgroup 6: SCLC, all stages, all treatment modalities, guideline adherence (vs. no guideline adherence)

Elegbede et al. addressed guideline adherence in a cohort of 404 SCLC-patients which correlated in five out of six recommendations with large effects on ***overall survival*** compared to non-adherence (effect results in ***Table 22***) [107].

[quality of evidence for overall survival: very low ⊕◯◯◯; downgraded because of inconsistency]

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 3, subgroup 6: SCLC, all stages, all treatment modalities, guideline adherence		
***Overall survival (OS)* – 1 observational study (404 patients)**		
Elegbede, 2019 **[107]**	404	*Overall survival – guideline implementation/adherence with large effect* (HR<1.0: guideline implementation/adherence correlating with higher OS)*:* LD-SCLC: -chemoradiotherapy: 1) guideline adherence: HR 0.35 [95% CI 0.14-0.90] 2) no guideline adherence: HR 1.0 (reference) -surgery ± adjuvant: 1) guideline adherence: HR 0.18 [95% CI 0.05-0.73] 2) no guideline adherence: HR 1.0 (reference) ED-SCLC: -chemotherapy: 1) guideline adherence: HR 0.33 [95% CI 0.22-0.48] 2) no guideline adherence: HR 1.0 (reference) -chemotherapy and other: 1) guideline adherence: HR 0.35 [95% CI 0.22-0.56] 2) no guideline adherence: HR 1.0 (reference) -chemotherapy and radiotherapy: 1) guideline adherence: HR 0.24 [95% CI 0.15-0.41] 2) no guideline adherence: HR 1.0 (reference) *Overall survival – guideline implementation/adherence with trivial effect* (HR<1.0: guideline implementation/adherence correlating with higher OS)*:* LD SCLC: -2nd line therapy: 1) guideline adherence: HR 0.88, 95% CI 0.55-1.43 2) no guideline adherence: HR 1.0 (reference)

Table 22*:* Effect results in the study by Elegbede et al. on overall survival for PICO 3, subgroup 6 (SCLC, all stages, all treatment modalities, guideline adherence; LD: limited disease, ED: extensive disease)

The GRADE evidence profile relating to the subgroup 6 in PICO 3 (SCLC, all stages, all treatment modalities, guideline adherence) is presented in ***Table 23***.

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Overall survival									
1 [107]	observational studies	not serious	serious [a]	not serious	not serious	none	In the study by Elegbede et al. (404 patients) guideline adherence resulted in large effects for chemoradiotherapy and surgery ± adjuvant chemotherapy in LD-SCLC: as well as chemotherapy, chemotherapy and other modalities and chemotherapy and radiotherapy in ED-SCLC. A trivial effect was seen for 2nd line therapy in LD-SCLC.	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations:

a. 1 subgroup with a trivial effect, while 5 subgroups showed large effects

Table 23: GRADE evidence profile for PICO 3, subgroup 6 (SCLC, all stages, all treatment modalities, guideline adherence)

C. PICO 3: GRADE evidence to decision framework

Table 24 depicts the GRADE evidence to decision framework relating to PICO 3 based upon on the GRADE evidence profiles as well as additional considerations by the task force panel.

PICO 3: In patients with lung cancer (or those suspected of having lung cancer), should guidelines or standard operating procedures (SOP) for lung cancer care be implemented or adhered to rather than non-implementation of or non-adherence to these guidelines or standard operating procedures?	
POPULATION:	All lung cancer types, all stages, all treatment modalities
INTERVENTION:	guideline implementation or adherence
COMPARISON:	no guideline implementation or adherence
MAIN OUTCOMES:	Overall survival; Morbidity; Accuracy of staging ; rate of curative treatment; Rate of any active tumour-specific treatment;
SETTING:	Both outpatient and inpatient
PERSPECTIVE:	Clinical recommendations – population perspective
BACKGROUND:	Large numbers of international and national lung cancer guidelines exist with significantly varying methodological quality and partially outdated recommendations.
CONFLICT OF INTERESTS:	N/A

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	A surplus on international and national clinical lung cancer guidelines with significant variance in terms of up-to-dateness and methodological quality has been previously reported. Higher national financial resources correlated with enhanced systematic guideline quality [117, 118]. Dissemination, implementation, adherence and update are the essential next steps within the guideline cycle introduced by the EU commission in 2004 ensuring a value-added utilization of well-developed guidelines [119]. Yet, in real life, difficulties in guideline implementation and adherence among professionals [120, 121] and stakeholders [122, 123] were identified, while some evidence indicated limited impact and substantial variation of assisting tools for guideline implementation [124].	Guideline implementation and adherence are considered as an essential topic in lung cancer care by the task force. Likewise, it is a key priority topic for ERS as well as ELF and the Patient Advisory Group

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Our systematic review revealed the following desirable effects of guideline implementation and adherence (see related PICO 3 evidence tables, subgroups 1-6 for details): *Regarding guideline implementation:* -improved overall survival, postsurgical 30-day mortality, accuracy of staging, rate of curative treatment and rate of any tumour-specific treatment were seen in the Danish national guideline implementation initiative linked to the re-organisation of lung cancer services and the set-up of a national clinical lung cancer registry, whereas a comparable earlier study from the United Kingdom showed positive effects on overall survival relating to some organisational standards, but not to clinical recommendations *Regarding guideline adherence:* -improved overall survival in some studies on single or combined recommendation-derived quality measures in NSCLC thoracic surgery, chemo-/radiotherapy in NSCLC stage III and various SCLC treatment modalities while other studies did not see certain overall survival effects in NSCLC thoracic surgery and chemotherapy in the more advanced stage IV NSCLC population -*postoperative 30-day mortality* was not correlating with guideline adherence in the two available smaller studies	From clinical experience, the TF members consider the following additional desirable effects of guideline implementation/adherence to be likely: -higher rates of treatments with curative intent, especially in more advanced stages -higher rates of treatments with palliatve intent in more advanced stages -higher satisfaction of patients and medical professionals

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	No harms were detected by our systematic review (see related PICO 3 evidence tables, subgroups 1-6 for details). The detected opposite effect on *overall survival* in the work by *Odell et al.* suggesting non-adherence to the evidence-based recommendation to initiate neo-adjuvant therapy before surgery in clinical stage IIIA NSCLC-patients was well invalidated by the authors due to a disproportionate, potentially non-representative control arm. Industry-sponsored guidelines may bear specific risks (i.e. less transparency, fewer reservations, more favourable conclusions) [125].	From clinical experience, the TF members are concerned about the following additional undesirable effects of guideline implementation/adherence: -risk of outdated guideline recommendations -surplus of available guidelines on a certain topic with risk of contradicting or only partially matching guideline recommendations -potentially insufficient methodological quality (i.e. ascertainable using the AGREE II tool) -health care authority financed/issued guidelines may be limited to national resources only

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the evidence was graded as very low (see related PICO 3 evidence tables, subgroups 1-6 for details)	None

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	We did not perform a systematic literature search specifically on patient values relating to guideline implementation and adherence. Our systematic review did not retrieve any related pieces of evidence.	Guideline implementation and adherence are a key priority of patients as confirmed by patient and ELF representatives in our task force panel. In addition, the following points were stated: -patients would like to receive optimal diagnostics and treatments recommended in guidelines -risk of adverse events if patient unfit for guideline recommended therapy -routine care may be driven more by locally available infrastructure and resources than by guideline recommended care -guidelines may withhold clinicians from coming up with individual treatment approaches not backed-up by guidelines recommendations

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Our systematic evidence assessment resulted in moderate desirable effects and no undesirable effects.	Weighing desirable and undesirable effects based on our systematic evidence assessment, our task force panel discussions and clinical experience, we see benefits in guideline implementation and adherence in principle. Yet, we are precautious about the above-mentioned potential risks.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	We did not perform a systematic literature search specifically on required resources relating to guideline implementation and adherence. Our systematic review did not retrieve any related pieces of evidence.	We estimate at least moderate costs to facilitate guideline implementation and adherence in lung cancer care on the various level of care.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● No included studies	not applicable	Required resources are depending on multiple factors, especially the capacities and outreach of already existing (national) guideline programmes. A substantial variation across European countries is suspected impeding general cost estimates.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	We did not perform a systematic literature search specifically on cost effectiveness relating to guideline implementation and adherence. Our systematic review retrieved two studies: *Casebeer et al.* demonstrated no increase of costs after guideline implementation were after multivariate analysis [106]. *Neubauer et al.* could even demonstrate lower costs for guideline-concordant care within a period of 1 year after initiation of 1st line chemotherapy in NSCLC patients in a regional outpatient US-oncology network (1,409 patients; average 12-month on/off pathway costs: $18,042 v $27,737; on/off cost ratio 0.71, 95% CI 0.64-0.80) [111].	Despite increased short-term/ongoing costs for set-up of guideline implementation and adherence initiatives, we assume mid- and long-term savings due to more efficient utilization of diagnostic and therapeutic capacities as well as reduction of mis-, over- and undertreatment rates.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	We did not perform a systematic literature search specifically on equity relating to guideline implementation and adherence. Our systematic review did not retrieve any related pieces of evidence. Ensuring equity in all patients receiving guideline-concordant care should be an unquestionable goal. Based on Surveillance, Epidemiology, and End Results Medicare US data, *Fang et al.* detected that black patients compared to white patients were less likely to receive stereotactic radiation or surgery in stage I NSCLC (14,605 patients; 61% vs. 75%, p<0.0001) as well as chemotherapy in addition to radiotherapy or surgery in stage III NSCLC (15,609 patients; 36% vs. 41%, p<0.0001) [126].	Improving guideline implementation may facilitate better patient adherence to guideline recommendations. Conversely, appropriate guideline implementation and adherence is not expected to create inequality.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	We did not perform a systematic literature search specifically on acceptability to key stakeholders relating to guideline implementation and adherence. Our systematic review did not retrieve any related pieces of evidence.	We assume that guideline implementation and adherence will be accepted very well by patients, medical professionals and healthcare providers alike.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not perform a systematic literature search specifically on feasibility of implementing and adhering to guidelines. Our systematic review did not retrieve any related pieces of evidence.	If sufficient resources are made available, we do see a chance to improve guideline implementation and adherence well.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know

	JUDGEMENT						
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

In patients with lung cancer, we suggest that methodologically robust, evidence-based guidelines and standard operating procedures should be implemented and adhered to (based on informed consent by the patient) [conditional recommendation for the intervention; very low overall quality of evidence].

Remark: We acknowledge that clinical practice guidelines are generally perceived as highest level of evidence-based medicine and have been created frequently in lung cancer care. Yet, even if guidelines are issued in good metholodogical and contentual quality, their overall impact strongly depends on the recognition and adherence by the target audience. Stakeholder need assessments, measures to improve implementation and applicability as well as

regular updates of guidelines may facilitate user acceptation. At the same time guidelines are not mandates but do need unsolicitous approval by competent patients after provision of understandable information on recommended practices by physicians and time for discussion on their benefits and risks as well as alternatives.

Justification

The very low level of certainty in the effect estimates has led to a conditional recommendation for guideline implementation and adherence. No substantial harms became evident by the systematic review or are foreseen by us related to guideline implementation and adherence when applied properly in clinical practice.

Subgroup considerations

None

Implementation considerations

Guideline implementation and adherence is crucial for an adequate, state-of-the-art management of lung cancer patients. The above-mentioned potential problems of dissemination and implementation as well as up-to-dateness should be considered and actively addressed in respective national and local settings.

Monitoring and evaluation

Active guideline cycles linking guideline development (including vivid monitoring and adaption processes), guideline implementation on the lung cancer service level and quality assurance of guideline-recommended care by clinical lung cancer registries should be facilitated. As a result, we expect improved contentual quality, up-to-dateness and by that acceptance of guideline-based lung cancer care. Likewise, equity in receipt of guideline-concordant care should be monitored as well as causes for potential inequities be further explored and solutions be striven for.

Research priorities

Valuable financial and human resources for guideline development may be saved by multidisciplinary collaborations across societies and governmental bodies within and among countries as well as on the international level avoiding unnecessary duplication of work within the qualitative evidence synthesis. However, evidence-based guideline recommendations are usually adapted according to different national health care system organization and resources (amongst many others, a positive example is the conjoint development and implementation of the Belgian Lung Cancer Guideline led by the Belgian Health Care Knowledge Centre KCE [25]).

Table 24: GRADE evidence to decision framework relating to PICO 3

PICO question 4: Should patients with lung cancer (or those suspected of having lung cancer) receive lung cancer-specific diagnostic or therapeutic procedures in hospitals/from professionals with higher volumes of activity/with a higher grade of specialization for these procedures rather than receiving them in hospitals/from professionals with lower volumes of activity/with lower grade of specialization for these procedures?

A. PICO 4: General summary of the evidence

A total of 76 observational studies were selected out of the 440 initially identified abstracts within the scope of this search question (PRISMA flow diagram: ***online supplement A***) [67, 68, 88, 127-199].

64 observational studies focussed on *hospital volume of care* [67, 127-189]. Two of those [152, 154] were extracted out of a review by *von Meyenfeld et al.* [200]. 30 studies originated from the United States of America [127, 129, 132-135, 138, 141, 143, 145-149, 152, 155-157, 160, 163-166, 169, 172, 175, 176, 179, 185, 188], nine from Japan [139, 150, 153, 167, 168, 170, 171, 173, 177], four each from France [130, 131, 142, 174] and the Netherlands [136, 140, 158, 189], three from Canada [180, 186, 187], two each from Germany [128, 151], South Korea [67, 154], Taiwan [137, 159] and the United Kingdom [161, 162] as well as one each from Australia [184], Belgium [178], Finland [181], Norway [183] and Spain [144]. One multinational study included patients from six South-American and European countries [182].

The majority of studies (53 studies) focused on the impact of *hospital volume of care in patients with surgical resections* (2,412,411 patients) [67, 127-135, 137-140, 142-144, 147-149, 151, 152, 154-156, 158-165, 167-171, 173-181, 183-188]. The relationship between *hospital volume of care in procedures other than surgical resection* was investigated in eleven studies [136, 141, 145, 146, 150, 153, 157, 166, 172, 182, 189]. Two studies each addressed chemoradiochemotherapy in stage II and IIIA/B NSCLC (734 patients) [141, 157] and diagnostic bronchoscopy including EBUS (78,646 patients) [150, 172]. Likewise, single studies explored the impact of hospital volumes relating to: quality of pathological lung cancer diagnostics (89,409 patients) [145], different tumour-specific therapies in stage IIIA NSCLC (83,673 patients) [166], systemic therapy in stage III/IV lung cancer (26,277 patients) [136], different tumour-specific therapies in stage IV NSCLC (338,445 patients) [146], different tumour-specific therapies in all-stage NSCLC (43,544 patients) [189], different tumour-specific therapies in all-stage lung cancers (9,235 patients) [153], and ICU therapy in lung cancer patients (449 patients) [182].

The impact of *hospital specialization* was subject matter in 19 observational studies (786,242 patients) [68, 127, 131, 138, 142, 145, 156, 158, 160, 163, 174, 176, 180, 181, 189-192, 196]. Eleven studies derived from the United States of America [68, 127, 138, 145, 156, 160, 163, 176, 191, 192, 196], three from France [131, 142, 174], two each from from Canada [180, 190] and the Netherlands [158, 189] as well as one from Finland [181]. 17 studies covered lung cancer patients with surgical resections (653,289 patients) [68, 127, 131, 138, 145, 158, 160, 163, 174, 176, 180, 181, 189-192, 196], one study observed quality of pathological lung cancer diagnostics (89,409 patients) [145], and another different tumour-specific therapies in all-stage NSCLC (43,544 patients) [189].

Seven observational studies dealt with *surgeon volumes of care* exclusively relating to surgical resections (63,505 patients) [133, 137, 142, 148, 159, 198, 199]. Studies emanated from the Canada , France [142], Taiwan [137, 159], the United Kingdom [199], and the United States of America [133, 148, 198].

Surgeon specialization was addressed in eight observational studies, again exclusively relating to surgical resections (492,135 patients) [88, 140, 158, 168, 193-195, 197]. One of of these studies [193] were obtained through the review by *Tieu et al.* [201]. Studies were performed in the Japan [168], the Netherlands [140, 158], the United Kingdom [88], and the United States of America [193-195, 197].

B. PICO 4: Summary, rating of the quality of evidence and GRADE evidence profiles in specific subgroups

Individual studies, their main characteristics, and assessments of respective limitations per outcome are depicted in ***online supplement C***. We formed six groups to assess the body of evidence: 1) hospital volume of care, surgical resection, 2) hospital specialization, surgical resection, 3) surgeon volume of care, surgical resection, 4) surgeon specialization, surgical resection, 5) hospital volume of care, procedures other than surgical resection, and 6) hospital specialization, procedures other than surgical resection.

A priori, all outcomes were considered either critical or important related to this PICO (***online supplement A***). Effectively, only *overall survival*, *progression-free survival, mortality*, *morbidity*, *accuracy of staging*, *pathological confirmation*, and *receipt of curative treatment* were addressed in the selected study groups.

No evidence was found relating to *disease-free survival, staging, receipt of any active tumour-specific treatment, quality of life, patient satisfaction, and performance status*.

1) PICO 4, subgroup 1: All lung cancer, all stages, higher hospital volume of surgical resections (vs. lower hospital volume)

53 obervational studies investigated the impact of hospital volume of care in lung cancer patients with surgical resections (2,412,411 patients) [67, 127-135, 137-140, 142-144, 147-149, 151, 152, 154-156, 158-165, 167-171, 173-181, 183-188]. 34 studies were based upon lung cancer patients only [67, 127, 128, 130, 131, 138, 140, 142, 144, 147, 149, 151, 154, 155, 158-165, 167, 168, 171, 173-176, 178, 181, 183-185, 188] while 19 studies applied mixed patient populations involving different types of primary cancers or cancer surgery and/or other non-malignant diseases with other types of major surgeries [67, 129, 132-135, 137, 139, 143, 148, 152, 156, 169, 170, 177, 179, 180, 186, 187]. Types of lung cancer regarding stage and histologies as well as those of exact surgical pulmonary resection procedures differed among studies or were not further specified. Likewise, the sources of study data varied with underlying clinical cancer registries, administrative databases or combinations of both. Moreover, studies established various types of volume strata and numeric thresholds which were defined either a priori or ex post. Thus, we purposely omitted any meta-analyses. Instead, we described results across outcomes narratively after estimating the effect size on a self-selected classification per outcome for each study.

A priori, all outcomes were considered either critical or important related to this PICO. Effectively, only *overall survival*, *mortality*, *morbidity* and *receipt of curative treatment* were addressed within the rated body of evidence.

Overall survival was utilized as an outcome parameter in 18 studies with surgically resected lung cancer patients (448,402 patients) [67, 127, 132, 135, 137, 138, 144, 158, 161, 164, 167, 170, 171, 178, 180, 181, 184, 188].

We detected twelve studies with a large effect (275,995 patients) [67, 127, 135, 137, 161, 167, 170, 171, 178, 180, 181], three studies with a moderate effect (57,643 patients) [132, 138, 184], and three studies with a trivial effect (154,764 patients) [144, 158, 188] (effect results in ***Table 25***).

[quality of evidence for *overall survival*: very low ⊕◯◯◯, rated down for risk of bias -1, indirectness -1, inconsistency -1 and imprecision -1, rated up for large effect +1].

Group Outcome Author, year	total number of patients	study effect per outcome
PICO 4, subgroup 1: Hospital volume of care, surgical resection		
***Overall survival (OS)* – 18 observational studies (448,402 patients)**		
Bach PB et al., 2001 **[127]**	2,118 pts.	Overall survival - *higher hospital volume of care with large effect* (HR<1.0: higher hospital volume of care correlating with higher OS)*:* 1) 1–8 resections p.a.: 407 pts.; 2-year OS 58%; 5-year 33%; adjusted HR 1.0 (reference) 2) 9–14 resections p.a.: 466. pts.; 2-year OS 62%; 5-year 36%; adjusted HR 0.91 3) 15–19 resections p.a.: 407 pts.; 2-year OS 62%; 5-year 39%; adjusted HR 0.80 4) 20–66 resections p.a.: 457 pts.; 2-year OS 69%; 5-year 40%; adjusted HR 0.75 5) 67–100 resections p.a.: 381 pts.; 2-year OS 69%; 5-year OS 44%; adjusted HR 0.77
Bilimoria KY et al., 2008 **[132]**	40,754 pts.	Overall survival - *higher hospital volume of care with moderate effect* (HR<1.0: higher hospital volume of care correlating with higher OS)*:* 1) 1–20 resections p.a.: 5-year OS 32.7%; adjusted HR 1.0 (reference) 2-4) 21–83 resections p.a.: 5-year OS 34.8%; adjusted HR not stated 5) >83 resections p.a.: 5-year OS 36.0%; HR 0.92, 95% CI 0.88-0.96
Birkmeyer JD et al., 2007 **[135]**	12,967 pts.	Overall survival - *higher hospital volume of care with large effect* (HR<1.0: higher hospital volume of care correlating with higher OS)*:* 1) low volume hospitals: 4,325 pts.; 5-year OS 37.5%; adjusted HR 1.0 (reference) 2) medium volume hospitals: 4,418 pts.; 5-year OS and adjusted HR not stated 3) high volume hospitals: 4,224 pts.; 5-year OS 43.5%; adjusted HR 0.84, 95% CI 0.79-0.90
Chang CM et al., 2012 **[137]**	655	Overall survival - *higher hospital volume of care with large effect* (***cave:*** higher hospital volume of care/higher individual volume of care as reference - HR>1.0: ***lower*** hospital volume of care correlating with ***lower*** OS)*:* 1) hospital <62 resections p.a.; surgeon <6 resections p.a.: 108 deaths/155 pts.; 5-year OS 30.37%); adjusted HR 1.82, 95% CI 1.35-2.46 2) hospital <62 resections p.a.; surgeon ≥6 resections p.a.: 152 deaths/275 pts.; 5-year OS 44.7%); adjusted HR 1.10, 95% CI 0.83-1.46 3) hospital ≥62 resections p.a.; surgeon <6 resections p.a.: 26 deaths/46 pts.; 5-year OS 43.5%; adjusted HR 1.33, 95% CI 0.85-2.08 4) hospital ≥62 resections p.a.; surgeon ≥6 resections p.a.: 84 deaths/179 pts.; 5-year OS 53.19%; ***adjusted HR 1.0 (reference)***
Cheung MC et al., 2009 **[138]**	13,469 pts.	Overall survival - *higher hospital volume of care with moderate effect* (HR<1.0: higher hospital volume of care correlating with higher OS)*:* 1) low volume hospitals: 8,871 pts.; median OS 39.8 months; adjusted HR 1.0 (reference) 2) high-volume hospitals: 4,598 pts.; median OS 45.1 months; adjusted HR 0.93, 95% CI 0.879-0.992

Freixinet JL et al., 2006 **[144]**	2,994 pts.	Overall survival - *higher hospital volume of care with trivial effect:* 1) 1-43 resections p.a.: 565 pts; 5-year OS 40%; median OS 39.82 months 2) 44-54 resections p.a.: 1,044 pts.; 5-year OS 37%; median OS 32.88 months 3) >54 resections p.a.: 1,386 pts.; 5-year OS 38%; median OS 34.39 months p=0.18
Kunisawa S et al., 2014 **[167]**	7,064 pts.	Overall survival - *higher hospital volume of care with large effect:* 1) 1-29 resections p.a.: 792 pts.; 1-year OS 97.8%, 95% CI ±1.2; 2-year OS 94.9%, 95% CI ±2.4; 3-year OS 90.6%, 95% CI ±4.5; 4-year OS 81.4%, 95% CI ±11.1; 5-year OS 81.4%, 95% CI ±11.1 2) ≥30 resections p.a.: 2587 pts.; 1-year OS 98.5%, 95% CI ±0.6; 2-year OS 97.3%, 95% CI ±0.5; 3-year OS 93.9%, 95% CI ±1.1; 4-year OS 92.1%, 95% CI ±2.9; 5-year OS 92.1%, 95% CI ±2.9 p=0.05
Li WW et al., 2008 **[158]**	1,097 pts	Overall survival - *higher hospital volume of care with trivial effect* (HR<1.0: higher hospital volume of care correlating with higher OS)*:* 1) 1-39 resections p.a.: 163 pts.; 5-year OS 53%; adjusted HR 1.0 (reference) 2) 40-59 resections p.a.: 529 pts.; 5-year OS 50%; adjusted HR 0.99, 95% CI 0.76-1.30 3) ≥60 resections p.a.: 358 pts.; 5-year OS 50%; adjusted HR 1.18, 95% CI 0.88-1.60
Luchtenborg M et al., 2013 **[161]**	134,293 pts.	Overall survival - *higher hospital volume of care with large effect* (HR<1.0: higher hospital volume of care correlating with higher OS) 1) 1-69 resections p.a.: 2,582 pts.; adjusted HR 1.0 (reference) 2) 70-99 resections p.a.: 2,662 pts.; adjusted HR 0.86, 95% CI 0.77-0.97 3) 100-129 resections p.a.: 2,378 pts.; adjusted HR 0.90, 95% CI 0.79-1.02 4) 130-149 resections p.a.: 2,651 pts.; adjusted HR 0.89, 95% CI 0.78-1.02 5) ≥150 resections p.a.: 2,589 pts.; adjusted HR 0.78, 95% CI 0.67-0.90
Mulvihill MS et al., 2018 **[164]**	139,802 pts.	Overall survival - *higher hospital volume of care with large effect* (***cave:*** highest hospital volume stratum as reference - HR>1.0: ***lower*** hospital volume of care correlating with ***lower*** OS)*:* 1) Bottom 25th percentile volume hospitals: 26,227 pts.; 1.40, 95% CI 1.37-1.43 2) 25-50th percentile volume hospitals: 48,934 pts.; adjusted HR 1.21, 95% CI 1.19-1.23 3) 50-75th percentile volume hospitals: 54,552 pts.; adjusted HR 1.12, 95% CI 1.10-1.14 4) Top 25th percentile volume hospitals: 56,431 pts.; ***adjusted HR 1.0 (reference)***

Okawa S et al., 2020 **[170]**	9,095 pts.	Overall survival - *higher hospital volume of care with large effect* (***cave:*** highest hospital volume stratum as reference - HR>1.0: ***lower*** hospital volume of care correlating with ***lower*** OS)*:* 1) very low volume hospitals – mean 5.5 (0.2-26.0): 2,420 pts.; adjusted HR 1.49, 95% CI 1.09-2.04 2) low volume hospitals – mean 44.2 (31.2-65.4): 2,205 pts.; adjusted HR 1.03, 95% CI 0.75-1.42 3) medium volume hospitals – mean 83.0 (68.0-109.0): 2,422 pts.; adjusted HR 1.20, 95% CI 0.87-1.67 4) high volume hospitals – mean 140.0 (111.2-164.2): 2,048 pts.; ***adjusted HR 1.0 (reference)***
Osada H et al., 2007 **[171]**	72,217 pts.	Overall survival - *higher hospital volume of care with large effect* (***cave:*** highest hospital volume stratum as reference - HR>1.0: ***lower*** hospital volume of care correlating with ***lower*** OS)*:* 1) 1-19 resections p.a.: 201 pts.; adjusted HR 1.5589, 95% CI 1.0036-2.4216 2) 20–29 resections p.a.: 544 pts.; adjusted HR 1.2556, 95% CI 0.8012-1.9676 3) 30–49 resections p.a.: 1,095 pts.; adjusted HR 1.3267, 95% CI 0.8657-2.0332 4) 50–79 resections p.a.: 761 pts.; adjusted HR 1.2607, 95% CI 0.8219-1.9340 5) >79 resections p.a.: 632 pts.; ***adjusted HR 1.0 (reference)***
Schillemans V et al., 2019 **[178]**	2,084 pts.	Overall survival - *higher hospital volume of care with large effect:* 1) 1-9 resections p.a.: 1-year OS 85%; 3-year OS 66.9% 2) ≥10 resections p.a.: 1,730 pts.; 1-year OS 89%; 3-year OS 69.2%
Simunovic M et al., 2006 **[180]**	2,698 pts.	Overall survival - *higher hospital volume of care with large effect* (HR<1.0: higher hospital volume of care correlating with higher OS)*:* 1) 1-32 resections per 3 years: 653 pts.; adjusted HR 1.0 (reference) 2) 32-85 resections per 3 years: 730 pts.; adjusted HR not stated 3) 86-130 resections per 3 years: 644 pts.; adjusted HR not stated 4) ≥131 resections per 3 years: 671 pts.; adjusted HR 0.8, 95% CI 0.6–0.9
Sioris T et al., 2008 **[181]**	5,339 pts.	Overall survival - *higher hospital volume of care with large effect* (HR<1.0: higher hospital volume of care correlating with higher OS)*:* 1) 0-4 resections p.a.: 334 pts.; adjusted HR 1.0 (reference) 2) 5-10 resections p.a.: 840 pts.; adjusted HR not stated 3) 11-20 resections p.a.: 1,102 pts.; adjusted HR not stated 4) >20 resections p.a.: 2,602 pts.; adjusted HR 0.8, 95% CI 0.7-0.9

Thai AA et al., 2019 **[184]**	3,420 pts.	Overall survival - *higher hospital volume of care with moderate effect* (HR<1.0: higher hospital volume of care correlating with higher OS)*:* 1) 1–17 resections p.a.: 866 pts.; adjusted HR 1.0 (reference) 2) 18-34 resections p.a.: 1,026 pts.; adjusted HR 0.92, 95% CI 0.78-1.09 3) 35-58 resections p.a.: 753 pts.; adjusted HR 0.88, 95% CI 0.73-1.05 4) ≥59 resections p.a.: 775 pts.; adjusted HR 0.94, 95% CI 0.79-1.12
von Itzstein MS et al., 2020 **[188]**	150,179 pts.	Overall survival - *higher hospital volume of care with moderate effect* (HR<1.0: higher hospital volume of care correlating with higher OS) 1) 1-5 resections p.a.: 7,027 pts.: adjusted HR 1.0 (reference) 2) 6-15 resections p.a.: 17,250 pts.: adjusted HR 0.97, 95% CI 0.87-1.07 3) 16-34 resections p.a.: 35,839 pts.: adjusted HR 0.97, 95% CI 0.88-1.07 4) >34 resections p.a.: 90063 pts.: adjusted HR 0.95, 95% CI 0.87-1.05
Yun et al., 2012 **[67]**	9,094 pts.	Overall survival - *higher hospital volume of care with large effect* (HR<1.0: higher hospital volume of care correlating with higher OS)*:* 1) 1-25 resections p.a.: adjusted HR 0.54, 95% CI 0.47-0.62 2) 26-67 resections p.a.: adjusted HR not stated 3) 67-84 resections p.a.: adjusted HR not stated 4) >84 resections p.a.: adjusted HR 1.0 (reference)

Table 25: Effect results of studies ineligible for meta-analyses on overall survival for PICO 4, subgroup 1 (Hospital volume of care, surgical resection)

Mortality was investigated in 46 observational studies (2,215,968 patients) [127-134, 138-140, 142-144, 147-149, 151, 152, 154-156, 159, 160, 162-165, 167-169, 171, 173-181, 183-187]. Studies applied different mortality-measures, namely *in-hospital mortality* (12 studies; 434,948 patients [128, 143, 147, 149, 151, 155, 156, 159, 167, 171, 173, 185]), *30-day mortality* (31 studies; 1,729,606 patients [127, 129-131, 133, 134, 138-140, 142, 144, 148, 152, 154, 160, 162-165, 168, 169, 171, 175-177, 179-181, 183, 186, 187]), *60-day mortality* (2 studies; 42,843 patients [132, 178]), *90-day mortality* (5 studies; 477,743 patients [138, 162-164, 184]), and *conditional 90-day mortality* (1 study; 124,418 patients [175]).

The effect of higher volume of surgical resections on ***in-house mortality*** was large in nine studies (388,079 patients) [128, 147, 151, 155, 156, 167, 173, 174, 185], small in two studies (26,731 patients) [143, 159] and trivial in one study (20,138 patients) [149].

[quality of evidence for in-house mortality: very low ⊕○○○, rated down for risk of bias -1, indirectness -1, inconsistency -1 and imprecision -1, rated up for large effect +1]

Relating to ***30-day mortality***, we saw large, moderate, small and trivial effects in 20 studies (965,608 patients) [127, 129-131, 139, 148, 152, 154, 160, 162, 163, 165, 169, 171, 175-177, 180, 187], four studies (364,835 patients) [133, 138, 179, 183], four studies (384,345 patients) [140, 144, 164, 168], and three studies (31,135 patients) [142, 181, 186], respectively.

[quality of evidence for *30-day mortality*: very low ⊕○○○, rated down for risk of bias -1, indirectness -1, inconsistency -1 and imprecision -1, rated up for large effect +1]

The effects on ***60-day mortality*** were large (2,084 patients) [178] and moderate (40,754 patients) [132] in one study each.

[quality of evidence for *60-day mortality*: very low ⊕○○○, rated down for indirectness -1, inconsistency -1 and imprecision -1, rated up for large effect +1]

In the context of ***90-day mortality***, there were three studies with a large effect (332,785 patients) [138, 162, 163] as well as one study each with a moderate (139,802 patients) [164] and small effect (3,420 patients) [184], respectively. The impact on ***conditional 90-day mortality*** was large in another study (124,418 patients) [175].

[quality of evidence for *90-day mortality*: very low ⊕○○○, rated down for risk of bias -1, indirectness -1, inconsistency -1 and imprecision -1, rated up for large effect +1]

The effect results for all types of mortality are listed in ***Table 26***.

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 4, subgroup 1: Hospital volume of care, surgical resection		
Mortality		
***In-hospital mortality* – 12 observational studies (434,948 patients)**		
Baum P et al., 2001 **[128]**	36,051 pts.	in-hospital mortality - *higher hospital volume of care with large effect* (OR<1.0: higher hospital volume of care correlating with lower mortality)*:* 1) very low volume hospitals: 7,167 pts.; 286 deaths; in-hospital mortality 4.0%; adjusted OR 1 (reference) 2) low volume hospitals: 7,078 pts.; 245 deaths; in-hospital mortality 3.5%; adjusted OR 0.81, 95% CI 0.62-1.00 3) medium volume hospitals: 7,088 pts.; 193 deaths; in-hospital mortality 2.7%; adjusted OR 0.77, 95% CI 0.62-0.96 4) high volume hospitals: 7,122 pts.; 179 deaths; in-hospital mortality 2.5%; adjusted OR 0.53, 95% CI 0.42-0.66 5) very high volume hospitals: 7,596 pts.; 159 deaths; in-hospital mortality 2.1%; adjusted OR 0.58, 95% CI 0.46-0.72

Finlayson EV et al., 2013 (Arch Surg) **[143]**	21,890 pts.	in-hospital mortality – *higher hospital volume of care with small effect:* Lobectomy 1) <19 resections p.a.: in-hospital mortality 4.3% 2) 19-37 resections p.a.: in-hospital mortality 2.9% 3) >37 resections p.a.: in-hospital-day mortality 3.5% Pneumonectomy 1) <19 resections p.a.: in-hospital mortality 10.6% 2) 19-37 resections p.a.: in-hospital mortality 10.1% 3) >37 resections p.a.: in-hospital mortality 8.9%
Hadaya J et al., 2020 **[147]**	22,739 pts.	in-hospital mortality - *higher hospital volume of care with large effect* (***cave:*** highest hospital volume stratum as reference - OR>1.0: ***lower*** hospital volume of care correlating with ***lower*** mortality)*:* 1) low volume hospitals: 5,928 pts.; in-hospital mortality 9%; adjusted OR 1.74, 95% CI 1.14-2.66 2) medium volume hospitals: 4,704 pts.; in-hospital mortality 7.3%; adjusted OR 1.38, 95% CI 0.90-2.11 3) high volume hospitals: 5,830 pts.; in-hospital mortality 6.6%; adjusted OR 1.31, 95% CI 0.88-1.93 4) very high volume hospitals: 6,277 pts.; in-hospital mortality 5.3%, ***adjusted OR 1.0 (reference)***
Harrison S et al., 2018 **[149]**	12,698 pts.	in-hospital mortality - *higher hospital volume of care with trivial effect* (***cave:*** highest hospital volume stratum as reference - OR>1.0: ***lower*** hospital volume of care correlating with ***lower*** mortality)*:* 1) 1-39 resections p.a.: 6,349 pts.; in-hospital mortality 134 deaths (2.1%); adjusted OR 1.0 (reference) 2) ≥40 resections p.a.: 6,349 pts.; in-hospital mortality 113 deaths (1.8%); adjusted OR 0.84, 95% CI 0.65-1.08
Hoffmann H et al., 2019 **[151]**	114,818 pts.	in-hospital mortality - *higher hospital volume of care with large effect* (***cave:*** highest hospital volume stratum as reference - OR>1.0: ***lower*** hospital volume of care correlating with ***lower*** mortality)*:* 1) 1-25 resections p.a.: 17,166 pts.; in-hospital mortality 920 deaths (5.36%); unadjusted OR 2.3, 95% CI 2.07-2.55 2) 26-50 resections p.a.: 19,269 pts.; in-hospital mortality 871 deaths (4.52%); unadjusted OR 1.92, 95% CI 1.73-2.13 3) 51-74 resections p.a.: 14,045 pts.; in-hospital mortality 526 deaths (3.75%); unadjusted OR 1.58, 95% CI 1.4-1.78

		4) 75-100 resections p.a.: 14,659 pts.; in-hospital mortality 476 deaths (3.25%); unadjusted OR 1.36, 95% CI 1.21-1.53 5) 101-175 resections p.a.: 22,508 pts.; in-hospital mortality 841 deaths (3.60%); unadjusted OR 1.51, 95% CI 1.36-1.68 6) >175 resections p.a.: 26,330 pts.; in-hospital mortality 634 deaths (2.41%); ***unadjusted OR 1.0 (reference)***
Kozower BD et al., 2011 **[155]**	40,460 pts.	in-hospital mortality - *higher hospital volume of care with large effect* (***cave:*** highest hospital volume stratum as reference - OR>1.0: ***lower*** hospital volume of care correlating with ***lower*** mortality)*:* 1) 1-2 resections p.a.: 1,051 pts.; adjusted OR 3.52, 95% CI 0.92-13.52 2) 3-6 resections p.a.: 1,823 pts.; adjusted OR 0.85, 95% CI 0.23-3.14 3) 7-12 resections p.a.: 3,990 pts.; adjusted OR 0.82, 95% CI 0.20-3.30 4) 13-23 resections p.a.: 7,632 pts.; adjusted OR 0.37, 95% CI 0.10-1.41 3) ≥24 resections p.a.: 25,964 pts.; ***adjusted OR 1 (reference)***
Kunisawa S et al., 2014 **[167]**	7,064 pts.	in-hospital mortality - *higher hospital volume of care with large effect:* 1) 1-29 resections p.a.: 792 pts.; in-hospital mortality 29 deaths (3.7%), unadjusted OR 1.0 (reference) 2) ≥30 resections p.a.: 2587 pts.; in-hospital mortality 52 deaths (2.0%), unadjusted OR 0.54, 95% CI 0.34-0.85
Learn PA et al., 2010 **[156]**	62,628 pts.	in-hospital mortality - *higher hospital volume of care with large effect* (OR<1.0: higher hospital volume of care ***as continuous variable*** correlating with lower mortality)*:* 1) 1-16 resections p.a.: 19,067 pts. 2) 17-33 resections p.a.: 18,423 pts. 3) >33 resections p.a.: 25,222 pts. ***continuous adjusted OR per case*** 0.996, 95% CI 0.994-0.998
Lien YC et al., 2007 **[159]**	4,841 pts.	in-hospital mortality - *higher hospital volume of care with small effect* (OR<1.0: higher hospital volume of care correlating with lower mortality)*:* 1) 1-135 resections p.a.: 1,601 pts.; 26 deaths (1.6%); unadjusted OR 1.0 (reference) 2) 136-467 resections p.a.: 1,623 pts.; 19 deaths (1.2%); unadjusted OR 0.72, 95% CI 0.40-1.30 3) ≥468 resections p.a.: 1,617 pts.; 18 deaths (1.1%); unadjusted OR 0.68, 95% CI 0.37-1.25

Otake H et al., 2011 **[173]**	19,831 pts.	in-hospital mortality - *higher hospital volume of care with large effect* (OR<1.0: higher hospital volume of care correlating with lower mortality)*:* 1) 1-24 resections p.a.: 5,013 pts.; adjusted HR 1.0 (reference) 2) 25-43 resections p.a.: 5,127 pts.; adjusted HR 0.68, 95% CI 0.43-1.08 3) 44-67 resections p.a.; 4,856 pts.; adjusted HR 0.82, 95% CI 0.53-1.28 4) ≥68 resections p.a.; 4,835 pts.; adjusted HR 0.60, 95% CI 0.36-0.99
Pages PB et al., 2016 **[174]**	76,235 pts.	In-hospital mortality- *higher hospital volume of care with large effect (**cave:*** highest hospital volume stratum as reference - OR>1.0: ***lower*** hospital volume of care correlating with ***lower*** mortality)*:* 1) 1-13 resections p.a.: 4,151 pts.; in-hospital mortality 218 deaths (5.15%); adjusted HR 1.5, 95% CI 1.2-1.8 2) 13-43 resections p.a.: 14,868 pts.; in-hospital mortality 610 deaths (4%); adjusted HR 1.1, 95% CI 0.94-1.3 3) >43 (n=71): 57,216 pts.; in-hospital mortality 2,147 deaths (3.75%); ***adjusted HR 1.0 (reference)***
Tchouta LN et al., 2017 **[185]**	8,523 pts.	in-hospital mortality - *higher hospital volume of care with large effect* (OR<1.0: higher hospital volume of care correlating with lower mortality)*:* 1) 1-3 resections p.a.: 2,373 pts.; in-hospital mortality 1.9%; adjusted OR 1.0 (reference) 2) 4-6 resections p.a.: in-hospital mortality 0.8%; adjusted OR 0.474, 95% CI 0.262-0.857 3) 7-14 resections p.a.: in-hospital mortality 2.1% 4) ≥15 resections p.a.: 1,890 pts.; in-hospital mortality 0.5%; adjusted OR 0.134, 95% CI 0.051-0.353
30-day mortality **– 31 observational studies (1,729,606 patients)**		
Bach PB et al. **[127]**	2,118 pts.	30-day mortality - *higher hospital volume of care with large effect* (OR<1.0: higher hospital volume of care correlating with lower mortality)*:* 1) 1–8 resections p.a.: 407 pts.; 6; adjusted OR 1.0 (reference) 2) 9–14 resections p.a.: 466. pts.; 6%; adjusted OR 0.86 3) 15–19 resections p.a.: 407 pts.; 4%; adjusted OR 0.50 4) 20–66 resections p.a.: 457 pts.; 3%; adjusted OR 0.48 5) 67–100 resections p.a.: 381 pts.; 3%; adjusted OR 0.48 (95% CI not stated)
Begg CB et al., 1998 **[129]**	1,375 pts.	30-day mortality – *higher hospital volume of care with large effect:* 1) 1–5 resections p.a.: 484 pts.; 30-day mortality 13.8% (95% CI 10.9-17.2%) 2) 6–10 resections p.a.: 453 pts.; 30-day mortality 14.1% (95% CI not stated) 3) ≥11 resections p.a.: 438 pts.; 30-day mortality 10.7% (95% CI 8.0-14.0%)

Bernand A et al., 2018 **[130]**	108,571 pts.	30-day mortality - *higher hospital volume of care with large effect* (OR<1.0: higher hospital volume of care correlating with lower mortality)*:* 1) 1–10 resections p.a.: 2,495 pts.; 30-day mortality 5.2%; 1.0 (reference) 2) 11-15 resections p.a.: 2,304 pts.; 30-day mortality 4%; adjusted OR 0.84, 95% CI 0.6-1.20 3) 16-35 resections p.a.: 12,881 pts.; 30-day mortality 4%; adjusted OR 0.73, 95% CI 0.57-0.94 4) 36-70 resections p.a.: 24,397 pts.; 30-day mortality 3.5%; adjusted OR 0.71, 95% CI 0.55-0.90 5) >70 resections p.a.: 66,044 pts.; 30-day mortality 3.5%; adjusted OR 0.65, 95% CI 0.5-0.84
Bernard A. et al., 2019 **[131]**	10,675 pts.	30-day mortality - *higher hospital volume of care with large effect:* 1) 1–14 resections p.a.: 320 pts.; 30-day mortality 3-4%: 100% of hospitals 2) 15-39 resections p.a.: 2,264 pts.; 30-day mortality <3%: 7% of hospitals, 3-4%: approx. 78-83% of hospitals, >4%: approx. 10-15% of hospitals 3) >39 resections p.a.: 8,091 pts.; 30-day mortality rate <3%: 20% of hospitals, 3-4%: approx. 60-65% of hospitals, >4%: approx. 15-20% of hospitals
Birkmeyer JD et al., 2003 **[133]**	24,092 pts.	30-day mortality - *higher hospital volume of care with moderate effect (**cave:*** highest hospital volume stratum as reference - OR>1.0: ***lower*** hospital volume of care correlating with ***lower*** mortality)*:* 1) 1–16 resections p.a.: adjusted OR 1 (reference) 2) 17-35.5 resections p.a.: adjusted OR not stated 3) >35.5 resections p.a.: adjusted OR 0.82, 95% CI 0.69-0.96
Birkmeyer JD et al., 2006 **[134]**	49,280 pts.	30-day mortality - *higher hospital volume of care with small effect (**cave:*** highest hospital volume stratum as reference - OR>1.0: ***lower*** hospital volume of care correlating with ***lower*** mortality)*:* 1) very low volume hospitals- lowest 20th (1965 hospitals): 9,838 pts.; 5.9%; adjusted OR OR 1.0 (reference) 2) low volume hospitals: 10,420 pts.; 5.1%; adjusted OR not stated 3) medium volume hospitals: 10,339 pts.; 4.9%; adjusted OR not stated 4) high volume hospitals: 10,116 pts.; 5.1%; adjusted OR not stated 5) very high volume hospitals - highest 20th (72 hospitals): 8,507 pts.; 5.0%; adjusted 0.85, 95% CI 0.72-1.00
Cheung MC et al., 2009 **[138]**	13,469 pts.	30-day mortality - *higher hospital volume of care with moderate effect:* 1) low volume hospitals: 8,871 pts.; 30-day mortality 2.7% 2) high-volume hospitals: 4,598 pts.; 30-day mortality 1.6%, p<0.001

Committee for Scientific Affairs, 2007 **[139]**	94,854 pts.	30-day mortality - *higher hospital volume of care with large effect, no adjusted ORs stated (**cave:*** highest hospital volume stratum as reference - OR>1.0: ***lower*** hospital volume of care correlating with ***lower*** mortality)*:* 1) 1-9 resections p.a.: 3,011 pts.; 30-day mortality 1.96%; unadjusted OR 4.94, 95% CI 3.10-7.86 2) 10-24 resections p.a.: 15,025 pts.; 30-day mortality 0.95%; unadjusted OR 3.41, 95% CI 1.85-6.26 3) 25-49 resections p.a.: 29,745 pts.; 30-day mortality 0.60%; unadjusted OR 2.25, 95% CI 1.56-3.25 4) 50-74 resections p.a.: 17,680 pts.; 30-day mortality 0.63%; unadjusted OR 2.11, 95% CI 1.39-3.20 5) 75-99 resections p.a.: 13,995 pts.; 30-day mortality 0.52%; unadjusted OR 1.77, 95% CI 1.05-2.96 5) 100-149 resections p.a.: 10,236 pts.; 30-day mortality 0.73%; unadjusted OR 2.32, 95% CI 1.43-3.78 6) ≥ 150 resections p.a.: 3,011 pts.; 30-day mortality 0.26%; ***unadjusted OR 1.0 (reference)***
Damhuis RA et al., 2015 **[140]**	9,579 pts.	30-day mortality - *higher hospital volume of care with small effect* (OR<1.0: higher hospital volume of care correlating with lower mortality)*:* 1) 1-19 resections p.a.: 2,778 pts.; 30-day mortality 3.1%; adjusted OR 1.0 (reference) 2) 20-49 resections p.a.: 4,694 pts.; 30-day mortality 2.5%; adjusted OR 0.86, 95% CI 0.65-1.15 3) >49 resections p.a.: 2,107 pts.; 30-day mortality 2.5%; adjusted OR 0.87, 95% CI 0.61-1.24
Falcoz PE et al., 2017 **[142]**	20,640 pts.	30-day mortality - *higher hospital volume of care with trivial effect:* no statistically significant variation of 30-day mortality for hospital volume (mean annual hospital volume: 98)
Freixinet JL et al., 2006 **[144]**	2,994 pts.	30-day mortality - *higher hospital volume of care with small effect* (OR<1.0: higher hospital volume of care correlating with lower mortality)*:* 1) 1-43 resections p.a.; 565 pts; 30-day mortality 7.6%; adjusted OR 1.0 (reference) 2) 44-54 resections p.a.; 1,044 pts.; 30-day mortality 6.6%; adjusted OR 0.89, 95% CI 0.71-1.13 3) >54 resections p.a.; 1,386 pts.; 30-day mortality 6.7%; adjusted OR 1.04, 95% CI 0.83-1.31

Hannan EL et al., 2002 **[148]**	6,954 pts.	30-day mortality - *higher hospital volume of care with large effect (**cave:*** highest hospital volume stratum as reference - ***risk-adjusted rate*** >0: ***lower*** hospital volume of care correlating with ***higher*** mortality)*:* 1) 1-37 resections p.a.: 1,672 pts; 30-day mortality 3.05; risk-adjusted rate 1.65 2) 38-114 resections p.a.: 1,781 pts; 30-day mortality 2.13; risk-adjusted rate 0.82 3) 115-168 resections p.a.: 1,665 pts; 30-day mortality 1.44; risk-adjusted rate 0.34 4) ≥169 resections p.a.: 1,836 pts; 30-day mortality 0.87; ***risk-adjusted rate 0 (reference)***
Hollenbeck BK et al., 2007 **[152]**	8,183 pts.	30-day mortality (Medicare) - *higher hospital volume of care with large effect **risk-adjusted rate** t:* 1) low volume hospitals: 3,396 pts.; adjusted OR 1.48, 95% CI 1.13-1.94 2) medium volume hospitals: 2,513 pts.; adjusted OR not stated 3) high volume hospitals: 2,274 pts.; adjusted OR 1.0 (reference) 30-day mortality (SEER) - *higher hospital volume of care with large effect:* 1) low volume hospitals: 2,735 pts.; adjusted OR 1.32, 95% CI 1.07-1.71 2) medium volume hospitals: 2,723 pts.; adjusted OR not stated 3) high volume hospitals: 2,725 pts.; adjusted OR 1 (reference)
Khuri SF et al., 1999 **[165]**	4,890 pts.	30-day mortality (Medicare) - *higher hospital volume of care with large effect:* 1) 0-5 resections p.a.: 30-day mortality 7.16±19.1% 2) 6-7 resections p.a.: 30-day mortality 5.0±4.9% 3) 8-13 resections p.a.: 30-day mortality 6.3±3.2% 4) 14-44 resections p.a.: 30-day mortality 5.2±3.0%
Kim SY et al., 2010 **[154]**	987 pts.	30-day mortality (Medicare) - *higher hospital volume of care with large effect (**cave:*** highest hospital volume stratum as reference - OR>1.0: ***lower*** hospital volume of care correlating with ***lower*** mortality)*:* 1) 1-4 resections p.a.: 343 pts.; 30-day mortality 2.92%; adjusted OR 3.48; 95% CI 1.0-approx. 13.1 2) 5-20 resections p.a.: 337 pts.; 30-day mortality 2.67%; adjusted OR not stated 3) >20 resections p.a.: 307 pts.; pts.; 30-day mortality 0.98%; ***adjusted OR 1.0 (reference)***
Little AG et al., 2005 **[160]**	40,090 pts.	30-day mortality - *higher hospital volume of care with large effect:* 1) 1-90 resections p.a.: 30-day mortality 4.8% 2) >90 resections p.a.: 30-day mortality 3.2%, p=0.037

Moller H et al., 2016 **[162]**	15,737 pts.	30-day mortality - *higher hospital volume of care with large effect* (OR<1.0: higher hospital volume of care correlating with lower mortality)*:* 1) 1-75 resections p.a.: 3,190 pts.; 30-day mortality 33 deaths (1.0%); adjusted OR 1.0 (reference) 2) 77-112 resections p.a.: 3,230 pts.; 30-day mortality 42 deaths (1.3%); adjusted OR 1.26, 95% CI 0.75-2.11 3) 114-155 resections p.a.: 3,026 pts.; 30-day mortality 24 deaths (0.8%); adjusted OR 0.77, 95% CI 0.43-1.38 4) 156-186 resections p.a.: 3,189 pts.; 30-day mortality 29 deaths (0.9%); adjusted OR 0.84, 95% CI 0.47-1.50 5) 189-287 resections p.a.: 3,103 pts.; 30-day mortality 17 deaths (0.5%); adjusted OR 0.50, 95% CI 0.25-1.01
Moore CB et al., 2019 **[163]**	303,579 pts.	30-day mortality - *higher hospital volume of care with large effect* (OR<1.0: higher hospital volume of care correlating with lower mortality)*:* 1) 1-3 resections p.a.: 1,627 pts.; 30-day mortality 5.5%; adjusted OR 1.0 (reference) 2) 4-9 resections p.a.: 11,840 pts.; 30-day mortality 4.0%; adjusted OR 0.79, 95% CI 0.61-1.02 3) 10-20 resections p.a.: 45,877 pts.; 30-day mortality 3.5%; adjusted OR 0.75, 95% CI 0.58-0.96 4) >20 resections p.a.: 244,325 pts.; 30-day mortality 2.8%; adjusted OR 0.68, 95% CI 0.53-0.88
Mulvihill MS et al., 2018 **[164]**	139,802 pts.	30-day mortality - *higher hospital volume of care with small effect:* 1) Bottom 25th percentile volume hospitals: 13,284 pts.; 30-day mortality 315 deaths (2.7%) 2) 25-50th percentile volume hospitals: 34,092 pts.; 30-day mortality 682 deaths (2,3%) 3) 50-75th percentile volume hospitals: 44,126 pts.; 30-day mortality 896 deaths (2.3%) 4) Top 25th percentile volume hospitals: 52,850 pts.; 30-day mortality 859 deaths (1.9%)
Nagayasu T et al., 2016 **[168]**	211,619 pts.	30-day mortality - *higher hospital volume of care with small effect* (OR<1.0: higher hospital volume of care correlating with lower mortality)*:* 1) 1-49 resections p.a.; 59,526 pts; 30-day mortality 290 deaths (0,49%); adjusted OR 1.0 (reference) 2) ≥50 resections p.a.; 152,093 pts.; 30-day mortality 551 deaths 0.36%); adjusted OR 0.856, 95% CI 0.732-1.001

Nathan H et al., 2015 **[169]**	10,151 pts.	30-day mortality - *higher hospital volume of care with large effect:* 1) 1-7 resections p.a.: 30-day mortality 3.6% 2) 8-16 resections p.a.: 30-day mortality 3.1% 3) 17-99 resections p.a.: 30-day mortality 1.9%
Osada H et al., 2007 **[171]**	72,217 pts.	30-day mortality - *higher hospital volume of care with large effect(**cave:** highest hospital volume stratum as reference - OR>1.0: **lower** hospital volume of care correlating with **lower** mortality) :* 1) 1-24 resections p.a.: 13,572 pts.; adjusted OR 1.4300, 95% CI 0.9557- 2.1397 2) 25–49 resections p.a.: 23,275 pts.; adjusted OR 1.1062, 95% CI 0.7461-1.6399 3) 50–99 resections p.a.: 23,737 pts.; adjusted OR 1.0809, 95% CI 0.7121-1.6406 4) ≥100 resections p.a.: 11,633 pts.; ***adjusted OR 1.0 (reference)***
Pezzi CM et al., 2014 **[175]**	124,418 pts.	30-day mortality - *higher hospital volume of care with large effect (**cave:** highest hospital volume stratum as reference - OR>1.0: **lower** hospital volume of care correlating with **lower** mortality):* 1) 0-9 resections p.a.: 10,860 pts.; 30-day mortality 404 deaths (3.7%); adjusted OR 2.1, 95% CI 1.7-2.6 2) 10-29 resections p.a.: 43,409 pts.; 30-day mortality 1,363 deaths (3.1%); adjusted OR 1.7, 95% CI 1.4-2.1 3) 30-89 resections p.a.: 53,155 pts.; 30-day mortality 1,384 deaths (2.6%); adjusted OR 1.4, 95% CI 1.1-1.7 4) ≥90 resections p.a.: 13,675 pts.; 30-day mortality 238 deaths (1.7%); ***adjusted OR 1.0 (reference)***
Romano PS et al., 1992 **[176]**	12,439 pts.	30-day mortality - *higher hospital volume of care with large effect* (OR<1.0: higher hospital volume of care correlating with lower mortality)*:* 1) 0-8 resections p.a.: 143 deaths (5.5%); adjusted OR 1.0 (reference) 2) 9-16 resections p.a.: 120 deaths (4.1%); adjusted OR 0.7, 95% CI 0.6-1.0 3) 17-24 resections p.a.: 90 deaths (3.5%); adjusted OR 0.6, 95% CI 0.5-0.8 4) >24 resections p.a.: 89 deaths (3.2%); adjusted OR 0.6, 95% CI 0.4-0.8
Sakata R et al., 2012 **[177]**	128,848 pts.	30-day mortality - *higher hospital volume of care with large effect (**cave:** highest hospital volume stratum as reference - OR>1.0: **lower** hospital volume of care correlating with **lower** mortality):* 1) 1-9 resections p.a.: 2,555 pts.; 30-day mortality 2.58%; adjusted OR 4.09, 95% CI 2.39-7.02 2) 10-24 resections p.a.: 14,023 pts.; 30-day mortality 0.53%; adjusted OR 1.79, 95% CI 1.24-2.60 3) 25-49 resections p.a.: 30,711 pts.; 30-day mortality 0.53%; adjusted OR 1.85, 95% CI 1.33-2.56 4) 50-74 resections p.a.: 26,448 pts.; 30-day mortality 0.42%; adjusted OR 1.49, 95% CI 1.07-2.09

		5) 75-99 resections p.a.: 19,580 pts.; 30-day mortality 0.40%; adjusted OR 1.38, 95% CI 0.96-2.00 6) 100-149 resections p.a.: 17,373 pts.; 30-day mortality 0.4%; adjusted OR 1.52, 95% CI 1.00-2.30 7) ≥150 resections p.a.: 18,159 pts.; 30-day mortality 0.29%; ***adjusted OR 1.0 (reference)***
Sheetz KH et al., 2019 **[179]**	322,879 pts.	30-day mortality - *higher hospital volume of care with moderate effect* (OR<1.0: higher hospital volume of care correlating with lower mortality) 1) lowest volume hospitals – median 14 resections p.a. (IQR 9-18): 30-day mortality 3.0%; adjusted OR 1.0 (reference) 2) highest volume hospitals – median 178 resections p.a. (IQR 135-279): 30-day mortality 2.3%; adjusted OR 0.76, 95% CI 0.62-0.94
Simunovic M et al., 2006 **[180]**	2,698 pts.	30-day mortality - *higher hospital volume of care with large (**cave:*** highest hospital volume stratum as reference - OR>1.0: ***lower*** hospital volume of care correlating with ***lower*** mortality)*:* 1) 1-32 resections per 3 years: 653 pts.; 30-day mortality 5.8%; adjusted OR 2.2, 95% CI 0.8–5.6 2) 32-85 resections per 3 years: 730 pts.; 30-day mortality 5.9; adjusted OR not stated 3) 86-130 resections per 3 years: 644 pts.; 30-day mortality 3.7%; ***adjusted OR not stated*** 4) ≥131 resections per years: 671 pts.; 30-day mortality 2.4%; ***adjusted OR 1.0 (reference)***
Sioris T et al., 2008 **[181]**	5,339 pts.	30-day mortality - *higher hospital volume of care with trivial effect (**cave:*** highest hospital volume stratum as reference - OR>1.0: ***lower*** hospital volume of care correlating with ***lower*** mortality)*:* 1) 0-4 resections p.a.: 334 pts.; adjusted OR not significant (exact OR not stated) 2) 5-10 resections p.a.: 840 pts.; adjusted HR not significant (exact OR not stated) 3) 11-20 resections p.a.: 1,102 pts.; adjusted HR not significant (exact OR not stated) 4) >20 resections p.a.: 2,602 pts.; adjusted HR 1.0 (reference)
Strand TE et al., 2007 **[183]**	4,395 pts.	30-day mortality - *higher hospital volume of care with moderate effect* (OR<1.0: higher hospital volume of care correlating with lower mortality)*:* 1) 1-19 resections p.a.: 1,476 pts.; 30-day mortality 77 deaths (5.2%); adjusted OR 1.0 (reference) 2) ≥20 resections p.a.: 2,919 pts.; 30-day mortality 116 deaths (4.0%); adjusted OR 0.75, 95% CI 0.56-1.00

Urbach DR et al., 2003 **[186]**	5,156 pts.	30-day mortality - *higher hospital volume of care with trivial effect (**cave:** highest hospital volume stratum as reference - OR>1.0: **lower** hospital volume of care correlating with **lower** mortality)*: 1) quartile 1 – mean 18.2 resections p.a.: 1,442 pts.; 65 deaths (4.5%); adjusted OR 1.2, 95% CI 0.8-1.7 2) quartile 2 – mean 45.0 resections p.a.: 1,155 pts.; 61 deaths (5.3%); adjusted OR 1.8, 95% CI 1.2-2.8 3) quartile 3 – mean 86.0 resections p.a.: 1,439 pts.; 40 deaths (2.8%); adjusted OR 1.0, 95% CI 0.7-1.5 4) quartile 4 – mean 129.4 resections p.a.: 1,120 pts.; 49 deaths (4.4%); ***adjusted OR 1.0 (reference)***
Urbach DR et al., 2004 **[187]**	5,156 pts.	30-day mortality - *higher hospital volume of care with large effect* (OR<1.0: higher hospital volume of care correlating with lower mortality)*:* 1) <45 resections p.a.: 2,597 pts.; 30-day mortality 126 deaths (4.85%); adjusted OR 1.0 (reference) 2) >45 resections p.a.: 2,559 pts.; 30-day mortality 89 deaths (3.48); adjusted OR 0.64, 95% CI 0.44-0.94
***60-day mortality* – 2 observational studies (42,843 patients)**		
Bilimoria KY et al., 2008 **[132]**	40,754 pts.	60-day mortality - *higher hospital volume of care with moderate effect* (OR<1.0: higher hospital volume of care correlating with lower mortality)*:* 1) 1–20 resections p.a.: 60-day mortality 6.4%; adjusted HR 1.0 (reference) 2-4) 21–83 resections p.a.: 60-day mortality 6.1%; adjusted HR not stated 5) >83 resections p.a.: 60-day mortality 5.5%; adjusted HR 0.76, 95% CI 0.66-0.83
Schillemans V et al., 2019 **[178]**	2,084 pts.	60-day mortality - *higher hospital volume of care with large effect:* 1) 1-9 resections p.a.: 354 pts.; 60-day mortality 5.6% 2) ≥10 resections p.a.: 1,730 pts.; 60-day mortality 3.5%
***90-day mortality* – 5 observational studies (477,743 patients)**		
Cheung MC et al., 2009 **[138]**	13,469 pts.	90-day mortality - *higher hospital volume of care with large effect:* 1) low volume hospitals: 8,871 pts.; 90-day mortality 7.5% 2) high-volume hospitals: 4,598 pts.; 90-day mortality 4.0%
Moller H et al., 2016 **[162]**	15,737 pts.	90-day mortality - *higher hospital volume of care with large effect* (OR<1.0: higher hospital volume of care correlating with lower mortality)*:* 1) 1-75 resections p.a.: 3,190 pts.; 90-day mortality 98 deaths (3.1%); adjusted OR 1.0 (reference) 2) 77-112 resections p.a.: 3,230 pts.; 90-day mortality 111 deaths (3.4%); adjusted OR 1.15, 95% CI 0.85-1.56 3) 114-155 resections p.a.: 3,026 pts.; 90-day mortality 72 deaths (2.4%); adjusted OR 0.79, 95% CI 0.56-1.11

		4) 156-186 resections p.a.: 3,189 pts.; 90-day mortality 95 deaths (3.0%); adjusted OR 0.95, 95% CI 0.68-1.31 5) 189-287 resections p.a.: 3,103 pts.; 90-day mortality 67 deaths (2.2%); adjusted OR 0.67, 95% CI 0.46-0.96
Moore CB et al., 2019 **[163]**	303,579 pts.	90-day mortality - *higher hospital volume of care with large effect* (OR<1.0: higher hospital volume of care correlating with lower mortality)*:* 1) 1-3 resections p.a.: 1,622 pts.; 90-day mortality 9%; adjusted OR 1.0 (reference) 2) 4-9 resections p.a.: 11,787 pts.; 90-day mortality 7%; adjusted OR 0.85, 95% CI 0.69-1.04 3) 10-20 resections p.a.: 45,647 pts.; 90-day mortality 6.6%; adjusted OR 0.86, 95% CI 0.70-1.06 4) >20 resections p.a.: 242,821 pts.; 90-day mortality 5.4%; adjusted OR 0.77, 95% CI 0.63-0.95
Mulvihill MS et al., 2018 **[164]**	139,802 pts.	90-day mortality - *higher hospital volume of care with moderate effect:* 1) Bottom 25th volume hospitals: 13,284 pts.; 30-day mortality 522 deaths (4.8%) 2) 25-50th percentile volume hospitals: 34,092 pts.; 30-day mortality 1,222 deaths (4.1%) 3) 50-75th percentile volume hospitals: 44,126 pts.; 30-day mortality 1,562 deaths (4.1%) 4) Top 25th percentile volume hospitals: 52,850 pts.; 30-day mortality 1,629 deaths (3.5%)
Thai AA et al., 2019 **[184]**	3,420 pts.	90-day mortality - *higher hospital volume of care with small effect* (OR<1.0: higher hospital volume of care correlating with lower mortality)*:* 1) 1–17 resections p.a.: 866 pts.; 34 deaths (3,9%); adjusted OR 1.0 (reference) 2) 18-34 resections p.a.: 1,026 pts.; 38 deaths (3,7%); adjusted OR 0.93, 95% CI 0.57-1.56 3) 35-58 resections p.a.: 753 pts.; 24 deaths (3,2%); adjusted HR 0.83, 95% CI 0.48-1.42 4) ≥59 resections p.a.: 775 pts.; 24 deaths (3,1%); adjusted HR 0.82, 95% CI 0.47-1.40

***conditional 90-day mortality* – 1 observational study (124,418 patients)**		
Pezzi CM et al., 2014 **[175]**	124,418 pts.	conditional 90-day mortality - *higher hospital volume of care with large effect (**cave:** highest hospital volume stratum as reference - OR>1.0: **lower** hospital volume of care correlating with **lower** mortality):* 1) 0-9 resections p.a.: 10,278 pts.; conditional 90-day mortality 303 deaths (2.9%); adjusted HR 1.3, 95% CI 1.1-1.6 2) 10-29 resections p.a.: 41,035 pts.; conditional 90-day mortality 1,146 deaths (2.8%); adjusted HR 1.2, 95% CI 1.0-1.4 3) 30-89 resections p.a.: 50,165 pts.; conditional 90-day mortality 1,238 deaths (2.4%); adjusted HR 1.0, 95% CI 0.9-1.2 4) ≥90 resections p.a.: 12,977 pts.; conditional 90-day mortality 281 deaths (2.2%); ***adjusted HR 1.0 (reference)***

Table 26: Effect results of studies ineligible for meta-analyses on different types of mortality for PICO 4, subgroup 1 (Hospital volume of care, surgical resection)

Seven studies investigated various aspects of ***morbidity*** (75,972 patients) [127, 140, 144, 147, 149, 169, 185].

Observed effects on specific types of morbidities ranged from large in one study (2,118 patients) over trivial-moderate in one study (22,739 patients) [147] and trivial-small in two studies (28,391 patients) [149, 185] to trivial in three studies (22,724 patients) [140, 144, 169] (see effect results in ***Table 27***).

[quality of evidence for *morbidity*: very low ⊕◯◯◯, rated down for risk of bias -1, indirectness -1, inconsistency -1 and imprecision -1]

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 4, subgroup 1: Hospital volume of care, surgical resection		
***Morbidity* – 7 observational studies (75,972 patients)**		
Bach PB et al., 2001 **[127]**	2,118 pts.	Morbidity (operative) - *higher hospital volume of care with large effect:* -1–8 resections p.a.: 407 pts.; operative 122 pts. (30%) -9–14 resections p.a.: 466. pts.; operative 74 pts. (16%) -15–19 resections p.a.: 407 pts.; operative 84 pts. (21%) -20–66 resections p.a.: 457 pts.; operative 76 pts. (17%) -67–100 resections p.a.: 381 pts.; operative 53 pts. (14%) Morbidity (pulmonary) - *higher hospital volume of care with large effect:* -1–8 resections p.a.: 407 pts.; pulmonary 112 pts. (28%)

		-9–14 resections p.a.: 466. pts.; pulmonary 86 pts. (18%) -15–19 resections p.a.: 407 pts.; pulmonary 82 pts. (20%) -20–66 resections p.a.: 457 pts.; pulmonary 92 pts. (20%) -67–100 resections p.a.: 381 pts.; pulmonary 48% (13%) Morbidity (any) - *higher hospital volume of care with large effect:* -1–8 resections p.a.: 407 pts.; any 181 pts. (44%) -9–14 resections p.a.: 466. pts.; any 131 pts. (28%) -15–19 resections p.a.: 407 pts.; any 145 pts. (32%) -20–66 resections p.a.: 457 pts.; any 145 pts. (32%) -67–100 resections p.a.: 381 pts.; any 78 pts. (20%)
Damhuis RA et al., 2015 **[140]**	9,579 pts.	Morbidity (major) - *higher hospital volume of care with trivial effect:* correlation of hospital volume and major morbidity rate presented only as Funnel plot
Freixinet JL et al., 2006 **[144]**	2,994 pts.	Morbidity (general) - *higher hospital volume of care with trivial effect:* 1) 1-43 resections p.a.: 565 pts; general morbidity 197 pts. (34.9%) 2) 44-54 resections p.a.: 1,044 pts.; general morbidity 376 pts. (36%) 3) >54 resections p.a.: 1,386 pts.; general morbidity 484 pts. (34.9%), p=n.s.
Hadaya J et al., 2020 **[147]**	22,739 pts.	Morbidity (any) - *higher hospital volume of care with moderate effect (**cave:*** highest hospital volume stratum as reference - OR>1.0: ***lower*** hospital volume of care correlating with ***lower*** morbidity)*:* 1) low volume hospitals– median 13 resections p.a., IQR 9-18: 5,928 pts.; any morbidity 46.5%; adjusted OR 1.16, 95% CI 0.84-1.60 2) medium volume hospitals: 4,704 pts.; any morbidity 40.2%; adjusted OR 0.93, 95% CI 0.69-1.27 3) high volume hospitals: 5,830 pts.; any morbidity 36.0%; adjusted OR 0.77, 95% CI 0.58-1.03 4) very high volume hospitals– median 130 resections p.a., IQR 100-210: 6,277 pts.; any morbidity 39.3%, ***adjusted OR 1.0 (reference)*** Morbidity (neurologic) - *higher hospital volume of care with trivial effect (**cave:*** highest hospital volume stratum as reference - OR>1.0: ***lower*** hospital volume of care correlating with ***lower*** morbidity)*:* 1) low volume hospitals– median 13 resections p.a., IQR 9-18: 5,928 pts.; neurologic morbidity 2.1%; adjusted OR 1.34, 95% CI 0.58-3.10 2) medium volume hospitals: 4,704 pts.; neurologic morbidity 1.2%; adjusted OR 0.93, 95% CI 0.38-2.26 3) high volume hospitals: 5,830 pts.; neurologic morbidity 1.2%; adjusted OR 0.67, 95% CI 0.30-1.50

4) very high volume hospitals – median 130 resections p.a., IQR 100-210: 6,277 pts.; neurologic morbidity 1.3%, ***adjusted OR 1.0 (reference)***

Morbidity (cardiovascular) - *higher hospital volume of care with small effect (**cave:*** highest hospital volume stratum as reference - OR>1.0: ***lower*** hospital volume of care correlating with ***lower*** morbidity)*:*
1) low volume hospitals – median resections p.a. 13, IQR 9-18: 5,928 pts.; cardiovascular morbidity 31.7%; adjusted OR 1.04, 95% CI 0.75-1.46
2) medium volume hospitals: 4,704 pts.; cardiovascular morbidity 27.1%; adjusted OR 0.90, 95% CI 0.66-1.24
3) high volume hospitals: 5,830 pts.; cardiovascular morbidity 22.6%; adjusted OR 0.70, 95% CI 0.52-0.93
4) very high volume hospitals – median 130 resections p.a., IQR 100-210: 6,277 pts.; cardiovascular morbidity 27.6%, ***adjusted OR 1.0 (reference)***

Morbidity (pulmonary) - *higher hospital volume of care with trivial effect (**cave:*** highest hospital volume stratum as reference - OR>1.0: ***lower*** hospital volume of care correlating with ***lower*** morbidity)*:*
1) low volume hospitals – median 13 resections p.a., IQR 9-18: 5,928 pts.; pulmonary morbidity 26.7%; adjusted OR 1.19, 95% CI 0.78-1.82
2) medium volume hospitals: 4,704 pts.; pulmonary morbidity 21%; adjusted OR 0.99, 95% CI 0.66-1.50
3) high volume hospitals: 5,830 pts.; pulmonary morbidity 18.9%; adjusted OR 0.90, 95% CI 0.59-1.37
4) very high volume hospitals – median 130 resections p.a., IQR 100-210: 6,277 pts.; pulmonary morbidity 18.3%, ***adjusted OR 1 (reference)***

Morbidity (infectious) - *higher hospital volume of care with small effect (**cave:*** highest hospital volume stratum as reference - OR>1.0: ***lower*** hospital volume of care correlating with ***lower*** morbidity)*:*
1) low volume hospitals– median 13 resections p.a., IQR 9-18: 5,928 pts.; infectious morbidity 19.3%; adjusted OR 1.03, 95% CI 0.74-1.43
2) medium volume hospitals: 4,704 pts.; infectious morbidity 15.3%; adjusted OR 0.79, 95% CI 0.57-1.10
3) high volume hospitals: 5,830 pts.; infectious morbidity 16.1%; adjusted OR 0.91, 95% CI 0.67-1.23
4) very high volume hospitals – median 130 resections p.a., IQR 100-210: 6,277 pts.; infectious morbidity 15.5%, ***adjusted OR 1.0 (reference)***
p=0.052

		Morbidity (renal) - *higher hospital volume of care with trivial effect (**cave:** highest hospital volume stratum as reference - OR>1.0: **lower** hospital volume of care correlating with **lower** morbidity)*: 1) low volume hospitals – median 13 resections p.a., IQR 9-18: 5,928 pts.; renal morbidity 7.5%; adjusted OR 1.30, 95% CI 0.86-1.98 2) medium volume hospitals: 4,704 pts.; renal morbidity 7.3%; adjusted OR 0.98, 95% CI 0.65-1.47 3) high volume hospitals: 5,830 pts.; infectious morbidity 6.4%; adjusted OR 0.92, 95% CI 0.64-1.32 4) very high volume hospitals – median 130 resections p.a., IQR 100-210: 6,277 pts.; infectious morbidity 7%, ***adjusted OR 1.0 (reference)***
Harrison S et al., 2018 **[149]**	12,698 pts.	Morbidity (cardiovascular) - higher hospital volume of care with trivial effect (OR<1.0: higher hospital volume of care correlating with lower morbidity): 1) 1-39 resections p.a.: 6,349 pts.; cardiovascular 1,075 events (16.9%); adjusted OR 1.0 (reference) 2) ≥40 resections p.a.: 6,349 pts.; cardiovascular 1,087 events (17.1%); adjusted OR 1.01, 95% CI 0.93-1.11; p=0.78 Morbidity (pulmonary) - higher hospital volume of care with small effect (OR<1.0: higher hospital volume of care correlating with lower morbidity): 1) 1-39 resections p.a.: 6,349 pts.; pulmonary 2,224 events (35.0%); adjusted OR1.0 (reference) 2) ≥40 resections p.a.: 6,349 pts.; pulmonary 2,129 events (33.5%); adjusted OR 0.93, 95% CI 0.87-1.01; p=0.07 Morbidity (infectious) - higher hospital volume of care with trivial effect (OR<1.0: higher hospital volume of care correlating with lower morbidity): 1) 1-39 resections p.a.: 6,349 pts.; infectious 310 events (4.9%); adjusted OR 1.0 (reference) 2) ≥40 resections p.a.: 6,349 pts.; infectious 266 events (4.2%); adjusted OR 0.85, 95% CI 0.68-0.72; p=0.06 Morbidity (intraoperative) - higher hospital volume of care with trivial effect (OR<1.0: higher hospital volume of care correlating with lower i): 1) 1-39 resections p.a.: 6,349 pts.; intraoperative 180 events (2.8%); adjusted OR 1.0 (reference) 2) ≥40 resections p.a.: 6,349 pts.; intraoperative 181 events (2.9%); adjusted OR 1.01, 95% CI 0.82-1.23; p=0.96

Nathan H et al., 2015 **[169]**	10,151 pts.	Morbidity - *higher hospital volume of care with trivial effect:* 1) 1-7 resections p.a.: 30-day morbidity 56% 2) 8-16 resections p.a.: 30-day morbidity 57% 3) 17-99 resections p.a.: 30-day morbidity 56%; p=n.s.
Tchouta LN et al., 2017 **[185]**	8,523 pts.	Morbidity (pulmonary) - *higher hospital volume of care with trivial effect:* 1) 1-3 resections p.a.: 2,373 pts.; pulmonary 13.4% 2) 4-6 resections p.a.: pulmonary 13.9% 3) 7-14 resections p.a.: pulmonary 12.5% 4) ≥15 resections p.a.: 1,890 pts.; pulmonary 14.1%; p=0.480 Morbidity (cardiovascular) - *higher hospital volume of care with trivial effect:* 1) 1-3 resections p.a.: 2,373 pts.; cardiovascular 5.9% 2) 4-6 resections p.a.: cardiovascular 7.9% 3) 7-14 resections p.a.: cardiovascular 5.75% 4) ≥15 resections p.a.: 1,890 pts.; cardiovascular 6.5%; p=0.022 Morbidity (intraoperative) - *higher hospital volume of care with trivial effect* (OR<1.0: higher hospital volume of care correlating with lower morbidity)*:* 1) 1-3 resections p.a.: 2,373 pts.; intraoperative 4.4%; adjusted OR 1.0 (reference) 2) 4-6 resections p.a.: intraoperative 3.8% 3) 7-14 resections p.a.: intraoperative 2.3%; adjusted OR 0.256, 95% CI 0.139-0.470 4) ≥15 resections p.a.: 1,890 pts.; intraoperative 4.5%; adjusted OR 0.595, 95% CI 0.353-1.003, p<0.001 Morbidity (infectious) - *higher hospital volume of care with small effect:* 1) 1-3 resections p.a.: 2,373 pts.; infectious 6.7%; adjusted OR 1 (reference) 2) 4-6 resections p.a.: infectious 7.7% 3) 7-14 resections p.a.: infectious 9.1% 4) ≥15 resections p.a.: 1,890 pts.; infectious 7.7%, p=0.030 Morbidity (wound) - *higher hospital volume of care with trivial effect:* 1) 1-3 resections p.a.: 2,373 pts.; wound 0.2% 2) 4-6 resections p.a.: wound 0.3% 3) 7-14 resections p.a.: wound 0.0% 4) ≥15 resections p.a.: 1,890 pts.; wound 0.0%; p=0.023

Table 27: Effect results of studies ineligible for meta-analyses on different types of morbidity for PICO 4, subgroup 1 (Hospital volume of care, surgical resection)

The effect of higher surgical hospital volumes on the ***receipt of curative treatment*** was large in the only retrieved study by *Li et al.* (1,591 patients) [158] (see effect results in ***Table 28***).

[quality of evidence for rate of curative treatment: low ⊕⊕◯◯]

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 4, subgroup 1: Hospital volume of care, surgical resection		
***Receipt of curative treatment* – 1 observational study (1,591 patients)**		
Li et al., 2008 **[158]**	1,591 pts.	Receipt of curative treatment - *higher hospital volume of care with large effect* (OR>1.0: higher hospital volume of care correlating with higher resection rate)*:* 1) 1-39 resections p.a.: 283 pts.; resection rate 58%; adjusted OR 1.0 (reference) 2) 40-59 resections p.a.: 721 pts.; resection rate 73%; adjusted OR 1.82, 95% CI 1.27-2.61 3) ≥60 resections p.a.: 528 pts.; resection rate 68%; adjusted OR 1.58, 95% CI 1.07-2.35

Table 28: Effect results of the study by *Li et al.* on receipt of curative treatment for PICO 4, subgroup 1 (Hospital volume of care, surgical resection)

The GRADE evidence profile relating to the subgroup 1 in PICO 4 (Hospital volume of care, surgical resection) is presented in ***Table 29***.

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Overall survival									
18 [67, 127, 132, 135, 137, 138, 144, 158, 161, 164, 167, 170, 171, 178, 180, 181, 184, 188]	observational studies	serious [a,b]	serious [c]	serious [d]	serious [e]	strong association	We detected 12 studies with a large effect (275,995 patients), 3 studies with a moderate effect (57,643 patients), and 3 studies with a trivial effect (154,764 patients).	⨁◯◯◯ VERY LOW	CRITICAL
In-hospital mortality									
12 [128, 143, 147, 149, 151, 155, 156, 159, 167, 171, 173, 185]	observational studies	serious [a,b]	serious [c]	serious [d]	serious [e]	strong association	The effect of higher volume of surgical resections on in-house mortality was large in nine studies (388,079 patients), small in two studies (26,731 patients), and trivial in one study (20,138 patients).	⨁◯◯◯ VERY LOW	CRITICAL
30-day mortality									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
31 [127, 129-131, 133, 134, 138-140, 142, 144, 148, 152, 154, 160, 162-165, 168, 169, 171, 175-177, 179-181, 183, 186, 187]	observational studies	serious [a,b]	serious [c]	serious [d]	serious [e]	strong association	Relating to 30-day mortality, we saw large, moderate, small and trivial effects in 20 studies (965,608 patients), four studies (364,835 patients), four studies (384,345 patients), and three studies (31,135 patients), respectively.	⨁◯◯◯ VERY LOW	CRITICAL
60-day mortality									
2 [132, 178]	observational studies	not serious	serious [c]	serious [d]	serious [e]	strong association	The effects on 60-day mortality were large (2,084 patients) and moderate (40,754 patients) [6] in one study each.	⨁◯◯◯ VERY LOW	CRITICAL
90-day mortality									
6 [138, 162-164, 184]	observational studies	serious [f]	serious [c]	serious [d]	serious [e]	strong association	In the context of 90-day mortality, there were three studies with a large effect (332,785 patients) as well as one study each with a moderate (139,802 patients) and small effect (3,420 patients), respectively. The impact on conditional 90-day mortality was large in another study (124,418 patients).	⨁◯◯◯ VERY LOW	CRITICAL
Morbidity									
7 [127, 140, 144, 147, 149, 169, 185]	observational studies	serious [a,b]	serious [c]	serious [d]	serious [e]	none	Observed effects on specific types of morbidities ranged from large in one study (2,118 patients) over trivial-moderate in one study (22,739 patients) and trivial-small in two studies (28,391 patients) to trivial in three studies (22,724 patients).	⨁◯◯◯ VERY LOW	CRITICAL
Rate of curative treatment									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
1 [158]	observational studies	not serious	not serious	not serious	not serious	none	The effect of higher surgical hospital volumes on the *receipt of curative treatment* was large in the only retrieved study (1,591 patients; adjusted OR 1.58, 95% CI 1.07-2.35).	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval

Explanations:

a. some studies did not adequately control for confounding
b. some studies did not state 95% CIs or other data needed to fully estimate the effect and certainty
c. varying effect sizes across studies raise concerns about high heterogeneity
d. studies used different thresholds and volume strata
e. pooling of studies not feasible
f. one study did not adequately control for confounding

Table 29: GRADE evidence profile for PICO 4, subgroup 1 (Hospital volume of care, surgical resection)

2) PICO 4, subgroup 2: All lung cancer, all stages, better hospital specialization in, surgical resections (vs. less hospital specialization)

17 observational studies focused on *hospital specialization* in surgically resected lung cancer patients (653,289 patients) [68, 127, 131, 138, 142, 156, 158, 160, 163, 174, 176, 180, 181, 190-192, 196]. Definitions of hospital specialization varied amongst studies discriminating between teaching and non-teaching hospitals, designated and non-designated hospitals, university and non-university hospitals as well as NCI Comprehensive Cancer Centers, academic, community and comprehensive community centres. Due to heterogeneity of patient populations, data sources and types of hospital specialization, we abstained from pooling studies. Instead, we described results across outcomes narratively after estimating the effect size on a self-selected classification per outcome for each study.

A priori, all outcomes were considered either critical or important related to this PICO. Effectively, only *overall survival*, *mortality*, *morbidity* and *receipt of curative treatment* were addressed within the rated body of evidence.

Overall survival was targeted in eight studies (95,099 patients) [68, 127, 138, 158, 180, 181, 191, 192].

Seven studies demonstrated either large (53,563 patients) [127, 138, 181, 192] or moderate effects (39,945 patients) [68, 180, 191]. One study revealed a trivial effect (1,591 patients) [158] (see effect results in ***Table 30***).

[quality of evidence for *overall survival*: very low ⊕◯◯◯, rated down for risk of bias -1, indirectness -1, inconsistency -1 and imprecision -1]

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 4, subgroup 2: Hospital specialization, surgical resection		
***Overall survival (OS)* – 8 observational studies (95,099 patients)**		
Bach PB et al., 2001 **[127]**	2,118 pts.	Overall survival - *better hospital specialization with large effect:* 1) teaching hospitals: 1,129 pts.; 5-year OS 42% 2) non-teaching hospitals: 989 pts.; 5-year OS 31% p<0.001
Birkmeyer NJ et al., 2005 **[191]**	18,012 pts.	Overall survival - *better hospital specialization with moderate effect* (HR<1.0: higher hospital specialization correlating with higher OS)*:* 1) non-NCI cancer centres (n=51): 9,652 pts.; 5-year OS 41%; adjusted HR 1.0 (reference) 2) NCI cancer centres (n=51): 8,360 pts.; 5-year OS 43%; adjusted HR 0.93, 95% CI 0.86-1.00
Boffa DJ et al., 2020 **[192]**	32637 pts.	Overall survival - *better hospital specialization with large effect* (time ratio>1.0: higher hospital specialization correlating with higher survival time)*:* 1) affiliate hospitals (n=206): 9,657 pts.; adjusted time ratio 1.0 (reference)

		2) top-ranked hospitals (n=56): 22,980 pts.; adjusted time ratio 1.27, 95% CI 1.16-1.39
Cheung MC et al., 2009 **[138]**	13,469 pts.	Overall survival - *better hospital specialization with large effect* (HR<1.0: higher hospital specialization correlating with higher OS)*:* 1) non-teaching hospitals (n=239): 11,249 pts.; median OS 40.5 months; adjusted HR 1.0 (reference) 2) teaching hospitals (n=11): 2,220 pts.; median OS 47.1 months; adjusted HR 0.84, 95% CI 0.776-0.908
Li WW et al., 2008 **[158]**	1,097 pts	Overall survival - *better hospital specialization with trivial effect* (HR<1.0: higher hospital specialization correlating with higher OS)*:* 1) community hospitals: 939 pts.; 5-year OS 50%; adjusted HR 1.0 (reference) 2) specialized centres: 158 pts.; 5-year OS 50%; adjusted HR 1.26, 95% CI 0.94-1.70
Samson P et al., 2015 **[68]**		Overall survival – *better hospital specialization with moderate effect* (HR<1.0: higher hospital specialization correlating with higher OS)*:* 1) non-academic hospitals: 11,492 pts.; median OS 28.9 months; adjusted HR 1.0 (reference) 2) academic hospitals: 7,743 pts.; median OS 33.8 months; adjusted HR 0.91, 0.85-0.98
Simunovic M et al., 2006 **[180]**	2,698 pts.	Overall survival - *better hospital specialization with moderate effect* (HR<1.0: higher hospital specialization correlating with higher OS)*:* 1) non-teaching hospitals: 1,208 pts.; adjusted HR 1.0 (reference) 2) teaching hospitals: 1,472 pts.; adjusted HR 0.9, 95% CI 0.77–1.0
Sioris T et al., 2008 **[181]**	5,339 pts.	Overall survival - *better hospital specialization with large effect* (HR<1.0: higher hospital specialization correlating with higher OS)*:* 1) other hospital: 2,036 pts.; adjusted HR 1.0 (reference) 2) university hospital: 2,842 pts.; adjusted HR 0.8, 95% CI 0.7-0.9

Table 30: Effect results of studies ineligible for meta-analyses on overall survival for PICO 4, subgroup 2 (Hospital specialization, surgical resection)

15 studies assessed the impact of hospital specialization on *mortality* in resected lung cancer patients [68, 131, 138, 142, 156, 160, 163, 174, 176, 180, 181, 190-192, 196].

The effect on ***in-hospital mortality*** was small in two studies (122,826 patients) [174, 196] and trivial in one study (62,628 patients) [156].

[quality of evidence for *in-hospital mortality*: very low ⊕◯◯◯, rated down for risk of bias -1, indirectness -1, inconsistency -1 and imprecision -1]

Relating to ***30-day mortality***, five out of eleven studies showed a large effect (344,156 patients) [131, 138, 163, 180, 190], a moderate effect was seen in another three studies (49,686 patients) [68, 176, 191]. Two studies indicated a trivial effect (17,007 patients) [160, 181]. One study compared only public and private hospitals (20,640 patients) [142].

[quality of evidence for *30-day mortality*: very low ⊕◯◯◯, rated down for risk of bias -1, indirectness -1, inconsistency -1 and imprecision -1, rated up for large effect +1]

All three studies addressing ***90-day mortality*** revealed a large effect (349,685 patients) [138, 163, 192].

[quality of evidence for *90-day mortality*: very low ⊕◯◯◯, rated down for risk of bias -1, indirectness -1 and imprecision -1, rated up for large effect +1]

The effect results for all types of mortality are listed in ***Table 31***.

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 4, subgroup 2: Hospital specialization, surgical resection		
***In-hospital mortality* – 3 observational studies (185,454 patients)**		
Learn PA et al., 2010 **[156]**	62,628 pts.	in-hospital mortality - *better hospital specialization with trivial effect* (OR<1.0: higher hospital specialization correlating with lower mortality)*:* 1) non-teaching hospital: 25,222 pts.; adjusted OR 1.0 (reference) 2) teaching hospital: 19,067 pts.; adjusted OR 0.98, 95% CI 0.88-1.09
Meguid RA et al., 2008 **[196]**	46,591 pts.	in-hospital mortality - *better hospital specialization with small effect* (OR<1.0: higher hospital specialization correlating with lower OS)*:* 1) non-teaching hospitals: 20,641 pts.; in-hospital mortality 818 deaths (4.0%); adjusted OR 1.0 (reference) 2) teaching hospitals: 26,310 pts.; in-hospital mortality 831 deaths (3.2%); adjusted OR 0.83, 95% CI 0.73-0.932)
Pages PB et al., 2016 **[174]**	76,235 pts.	in-hospital mortality - *better hospital specialization with small effect* (OR<1.0: higher hospital specialization correlating with lower mortality)*:* 1) non-teaching hospitals (n=83); 7,019 pts.; in-hospital mortality 331 deaths (4.7%); adjusted 1.0 (reference)

		2) private hospitals (n=232); 37,039 pts.; in-hospital mortality 1,388 deaths (3.7%); adjusted 0.94, 95% CI 0.76-1.5 3) teaching hospitals (n=30); 32,177 pts.; in-hospital mortality 1,256 deaths (3.9%); %); adjusted 0.94, 95% CI 0.7-1.2
***30-day mortality* – 11 observational studies (431,489 patients)**		
Bendzsak AM et al. **[190]**	16,641 pts.	30-day mortality - *better hospital specialization with large effect:* (OR<1.0: higher hospital specialization correlating with lower mortality) Pre-regionalization interval (2004-2007): 1) non-designated hospitals: 1,796 lung cancer pts. out of 1,975 pts.; adjusted OR 1.0 (reference) 2) designated hospitals: 4,129 lung cancer pts. out of 4,851 cancer pts.; adjusted OR 0.71, 95% CI 0.52-0.98 Regionalization interval (2008-2012): 1) non-designated hospitals: 949 lung cancer pts. out of 1,114 pts.; adjusted OR 1.0 (reference) 2) designated hospitals: 6,860 lung cancer pts. out of 8.701 cancer pts.; adjusted OR 0.64, 95% CI 0.43-0.98
Bernard A. et al., 2019 **[131]**	10,675 pts.	30-day mortality - *better hospital specialization with large effect:* Hospital volume strata based on mean annual number of procedures: number of pts. per strata; in-house mortality rate; adjusted OR, 95% CI: 1) public non-university hospitals (43 hospitals): 1,646 pts.; 30-day mortality rate <3%: approx. 5% of hospitals, 3-4%: approx. 85% of hospitals, >4%: approx. 10% of hospitals 2) private hospitals (87 hospitals): 4,387 pts.; 30-day mortality rate <3%: approx. 10% of hospitals, 3-4%: approx. 80-85% of hospitals, >4%: approx. 5-10% of hospitals 1) university hospitals (28 hospitals): 4,642 pts.; 30-day mortality rate <3%: 20% of hospitals, 3-4%: approx. 70% of hospitals, >4%: approx. 10% of hospitals
Birkmeyer NJ et al., 2005 **[191]**	18,012 pts.	30-day mortality - *better hospital specialization with moderate effect* (OR<1.0: higher hospital specialization correlating with lower mortality)*:* 1) non-NCI cancer centres (n=51): 9,652 pts.; 30-day mortality 5.1%; adjusted OR 1.0 (reference) 2) NCI cancer centres (n=51): 8,360 pts.; 30-day mortality 4.4%; adjusted OR 0.78, 95% CI 0.64-0.94
Cheung MC et al., 2009 **[138]**	13,469 pts.	30-day mortality - *better hospital specialization with large effect:*

		1) non-teaching hospitals (n=239): 11,249 pts.; 30-day mortality 3.8%; 90-day mortality 6.8% 2) teaching hospitals (n=11): 2,220 pts.; 30-day mortality 1.1%
Falcoz PE et al., 2017 **[142]**	20,640 pts.	30-day mortality - *better hospital specialization with large effect* (lower mortality in public hospitals compared to private hospitals)*:* 1) public hospitals: adjusted OR 1.0 (reference) 2) private hospitals: model 1 surgeon level activity adjusted OR 1.65, 95% CI 1.10-2.49; model 2 hospital level activity adjusted OR 1.65, 95% CI 1.08-2.52
Little AG et al., 2005 **[160]**	40,090 pts.	30-day mortality - *better hospital specialization with trivial effect:* 1) community cancer centres: 30-day mortality 5.3% 2) comprehensive community cancer centres: 30-day mortality 5.3% 3) teaching-research institutions: 30-day mortality 5.1%
Moore CB et al., 2019 **[163]**	303,579 pts.	30-day mortality - *better hospital specialization with large effect* (OR<1.0: higher hospital specialization correlating with lower mortality)*:* 1) community cancer centres: 20,802 pts.; 30-day mortality 4.4%; adjusted OR 1.0 (reference) 2) comprehensive community cancer centres: 132,402,802 pts.; 30-day mortality 3.3%; adjusted OR 0.87, 95% CI 0.78-0.97 3) academic-research institutions: 115,669 pts.; 30-day mortality 2.3%; adjusted OR 0.68, 95% CI 0.60-0.77 4) integrated network: 32,102 pts.; 30-day mortality 3%; adjusted OR 0.80, 95% CI 0.69-0.94
Romano PS et al., 1992 **[176]**	12,439 pts.	30-day mortality - *better hospital specialization with moderate effect* (OR<1.0: higher hospital specialization correlating with lower mortality)*:* 1) non-teaching hospitals: 338 deaths (4.3%); adjusted OR 1.0 (reference) 2) low-intensity teaching hospitals: 54 deaths (3.7%); adjusted OR 1.0, 95% CI 0.7-1.4 3) high-intensity teaching hospitals: 50 deaths (3.2%); adjusted OR 0.9, 95% CI 0.6-1.3
Samson P et al., 2015 **[68]**		30-day mortality - *better hospital specialization with large effect* (OR<1.0: higher hospital specialization correlating with lower mortality)*:* 1) non-academic hospitals: 11,492 pts.; 30-day mortality 502 deaths (4.5%); adjusted OR 1.0 (reference) 2) academic hospitals: 7,743 pts.; 30-day mortality 246 deaths (3.3%); adjusted OR 0.69, 95% CI 0.54-0.90

Simunovic M et al., 2006 **[180]**	2,698 pts.	30-day mortality - *better hospital specialization with large effect* (OR<1.0: higher hospital specialization correlating with lower mortality)*:* 1) non-teaching hospital: 1,208 pts.; adjusted OR 1 (reference) 1) teaching hospital: 1,472 pts.; adjusted OR 0.7, 95% CI 0.4-1.3
Sioris T et al., 2008 **[181]**	5,339 pts.	30-day mortality - *better hospital specialization with trivial effect (**cave:** higher hospital specialization as reference - OR>1.0: **lower** hospital specialization correlating with **higher** mortality)*:* 1) other hospital: 2,036 pts.; adjusted HR n.s. 2) university hospital: 2,842 pts.; adjusted HR 1.0 (reference)
***90-day mortality* – 3 observational studies (349,685 patients)**		
Boffa DJ et al., 2020 **[192]**	32,637 pts.	90-day mortality - *better hospital specialization with large effect* (OR<1.0: higher hospital specialization correlating with lower mortality)*:* 1) affiliate hospitals (n=206): 9,657 pts.; exact 90-day mortality rate not stated; lobectomy: adjusted OR 1.0 (reference) 2) top-ranked hospitals (n=56): 22,980 pts.; exact 90-day mortality rate not stated; adjusted OR 0.54, 95% CI 0.43-0.68, pneumonectomy: adjusted OR 0.60, 95% CI 0.40-0.88
Cheung MC et al., 2009 **[138]**	13,469 pts.	90-day mortality - *better hospital specialization with large effect:* 1) non-teaching hospitals (n=239): 11,249 pts; 90-day mortality 6.8% 2) teaching hospitals (n=11): 2,220 pts.; 90-day mortality 3.8%
Moore CB et al., 2019 **[163]**	303,579 pts.	90-day mortality - *better hospital specialization with large effect* (OR<1.0: higher hospital specialization correlating with lower mortality)*:* 1) community cancer centres: 20,703 pts.; 90-day mortality 7.9%; adjusted OR 1.0 (reference) 2) comprehensive community cancer centres: 131,863 pts.; 90-day mortality 6.2%; adjusted OR 0.88, 95% CI 0.80-0.96 3) academic-research institutions: 114,837 pts.; 90-day mortality 4.7%; adjusted OR 0.72, 95% CI 0.65-0.80 4) integrated network: 31,891 pts.; 90-day mortality 5.2%; adjusted OR 0.83, 95% CI 0.72-0.94

Table 31: Effect results of studies ineligible for meta-analyses on different types of mortality for PICO 4, subgroup 2 (Hospital specialization, surgical resection)

The only retrieved study on ***morbidity*** in highlighted a large effect with less surgical complications in better specialized hospitals (13,735 patients) [190] (effect results in ***Table 32***).

[quality of evidence for *morbidity*: low ⊕⊕◯◯]

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 4, subgroup 2: Hospital specialization, surgical resection		
***Morbidity* – 1 observational study (13,735 patients)**		
Bendzsak AM et al. **[190]**	13,735 pts.	Morbidity (surgical complications) - *better hospital specialization with trivial effect* (OR<1.0: higher hospital specialization correlating with lower morbidity)*:* Preregionalization Interval (2004-2007): 1) non-designated hospitals: 1,796 lung cancer pts. out of 1,975 pts.; adjusted OR 1.0 (reference) 2) designated hospitals: 4,129 lung cancer pts. out of 4,851 cancer pts.; adjusted OR 0.74, 95% CI 0.57-0.98 Regionalization Interval (2008-2012): 1) non-designated hospitals: 949 lung cancer pts. out of 1,114 pts.; adjusted OR 1.0 (reference) 2) designated hospitals: 6,860 lung cancer pts. out of 8.701 cancer pts.; adjusted OR 0.60, 95% CI 0.46-0.77

Table 32: Effect results of the study by *Bendzsak et al.* on morbidity for PICO 4, subgroup 2 (Hospital specialization, surgical resection)

Accuracy of staging was solely explored by *Little et al.* revealing a large effect with higher mediastinal lymph node sampling rates in teaching-research hospitals (40,090 patients) [160] (effect results in ***Table 33***).

[quality of evidence for *accuracy of staging*: very low ⊕◯◯◯, rated down for risk of bias -1]

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 4, subgroup 2: Hospital specialization, surgical resection		

***Accuracy of staging* – 1 observational study (40,090 patients)**		
Little AG et al., 2005 **[160]**	40,090 pts.	Accuracy of staging - *better hospital specialization with large effect:* 1) community cancer centres: rate mediastinal lymph node sampling 48.1%, 95% CI 45.5-50.6% 2) comprehensive community cancer centres: rate mediastinal lymph node sampling 55.6%, 95% CI 53.9-57.4% 3) teaching-research institutions: rate mediastinal lymph node sampling 67.9%, 95% CI 65.8-69.9%

Table 33: Effect results of the study by *Little et al.* on accuracy of staging for PICO 4, subgroup 2 (Hospital specialization, surgical resection)

The only work on ***receipt of curative treatment*** by *Li et al.* demonstrated largely increased resection rates in more advanced thoracic surgery services (1,591 patients) [158] (see effect results in ***Table 34***).

[quality of evidence for *receipt of curative treatment*: very low ⊕◯◯◯, rated down for imprecision -1]

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 4, subgroup 2: Hospital specialization, surgical resection		
***Receipt of curative treatment* – 1 observational study (1,591 patients)**		
Li et al., 2008 **[158]**	1,591 pts.	Receipt of curative treatment - *better hospital specialization with large effect* (OR>1.0: higher hospital specialization correlating with higher resection rate)*:* 1) community hospitals: 1,395 pts.; resection rate 67%; adjusted OR 1.0 (reference) 2) specialized centres: 196 pts.; resection rate 81%; adjusted OR 1.72, 95% CI 1.06-2.80

Table 34: Effect results of the study by *Li et al.* on receipt of curative treatment for PICO 4, subgroup 2 (Hospital specialization, surgical resection)

The GRADE evidence profile relating to the subgroup 2 in PICO 4 (Hospital specialization, surgical resection) is presented in ***Table 35***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	better hospital specialization	less hospital specialization	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
8 [68, 127, 138, 158, 180, 181, 191, 192]	observational studies	serious [a]	serious [b]	serious [c]	serious [d]	none	Seven studies demonstrated either large (53,563 patients) or moderate effects (39,945 patients). One study revealed a trivial effect (1,591 patients).				⊕◯◯◯ VERY LOW	CRITICAL
In-hospital mortality												
3 [156, 174, 196]	observational studies	serious [e]	serious [b]	serious [c]	serious [d]	none	The effect on *in-hospital mortality* was small in two studies (122,826 patients) and trivial in one study (62,628 patients).				⊕◯◯◯ VERY LOW	CRITICAL
30-day mortality												
11 [68, 131, 138, 142, 160, 163, 176, 180, 181, 190, 191]	observational studies	serious [a]	serious [b]	serious [c]	serious [d]	none	Relating to *30-day mortality*, five out of eleven studies showed a large effect (344,156 patients), a moderate effect was seen in another three studies (49,686 patients). Two studies indicated a trivial effect (17,007 patients). One study compared only public and private hospitals (20,640 pts.)				⊕◯◯◯ VERY LOW	CRITICAL
90-day mortality												
3 [138, 163, 192]	observational studies	serious [e]	not serious	serious [c]	serious [d]	strong association	All three studies addressing *90-day mortality* revealed a large effect (349,685 patients).				⊕◯◯◯ VERY LOW	CRITICAL
Morbidity												
1 [190]	observational studies	not serious	not serious	not serious	not serious	none	The only retrieved study on *morbidity* highlighted a large effect with less surgical complications in better specialized hospitals (13,735 patients).				⊕⊕◯◯ LOW	CRITICAL
Accuracy of staging												
1 [160]	observational studies	serious [e]	not serious	not serious	not serious	none	*Accuracy of staging* was solely explored by Little et al. revealing a large effect with higher mediastinal lymph node sampling rates in teaching-research hospitals (40,090 patients)				⊕◯◯◯ VERY LOW	CRITICAL
Receipt of curative treatment												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	better hospital specialization	less hospital specialization	Relative (95% CI)	Absolute (95% CI)		
1 [158]	observational studies	not serious	not serious	not serious	serious [f]	none	159/196 (81.1%)	935/1395 (67.0%)	**OR 1.72** (1.06 to 2.80)	**107 more per 1.000** (from 13 more to 180 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

Explanations:

a. some studies did not adequately control for confounding
b. varying effect sizes across studies raise concerns about high heterogeneity
c. studies used different thresholds and volume strata
d. pooling of studies not feasible
e. one study did not adequately control for confounding
f. few events raises concerns about imprecision

Table 35: GRADE evidence profile for PICO 4, subgroup 2 (Hospital specialization, surgical resection)

3) PICO 4, subgroup 3: All lung cancer, all stages, higher surgeon volume of surgical resections (vs. lower surgeon volume)

Seven observational studies dealt with *surgeon volume of care* in the context of surgical resections (63,505 patients) [133, 137, 142, 148, 159, 198, 199]. Subdivision and thresholds for distinction of individual surgeon volumes differed substantially in all studies as did patient populations, sources of patient data and types of surgical procedures so that data pooling was omitted.

Both studies on ***overall survival*** revealed a large effect with higher 5-year overall survival rates in the cohorts operated by surgeons with higher individual volumes (2,950 patients) [137, 198] (see effect results in ***Table 36***).

[quality of evidence for *overall survival*: low for surgical resections ⊕⊕◯◯]

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 4, subgroup 3: Surgeon volume of care, surgical resection		
***Overall survival (OS)* – 2 observational studies (2,950 patients)**		
Chang CM et al., 2012 **[137]**	655	Overall survival - *higher individual volume of care with large effect* (***cave:*** higher hospital volume of care/higher individual volume of care as reference - HR>1.0: ***lower*** indiviudal volume of care correlating with ***lower*** OS)*:* 1) hospital <62 resections p.a.; surgeon <6 resections p.a.: 108 deaths/155 pts.; 5-year OS 30.37%); adjusted HR 1.82, 95% CI 1.35-2.46 2) hospital <62 resections p.a.; surgeon ≥6 resections p.a.: 152 deaths/275 pts.; 5-year OS 44.7%); adjusted HR 1.10, 95% CI 0.83-1.46 3) hospital ≥62 resections p.a.; surgeon <6 resections p.a.: 26 deaths/46 pts.; 5-year OS 43.5%; adjusted HR 1.33, 95% CI 0.85-2.08 4) hospital ≥62 resections p.a.; surgeon ≥6 resections p.a.: 84 deaths/179 pts.; 5-year OS 53.19%; ***adjusted HR 1.0 (reference)***
Smith CB et al., 2007 **[198]**	2,295 pts.	Overall survival - *higher individual volume of care with large effect* (HR<1.0: higher individual volume of care correlating with higher OS)*:* 1) low volume hospitals: 774 pts.; adjusted HR 1.0 (reference) 2) intermediate volume hospitals: 776 pts.; adjusted HR 0.93, 9% CI 0.77-1.13 3) high volume hospitals: 745 pts.; adjusted HR 0.70, 95% CI 0.58-0.84

Table 36: Effect results of studies ineligible for meta-analyses on overall survival for PICO 4, subgroup 3 (Surgeon volume of care, surgical resection)

Mortality was addressed in six observational studies (62,850 patients) [133, 142, 148, 159, 198, 199].

The effects on ***in-hospital mortality*** were large and trivial in the two studies by *Lien et al.* (4,841 patients) [159] and *Treasure et al.* (4,028 patients) [199], respectively.

[quality of evidence for *in-hospital mortality*: very low ⊕○○○, rated down for risk of bias -1, indirectness -1, inconsistency -1 and imprecision -1]

Three out of four studies demonstrated large (9,249 patients) [148, 198] and moderate effects (24,092 patients) [133] on ***30-day mortality***. A trivial effect was seen in the remaining study (20,640 patients) [142].

[quality of evidence for *30-day mortality*: very low ⊕○○○, rated down for risk of bias -1, indirectness -1, inconsistency -1 and imprecision -1]

The effect results for all types of mortality are listed in ***Table 37***.

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 4, subgroup 3: Surgeon volume of care, surgical resection		
***In-hospital mortality* – 2 observational studies (8,869 patients)**		
Lien YC et al., 2007 **[159]**	4,841 pts.	in-hospital mortality - *higher individual volume of care with large effect* (OR<1.0: higher individual volume of care correlating with lower mortality)*:* 1) 1-46 resections p.a. (n=347): 1,605 pts.; 37 deaths (2.3%); unadjusted OR 1.0 (reference) 2) 47-131 resections p.a. (n=22): 1,597 pts.; 16 deaths (1.0%); unadjusted OR 0.49, 95% CI 0.27-0.89 3) ≥132 resections p.a. (n=8): 1,639 pts.; 10 deaths (0.6%); unadjusted OR 0.38, 95% CI 0.17-0.86
Treasure T et al., 2003 **[199]**	4,028 pts.	in-hospital mortality - *higher individual volume of care with trivial effect:* 1) 1-15 resections p.a. (n=49): 806 pts.; in-hospital mortality 22 deaths (2.7%) 2) 16-23 resections p.a. (n=21): 811 pts.; in-hospital mortality 21 deaths (2.6%) 3) 24-32 resections p.a. (n=15): 825 pts.; in-hospital mortality 21 deaths (2.5%) 4) 33-40 resections p.a. (n=11): 797 pts.; in-hospital mortality 19 deaths (2.4%) 5) 47-96 resections p.a. (n=6): 789 pts.; in-hospital mortality 20 deaths (2.5%)
***30-day mortality* – 4 observational studies (53,981 patients)**		
Birkmeyer JD et al., 2003 **[133]**	24,092 pts.	30-day mortality - *higher individual volume of care with moderate effect* (***cave:*** highest individual volume of care stratum as reference - OR>1.0: ***lower*** individual volume of care correlating with ***higher*** mortality)*:* 1) 1–16 resections p.a.: 7,668 pts.; 30-day mortality 6.1%; adjusted OR 1.16, 95% CI 0.99-1.36

		2) 17-35.5 resections p.a.: 8,360 pts.; 30-day mortality 5.6%; adjusted OR not stated 3) >35.5 resections p.a.: 8,064 pts.; 30-day mortality 5.0%; ***adjusted OR 1.0 (reference)***
Falcoz PE et al., 2017 **[142]**	20,640 pts.	30-day mortality - *higher individual volume of care with trivial effect:* no clear correlation of 30-day mortality and individual volume (mean annual individual volume: 46); lowest OR estimated for 89 annual procedures (OR 0.722), highest OR estimated for 30 annual procedures (OR 1.081)
Hannan EL et al., 2002 **[148]**	6,954 pts.	30-day mortality - *higher hospital volume of care with large effect (**cave:** highest individual volume stratum as reference - **risk-adjusted rate** >0: **lower** individual volume of care correlating with **higher** mortality):* 1) 1-22 resections p.a. (n=291): 1,719 pts; 30-day mortality 2.56; risk-adjusted rate 1.12 2) 23-49 resections p.a. (n=50): 1,727 pts; 30-day mortality 2.43; risk-adjusted rate 0.96 3) 50-130 resections p.a. (n=23): 1,709 pts; 30-day mortality 1.52; risk-adjusted rate 0.27 4) ≥131 resections p.a. (n=9): 1,799 pts; 30-day mortality 0.94; risk-adjusted rate 0 (reference)
Smith CB et al., 2007 **[198]**	2,295 pts.	30-day mortality - *higher individual volume of care with trivial effect* (OR<1.0: higher individual volume of care correlating with lower mortality)*:* 1) low individual volume : 774 pts.; 30-day mortality ≤11 deaths (< 3.0%); adjusted OR 1.0 (reference) 2) intermediate individual volume: 776 pts.; 30-day mortality ≤11 deaths (< 3.0%); adjusted OR not stated 3) high individual volume: 745 pts.; 30-day mortality ≤11 deaths (< 3.0%); adjusted OR 1.07, 95% CI 0.70-1.65

Table 37: Effect results of studies ineligible for meta-analyses on different types of mortality for PICO 4, subgroup 3 (Surgeon volume of care, surgical resection)

The only study on ***morbidity*** showed large effects on any and respiratory complications as well as trivial effects on extrapulmonary infection, cardiovascular and thromboembolic complications when video-assisted thoracoscopic surgery was conducted by surgeons with higher individual volumes (2,295 patients) [198] (see effect results in ***Table 38***).

[quality of evidence for *morbidity*: very low ⊕○○○, rated down for risk of bias -1]

Group	**total number of patients**	**study effect per outcome**

Outcome **Author, year**		
PICO 4, subgroup 3: Surgeon volume of care, surgical resection		
***Morbidity* – 1 observational study (2,295 patients)**		
Smith CB et al., 2007 **[198]**	2,295 pts.	Morbidity (any complication) - *higher individual volume of care with large effect* (OR<1.0: higher individual volume of care correlating with lower morbidity)*:* 1) low individual volume: 774 pts.; any complication 301 events (39%); adjusted OR 1.0 (reference) 2) intermediate individual volume: 776 pts.; any complication 264 events (34%); adjusted OR not started 3) high individual volume: 745 pts.; any complication 236 events (31%); adjusted OR 0.84, 95% CI 0.73-0.97 Morbidity (extrapulmonary infection) - *higher individual volume of care with trivial effect* (OR<1.0: higher individual volume of care correlating with lower morbidity)*:* 1) low individual volume: 774 pts.; extrapulmonary infection 25 events (4%); adjusted OR 1.0 (reference) 2) intermediate individual volume: 776 pts.; extrapulmonary infection 21 events (3%); adjusted OR not started 3) high individual volume: 745 pts.; extrapulmonary infection 29 events (5%); adjusted =R 0.99, 95% CI 0.76-1.29 Morbidity (cardiovascular) - *higher individual volume of care with trivial effect* (OR<1.0: higher individual volume of care correlating with lower morbidity)*:* 1) low individual volume: 774 pts.; cardiovascular ≤11 deaths (< 3.0%); adjusted OR 1.0 (reference) 2) intermediate individual volume: 776 pts.; cardiovascular 16 events (3%); adjusted OR not started 3) high individual volume: 745 pts.; cardiovascular 20 events (3%); adjusted OR 1.22, 95% CI 0.79-1.88 Morbidity (thromboembolic) - *higher individual volume of care with trivial effect* (OR<1.0: higher individual volume of care correlating with lower morbidity)*:* 1) low individual volume: 774 pts.; thromboembolic 16 events (3%); adjusted OR 1.0 (reference) 2) intermediate individual volume: 776 pts.; thromboembolic 32 events (5%); adjusted OR not started

	3) high individual volume: 745 pts.; thromboembolic 35 events (6%); adjusted OR 1.18, 95% CI 0.91-1.50 Morbidity (respiratory) - *higher individual volume of care with large effect* (OR<1.0: higher individual volume of care correlating with lower morbidity)*:* 1) low individual volume: 774 pts.; respiratory 194 events (33%); adjusted OR 1.0 (reference) 2) intermediate individual volume: 776 pts.; respiratory 191 events (29%); adjusted OR not started 3) high individual volume: 745 pts.; respiratory 149 events (25%); adjusted OR 0.85, 95% CI 0.72-0.99

Table 38: Effect results of the study by *Smith et al.* on morbidity for PICO 4, subgroup 3 (Surgeon volume of care, surgical resection)

The GRADE evidence profile relating to the subgroup 3 in PICO 4 (Surgeon volume of care, surgical resection) is presented in ***Table 39***.

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Overall survival									
2 [137, 198]	observational studies	not serious	not serious	not serious	not serious	none	Both studies on *overall survival* revealed a large effect with higher 5-year overall survival rates in the cohorts operated by surgeons with higher individual volumes (2,950 patients).	⊕⊕◯◯ LOW	CRITICAL
In-hospital mortality									
2 [159, 199]	observational studies	serious [a]	serious [b]	serious [c]	serious [d]	none	The effects on *in-hospital mortality* were large and trivial in the two studies by *Lien et al.* (4,841 patients) and *Treasure et al.* (4,028 patients), respectively.	⊕◯◯◯ VERY LOW	CRITICAL
30-day mortality									
4 [133, 142, 148, 198]	observational studies	serious [e]	serious [b]	serious [c]	serious [d]	none	Three out of four studies demonstrated large (9,249 patients) and moderate effects (24,092 patients) on *30-day mortality*. A trivial effect was seen in the remaining study (20,640 patients).	⊕◯◯◯ VERY LOW	CRITICAL
Morbidity									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
1 [198]	observational studies	serious [f]	not serious	not serious	not serious	none	The only study on *morbidity* showed large effects on any and respiratory complications as well as trivial effects on extrapulmonary infection, cardiovascular and thromboembolic complications when video-assisted thoracoscopic surgery was conducted by surgeons with higher individual volumes (2,295 patients).	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence intervals

Explanations:

a. some studies did not adequately control for confounding
b. varying effect sizes across studies raise concerns about high heterogeneity
c. studies used different thresholds and volume strata
d. pooling of studies not feasible, thus the 95% CI cannot exclude the potential of no meaningful effect.
e. one study did not adequately control for confounding
f. no adequately control for confounding

Table 39: GRADE evidence profile for PICO 4, subgroup 3 (Surgeon volume of care, surgical resection)

4) PICO 4, subgroup 4: All lung cancer, all stages, better surgeon specialization in surgical resections (vs. less surgeon specialization)

Eight observational studies investigated the impact of *surgeon specialization* of surgeons on our outcomes of interest in patients with surgical resections (492,135 patients) [88, 140, 158, 168, 193-195, 197].

Studies encompassed thoracic surgical lung cancer patients resected by either general surgeons, cardiac surgeons, cardiothoracic surgeons and/or thoracic surgeons.

Overall survival was analyzed in the study by *Farjah et al.* [194] as well as those by *Li et al.* [158] and *Martin-Ucar et al.* [88], the former one displaying a large effect (19,745 patients), the latter two with trivial effects (1,831 patients) based on our self-selected scheme (see effect results in ***Table 40***).

[quality of evidence for *overall survival*: very low ⊕◯◯◯, rated down for risk of bias -1, indirectness -1, inconsistency -1 and imprecision -1]

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 4, subgroup 4: Surgeon specialization, surgical resection		
***Overall survival* – 3 observational studies (21,576 patients)**		
Farjah F et al., 2009 **[194]**	19,745 pts.	Overall survival - *better individual specialization with large effect* (OR<1.0: higher individual specialization correlating with higher OS)*:* 1) general surgeons: 4,677 pts.; 5-year OS 37%; adjusted HR 1.0 (reference) 2) cardiothoracic surgeons: 8,807 pts.; 5-year OS 39%; adjusted HR 0.94, 95% CI 0.88-1.01 3) general thoracic surgeons: 6,261 pts.; 5-year OS 41%; adjusted HR 0.89, 95% CI 0.82-0.97
Li et al., 2008 **[158]**	1,591 pts.	Overall survival - *better individual specialization with trivial effect* (OR<1.0: higher individual specialization correlating with higher OS)*:* 1) centres without cardiothoracic surgery: 939 pts.; 5-year OS 50%; adjusted HR 1.0 (reference) 2) centres with cardiothoracic surgery: 158 pts.; 5-year OS 52%; adjusted HR 0.73, 95% CI 0.53-1.01
Martin-Ucar AE et al., 2004 **[88]**	240 pts.	Overall survival - *better individual specialization with trivial effect:* 1) cardio-thoracic surgeon: 1-year OS 62%, 5-year OS 32% 2) specialist thoracic surgeon: 1-year OS 63%, 5-year OS 31% p=n.s.

Table 40: Effect results of studies ineligible for meta-analyses on overall survival for PICO 4, subgroup 4 (Surgeon specialization, surgical resection)

Mortality was investigated in seven studies (490,544 patients) [88, 140, 168, 193-195, 197].

All three studies exploring ***in-hospital mortality*** showed large effects with improved mortality rated in pulmonary resections by more specialized surgeons (224,056 patients) [88, 193, 197].

[quality of evidence for *in-hospital mortality*: very low ⊕◯◯◯, rated down for risk of bias -1, indirectness -1 and imprecision -1]

Regarding ***30-day mortality***, three studies exhibited large (45,290 patients) [194, 195] and moderate effects (9,579 patients) [140]. The fourth and largest study by Nagayasu et al. demonstrated only a small prognostic impact, yet comparing number of general thoracic surgeons in both cohorts both with very low mortality rates (211,619 patients) [168].

[quality of evidence for *30-day mortality*: very low ⊕◯◯◯, rated down for indirectness -1, inconsistency -1 and imprecision -1]

The effect results for all types of mortality are listed in ***Table 41***.

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 4, subgroup 4: Surgeon specialization, surgical resection		
***In-house mortality* – 3 observational studies (224,056 patients)**		
Ellis MC et al., 2011 **[193]**	222,233 pts.	In-house mortality - *better individual specialization with large effect (**cave:** highest individual specialization stratum as reference - OR>1.0: **lower** individual specialization correlating with **higher** mortality):* 1) general surgeons: 118,843 pts.; in-house mortality adjusted OR 1.79, 95% CI 1.41-2.05 2) cardiac surgeons: 85,106 pts.; in-house mortality adjusted OR 1.50, 95% CI 1.18-1.91 3) general thoracic surgeons: 18,284 pts.; ***adjusted OR 1.0 (reference)***
Martin-Ucar AE et al., 2004 **[88]**	240 pts.	In-hospital mortality – *better individual specialization with large effect:* 1) cardio-thoracic surgeon: in-hospital mortality 5 deaths (7.7%) 2) specialist thoracic surgeon: in-hospital mortality 5 deaths (5.5%), p=n.s.
Silvestri GA et al., 1998 **[197]**	1,583 pts.	In-hospital mortality - *better individual specialization with large effect:* 1) general surgeons (n=85): 711 pts.; in-hospital mortality 38 deaths (5.3%) 2) thorax surgeons (n=35): 705 pts.; in-hospital mortality 21 deaths (3.0%), p=0.04

***30-day mortality* – 3 observational studies (266,488 patients)**

Damhuis RA et al., 2015 **[140]**	9,579 pts.	30-day mortality - *better individual specialization with moderate effect* (OR<1.0: higher individual specialization correlating with lower mortality)*:* Surgical specialty 2005-2007 1) General surgery: 3.7%; adjusted OR 1.0 (reference) 2) Cardiothoracic surgery: 2.4%; adjusted OR 0.67, 95% CI 0.45-1.00 Surgical training 2008-2010 1) General surgery: 2.1%; adjusted OR 1.0 (reference) 2) Cardiothoracic surgery: 2%; adjusted OR 0.99, 95% CI 0.64-1.52
Farjah F et al., 2009 **[194]**	19,745 pts.	30-day mortality - *better individual specialization with large effect* (OR<1.0: higher individual specialization correlating with lower mortality)*:* 1) general surgeons: 4,677 pts.; 30-day mortality 6.0%; adjusted HR 1.0 (reference) 2) cardiothoracic surgeons: 8,807 pts.; 30-day mortality 5.0%; adjusted HR 0.92, 95% CI 0.73-1.16 3) general thoracic surgeons: 6,261 pts.; 30-day mortality 4.4%; adjusted HR 0.92, 95% CI 0.68-1.25
Goodney PP et al., 2005 **[195]**	25,545 pts.	30-day mortality - *better individual specialization with large effect* (OR<1.0: higher individual specialization correlating with lower mortality)*:* 1) general surgeons: 9,263 pts.; 30-day mortality 7.6%; adjusted OR 1.0 (reference) 2) non-cardiac thoracic surgeons: 6,490 pts.; 30-day mortality 5.8%; adjusted OR 0.77, 95% CI 0.68-0.89 3) cardiothoracic surgeons: 9,782 pts.; 30-day mortality 5.6%; adjusted OR 0.72, 95% CI 0.64-0.82
Nagayasu T et al., 2016 **[168]**	211,619 pts.	30-day mortality - *better individual specialization with large effect* (OR<1.0: higher individual specialization correlating with lower mortality)*:* 1) <3 certified general thoracic surgeons: 132,062 pts; 30-day mortality 569 deaths (0.043%); adjusted OR 1.0 (reference) 2) ≥3 certified general thoracic surgeons: 88,557 pts.; 30-day mortality 272 deaths (0.031); adjusted OR 0.688, 95% CI 0.587-0.806

Table 41: Effect results of studies ineligible for meta-analyses on different types of mortality for PICO 4, subgroup 4 (Surgeon specialization, surgical resection)

A large effect relating to ***accuracy of staging*** with higher lymphadenectomy rates by general thoracic surgeons compared to general and cardiothoracic surgeons was seen in the study by *Ellis et al.* (222,233 patients) [193] (see effect results in ***Table 42***).

[quality of evidence for *accuracy of staging*: low ⊕⊕◯◯]

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 4, subgroup 4 Surgeon specialization, surgical resection		
***Accuracy of staging* – 1 observational study (222,233 patients)**		
Ellis MC et al., 2011 **[193]**	222,233 pts.	Accuracy of staging (lymphadenectomy) - *better individual specialization with large effect (**cave:*** highest individual specialization stratum as reference – OR<1.0: ***lower*** individual specialization correlating with ***lower*** accuracy of staging)*:* 1) general surgeons: 118,843 pts.; lymphadenectomy adjusted OR 0.47, 95% CI 0.35-0.652) cardiac surgeons: 85,106 pts.; lymphadenectomy; adjusted OR 0.47, 95% CI 0.35-0.64 3) general thoracic surgeons: 18,284 pts.; lymphadenectomy; adjusted OR 1.0 (reference)

Table 42: Effect results of the study by *Ellis et al.* on accuracy of staging for PICO 4, subgroup 4 (Surgeon specialization, surgical resection)

Receipt of curative treatment was assessed in two studies showing a large effect in the work by *Martin-Ucar et al.* with increased resection rates when more specialized surgeon care was applied (2,891 patients) [88] opposed by a trivial effect in the study by *Li et al.* (1,591 patients) [158] (see effect results in ***Table 43***).

[quality of evidence for *receipt of curative treatment*: very low ⊕◯◯◯, ⊕◯◯◯, rated down for risk of bias -1, indirectness -1, inconsistency -1 and imprecision -1]

Group Outcome Author, year	total number of patients	study effect per outcome
PICO 4, subgroup 4: Surgeon specialization, surgical resection		
***Receipt of curative treatment* – 2 observational studies (4,482 patients)**		
Li et al., 2008 **[158]**	1,591 pts.	Receipt of curative treatment - *better individual specialization with trivial effect* (OR>1.0: higher individual specialization correlating with higher resection rate)*:* 1) centres without cardiothoracic surgery: 1,393 pts.; resection rate 69%; adjusted OR 1.0 (reference) 2) centres with cardiothoracic surgery: 198 pts.; resection rate 69%; adjusted OR 0.73, 95% CI 0.47-1.14
Martin-Ucar AE et al., 2004 **[88]**	2,891 pts.	Receipt of curative treatment - *better individual specialization with large effect:* 1) cardio-thoracic surgeon: resection rate 12% 2) specialist thoracic surgeon: resection rate 23.4% p<0.001

Table 43: Effect results of the study by *Martin-Ucar et al.* on receipt of curative treatment for PICO 4, subgroup 4 (Surgeon specialization, surgical resection)

The GRADE evidence profile relating to the subgroup 4 in PICO 4 (Surgeon specialization, surgical resection) is presented in **Table 44**.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	better individual specialization	less individual specialization	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
3 [88, 158, 194]	observational studies	serious [a]	serious [b]	serious [c]	serious [d]	none	One study displayed a large effect (19,745 patients), two studies reporrted trivial effects (1,831 patients).				⊕◯◯◯ VERY LOW	CRITICAL
In-hospital mortality												
3 [88, 193, 197]	observational studies	not serious	not serious	serious [c]	serious [d]	none	All three studies exploring *in-hospital mortality* showed large effects with improved mortality rated in pulmonary resections by more specialized surgeons (224,056 patients).				⊕◯◯◯ VERY LOW	CRITICAL
30-day mortality												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	better individual specialization	less individual specialization	Relative (95% CI)	Absolute (95% CI)		
4 [140, 168, 194, 195]	observational studies	not serious	serious [b]	serious [c]	serious [d]	none	, three studies exhibited large (45,290 patients) and moderate effects (9,579 patients). The fourth study by Nagayasu et al. demonstrated only a small prognostic impact211,619 patients).				⨁◯◯◯ VERY LOW	CRITICAL
Accuracy of staging												
1 [193]	observational studies	not serious	not serious	not serious	not serious	none	-/118843 [e]	-/18284 [e]	**OR 0.47** (0.35 to 0.65)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL
Receipt of curative treatment												
2 [88, 158]	observational studies	serious [a]	serious [b]	serious [c]	serious [d]	none	*Receipt of curative treatment* was assessed in two studies showing a large effect in the work by *Martin-Ucar et al.* with increased resection rates when more specialized surgeon care was applied (2,891 patients) opposed by a trivial effect in the study by *Li et al.* (1,591 patients).				⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

Explanations:

a. one study did not adequately control for confounding
b. varying effect sizes across studies raise concerns about high heterogeneity
c. studies used different types of specialization
d. pooling of studies not feasible
e. no events stated

Table 44: GRADE evidence profile for PICO 4, subgroup 4 (Surgeon specialization, surgical resection)

5) PICO 4, subgroups 5a-5i: Hospital volume of care, procedures other than surgical resection

Eleven observational studies explored the impact of *hospital volume in procedures other than surgical resection* (591,766 patients) [136, 141, 145, 146, 150, 153, 157, 166, 172, 182, 189].

5a) All lung cancer, all stages, higher hospital volume of diagnostic bronchoscopies including EBUS (vs. lower hospital volume)

Two studies looked at **diagnostic bronchoscopies including EBUS** (78,646 patients) [150, 172].

Hiraishi et al. described large effects with improved rates in high volume hospitals for ***7-day mortality***, ***15-day mortality*** and ***30-day mortality***, yet a trivial effect regarding pneumothorax as peri-intervenional ***morbidity*** (77,755 patients) [150].

[quality of evidence for *7-day mortality*: very low ⊕〇〇〇, rated down for imprecision -1]

[quality of evidence for *15-day mortality*: low ⊕⊕〇〇]

[quality of evidence for *30-day mortality*: low ⊕⊕〇〇]

[quality of evidence for *morbidity*: very low ⊕〇〇〇, rated down for risk of bias -1 and imprecision -1]

Ost et al. revealed a trivial volume-dependent effect on rates of ***pathological confirmation*** (891 patients) [172]

[quality of evidence for *pathological confirmation*: very low ⊕〇〇〇, rated down for imprecision -1]

The effect results for all types of mortality are listed in ***Table 45***.

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 4, subgroup 5a: Hospital volume of care, procedures other than surgical resection		
Diagnostic bronchoscopy including EBUS		
***7-day mortality* – 1 observational study (77,755 patients)**		
Hiraishi Y et al., 2019 **[150]**	77,755 pts.	7-day mortality - *higher hospital volume of care with large effect* (OR<1.0: higher hospital volume of care correlating with lower mortality): 1) 1-50 procedures p.a.: 11,086 pts.; 7-day mortality 89 deaths (0.8%); adjusted OR 1.0 (reference) 2) 51-100 procedures p.a.: 16,616 pts.; 7-day mortality 104 deaths (0,6%); adjusted OR 0.93, 95% CI 0.68-1.27 3) 101-300 procedures p.a.: 37,777 pts.; 7-day mortality 143 deaths (0.4%); adjusted OR 0.69, 95% CI 0.5-0.92 4) >300 procedures p.a.: 12,276 pts.; 7-day mortality 38 deaths (0.3%); adjusted OR 0.67, 95% CI 0.45-1.05
***15-day mortality* – 1 observational study (77,755 patients)**		
Hiraishi Y et al., 2019 **[150]**	77,755 pts.	15-day mortality – *higher hospital volume of care with large effect* (OR<1.0: higher hospital volume of care correlating with lower mortality):

		1) 1-50 procedures p.a.: 11,086 pts.; 15-day mortality 220 deaths (2.0%); unadjusted OR 1.0 (reference) 2) 51-100 procedures p.a.: 16,616 pts.; 15-day mortality 285 deaths (1.7%); unadjusted OR 0.86, 95% CI 0.72-1.03 3) 101-300 procedures p.a.: 37,777 pts.; 15-day mortality 405 deaths (1.1%); unadjusted OR 0.54, 95% CI 0.46-0.64 4) >300 procedures p.a.: 12,276 pts.; 30-day mortality 112 deaths (0.9%); unadjusted OR 0.45, 95% CI 0.36-0.57
***30-day mortality* – 1 observational study (77,755 patients)**		
Hiraishi Y et al., 2019 **[150]**	77,755 pts.	30-day mortality - *higher hospital volume of care with large effect* (OR<1.0: higher hospital volume of care correlating with lower mortality)*:* 1) 1-50 procedures p.a.: 11,086 pts.; 30-day mortality 509 deaths (4.6%); adjusted OR 1.0 (reference) 2) 51-100 procedures p.a.: 16,616 pts.; 30-day mortality 680 deaths (4.1%); adjusted OR 1.02, 95% CI 0.88-1.18 3) 101-300 procedures p.a.: 37,777 pts.; 30-day mortality 973 deaths (2.6%); adjusted OR 0.77, 95% CI 0.66-0.88 4) >300 procedures p.a.: 12,276 pts.; 30-day mortality 262 deaths (2.1%); adjusted OR 0.73, 95% CI 0.58-0.91
***Morbidity* – 1 observational study (77,755 patients)**		
Hiraishi Y et al., 2019 **[150]**	77,755 pts.	Morbidity (pneumothorax) - *higher hospital volume of care with trivial effect* (OR<1.0: higher hospital volume of care correlating with lower morbidity): 1) 1-50 procedures p.a.: 11,086 pts.; pneumothorax 112 events (1.0%); unadjusted OR 1.0 (reference) 2) 51-100 procedures p.a.: 16,616 pts.; pneumothorax 173 events (1.0%) 3) 101-300 procedures p.a.: 37,777 pts.; pneumothorax 349 events (0.9%) 4) >300 procedures p.a.: 12,276 pts.; pneumothorax 116 events (0.9%); unadjusted OR 0.93, 95% CI 0.72-1.21
***Pathological confirmation* – 1 observational study (891 patients)**		
Ost DE et al. **[172]**	891 pts.	Pathologic confirmation - *higher hospital volume of care with trivial effect*: 1) 97 procedures p.a.: diagnostic yield 0.38, 95% CI 0.25-0.56 2) 166 procedures p.a.: diagnostic yield 0.35, 95% CI 0.24-0.49 3) 169 procedures p.a.: diagnostic yield 0.44, 95% CI 0.33-0.59 4) 276 procedures p.a.: diagnostic yield 0.53, 95% CI 0.43-0.64 5) 325 procedures p.a.: diagnostic yield 0.48, 95% CI 0.36-0.64 6) 435 procedures p.a.: diagnostic yield 0.58, 95% CI 0.50-0.67

Table 45: Effect results of the studies by *Hiraishi et al.* and *Ost et al.* sorted by outcomes for PICO 4, subgroup 5a (Hospital volume of care, procedures other than surgical resection – diagnostic bronchoscopy including EBUS)

The GRADE evidence profile relating to the subgroup 5a in PICO 4 (Hospital volume of care, procedures other than surgical resection - diagnostic bronchoscopy including EBUS) is presented in ***Table 46***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	higher hospital volume of care	lower hospital volume of care	Relative (95% CI)	Absolute (95% CI)		
7-day mortality												
1 [150]	observational studies	not serious	not serious	not serious	serious [a]	none	38/12276 (0.3%)	89/11086 (0.8%)	**OR 0.67** (0.45 to 1.05)	**3 fewer per 1.000** (from 4 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
15-day mortality												
1 [150]	observational studies	not serious	not serious	not serious	not serious	none	112/12276 (0.9%)	220/11086 (2.0%)	**OR 0.45** (0.36 to 0.57)	**11 fewer per 1.000** (from 13 fewer to 8 fewer)	⊕⊕◯◯ LOW	CRITICAL
30-day mortality												
1 [150]	observational studies	not serious	not serious	not serious	not serious	none	262/12276 (2.1%)	509/11086 (4.6%)	**OR 0.73** (0.58 to 0.91)	**12 fewer per 1.000** (from 19 fewer to 4 fewer)	⊕⊕◯◯ LOW	CRITICAL
Morbidity (pneumothorax)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	higher hospital volume of care	lower hospital volume of care	Relative (95% CI)	Absolute (95% CI)		
1 [150]	observational studies	serious [b]	not serious	not serious	serious [a]	none	116/12276 (0.9%)	112/11086 (1.0%)	**OR 0.93** (0.72 to 1.21)	**1 fewer per 1.000** (from 3 fewer to 2 more)	⊕◯◯◯ VERY LOW	CRITICAL
Pathological confirmation												
1 [172]	observational studies	not serious	not serious	not serious	serious [c]	none	1 study revealed a trivial volume-dependent effect on rates of pathological confirmation (891 patients)				⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio

Explanations:

a. The 95% CI includes the potential for benefit; however, cannot exclude the possibility of no benefit.

b. not adequately controlled for confounding

c. small sample size of study raises concerns about potential imprecision.

Table 46: GRADE evidence profile for PICO 4, subgroup 5a (Hospital volume of care, procedures other than surgical resection - diagnostic bronchoscopy including EBUS)

5b) All lung cancer, all stages, higher hospital volume of pathological lung cancer diagnostics (vs. lower hospital volume)

We retrieved only one study on the impact of hospital volumes on *quality of pathological lung cancer diagnostics*. *Gansler et al.* concluded a large effect with better ***pathological confirmation*** expressed as lower rates of unspecified histologies if pathology testing was performed in more specialized institutions (89,409 specimens from lung cancer patients) [145] (effect results in ***Table 47***).

[quality of evidence for *pathological confirmation*: low ⊕⊕◯◯]

Group **Outcome**	**total number of patients**	**study effect per outcome**

Author, year		
PICO 4, subgroup 5b: Hospital volume of care, procedures other than surgical resection		
Quality of pathological lung cancer diagnostics		
***Pathological confirmation* – 1 observational study (89,409 patients)**		
Gansler T et al. **[172]**	89,409 pts.	Pathologic confirmation (rate of unspecified histologies=broad diagnoses) - *higher hospital volume of care with large effect* (prevalence ratio<1.0: higher hospital volume of care correlating with less unspecified histologies): 1) low volume hospitals: broad diagnoses 482 events (8.55%); adjusted prevalence ratio 1.0 (reference) 2) medium volume hospitals: broad diagnoses 1,489 events (7.50%); adjusted prevalence ratio 0.88, 95% CI 0.79-0.98 3) high volume hospitals: broad diagnoses 3,688 events (5.77%); adjusted prevalence ratio 0.72, 95% CI 0.63-0.82

Table 47: Effect results of the study by *Gansler et al.* on pathological confirmation for PICO 4, subgroup 5b (Hospital volume of care, procedures other than surgical resection – quality of pathological lung cancer diagnostics)

The GRADE evidence profile relating to the subgroup 5b in PICO 4 (Hospital volume of care, procedures other than surgical resection - quality of pathological lung cancer diagnostics) is presented in ***Table 48***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	higher hospital volume of care	lower hospital volume of care	Relative (95% CI)	Absolute (95% CI)		
Pathologic confirmation												
1 [172]	observational studies	not serious	not serious	not serious	not serious	none	3688/63917 (5.8%)	482/5637 (8.6%)	**OR 0.72** (0.63 to 0.82)	**22 fewer per 1.000** (from 30 fewer to 14 fewer)	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio

Table 48: GRADE evidence profile for PICO 4, subgroup 5b (Hospital volume of care, procedures other than surgical resection - quality of pathological lung cancer diagnostics)

5c) NSCLC, stage II/IIIA, higher hospital volume of chemoradiotherapy (vs. lower volume)

Two studies addressed **chemoradiotherapy in stage II and IIIA/B NSCLC** (734 patients). Both described large effects on ***overall survival*** , yet discriminating lower versus higher hospital volumes at rather low thresholds [141, 157] (effect results in ***Table 49***).

[quality of evidence for *overall survival*: very low ⊕◯◯◯, rated down for indirectness -1 and imprecision -1]

Eaton et al. saw a moderate effect in terms of ***progression-free survival*** (495 patients) [141].

[quality of evidence for *progression-free survival*: very low ⊕◯◯◯, rated down for imprecision -1]

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 4, subgroup 5c: Hospital volume of care, procedures other than surgical resection		
Chemoradiotherapy in stage II and IIIA/B NSCLC		
***Overall survival* – 2 observational studies (734 patients)**		
Eaton BR et al., 2016 **[141]**	495 pts.	Overall survival - *higher hospital volume of care with large effect* (HR<1.0: higher hospital volume of care correlating with higher OS)*:* 1) low+medium volume hospitals: 195 pts; median OS 19.8 months; adjusted HR 1.0 (reference) 2) high volume hospitals: 300 pts.; median OS 26.2 months; adjusted HR 0.75, 95% CI 0.59-0.97
Lee JS et al., 2002 **[157]**	239 pts.	Overall survival – *higher hospital volume of care with large effect:* 1) 1-4 procedures p.a.: 92 pts.; median OS 14.8 months; 1-year OS 54%; 2-year OS 20%; 3-year OS 13%; 2) ≥5 procedures p.a.: 147 pts.; median OS 20.5 months1-year OS 69%; 2-year OS 45%; 3-year OS 31%; Exp (Coefficient) 1.66; p=0.001
***Progression-free survival* – 1 observational study (495 patients)**		
Eaton BR et al., 2016 **[141]**	495 pts.	Progression-free survival - *higher hospital volume of care with moderate effect* (HR<1.0: higher hospital volume of care correlating with higher PFS)*:* 1) low+medium volume hospitals: 195 pts; median OS 9.7 months; adjusted HR 1.0 (reference) 2) high volume hospitals: 300 pts.; median OS 11.4 months; adjusted HR 0.85, 95% CI 0.68-1.06

Table 49: Effect results of the studies by *Eaton et al.* and *Lee et al.* sorted by outcomes for PICO 4, subgroup 5c (Hospital volume of care, procedures other than surgical resection – chemoradiotherapy in stage II and IIIA/B NSCLC)

The GRADE evidence profile relating to the subgroup 5c in PICO 4 (Hospital volume of care, procedures other than surgical resection - chemoradiotherapy in stage II and IIIA/B NSCLC) is presented in ***Table 50***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	higher hospital volume of care	lower hospital volume of care	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
2 [141, 157]	observational studies	not serious	not serious	serious [a]	serious [b]	none	Both studies described large effects on *overall survival* (734 patients).				⊕◯◯◯ VERY LOW	CRITICAL
Progression-free survival												
1 [141]	observational studies	not serious	not serious	not serious	serious [b]	none	-/300 [c]	-/195 [c]	**HR 0.85** (0.68 to 1.06)	**-- per 1.000** (from -- to --)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio

Explanations:

a. studies used different thresholds and volume strata

b. small sample size of study raises concerns about potential imprecision.

c. number of events not stated

Table 50: GRADE evidence profile for PICO 4, subgroup 5c (Hospital volume of care, procedures other than surgical resection - chemoradiotherapy in stage II and IIIA/B NSCLC)

5d) NSCLC, stage IIIA, higher hospital volume of different tumour-specific therapies (vs. lower volume)

Different tumour-specific therapies in stage IIIA NSCLC was solely explored in one study highlighting large effects on ***overall survival*** and ***receipt of curative treatment*** (83,673 patients) [166] (effect results in ***Table 51***).

[quality of evidence for *overall survival*: low ⊕⊕◯◯]

[quality of evidence for *receipt of curative treatment*: low ⊕⊕◯◯]

Group
Outcome **total number of patients** **study effect per outcome**
Author, year

PICO 4, subgroup 5d: Hospital volume of care, procedures other than surgical resection		
Different tumour-specific therapies in stage IIIA NSCLC		
***Overall survival* – 1 observational study (83,673 patients)**		
Kommalapati A et al., 2019 **[166]**	83,673 pts.	Overall survival - *higher hospital volume of care with large effect* (***cave:*** highest hospital volume stratum as reference - HR>1.0: ***lower*** hospital volume of care correlating with ***lower*** OS): 1) 1-8 procedures p.a.: 30,919 pts.; median OS 13 months; 1-year OS 57%; 3-year OS 26%; 5-year OS 17%; adjusted HR 1.11, 95% CI 1.09-1.13 2) 9-14 procedures p.a.: 28,404 pts.; median OS 15 months; 1-year OS 59%; 3-year OS 27%; 5-year OS 18%; adjusted HR 1.09, 95% CI 1.07-1.11 3) ≥15 procedures p.a.: 24,350 pts.; median OS 16 months; 1-year OS 63%; 3-year OS 32%; 5-year OS 22%; ***adjusted HR 1.0 (reference)***
***Receipt of curative treatment* – 1 observational study (83,673 patients)**		
Kommalapati A et al., 2019 **[166]**	83,673 pts.	Receipt of curative treatment - *higher hospital volume of care with large effect* (OR>1.0: higher hospital volume of care correlating with higher receipt of curative treatment): 1) 1-8 procedures p.a.: 30,919 pts.; surgery alone/combination 18%; adjusted OR 1.0 (reference) 2) 9-14 procedures p.a.: 28,404 pts.; surgery alone/combination 20%; adjusted OR 1.15, 95% CI 1.10-1.20 3) ≥15 procedures p.a.: 24,350 pts.; surgery alone/combination 25%; adjusted OR 1.55, 95% CI 1.49-1.62

Table 51: Effect results of the study by *Kommalapati et al.* sorted by outcomes for PICO 4, subgroup 5d (Hospital volume of care, procedures other than surgical resection – different tumour-specific therapies in stage IIIA NSCLC)

The GRADE evidence profile relating to the subgroup 5d in PICO 4 (Hospital volume of care, procedures other than surgical resection - different tumour-specific therapies in stage IIIA NSCLC) is presented in ***Table 52****.*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	higher hospital volume of care	lower hospital volume of care	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
1 [166]	observational studies	not serious	not serious	not serious	not serious	none	-/24350 [a]	-/30919 [a]	**HR 1.11** (1.09 to 1.13)	**-- per 1.000** (from -- to --)	⊕⊕◯◯ LOW	CRITICAL
Receipt of curative treatment												
1 [166]	observational studies	not serious	not serious	not serious	not serious	none	-/24350 [a]	-/30919 [a]	**OR 1.55** (1.49 to 1.62)	**-- per 1.000** (from -- to --)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio

Explanations:

a. number of events not stated

Table 52: GRADE evidence profile for PICO 4, subgroup 5d (Hospital volume of care, procedures other than surgical resection - different tumour-specific therapies in stage IIIA NSCLC)

5e) All lung cancer, stage III/IV, higher hospital volumes of systemic therapies (vs. lower volume)

Burgers et al. investigated the impact of hospital volumes as a continuous variable in **systemic therapy in stage III/IV lung cancer** showing a trivial effect on ***30-day mortality*** (26,277 patients) [136] (see effect results in ***Table 53***).

[quality of evidence for *receipt of curative treatment*: very low ⊕◯◯◯, rated down imprecision -1]

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 4, subgroup 5e: Hospital volume of care, procedures other than surgical resection		
Systemic therapy in stage III/IV lung cancer		
***30-day mortality* – 1 observational study (26,277 patients)**		
Burgers JA et al., 2018 **[136]**	26,277 pts.	30-day mortality - *higher hospital volume of care with trivial effect*(OR<1.0: higher hospital volume of care ***as continuous variable*** correlating with lower mortality)*:* continuous: n.s.

Table 53: Effect results of the study by *Burgers et al.* on 30-day mortality for PICO 4, subgroup 5e (Hospital volume of care, procedures other than surgical resection – systemic therapy in stage III/IV lung cancer)

The GRADE evidence profile relating to the subgroup 5e in PICO 4 (Hospital volume of care, procedures other than surgical resection - systemic therapy in stage III/IV lung cancer) is presented in ***Table 54***.

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
30-day mortality									
1 [136]	observational studies	not serious	not serious	not serious	serious [a]	none	The impact of hospital volumes was assessed as a continuous variable in systemic therapy in stage III/IV lung cancer showing a trivial effect on *30-day mortality* (26,277 patients).	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval
Explanations:
a. The 95% CI cannot exclude no meaningful change on mortality.

Table 54: GRADE evidence profile for PICO 4, subgroup 5e (Hospital volume of care, procedures other than surgical resection - systemic therapy in stage III/IV lung cancer)

5f) NSCLC, stage IV, higher hospital volume of different tumour-specific therapies in stage IV NSCLC(vs. lower volume)

Goyal et al. analyzed volume-dependency of ***overall survival*** and ***receipt of any tumour-specific treatment*** in **different tumour-specific therapies in stage IV NSCLC**, both largely improved by higher volumes (338,445 patients) [146] (effect results in ***Table 55***).

[quality of evidence for *overall survival*: low ⊕⊕◯◯]

[quality of evidence for *receipt of any tumour-specific treatment*: low ⊕⊕◯◯]

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 4, subgroup 5f: Hospital volume of care, procedures other than surgical resection		
Different tumour-specific therapies in stage IV NSCLC		
***Overall survival* – 1 observational study (338,445 patients)**		
Goyal G et al., 2018 **[146]**	338,445 pts.	Overall survival - *higher hospital volume of care with large effect* (***cave:*** highest hospital volume stratum as reference - HR>1.0: ***lower*** hospital volume of care correlating with ***lower*** OS)*:* 1) 1-23 procedures p.a.): 85,500 pts.; median OS 6 months; 1-year OS 30%; 3-year OS 8%; 5-year OS 4%; adjusted HR 1.11, 95% CI 1.10-1.12

		2) 24-36 procedures p.a.: 85,101 pts.; median OS 6 months; 1-year OS 29%; 3-year OS 8%; 5-year OS 4%; adjusted HR 1.12, 95% CI 1.11-1.14 3) 37-55 procedures p.a.: 85,227 pts.; median OS 7 months; 1-year OS 32%; 3-year OS 9%; 5-year OS 5%; adjusted HR 1.05, 95% CI 1.04-1.06 4) ≥56 procedures p.a.: 82,617 pts.; median OS 8 months; 1-year OS 35%; 3-year OS 11%; 5-year OS 6%; ***adjusted HR 1.0 (reference)***
Receipt of any tumour-specific treatment **– 1 observational study (338,445 patients)**		
Goyal G et al., 2018 **[146]**	338,445 pts.	Receipt of any tumour-specific treatment - *higher hospital volume of care with large effect* (HR<1.0: higher hospital volume of care correlating with higher OS)*:* 1) 1-23 procedures p.a.: 85,500 pts.; no treatment 26%; adjusted OR 1.0 (reference) 2) 24-36 procedures p.a.: 85,101 pts.; no treatment 24%; adjusted 1.12, 95% CI 1.09-1.15 3) 37-55 procedures p.a.: 85,227 pts.; no treatment 22%; adjusted OR 1.21, 95% CI 1.18-1.23 4) ≥56 procedures p.a.: 82,617 pts.; no treatment 18%; adjusted OR 1.42, 95% CI 1.39-1.46

Table 55: Effect results of the study by *Goyal et al.* sorted by outcomes for PICO 4, subgroup 5f (Hospital volume of care, procedures other than surgical resection – different tumour-specific therapies in stage IV NSCLC)

The GRADE evidence profile relating to the subgroup 5f in PICO 4 (Hospital volume of care, procedures other than surgical resection - different tumour-specific therapies in stage IV NSCLC) is presented in ***Table 56***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	higher hospital volume of care	lower hospital volume of care	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
1 [166]	observational studies	not serious	not serious	not serious	not serious	none	-/24350 [a]	-/30919 [a]	**HR 1.11** (1.09 to 1.13)	**-- per 1.000** (from -- to --)	⊕⊕◯◯ LOW	CRITICAL
Receipt of curative treatment												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	higher hospital volume of care	lower hospital volume of care	Relative (95% CI)	Absolute (95% CI)		
1 [166]	observational studies	not serious	not serious	not serious	not serious	none	-/24350 [a]	-/30919 [a]	**HR 1.55** (1.49 to 1.62)	**-- per 1.000** (from -- to --)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio
Explanations:
a. number of events not stated

Table 56: GRADE evidence profile for PICO 4, subgroup 5f (Hospital volume of care, procedures other than surgical resection - different tumour-specific therapies in stage IV NSCLC)

5g) NSCLC, all stages, higher hospital volume of different tumour-specific therapies (vs. lower volume)

The impact of hospital volumes on ***receipt of curative treatment*** in **different tumour-specific therapies in all-stage NSCLC** was the topic in the work by *Wouters et al.* in which a large effect was described (43,544 patients) [189] (effect results in ***Table 57***).

[quality of evidence for *receipt of curative treatment*: low ⊕⊕◯◯]

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 4, subgroup 5g: Hospital volume of care, procedure other than surgical resection		
Different tumour-specific therapies in all-stage NSCLC		
***Receipt of curative treatment* – 1 observational study (43,544 patients)**		
Wouters MW et al., 2010 **[189]**	43,544 pts.	Receipt of curative treatment - *higher hospital volume of care with large effect* (OR>1.0: higher hospital volume of care correlating with higher receipt of curative treatment): 1) 1-49 procedures p.a.: 3,910 pts.; adjusted OR 1.0 (reference) 2) 50-100 procedures p.a.: 16,209 pts.; adjusted OR 1.40, 95% CI 1.17-1.68 3) >100 procedures p.a.: 23,425 pts.; adjusted OR 1.69, 95% CI 1.40-2.04

Table 57: Effect results of the study by *Wouter et al.* on receipt of curative treatment for PICO 4, subgroup 5g (Hospital volume of care, procedures other than surgical resection – different tumour-specific therapies in all-stage NSCLC)

The GRADE evidence profile relating to the subgroup 5g in PICO 4 (Hospital volume of care, procedures other than surgical resection - different tumour-specific therapies in all-stage NSCLC) is presented in ***Table 58***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	higher hospital volume of care	lower hospital volume of care	Relative (95% CI)	Absolute (95% CI)		
Receipt of curative treatment												
1 [189]	observational studies	not serious	not serious	not serious	not serious	none	-/23425 [a]	-/3910 [a]	**OR 1.69** (1.40 to 2.04)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio
Explanations:
a. number of events not stated

Table 58: GRADE evidence profile for PICO 4, subgroup 5g (Hospital volume of care, procedures other than surgical resection - different tumour-specific therapies in all-stage NSCLC)

5h) All lung cancer, all stages, higher hospital volume of different tumour-specific therapies (vs. lower volume)

Ioka et al. revealed a large effect on ***overall survival*** in patients with **different tumour-specific therapies in all-stage lung cancers** treated at hospitals with higher volumes (9,235 patients) [153] (see effect results in ***Table 59***).

[quality of evidence for *overall survival*: low ⊕⊕◯◯]

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 4, subgroup 5h: Hospital volume of care, procedures other than surgical resection		
Different tumour-specific therapies in all-stage lung cancers		
***Overall survival* – 1 observational study (9,235 patients)**		
Ioka A et al., 2007 **[153]**	9,235 pts.	Overall survival - *higher hospital volume of care with large effect* (***cave:*** highest hospital volume stratum as reference - HR>1.0: ***lower*** hospital volume of care correlating with ***lower*** OS)*:* 1) very low volume hospitals: 2,316 pts.; relative 5-year survival 10.7%; adjusted HR 1.8, 95% CI 1.6-1.9

2) low volume hospitals: 2,460 pts.; relative 5-year survival 21.0%; adjusted HR 1.3, 95% CI 1.3-1.4
3) medium volume hospitals: 2,022 pts.; relative 5-year survival 18.8%; adjusted HR 1.3, 95% CI 1.2-1.4
4) high volume hospitals: 2,437 pts.; relative 5-year survival 31.7%; ***adjusted HR 1.0 (reference)***

Table 59: Effect results of the study by *Ioka et al.* on overall survival for PICO 4, subgroup 5h (Hospital volume of care, procedures other than surgical resection – different tumour-specific therapies in all-stage lung cancers)

The GRADE evidence profile relating to the subgroup 5h in PICO 4 (Hospital volume of care, procedures other than surgical resection - different tumour-specific therapies in all-stage lung cancers) is presented in ***Table 60***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	higher hospital volume of care	lower hospital volume of care	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
1 [153]	observational studies	not serious	not serious	not serious	not serious	none	-/2437 [a]	-/2316 [a]	**HR 1.8** (1.6 to 1.9)	**-- per 1.000** (from -- to --)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio
Explanations:
a. number of events not stated

Table 60: GRADE evidence profile for PICO 4, subgroup 5h (Hospital volume of care, procedures other than surgical resection - different tumour-specific therapies in all-stage lung cancers)

5i) All lung cancer, all stages, higher hospital volume of ICU-treated lung cancer patients (vs. lower volume)

In the multinational, multicenter study by *Soares et al.*, ***30-day mortality*** and ***180-day mortality*** in **ICU-treated lung cancer patients** was largely reduced when ICUs treated a higher proportion of lung cancer patients in all ICU patients (449 patients) [182] (effect results in ***Table 61***).

[quality of evidence for *30-day mortality*: very low ⊕◯◯◯, rated down for imprecision -1]

[quality of evidence for *180-day mortality*: very low ⊕◯◯◯, rated down for imprecision -1]

Group Outcome Author, year	total number of patients	study effect per outcome
PICO 4, subgroup 5i: Hospital volume of care, procedures other than surgical resection		
ICU therapy in lung cancer patients		
***30-day mortality* – 1 observational study (449 patients)**		
Soares et al., 2014 **[182]**	449 pts.	30-day mortality - *higher hospital volume of care with large effect* (OR<1.0: higher hospital volume of care correlating with lower mortality)*:* 1) <3%: 95 pts.; 30-day mortality 51 deaths (53.7%); adjusted OR 1.0 (reference) 2) 3-5%: 110 pts.; 30-day mortality 52 deaths (47.3%); adjusted OR 1.053, 95% CI 0.699-1.585 3) >5%-6.7%: 132 pts; 30-day mortality 55 deaths (41.7%); adjusted OR 1.064, 95% CI 0.704-1.607 4) >6.7%: 112 pts.; 30-day mortality 31 deaths (27.7%); adjusted OR 0.467, 95% CI 0.293-0.744
***180-day mortality* – 1 observational study (449 patients)**		
Soares et al., 2014 **[182]**	449 pts.	180-day mortality - *higher hospital volume of care with large effect* (OR<1.0: higher hospital volume of care correlating with lower mortality)*:* 1) <3%: 95 pts.; 180-day mortality 63deaths (66.3%); adjusted OR 1.0 (reference) 2) 3-5%: 110 pts.; 180-day mortality 71 deaths (64.5%); adjusted OR 1.123, 95% CI 0.630-2.003 3) >5%-6.7%; 132 pts; 180-day mortality 67 deaths (50.8%); adjusted OR 0.995, 95% CI 0.478-1.909 4) >6.7%: 112 pts.; 180-day mortality 48 deaths (42.9%); adjusted OR 0.559, 95% CI 0.307-1.017

Table 61: Effect results of the study by *Soares et al.* sorted by outcomes for PICO 4, subgroup 5i (Hospital volume of care, procedures other than surgical resection – ICU therapy in lung cancer patients)

The GRADE evidence profile relating to the subgroup 5i in PICO 4 (Hospital volume of care, procedures other than surgical resection - ICU therapy in lung cancer patients) is presented in ***Table 62***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	higher hospital volume of care	lower hospital volume of care	Relative (95% CI)	Absolute (95% CI)		
30-day mortality												
1 [182]	observational studies	not serious	not serious	not serious	serious [a]	none	31/112 (27.7%)	51/95 (53.7%)	**OR 0.467** (0.307 to 1.017)	**186 fewer per 1.000** (from 274 fewer to 4 more)	⊕◯◯◯ VERY LOW	CRITICAL
180-day mortality												
1 [182]	observational studies	not serious	not serious	not serious	very serious [a]	none	48/112 (42.9%)	63/95 (66.3%)	**OR 0.559** (0.307 to 1.017)	**139 fewer per 1.000** (from 286 fewer to 4 more)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

Explanations:

a. In addition to small sample size, the 95% CI includes the potential for benefit; however, cannot exclude the possibility of no benefit.

Table 62: GRADE evidence profile for PICO 4, subgroup 5i (Hospital volume of care, procedures other than surgical resection - ICU therapy in lung cancer patients)

6) PICO 4, subgroups 6a-6b: Hospital specialization, procedures other than surgical resection

Two studies focussed on the effect of hospital specialization in procedures other than surgical resection (132,953 patients) [145, 189].

6a) All lung cancer, all stages, better hospital specialization in pathological lung cancer diagnostics (vs. less specialization)

Gansler et al. observed a trivial effect on ***pathological confirmation*** regarding the **quality of pathological lung cancer diagnostics** in the context of hospital specialization (89,409 patients) revealing a trivial effect [145] (effect results in ***Table 63***).

[quality of evidence for *pathological confirmation*: very low ⊕◯◯◯, rated down for imprecision -1]

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 4, subgroup 6a: Hospital specialization, procedures other than surgical resection		
Quality of pathological lung cancer diagnostics		
***Pathological confirmation* – 1 observational study (89,409 patients)**		
Gansler T et al. **[172]**	89,409 pts.	Pathologic confirmation (rate of unspecified histologies=broad diagnoses) - *better hospital specialization with trivial effect* (prevalence ratio>1.0: higher hospital specialization correlating with less unspecified histologies)*:* 1) community hospitals: broad diagnoses 838 events (7.75%); adjusted prevalence ratio 1.0 (reference) 2) comprehensive community hospitals: broad diagnoses 3,064 events (6.69%); adjusted prevalence ratio 1.10, 95% CI 1.00-1.21 3) teaching/research hospitals: broad diagnoses 1,206 events (5,40%); adjusted prevalence ratio 0.86, 95% CI 0.75-0.98 4) NCI-designated comprehensive hospitals: : broad diagnoses 417 events (4.81%); adjusted prevalence ratio 1.01, 95% CI 0.81-1.29

Table 63: Effect results of the study by *Gansler et al.* on pathological confirmation for PICO 4, subgroup 6a (Hospital specialization, procedures other than surgical resection - quality of pathological lung cancer diagnostics)

The GRADE evidence profile relating to the subgroup 6a in PICO 4 (Hospital specialization, procedures other than surgical resection - quality of pathological lung cancer diagnostics) is presented in ***Table 64***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	better hospital specialization	less specialized hospitals	Relative (95% CI)	Absolute (95% CI)		
Pathological confirmation												
1 [172]	observational studies	not serious	not serious	not serious	serious [a]	none	417/8669 (4.8%)	838/10813 (7.7%)	**OR 1.01** (0.81 to 1.29)	**1 more per 1.000** (from 14 fewer to 20 more)	⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio

Explanations:

a. 95% CI includes the possibility that there may not be a benefit in pathological confirmation.

Table 64: GRADE evidence profile for PICO 4, subgroup 6a (Hospital specialization, procedures other than surgical resection - quality of pathological lung cancer diagnostics)

6b) NSCLC, all stages, better hospital specialization in different tumour-specific therapies (vs. less specialization

Wouters et al. reported a large beneficial effect on ***receipt of curative treatment*** in patients with **different tumour-specific therapies in all-stage NSCLC** when treated in more specialized lung cancer services (43,544 patients) [189] (effect results in ***Table 65***).

[quality of evidence for *receipt of curative treatment*: low ⊕⊕◯◯]

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 4, subgroup 6b: Hospital specialization, procedures other than surgical resection		
Different tumour-specific therapies in all-stage NSCLC		
***Receipt of curative treatment* – 1 observational study (43,544 patients)**		
Wouters MW et al., 2010 **[189]**	43,544 pts.	Receipt of curative treatment - *better hospital specialization with large effect* 1) non-teaching hospitals: 36,622 pts.; adjusted OR 1.0 (reference) 2) teaching hospitals: 6,922 pts.; adjusted OR 0.63, 95% CI 0.52-0.78

Table 65: Effect results of the study by *Wouter et al.* on pathological confirmation for PICO 4, subgroup 6b (Hospital specialization, procedures other than surgical resection - different tumour-specific therapies in all-stage NSCLC)

The GRADE evidence profile relating to the subgroup 6b in PICO 4 (Hospital specialization, procedures other than surgical resection - different tumour-specific therapies in all-stage NSCLC) is presented in ***Table 66***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	better hospital specialization	less specialized hospitals	Relative (95% CI)	Absolute (95% CI)		
Receipt of curative treatment												
1 [189]	observational studies	not serious	not serious	not serious	not serious	none	-/6922 [a]	-/366622 [a]	**OR 1.58** (1.28 to 1.94)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

Explanations:

a. number of events not stated

Table 66: GRADE evidence profile for PICO 4, subgroup 6b (Hospital specialization, procedures other than surgical resection - different tumour-specific therapies in all-stage NSCLC)

C. PICO 4: GRADE evidence to decision framework

Table 67 depicts the GRADE evidence to decision framework relating to PICO 4 based upon on the GRADE evidence profiles as well as additional considerations by the task force panel.

PICO 4: Should patients with lung cancer (or those suspected of having lung cancer) receive lung cancer-specific diagnostic or therapeutic procedures in hospitals/from professionals with higher volumes of activity/with a higher grade of specialization for these procedures rather than receiving them in hospitals/from professionals with lower volumes of activity/with lower grade of specialization for these procedures?	
POPULATION:	lung cancer patients with surgical resection and procedures other than surgical resection
INTERVENTION:	higher hospital volume of care; better specialized hospitals; higher surgeon or other professional volumes of care; better specialized surgeon or other professionals
COMPARISON:	lower hospital volume of care; less specialized hospitals; lower surgeon or other professional volumes of care; less specialized surgeons or other professionals
MAIN OUTCOMES:	Overall survival; Progression-free survival; In-hospital mortality; 7-day mortality 15-day mortality; 30-day mortality; 60-day mortality; 90-day mortality; 180-day mortality; Morbidity; Accuracy of staging; Pathological confirmation; Rate of curative treatment;
SETTING:	Both outpatient and inpatient
PERSPECTIVE:	Clinical recommendations – population perspective
BACKGROUND:	Higher procedural volumes or better specialization of care delivered by hospitals and clinicians may improve outcomes in lung cancer care.
CONFLICT OF INTERESTS:	N/A

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Over the last three decades, numerous studies reported that higher procedural volumes or better specialization of care delivered by hospitals and clinicians lead to improved outcomes in lung cancer patients. Yet, the knowledge of this positive correlation has still not been fully implemented into routine care [200].	Facilitating higher volumes of care and better specialization on the institutional and individual professional level is considered as an essential step by us to improve outcomes in lung cancer care. Likewise, it is a key priority topic for ERS as well as ELF and the Patient Advisory Group

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Our systematic review revealed the following desirable effects of higher volumes of care and better specialization (see related PICO 4 evidence tables, subgroups 1-6 for details): *Surgical resections* -improved overall survival in 1) hospitals with higher volumes, 2) better specialized hospitals, 3) surgeons with higher volumes, and 4) better specialized surgeons -reduced mortality rates in 1) better specialized hospitals, 3) surgeons with higher volumes, and 4) better specialized surgeons (studies applied in-hospital, 30-day, 60-day or 90-day mortality) -reduced rates of certain types of morbidity in 1) hospitals with higher volumes, 2) better specialized hospitals, 3) surgeons with higher volumes, and 4) better specialized surgeons -more accurate staging in 1) better specialized hospitals and 2) better specialized surgeons -higher surgical resection rates in 1) hospitals with higher volumes, 2) better specialized hospitals, and 3) better specialized surgeons *Procedures other than surgical resection* -diagnostic bronchoscopies including EBUS: improved 7-day, 15-day and 30-day mortality rates in hospitals with higher volumes (1 study, large effect, 77,755 patients) -quality of pathological lung cancer diagnostics: more accurate pathological diagnoses in 1) hospitals with higher volumes and 2) better specialized hospitals (both in 1 study, large effect, 89,409 lung cancer specimens) -chemoradiotherapy in stage II and IIIA/B NSCLC: improved overall survival (2 studies large effects, 734 patients) and progression-free survival (1 study, moderate effect, 495 patients) in hospitals with higher volumes -different tumour-specific therapies in stage IIIA NSCLC: improved overall survival and receipt of curative treatment in hospitals with higher volumes (both in 1 study, large effects, 83,673 patients) -different tumour-specific therapies in stage IV NSCLC: improved overall survival and receipt of curative treatment in hospitals with higher volumes (both in 1 study, large effects, 338,445 patients) -different tumour-specific therapies in all-stage NSCLC: improved receipt of curative treatment in 1) hospitals with higher volumes and 2) better specialized hospitals (both in 1 study, large effects, 43,544 patients) -different tumour-specific therapies in all-stage lung cancers: improved overall survival in hospitals with higher volumes (1 study, large effect, 9,235 patients) -ICU therapy in lung cancer patients: improved 30-day and 180-day mortality rates in hospitals with higher volumes (both in 1 study, large effects, 499 patients)	From clinical experience, the TF members consider the following additional desirable effects of higher volumes/better specialisation to be likely: -better rehabilitation of patients at-risk -better peri-operative management -better complication management -application of more advanced techniques that may improve outcomes per se

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	None of the evaluated studies indicated any substantial harms regarding performance of procedures by hospitals or professionals with higher volumes of care or better specialization.	From clinical experience, the TF members are concerned about the following additional undesirable effects of higher volumes/better specialisation: -regionalisation of care to achieve higher volumes and better specialization may reduce proximity to suitable lung cancer services and by that impose burden to some patients

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the evidence was graded as very low (see related PICO 4 evidence tables, subgroups 1-6 for details)	None

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	We did not perform a systematic literature search specifically on patient values relating to performance of procedures by hospitals or professionals with higher volumes of care or better specialization. Our systematic review did not retrieve any related pieces of evidence.	Performance of procedures by hospitals or professionals with higher volumes of care or better specialization is a key priority of patients as confirmed by patient and ELF representatives in our task force panel. While patients generally would like to be treated in hospitals with high volumes and experience as well as by skilled specialists, some patients are concerned about potentially long distances to these qualified lung cancer services.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	Our systematic evidence assessment resulted in large desirable effects and no undesirable effects.	Weighing desirable and undesirable effects based on our systematic evidence assessment, our task force panel discussions and clinical experience, we see clear benefits in performance of procedures by hospitals or professionals with higher volumes of care or better specialization.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	We did not perform a systematic literature search specifically on required resources relating to performance of procedures by hospitals or professionals with higher volumes of care or better specialization. Our systematic review did not retrieve any related pieces of evidence.	We estimate at least moderate costs to achieve performance of procedures by hospitals or clinicians with higher volumes of care or better specialization depending on national health care systems.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● No included studies	not applicable	Required resources are depending on multiple factors, especially re-organisation of lung cancer service networks and centralisation of certain procedures in lung cancer care.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	We did not perform a systematic literature search specifically on cost effectiveness relating to performance of procedures by hospitals or clinicians with higher volumes of care or better specialization. Our systematic review did not retrieve any related pieces of evidence.	Despite increased short-term costs to implement performance of procedures by hospitals or professionals with higher volumes of care or better specialization, we assume mid- and long-term savings due to centralisation of care and .better outcomes. Yet, cost-effectiveness analyses are missing taking into account variation on the local and national care level as well as among different health care systems.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	We did not perform a systematic literature search specifically on equity relating to performance of procedures by hospitals or clinicians with higher volumes of care or better specialization. Our systematic review did not retrieve any related pieces of evidence.	Implementation of performance of procedures by hospitals or professionals with higher volumes of care or better specialization may help to reduce inequalities of care provision. Conversely, appropriate implementation is not expected to create inequality.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	We did not perform a systematic literature search specifically on acceptability to key stakeholders relating to performance of procedures by hospitals or professionals with higher volumes of care or better specialization. Our systematic review did not retrieve any related pieces of evidence.	The idea of performance of procedures by hospitals or professionals with higher volumes of care or better specialization is already well-accepted by patients, medical professionals and healthcare providers alike.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	We did not perform a systematic literature search specifically on feasibility of performance of procedures by hospitals or professionals with higher volumes of care or better specialization. Our systematic review retrieved some pieces of evidence demonstrating successful achievements of performance of procedures by hospitals or clinicians with higher volumes of care or better specialization through re-organisation of care in Canada, Denmark and the USA [190, 202, 203].	If sufficient resources are made available, we assume that performance of procedures by hospitals or professionals with higher volumes of care or better specialization can be achieved in a broader context.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Recommendation

In lung cancer patients, we recommend performing lung cancer surgery a) in lung cancer services specialised in thoracic surgery with high institutional volumes of pulmonary resections and b) by surgeons specialised in thoracic surgery with high individual volumes of pulmonary resections. (Strong recommendation, very low certainty of evidence)

In lung cancer patients, we suggest performing procedures other than lung cancer surgery (*) a) in lung cancer services specialised in this procedure with high institutional volumes of these procedures and b) by professionals specialised in these procedure with high individual volumes of these procedures. (Strong recommendation, very low certainty of evidence)

(*) evidence available for diagnostic bronchoscopy including EBUS, quality of pathological diagnostics, different tumour-specific treatments in stage II-IV lung cancer, and ICU therapy in lung cancer patients

Justification

We have acknowledged that differing individual, institutional and healthcare system immanent factors as well as patient preferences could not be fully accounted for in the retrospective observational studies. Yet, regarding lung cancer surgery, the body of evidence contained a considerable number of studies from different countries and many with large patient figures or even population-based observational designs. The majority of studies demonstrated large effects and thereby justified the recommendation, none showed a converse correlation. Despite the very low overall certainty in the evidence, a strong recommendation for the above-mentioned lung cancer surgery performance is warranted given the life-threatening potential of lung cancer when actually curable tumour stages are not operated on properly, as underlined by significant differences seen in short-term mortality rates and long-term overall survival. This paradigmatic situation is in accordance to GRADE methodology [14]. No substantial harms are evident or foreseen by us. Nevertheless, patient preferences need to be addressed and acknowledged in joint decision making.

Given the limited body of evidence for the various other named diagnostic and therapeutic procedures, only conditional recommendations were consented.

Purposely, no lower thresholds narrowing the best volume of activity were defined at this stage for any of the appraised procedures since these would need in addition consensus by relevant stakeholders on the national level. Likewise, no upper thresholds were defined by us despite bearing in mind that resources are limited and that excessive volumes of care may lead to potentially harmful resource depletion within the processes of all procedures.

Subgroup considerations

None

Implementation considerations

Implementation strategies may require re-organisation of lung cancer service networks and centralisation of certain procedures in lung cancer care depending on national care systems and pre-existing conditions.

Monitoring and evaluation

Population-based and centre-based clinical cancer registries as well as administrative databases may help to monitor implementation processes.

Research priorities

Further quality of care research is needed to better identify and describe underlying factors leading to better hospital and surgeon quality as well as to define lower and upper thresholds for volumes of care in lung cancer surgery. In addition, patient characteristics and preferences should be explored and considered when re-organisation of lung cancer care is envisaged.

This kind of research should be applied to other diagnostic and therapeutic lung cancer interventions as well to those procedures in which similar correlations are likely, but evidence is so far limited.

Table 67: GRADE evidence to decision framework relating to PICO 4

PICO question 5: Should patients with lung cancer (or those suspected of having lung cancer) receive pathological confirmation of tumours or subtyping of lung cancers rather than no pathological confirmation of tumours or subtyping of lung cancers?

PICO 5a: Should pathological confirmation of tumours be obtained in lung cancer patients?

A. PICO 5a: General summary of the evidence

Seven observational studies investigating the impact of pathological confirmation (143,891 patients, range 55-136,993 patients) were finally selected out of initially 759 search results (PRISMA flow diagram: ***online supplement A***) [204-210]. Publication years ranged from 1997 to 2016.

Regarding study populations, three studies included unselected patients based on population-based registry data (143,410 patients) [204-206] while four focussed specifically on patients with stereotactic radiotherapy in stage I/II NSCLC (481 patients) [207-210].

All studies provided data on pathological confirmation (as intervention as per this PICO question) against clinical assumption alone (control) in pulmonary lesions treated as lung cancer.

Overall survival was addressed as an outcome parameter in all seven studies [204-210]. *Fujii et al.* observed in addition *progression-free survival* in patients with pathologically proven or clinically assumed stage I NSCLC [208], while *Erridge et al.* also assessed *rates of any tumour-specific treatments* in unselected lung cancer patients [204]. No evidence was found relating to *disease-free survival, mortality, morbidity, accuracy of staging, pathological confirmation, receipt of curative treatment* and *other treatment outcome, quality of life, patient satisfaction, performance status* and *other patient reported outcome measures (PROMs).*

B. PICO 5a: Summary, rating of the quality of evidence and GRADE evidence profiles in specific subgroups

Individual studies, their main characteristics, and assessments of respective limitations per outcome are depicted in ***online supplement C***. The following subgroups were formed for clinically meaningful quality assessments of outcomes across studies: 1) All lung cancer types, all stages, all treatment modalities, and 2) NSCLC, stage I/II, stereotactic radiotherapy.

A priori, all outcomes were considered either critical or important related to this PICO (***online supplement A***). Effectively, only *overall survival*, *progression-free survival* and *rates of any tumour-specific treatments* were addressed in the selected study groups.

1) PICO 5a, subgroup 1: All lung cancer, all stages, all treatment modalities, pathological confirmation (vs. no pathological confirmation)

All studies with unselected lung cancer patients were population-based (*Erridge et al.:* 3,833 patients in Scotland vs. 2,073 patients in British Columbia, Canada, both in 1995 [204]; *Imperatori et al.:* 268 patients in Teeside region, England vs. 243 patients in Varese region, Italy, both in 2000 [205]; *Khakwani et al.:* 136,993 patients in England from 2004 to 2010 [206]).

Overall survival estimates could not be aggregated in a meta-analysis due to substantial heterogeneity across the three studies (143,410 patients). Two studies revealed a large effect of pathological confirmation on overall survival: *Erridge et al.* revealed improved overall survival only in patients with confirmed NSCLC compared to those without pathological confirmation after adjusting for potential confounders, however data did not allow any direct conclusions about the effect in SCLC versus unconfirmed lesions [204]. *Imperatori et al.* could demonstrate the same effect in the entire cohort yet providing univariate analysis only [205].

Khakwani et al. stratified their large cohort into four subgroups according to performance status and age resulting in varying effects. Both factors attributed to overall survival rates at 6 months and 1 year in multivariate analysis revealing enhanced overall survival at both time points in pathologically confirmed patients with either ECOG 0/1 independent from age or ECOG 2 and age ≤75 years whereas this effect became uncertain in patients with ECOG 3 and age >75 years as well as all ECOG 4-age-combinations [206]. Quantitative results are provided in ***Table 68***.

[quality of evidence for *overall survival:* very low ⊕○○○, downgraded because of serious risk of bias and imprecision across studies]

Erridge et al. proved a large effect with higher ***receipt of any tumour-specific treatment*** in pathological confirmed NSCLC and SCLC patients compared to undetermined lung cancer patients in multi-variate analysis (5,906 patients; effect results in ***Table 68***) [204].

[quality of evidence for *receipt of any tumour-specific treatment:* low ⊕⊕○○]

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 5a, subgroup 1: All lung cancer types, all stages, all treatment modalities, pathological confirmation		
***Overall survival (OS)* – 3 observational studies (143,410 patients)**		
Erridge et al., 2009 **[204]**	5,906	*Overall survival – pathological confirmation with large effect* (HR<1.0: higher pathological confirmation correlating with higher OS)*:* NSCLC -region British Columbia, Canada: 1) unconfirmed pulmonary lesions: 277 pts.; adjusted HR 1.0 (reference) 2) confirmed NSCLC: 1,540 pts.; adjusted HR 0.6, 95% CI 0.5-0.7 -Scotland: 1) unconfirmed pulmonary lesions: 991 pts.; adjusted HR 1.0 (reference) 2) confirmed NSCLC: 2,168 pts.; adjusted HR 0.7, 95% CI 0.6-0.8 SCLC -HRs for SCLC vs. unconfirmed pulmonary lesions not provided/incalculable for both regions
Imperatori et al., 2006 **[205]**	511	*Overall survival – pathological confirmation with large effect* (HR<1.0: higher pathological confirmation correlating with higher OS)*:* *3-year OS*, all lung cancers -region Teeside, England: 1) unconfirmed pulmonary lesions: 75 pts.; unadjusted HR 1.0 (reference) 2) confirmed lung cancers: 193 pts.; unadjusted HR 0.82, 95% CI 0.72-0.95 -region Varese, Italy: 1) unconfirmed pulmonary lesions: 44 pts.; unadjusted HR 1.0 (reference) 2) confirmed lung cancers: 199 pts.; unadjusted HR 0.81, 95% CI 0.68-0.95
Khakwani et al., 2013 **[206]**	136,993	*Overall survival – pathological confirmation with large effect* (HR<1.0: higher pathological confirmation correlating with higher OS)*t:*

6-month OS, all lung cancers
1) unconfirmed pulmonary lesions: adjusted HR 1.0 (reference)
2) confirmed lung cancers (ECOG 0/1 & age≤65/ECOG 2 & age<65): adjusted HR 0.81 95% CI 0.77-0.86
3) confirmed lung cancers (ECOG 0/1 & age>75/ECOG 2 & age 65-75): adjusted HR 0.84 95% CI 0.79-0.88
4) confirmed lung cancers (ECOG 0/1 & age>75/ECOG 2 & age 65-75): adjusted HR 0.84 95% CI 0.79-0.88

Overall survival – pathological confirmation with moderate effect (HR<1.0: higher pathological confirmation correlating with higher OS)*:*
6-month OS, all lung cancers
1) unconfirmed pulmonary lesions: adjusted HR 1.0 (reference)
2) confirmed lung cancers (ECOG 2 & age>75/ECOG 3 & age≤75): adjusted HR 0.93, 95% CI 0.89-0.96
1-year OS, all lung cancers
1) unconfirmed pulmonary lesions: adjusted HR 1.0 (reference)
2) confirmed lung cancers (ECOG 0/1 & age≤65 years/ECOG 2 & age<65 years): adjusted HR 0.93 95% CI 0.88-0.97

Overall survival – pathological confirmation with small effect (HR<1.0: higher pathological confirmation correlating with higher OS)*:*
6-month OS, all lung cancers
1) unconfirmed pulmonary lesions: adjusted HR 1.0 (reference)
2) confirmed lung cancers (ECOG 3 & age>75/ECOG 4, any age): adjusted HR 0.98, 95% CI 0.95-1.02
1-year OS, all lung cancers
1) unconfirmed pulmonary lesions: adjusted HR 1.0 (reference)
2) confirmed lung cancers (ECOG 3 & age>75/ECOG 4, any age): adjusted HR 1.02 95% CI 0.98-1.05

Overall survival – pathological confirmation with trivial effect (HR<1.0: higher pathological confirmation correlating with higher OS)*:*
6-month OS, all lung cancers
1) unconfirmed pulmonary lesions: adjusted HR 1.0 (reference)
2) confirmed lung cancers (ECOG 2 & age>75/ECOG 3 & age≤75): adjusted HR 0.99, 95% CI 0.95-1.02

***Receipt of any tumour-specific treatment* – 1 observational study (5,906 patients)**

Erridge et al., 2009 **[204]**	5,906	*Receipt of any active tumour-specific treatment – pathological confirmation with large effect* (OR>1.0: higher pathological confirmation correlating with higher receipt of tumour-specific treatment)*:* NSCLC -region British Columbia, Canada: 1) unconfirmed pulmonary lesions: 277 pts.; adjusted OR 1.0 (reference) 2) confirmed NSCLC: 1,540 pts.; adjusted OR 10.0, 95% CI 5.0-25.0 -Scotland: 1) unconfirmed pulmonary lesions: 991 pts.; adjusted HR 1.0 (reference) 2) confirmed NSCLC: adjusted OR 10.0, 95% CI 5.0-14,3 SCLC -ORs for SCLC vs. unconfirmed pulmonary lesions not provided/incalculable for both regions

Table 68: Effect results of the study by *Erridge et al.*, *Imperatori et al.* and *Khakwani et al.* sorted by outcomes for PICO 5a, subgroup 1 (All lung cancer types, all stages, all treatment modalities, pathological confirmation)

The GRADE evidence profile relating to the subgroup 1 in PICO 5 (All lung cancer types, all stages, all treatment modalities, pathological confirmation) is presented in ***Table 69***.

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Overall survival									
3 [204-206]	observational studies	serious [a]	not serious	serious [b]	not serious	none	We detected 2 studies with a large effect (6,417 patients). 1 study showed varying effects according to sub-groups (136,993 pts.).	⊕◯◯◯ VERY LOW	CRITICAL
Receipt of any tumour-specific treatment									
1 [204]	observational studies	not serious	not serious	not serious	not serious	none	1 study showed a large effect on receipt of any tumour-specific treatment 5,906 patients).	⊕⊕◯◯ LOW	

CI: Confidence interval

Explanations:
a. Failure to adequately control confounding in 1 study
b. all studies explore different lung cancer patient subpopulations

Table 69: GRADE evidence profile for PICO 5, subgroup 1 (All lung cancer types, all stages, all treatment modalities, pathological confirmation)

2) PICO 5a, subgroup 2: NSCLC, stage I/II, stereotactic body radiation, pathological confirmation (vs. no pathological confirmation)

All four studies were monocentric and conducted between 2002-2012 in the United States of America (143 patients) [207, 209] or Japan (338 patients) [208, 210]. *Fujii et al.* applied particle therapy instead of conventional stereotactic radiotherapy [208].

Multivariate ***overall survival*** analyses regarding radiotherapy for solitary pulmonary nodules in four studies as well as the meta-analysis (HR 1.280, 95% CI 0.593-1.852) suggested that pathological confirmation may reduce overall survival but the evidence was very uncertain. Median follow-up times ranged between 20.3 to 42 months (481 patients; forest plot in ***Figure 16***) [207-210].

[quality of outcome: very low ⊕○○○, downgraded because of serious risk of bias and inconsistency across studies]

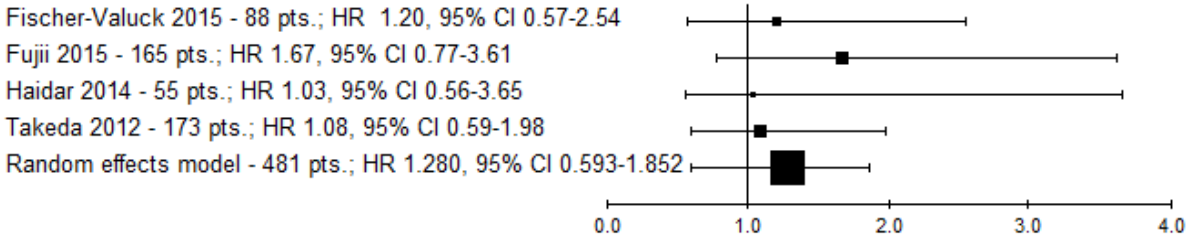


Figure 16: Forest plot with HR and 95% CI for effect of pathological confirmation in PICO 5a, subgroup 2 (NSCLC, stage I/II and stereotactic radiotherapy, pathological confirmation) on overall survival based on meta-analysis in four eligible observational studies (481 patients; I^2 0%; HR<1.0: pathological confirmation correlating with higher overall survival) [207-210]

Progression-free survival rates in solitary pulmonary nodule patients was explored by *Fujii et al.* (165 patients). After adjusting for potential confounders, a reversed large effect with better overall survival in the unconfirmed cohort was seen (adjusted HR 1.39, 95% CI 0.80-2.42) [208]

[quality of outcome: very low ⊕○○○, downgraded because of imprecision].

The GRADE evidence profile relating to the subgroup 2 in PICO 5 (NSCLC, stage I/II, stereotactic body radiation, pathological confirmation) is presented in ***Table 70***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pathological confirmation	no pathological confirmation	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
4 *[207-210]*	observational studies	serious [a]	not serious	not serious	Very serious [b,c]	none	-/323 [d]	-/158 [d]	**HR 1.280** (0.593 to 1.852)	**-- per 1.000** (from -- to --) [d]	⊕○○○ VERY LOW	CRITICAL
Progression-free survival												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pathological confirmation	no pathological confirmation	Relative (95% CI)	Absolute (95% CI)		
1 [208]	observational studies	not serious	not serious	not serious	Very serious [c,e]	none	-/111 [f]	-/54 [f]	**OR 1.39** (0.80 to 2.42)	**-- fewer per 1.000** (from - to -) [f]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio; **OR:** Odds ratio

Explanations:

a. Failure to adequately control confounding in 3 studies
b. Small sample sizes of all 4 studies raise concerns about potential imprecision.
c. The 95% CI includes the potential for no benefit; however, cannot exclude the possibility of benefit.
d. None of the studies provided number of events.
e. Small sample size of study raises concerns about potential imprecision.
f. Study did not provide event numbers.

Table 70: GRADE evidence profile for PICO 5, subgroup 2 (NSCLC, stage I/II, stereotactic body radiation, pathological confirmation)

C. PICO 5a: GRADE evidence to decision framework

Table 71 depicts the GRADE evidence to decision framework relating to PICO 5a based upon on the GRADE evidence profiles as well as additional considerations by the task force panel.

PICO 5a: Should pathological confirmation of tumours or subtyping of lung cancers be sought in lung cancer patients?	
POPULATION:	all lung cancer types, all stages and all treatment modalities
INTERVENTION:	pathological confirmation
COMPARISON:	no pathological confirmation
MAIN OUTCOMES:	Overall survival; progression-free survival; rate of any tumour-specific treatment;
SETTING:	Both outpatient and inpatient
PERSPECTIVE:	Clinical recommendations – population perspective
BACKGROUND:	Tumour biological profiling of lung cancers is perceived as a cornerstone in modern personalized care.
CONFLICT OF INTERESTS:	N/A

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Early diagnosis and treatment of lung cancer is central to improve outcomes. Yet, given the considerable expansion of therapeutic options over the last decade, diligent tumour biological profiling of lung cancers is an essential prerequisite to tailor personalized treatments [211].	Tumourbiological profiling of lung cancers is considered as an essential topic in lung cancer care by us. Likewise, it is a key priority topic for ERS as well as ELF and the Patient Advisory Group

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Our systematic review revealed the following desirable effects of pathological confirmation of tumours or subtyping of lung cancers (see related PICO 5 evidence tables, subgroups 1+2 for details): -improved overall survival in the entire cohort of unselected patients or in specific subgroups in one study and two studies, respectively No certain effects were seen in: -SCLC in one study exploring unselected patients	From clinical experience, the TF members consider the following additional desirable effects of pathological confirmation of tumours or subtyping of lung cancers to be likely: -higher efficacy and less harm in systemic therapies

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	The subgroup analysis by Khakwani et al. indicated that elderly as well as patients with poor performance status did not profit from pathological confirmation of suspicious lesions which may be due to lack of therapeutical benefit as well as higher diagnostic procedural risk and/or reduced fitness for subsequent therapy. Otherwise, no harms were detected by our systematic review (see related PICO 5 evidence tables, subgroups 1+2 for details). All four studies suggested that pathological confirmation in stage I/II NSCLC with stereotactic radiotherapy may reduce overall survival and progression-free survival, but the evidence was very uncertain. In fact, this may be well-explained by the unavoidable inclusion of patients with non-malignant solitary pulmonary nodules (with better prognosis) in the cohort without pathological confirmation.	From clinical experience, the TF members are concerned about the following additional undesirable effects of pathological confirmation of tumours and subtyping of lung cancers: -higher complication risk in patients at-risk for invasive diagnostics

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the evidence was graded as very low (see related PICO 5 evidence tables, subgroups 1+2 for details)	None

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	We did not perform a systematic literature search specifically on patient values relating to pathological confirmation of tumours and subtyping of lung cancers Our systematic review assessment did not retrieve any related pieces of evidence.	Pathological confirmation of tumours and subtyping of lung cancers are a key priority of patients as confirmed by patient and ELF representatives in our task force panel. However, there is also concern about performing invasive diagnostics in unfit patients.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Our systematic evidence assessment resulted in moderate desirable effects and only trivial undesirable effects.	Weighing desirable and undesirable effects based on our systematic evidence assessment, our task force panel discussions and clinical experience, we see benefits in pathological confirmation of tumours and subtyping of lung cancers in principle. Yet, we are precautious about the named potential undesirable effects. However, the panel felt that a substantial body of indirect evidence demonstrated the added value of pathological confirmation. While no direct evidence was retrieved with reference to histological subtyping and molecular profiling of lung cancers compared to their non-execution, both are also accepted mainstays for personalized therapy planning in lung cancer following several therapeutic randomized-controlled trials [211]. Additionally, the approval of several systemic drugs by the European Medicines Agency is based on this indirect, high-level evidence most often with the mandatory prerequisite to

		determine the respective molecular targets or predictive markers before prescription of any of these drugs [212].

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	We did not perform a systematic literature search specifically on required resources relating to pathological confirmation of tumours and subtyping of lung cancers. Our systematic review did not retrieve any related pieces of evidence.	We estimate at least moderate costs to improve pathological confirmation of tumours and subtyping of lung cancers.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● No included studies	not applicable	Required resources are depending on multiple factors, especially hardware (i.e. for modern molecular-genetic high-throughput investigations) and staff.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	We did not perform a systematic literature search specifically on cost effectiveness relating to pathological confirmation of tumours and subtyping of lung cancers. Our systematic review did not retrieve any related pieces of evidence.	Despite increased short-term costs to implement advanced diagnostic hardware for improved pathological confirmation of tumours and subtyping of lung cancers as well as ongoing costs, we assume mid- and long-term savings due to reduction of mis-, over- and undertreatment. Yet, cost-effectiveness analyses are missing taking into account variation on the local and national care level as well as among different health care systems.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	We did not perform a systematic literature search specifically on equity relating to pathological confirmation of tumours and subtyping of lung cancers. Our systematic review did not retrieve any related pieces of evidence.	Implementation of advanced techniques for pathological confirmation of tumours and subtyping of lung cancers within a lung cancer services may help to reduce inequalities of care provision. Conversely, appropriate implementation is not expected to create inequality.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	We did not perform a systematic literature search specifically on acceptability to key stakeholders relating to pathological confirmation of tumours and subtyping of lung cancers. Our systematic review did not retrieve any related pieces of evidence.	Pathological confirmation of tumours and subtyping of lung cancers are already well-accepted medical professionals and healthcare providers alike. However, the above mentioned potential undesirable effects may influence acceptance as well.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	We did not perform a systematic literature search specifically on feasibility of pathological confirmation of tumours and subtyping of lung cancers. Our systematic review did not retrieve any related pieces of evidence.	If sufficient resources are made available, we assume that implementation of improved techniques for pathological confirmation of tumours and subtyping of lung cancers is feasible.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies

	JUDGEMENT						
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	○	●

CONCLUSIONS

Recommendation

In patients with suspected lung cancer, we recommend seeking pathological confirmation where it determines management. (Strong recommendation, very low certainty of evidence)

In patients with confirmed lung cancer, we recommend further subtyping of lung cancers through application of the WHO Classification of Tumours: Thoracic Tumours, 5th edition [213] (*) as well as molecular characterisation for actionable targets or response to treatment. . (Strong recommendation, very low certainty of evidence)

(*) the WHO Classification represents the internationally accepted standard

Justification

Despite the limited direct evidence basis of very low overall quality, we consented two strong recommendations for pathological confirmation of suspected lung cancer and further subtyping of confirmed lung cancers. We justified the strength of both recommendations due to the above-mentioned indirect evidence of high quality showing less harm in treating patients when lung cancers are confirmed and well-subtyped fulfilling the criteria of a paradigmatic situation ('When low quality evidence suggests equivalence of two alternatives, but high quality evidence of less harm for one of the competing alternatives') according to GRADE methodology.

Subgroup considerations

None

Implementation considerations

Whilst pathological confirmation (whenever feasible), WHO lung cancer classification-compliant subtyping of adenocarcinoma, and characterization of treatable or predictive molecular targets is deemed as good clinical practice, valid evidence on their implementation in routine lung cancer diagnostics still lacks for the most part. Lung cancer services are highly encouraged to periodically review their practices on a cross-sectional basis and to strive for optimization accordingly.

Monitoring and evaluation

Research priorities

Beyond that, larger initiatives on regional, national or even international scales are needed. Population-based clinical cancer registries may serve as valid data sources, likewise centre-based data collection in high level lung cancer service networks as benchmarks.

Table 71: GRADE evidence to decision framework relating to PICO 5a

PICO 5b: Should histological subtyping of lung cancers be obtained in lung cancer patients?

A. PICO 5b: General summary of the Evidence

Initial and update evidence searches did not retrieve any studies comparing the effects of subtyping 1) SCLC and NSCLC vs. lung cancer, 2) histological subtyping of NSCLC vs. NSCLC, and 3) pulmonary adenocarcinoma (according to the 2015 WHO *Classification of Tumours of the Lung, Pleura, Thymus and Heart* [214] based on the 2011 IASLC/ATS/ERS *International Multidisciplinary Classification of Lung Adenocarcinoma* [215] which was the current edition at the time the search was performed) against their pathological characterisation following the previous version or no adenocarcinoma subtyping (PRISMA flow diagram: ***online supplement – section E***). Instead, the available evidence contained solely observational studies for the implementation of the 2015 WHO *Classification of Tumours of the Lung, Pleura, Thymus and Heart* assessing some of our predefined outcomes but without any retrospective controls. Thus, we decided to omit a full systematic review on this topic, but to formulate a good practice statement [216, 217].

PICO 5c: Should molecular characterisation of lung cancers for actionable targets or response to treatment be performed in lung cancer patients?

A. PICO 5c: General summary of the Evidence

Actionable targets were defined as molecular alterations in lung cancer that can be treated with drugs specifically targeting the respective alterations and that have been approved by the European Medicines Agency (EMA) for these indications, likewise targets predicting treatment response. At the time of the last evidence update, these targets encompassed activating EGFR- and BRAF V600E mutations, ALK- and ROS1-translocations as well as PD-L1 in NSCLC. All literature searches retrieved only evidence on the actionable targets of interest themselves and clinical trials on drugs targeting these actionable molecular alterations, but no evidence at all was found directly addressing the specific context of this PICO (PRISMA flow diagram: ***online supplement – section E***). Thus, we decided to omit a full systematic review on this topic, but to formulate a good practice statement [216, 217].

PICO question 6: In patients with lung cancer (or those suspected of having lung cancer), should palliative care or its delivery by specialists be integrated into lung cancer care already early during the course of the disease rather than no integration of palliative care or no palliative care delivery by specialists?

A. PICO 6: General summary of the Evidence

30 studies out of 269 initially retrieved abstracts (PRISMA flow diagram: ***online supplement A***) were included in the qualitative synthesis (49,864 lung cancer patients in 23 studies; seven studies without lung-cancer specific figures) [218-247] composed of 23 randomized-controlled trials (RCT) (2,342 lung cancer patients; seven studies without lung-cancer specific figures) [218-240], two non-randomized clinical trial with a prospective sequential control-intervention-group design (693 patients) [241, 242] and five observational studies (47,522 patients) [243-247]. All RCTs were unblinded.

17 RCTs (1,081 lung cancer patients; six studies without lung-cancer specific figures) [218-222, 224, 225, 228-236], the two non-randomized clinical trial (693 lung cancer patients) [241, 242] and three observational studies (46,927 lung cancer patients) [243, 245-247] were conducted in the United States of America. The remaining RCTs were performed in Belgium (51 lung cancer patients) [237], Canada (101 lung cancer patients) [231, 240], China (150 lung cancer patients) [239], Denmark (103 lung cancer patients) [226], Italy (163 lung cancer patients) [223] and the United Kingdom (no lung cancer specific figures) [227], and the two remaining observational studies in France (309 lung cancer patients) [244] and Norway (286 lung cancer patients) [246].

Single-centre and multi-centre designs were used in thirteen (914 lung cancer patients; three studies without lung cancer-specific figures) [218, 222, 225, 227, 228, 230-232, 234, 235, 237, 239, 240] and ten (735 lung cancer patients; four studies without lung cancer-specific figures) [220, 221, 223, 224, 226, 227, 229, 236, 238, 239] of the RCTs, respectively. One non-randomized clinical trial each was performed monocentric [241] and multicentric [242], respectively. While three of the five observational studies were undertaken in single centres [243, 244, 246], the large remaining two by *Lammers et al.* and *Sullivan et al.* observed multiple US centres including 46,720 Veterans diagnosed with stage IIIB/IV lung cancer [245, 247].

The compositions of study populations were heterogeneous among studies. The work by *Badr et al.* (39 patients), *Greer et al.* and *Temel et al.* (151 patients; same study) and by *Zhuang et al.* (150 patients) were the only RCTs encompassing solely lung cancer patients [218, 225, 234, 239], while thirteen enrolled patients with various cancer types (1,139 lung cancer patients in 11 studies; 2 studies without lung cancer-specific figures) [219, 220, 222, 223, 226, 228, 229, 235, 237, 238, 240] and six patients with malignant or chronic non-malignant diseases (19 lung cancer patients in one study; five studies without lung cancer-specific figures) [221, 224, 227, 231-233]. The two non-randomized clinical trials and the five observational studies included lung cancer patients only yet varying in stage [241-247].

Likewise, types of interventions differed substantially in all RCTs and observational studies regarding involved professions, institutional setting and applied measures.

As outcome parameters, *overall survival*, *receipt of any tumour-specific therapy*, *quality of life* and *patient satisfaction* were applied in fourteen (24,991 lung cancer patients in eleven studies; three studies without lung cancer-specific figures) [219-222, 224, 226, 227, 234, 237, 241, 243, 244, 246, 247], three (24,003 lung cancer patients) [225, 245, 246], 22 (2,191 lung cancer patients in 17 studies; five studies without lung cancer-specific figures) [218-223, 226-242], and four studies (101 lung cancer patients in one study; three studies without lung cancer-specific studies) [221, 224, 232, 240], respectively.

B. PICO 6: Summary, rating of the quality of evidence and GRADE evidence profile – all lung cancer, all stages, early palliative care integration (vs. no early palliative care integration)

Individual studies, their main characteristics, and assessments of respective limitations per outcome are depicted in ***online supplement C***. We focussed the GRADE assessment was on the RCTs and the prospective non-randomized clinical trials. A priori, all outcomes were considered either critical or important related to this PICO (***online supplement A***). Effectively, only *overall survival*, *rates of any tumour-specific treatment*, *quality of life* and *patient satisfaction* were addressed in the selected study groups.

Overall survival was assessed in nine RCTs [219-222, 224, 226, 227, 234, 237] and one prospective non-randomized clinical trial [241]. Only *Temel et al.* [234] and *Ferrell et al.* [241] provided lung cancer-specific analyses. The meta-analysis of those two studies revealed an improved overall survival with early integration of palliative care (forest plot in ***Figure 17***).

[quality of evidence for *overall survival*: very low ⊕○○○, downgraded because of serious risk of bias, indirectness and imprecision across studies]

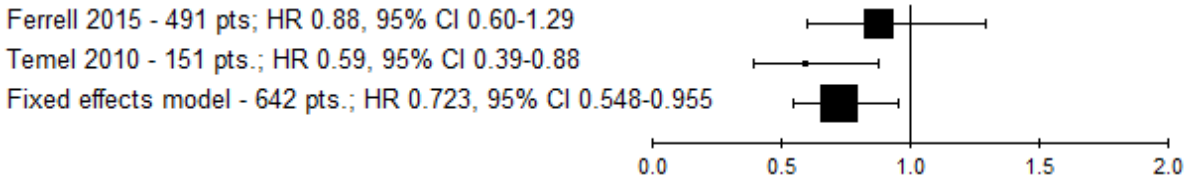


Figure 17: Forest plot with HR and 95% CI for effect of integrating early palliative care vs. standard care in lung cancer patients alone in PICO 6 (All lung cancer types, all stages, all treatment modalities, integration of early palliative care) on overall survival based on a meta-analysis in two eligible randomized controlled trials (642 patients; I^2 49%; HR<1.0: early integration of palliative care correlating with higher overall survival) [234, 241]

Receipt of any tumour-specific treatment as effect of early integration of palliative care was only explored in the study by *Greer et al.* [225] in which the authors performed a secondary analysis of the *Temel et al.* 2010 RCT-data (151 lung cancer patients) [234]. None of the treatment modalities assessed favoured either early integration or standard care (1st line chemotherapy: OR 0.68, 95% CI 0.34-1.36; 2nd line chemotherapy: OR 0.92, 95% CI 0.45-1.87; 3rd line chemotherapy: OR 1.19, 95% CI 0.51-2.78, 4th line chemotherapy: OR 1.38, 95% CI 0.54-3.51)

[quality of evidence for *receipt of active tumour therapy*: very low ⊕○○○, downgraded because of serious risk of bias and imprecision]

Out of the 20 RCTs and two non-randomized controlled trials assessing ***quality of life*** in patients obtaining various type of supplementary palliative care matched with standard care patients, one study showed a moderate (150 patients) [239] and three studies a small effect (359 patients) [235, 237, 241] relating to better *quality of life* in the interventional groups vs. controls , while 18 studies described trivial effects (1,238 patients in thirteen studies; five studies without lung cancer specific figures) [218-220, 222, 223, 226-234, 236, 238, 240, 242] (effect results in ***Table 72***).

[quality of outcome: very low ⊕○○○, downgraded because of serious risk of bias, indirectness, inconsistency and imprecision across studies]

Patient satisfaction was addressed in four RCTs which all displayed trivial effects below the minimal clinically important difference thresholds of the applied patient satisfaction assessment tools (effect results in ***Table 72***) [221, 224, 232, 240].

[quality of outcome: very low ⊕○○○, downgraded because of serious risk of bias, indirectness, inconsistency and imprecision across studies]

No evidence was found relating to *progression-free survival, disease-free survival, mortality, morbidity, staging, pathological confirmation, other treatment outcome, performance status* and *other patient reported outcome measures (PROMs).*

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 6: All lung cancer types, all stages, all treatment modalities, integration of early palliative care		
***Quality of life* – 20 randomized controlled trials and 2 non-randomized controlled trials (at least 1,747 lung cancer patients)**		
Badr et al., 2015 **[218]**	39	*Quality of life – depression, anxiety, competence, relatedness: early integration of palliative care with large effect; autonomy: early integration of palliative care with trivial effect:* raw score differences (intervention vs. control): -depression: -3.1 vs. 1.26; p<0.0001 -anxiety: -2.6 vs. 0.05; p<0.0001 -autonomy: 0.72 vs. 0.29; p=0.09 -competence: 2.41 vs. 0.1; p<0.0001 -relatedness: 1.6 vs. -0.26; p<0.0001
Bakitas et al., 2009 **[219]**	117	*Quality of life – early integration of palliative care with trivial effect (no lung cancer-specific results):* longitudinal estimated treatment effects (intervention minus control group): -QOL 4.6, standard error 2, p=0.02 -symptom intensity -27.8, standard error 15, p=0.06 -mood -1.8, standard error 0.81, p=0.02
Bakitas et al., 2015 **[220]**	88	*Quality of life – early integration of palliative care with trivial effect (no lung cancer-specific results):* mean raw scores 3, 6, 12 months after enrolment: (intervention vs control group): -QOL 129.9, 129.9, 129.9 vs. 127.2, 127.2, 129.1, p=0.34 -treatment impact 99.5, 99.5, 99.4 vs. 97.7, 97.7, 99.8, p=0.24
Cheville et al., 2013 **[222]**	39	*Quality of life – early integration of palliative care with trivial effect (no lung cancer -specific analysis):* mean difference between 8 weeks and baseline (intervention vs. control group): -QoL: 1.07 vs. 0.12, p=0.54
Ferrell et al., 2015 **[241]**	117	*Quality of life – early integration of palliative care with small effect:* adjusted mean score at 12 weeks (intervention vs. control group): -QoL: 109.1 vs. 101.4, p<0.001
Franciosi et al., 2019 **[223]**	88	*Quality of life – early integration of palliative care with trivial effect (no lung cancer -specific analysis):*

		mean difference between 12 weeks and baseline (intervention vs. control group): -QoL: -2.2 vs. -2.1, p>0.5
Groenvold et al., 2014 **[226]**	103	*Quality of life – early integration of palliative care with trivial-small effect (no lung cancer -specific analysis)* -mean weighted change between intervention and control group: -physical function -0.4, p=0.84 -role function 2.1, p=0.48 -emotional function -1.6, p=0.45 -pain -3.4, p=0.27 -dyspnea -4.2, p=0.20 -nausea/vomiting -5.8, p=0.013 -lack of appetite -2.0, p=0.57
Higginson et al., 2014 **[227]**	no lung cancer specific figures	*Quality of life – early integration of palliative care with trivial effect (no lung cancer-specific analysis):* difference between intervention and control group: -QoL 4.21, p=0.34 -QoL 1, p=0.67 -anxiety 0.1, p=0.8 -depression -1, p=0.16
McCorkle et al., 2015 **[228]**	no lung cancer specific figures	*Quality of life – early integration of palliative care with trivial effect (no lung cancer-specific analysis):* least square means in intervention vs. control group: -QoL at 1 month: 77.793 vs. 82.828, p=0.1062 -QoL at 3 months: 78.325 vs. 81.342, p=0.3718
Meyers et al., 2011 **[229]**	no lung cancer specific figures	*Quality of life – early integration of palliative care with trivial effect (no lung cancer-specific analysis):* -estimates of difference between rate of change per month in control and intervention group -0.10, p=0.70
Nguyen et al., 2018 **[242]**	202	*Quality of life – early integration of palliative care with trivial effect:* mean scores at baseline, 1 month and 3 months (interventional vs. control group): -QoL: 98.4, 100.8, 102.5 vs. 91.7, 102.0, 104.3, p<0.01
Nipp et al., 2020 **[230]**	27	*Quality of life – early integration of palliative care with trivial effect (no lung cancer-specific analysis):* mean differences from baseline to week 12 (intervention vs. control group): -QoL -0.77 vs.-3.84, Cohen's d effect size 0.21
Pantilat et al., 2010 **[231]**	19	*Quality of life – early integration of palliative care with trivial effect:* scores from baseline and follow-up (intervention vs. control group):

		--pain: 4.9, 2.4 vs. 3.5, 2.1, p=0.30 --dyspnea: 4.4, 2.4 vs. 3.0, 1.6, p=0.50 --anxiety: 5.5, 2.5 vs. 3.8, 2.5, p=0.08
Rabow et al., 2004 **[232]**	no lung cancer specific figures	*Quality of life – early integration of palliative care with trivial effect (no lung cancer-specific analysis):* scores at 6 and 12 months (intervention vs. control group): -QoL: 69.7, 69.3 vs. 65.4, 67.7, p=0.32
Steinhauser et al., 2008 **[233]**	no lung cancer specific figures	*Quality of life – early integration of palliative care with trivial effect:* mean scores for preparation for end of life from baseline to follow-ip (intervention group 1 vs. intervention group 2 vs. control group): 3.4 to 3.7 vs. 4.0 to 3.8 vs. 4.2 to 3.4
Temel et al., 2010 **[234]**	151	*Quality of life – early integration of palliative care with trivial effect:* change in scores from baseline to week 12 in control group vs. intervention group: -QoL: 4.6, 95% CI -0.8-9.9, p=0.09
Temel et al., 2017 **[235]**	191	Quality of life – early integration of palliative care with small effect: adjusted mean difference (control vs. intervention group): -QoL at 12 weeks: 5.04 (95% CI 0.68-9.41), p=0.024 -QoL at 24 weeks: 6.52 (95% CI 1.62-11.42), p=0.010
Temel et al., 2020 **[236]**	234	*Quality of life – early integration of palliative care with trivial effect (no lung cancer-specific analysis):* adjusted mean difference (control vs. intervention group): -QoL at 12 weeks: 3.23 (95% CI -0.67-7.13), p=0.10 -QoL at 24 weeks: 3.12 (95% CI -1.54-7.77), p=0.19
Vanbutsele et al., 2018 **[237]**	51	*Quality of life – early integration of palliative care with small effect (no lung cancer-specific analysis):* mean scores (intervention vs. control group): -QoL at 12 weeks: 61.98 vs. 54.39, p=0.03 -QoL at 24 weeks: 64.6 vs. 56.2, p=0.12
Wagner et al., 2014 **[238]**	30	*Quality of life – early integration of palliative care with trivial effect (no lung cancer-specific analysis):* mean scores (intervention vs. control group): -QoL at 4 months: 86.7 vs. 87.0, adjusted β 0.8 (95% CI -2.6-4.3) -QoL at 12 months: 90.8 vs. 90.4, adjusted β 0.6 (95% CI -2.2-3.5)
Zhuang et al., 2018 **[239]**	150	*Quality of life – early integration of palliative care with moderate effect:* -QoL in both scores better in interventional group, p<0.05
Zimmermann et al., 2014 **[240]**	101	*Quality of life – early integration of palliative care with trivial effect:*

		adjusted differences between change scores (intervention vs. control group): -QoL at 3 months: 3.56 (95% CI -0.27-7.40), p=0.07 -QoL at 4 months: 6.44 (95% CI 2.13-10.76), p=0.006
***Patient satisfaction* – 4 randomized controlled trials (at least 101 lung cancer patients)**		
Brumley et al., 2014 **[221]**	no lung cancer specific figures	*Patient satisfaction – early integration of palliative care with trivial effect (no lung cancer -specific analysis):* -patient satisfaction: no significant difference in the portion of participants reporting to be very satisfied at baseline or at 60 days after enrolment OR 1.79, 95% CI 0.65-4.96, p=0.26
Gade et al., 2008 **[224]**	no lung cancer specific figures	*Patient satisfaction – early integration of palliative care with trivial effect (no lung cancer -specific analysis):* mean at index hospitalisation discharge (intervention vs. control group): -place of care environment scale 6.8 vs. 6.4, p<0.001 -doctors, nurses/other health care providers communication scale 8.0 vs. 7.4, p<0.001
Rabow et al., 2004 **[232]**	no lung cancer specific figures	*Patient satisfaction – early integration of palliative care with trivial effect (no lung cancer-specific analysis):* scores at 6 and 12 months (intervention vs. control group): -patient satisfaction with care: 69.6, 70.1 vs. 74.5, 72.4, p=0.44
Zimmerman et al., 2014 **[240]**	101	*Patient satisfaction – early integration of palliative care with trivial effect:* adjusted differences between change scores (intervention vs. control group): -patient satisfaction at 3 months: 3.79 (95% CI 1.74-5.85), p=0.0003 - patient satisfaction at 4 months: 6.00 (95% CI 3.94-8.05), p<0.0001

Table 72: Effect results of studies ineligible for meta-analyses sorted by outcomes for PICO 6 (all lung cancer types, all stages, all treatment modalities, integration of early palliative care)

The GRADE evidence profile relating to PICO 6 (All lung cancer types, all stages, all treatment modalities) is presented in ***Table 73***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	early integration of palliative care into standard care	standard care alone	Relative (95% CI)	Absolute (95% CI)		
Overall survival												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	early integration of palliative care into standard care	standard care alone	Relative (95% CI)	Absolute (95% CI)		
2 [234, 241]	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	-/349	-/293	**HR 1.383** (1.047 to 1.824)	**-- per 1.000** (from -- to --)	⊕◯◯◯ VERY LOW	CRITICAL
Receipt of any tumour-specific treatment												
1 [225]	randomised trials	serious [d]	not serious	not serious	serious [c]	none	1 study showed varying effects depending on the line of chemotherapy.				⊕⊕◯◯ LOW	CRITICAL
Quality of life												
22 [218-220, 222, 223, 226-242]	randomised trials	serious [d]	serious [e]	serious [f]	serious [g]	none	1 study showed a moderate effect (150 lung cancer patients) and 3 studies a small effect, while 18 studies reported trivial effects (1,238 lung cancer patients)				⊕◯◯◯ VERY LOW	CRITICAL
Patient satisfaction												
4 [221, 224, 232, 240].	randomised trials	serious [d]	serious [e]	serious [b,h]	serious [g]	none	We detected 4 RCTs with trivial effects (101 patients).				⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio

Explanations:

a. Lack of blinding in both studies and uncertain allocation concealment in one study
b. Studies use different palliative care measures
c. The 95% CI in 1 study includes the potential for benefit; however, cannot exclude the possibility of no benefit.
d. Lack of blinding
e. Pooled effect was incalculable, studies favour intervention or aretrivial.
f. Studies apply different quality of life measures
g. Meta-analysis not feasible
h. Studies uses different patient satisfaction measures

Table 73: GRADE evidence profile for PICO 6: All lung cancer types, all stages, all treatment modalities

C. PICO 6: GRADE evidence to decision framework

Table 74 depicts the GRADE evidence to decision framework relating to PICO 6 based upon on the GRADE evidence profiles as well as additional considerations by the task force panel.

PICO 6: In patients with lung cancer (or those suspected of having lung cancer), should palliative care or its delivery by specialists be integrated into lung cancer care already early during the course of the disease rather than no integration of palliative care or no palliative care delivery by specialists?	
POPULATION:	lung cancer patients
INTERVENTION:	early integration of palliative care into standard care
COMPARISON:	standard care alone
MAIN OUTCOMES:	Overall survival; Receipt of any tumour-specific treatment; Quality of life; Patient satisfaction;
SETTING:	Both outpatient and inpatient
PERSPECTIVE:	Clinical recommendations – population perspective
BACKGROUND:	Lung cancer is the most common cancer-killer going along with high symptom-load for patients and their caretakers
CONFLICT OF INTERESTS:	N/A

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Integration of palliative care into standard lung cancer care at an early timepoint may positively influence quality of life and satisfaction in lung cancer patients as well as their prognosis. This beneficial practice is still not regularly implemented into routine processes, though [1]	Early integration of palliative care is considered as an essential topic in lung cancer care by us, Likewise, it is a key priority topic for ERS as well as ELF and the Patient Advisory Group

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Our systematic review revealed the following desirable effects of early integration of palliative care into standard lung cancer care (see related PICO 6 evidence table for details): -improved overall survival in the meta-analysis of two RCTs. -a moderate effect in 1 RCT and a small positive effect in 3 RCTs on quality of life(18 RCTs with trivial effects)	From clinical experience, the task force panel, considers the following additional desirable effects of early integration of palliative care into standard lung cancer care to be likely: -improved multidimensional assessment of symptoms and their treatment by a multiprofessional team

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	No harms were detected by our systematic review (see related PICO 6 evidence table for details).	From clinical experience, the task force panel is concerned about the following additional undesirable effects of early integration of palliative care into standard lung cancer care: -stigma of palliative care may impede its early implementation -risk of competing appraisal of patient fitness for tumour-specific treatments among standard care clinicians and palliative care specialists -risk of withholding of tumour-specific treatments

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall quality of the evidence was graded as very low (see related PICO 6 evidence table)	None

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	We did not perform a systematic literature search specifically on patient values relating to early integration of palliative care into standard lung cancer care. Our systematic review did not retrieve any related pieces of evidence.	Early integration of palliative care into standard lung cancer care is a key priority of patients as confirmed by patient and ELF representatives in our task force panel due to the appraisal and treatment of symptom burden load. Yet, the still existing stigma of palliative care needs to be overcome.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Our systematic evidence assessment resulted in moderate desirable effects and small undesirable effects.	Weighing desirable and undesirable effects based on our systematic evidence assessment, our task force panel discussions and clinical experience, we see benefits in early integration of palliative care into standard lung cancer care in principle. Yet, we are precautious about the named potential undesirable effects.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	We did not perform a systematic literature search specifically on required resources relating to early integration of palliative care into standard lung cancer care. Our systematic review did not retrieve any related pieces of evidence.	We estimate at least moderate costs to implement early integration of palliative care into standard lung cancer care. In particular, we do see a need for additional staff specialised in palliative care.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● No included studies	not applicable	Required resources are depending on multiple factors, especially already existing infrastructure, staff and palliative care network setting. A substantial variation across European countries is suspected impeding general cost estimates.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	We did not perform a systematic literature search specifically on cost effectiveness relating to early integration of palliative care into standard lung cancer care. Our systematic review did not retrieve any related pieces of evidence.	Despite increased short-term costs for implementation of early palliative care and on-going costs for its maintenance, we assume mid- and long-term savings due to better symptom control resulting in improved quality of life and patient satisfaction as well as more efficient utilization of diagnostic and therapeutic resources.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	We did not perform a systematic literature search specifically on equity relating to early integration of palliative care into standard lung cancer care. Our systematic review did not retrieve any related pieces of evidence.	Achieving early integration of palliative care into standard lung cancer care may facilitate better patient adherence to treatments due to more patient-focussed care. Conversely, appropriate implementation is not expected to create inequality.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not perform a systematic literature search specifically on acceptability to key stakeholders relating to early integration of palliative care into standard lung cancer care. Our systematic reiew did not retrieve any related pieces of evidence.	We assume that early integration of palliative care into standard lung cancer care will be accepted very well by patients, medical professionals and healthcare providers alike.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not perform a systematic literature search specifically on feasibility of implementing early integration of palliative care into standard lung cancer care. Our systematic review did not retrieve any related pieces of evidence.	If sufficient resources are made available, we assume early integration of palliative care into standard lung cancer care to be implemented and maintained well.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest integrating palliative care already at an early stage into lung cancer care pathways based on patient symptom load and well-linked to routine tumour-specific management [conditional recommendation for the intervention; very low overall quality of evidence].

Remark: Delivery of palliative care may be by palliative care specialists or palliative care teams.

Justification

Given the life-threatening potential and high symptom burden in lung cancer patients and the fact that there were no substantial harms evident of foreseen, we suggest early integration of palliative care into standard lung cancer care. The recommendation is conditional due to the very low certainty of evidence.

Subgroup considerations

None

Implementation considerations

The implementation of palliative care elements seems feasible when sufficient funding is provided. Joint strategies by governments and scientific societies are favoured.

Monitoring and evaluation

Processes of early integrated palliative care into standard lung cancer care and their interplay need to be assessed frequently and optimized if needed.

Research priorities

Clinical and quality of care research should focus on causes and mechanisms of the assumed positive impact on survival by palliative care integration as well as assess graduated models to better deliver flexible needs-based palliative care alongside of standard care throughout the lung cancer pathway, respectively.

Table 74: GRADE evidence to decision framework relating to PICO 6

PICO question 7: In patients with lung cancer (or those suspected of having lung cancer), should quality improvement measures be applied for lung cancer patients rather than no application of these methods in lung cancer care?

A. PICO 7: General summary of the evidence

A total of 13 observational studies were selected out of the 1,037 initially identified abstracts within the scope of this search question (PRISMA flow diagram: ***online supplement A***).

B. PICO 7: Summary, rating of the quality of evidence and GRADE evidence profiles in specific subgroups

Individual studies, their main characteristics, and assessments of respective limitations per outcome are depicted in ***online supplement C***. Due to the substantial heterogeneity across the body of evidence relating to different types of quality improvement measures, distinct subgroups were formed out of the 13 observational studies accordingly: a) cancer registries and quality indicator systems, b) specialized lung cancer services, c) individual quality improvement measures, and d) audits/quality indicator systems.

A priori, all outcomes were considered either critical or important related to this PICO (***online supplement A***). Effectively, only *overall survival*, *mortality*, *accuracy of staging*, *pathological confirmation*, *receipt of curative treatment*, and *receipt of any tumour-specific treatment* were addressed in the selected study groups.

No evidence was found relating to *disease-free survival, progression-free survival, morbidity, quality of life,* and *performance status*.

1) PICO 7, subgroup 1: All lung cancer, all stages, application of cancer registries and quality indicators (vs. no application)

We selected five observational studies [108, 203, 248-250] which evaluated the impact of lung cancer registries in combination with quality indicators as part of quality assurance measures (223,761 patients) originating from Denmark (Danish National Lung Cancer Registry: [108, 203]; the two publications from *Jakobsen et al.* with overlapping patient cohorts) and the United Kingdom (National Lung Cancer Audit: [248-250]). Three studies built upon unselected national lung cancer registry data [108, 203, 248], while one study each focussed on national NSCLC [249] and SCLC patient data [250].

Outcome parameters were adjusted for potential confounders in all five studies. A priori, all outcomes were considered either critical or important related to this PICO.

Regarding ***overall survival***, the two Danish studies, which covered different, but overlapping time periods (in total 52,435 patients between 2000-2012), demonstrated both large effects with improvement in all as well as surgically resected lung cancer patients over time [108, 203]. Trivial effects were seen in the two British studies in unselected NSCLC (120,745 patients; 2004-2010, *Khakwani et al.*: uncertain effect, only 1% annual improvement over the study period; adjusted HR 0.99, 95% CI 0.98-0.99) [249] and SCLC patients (18,513 patients; 2004-2011; *Khakwani et al.*: uncertain effect, median overall survival: 2011 190 days, 2004/2005 179 days, p=n.s.) (effect results in ***Table 75***) [250].

[quality of evidence for *overall survival*: very low ⊕○○○, downgraded because of indirectness, inconsistency and imprecision]

Mortality was addressed in the study by *Jakobsen et al.* (52,435 patients; 2000-2012) resulting in large effects on ***30-day-mortality*** (30-d survival increased from 93.7% in 2003 to 99.0% in 2012) (effect results in ***Table 75***) [203].

[quality of evidence for *mortality*: low ⊕⊕○○]

Accuracy of staging was improved according to the large effect with more complete staging observed by *Jakobsen et al.* (32,397 unselected patients; complete staging: 2010-2012 12,083/13,592 pts (88.9%), 2000-2004 10,378/18,805 pts (55.2%), p<0.0001, OR 6.5 (95% CI 6.12-6.91) [203]. Khakwani et al. demonstrated a large effect in SCLC patients (stage present: 2011 3,303/3,499 pts. (94.4%), 2004/2005 1,457/1,867 pts. (78.0%), p<0.001, OR 4,74, 95% CI 3,96-5,68) [250]. Due to different patient populations, we omitted a meta-analysis (effect results in ***Table 75***).

[quality of evidence for *accuracy of staging*: very low ⊕○○○, downgraded because of indirectness]

Beckett et al. (approx. 140,000 patients; 2005-2011) monitored an increasing ***pathological confirmation*** *rate* in England and Wales in 2009 compared to 2005 (effect results in ***Table 75***) [248].

[quality of evidence for *pathological confirmation*: very low ⊕○○○, downgraded because of risk of bias]

A temporal increase of ***receipt of curative treatment*** and ***receipt of any tumour-specific treatment*** in Denmark as well as the United Kingdom was recorded in the already cited studies by Jakobsen et al. [108, 203] and Beckett et al. (effect results in ***Table 75***) [248].

[quality of evidence for *receipt of curative treatment* and *receipt of any tumour-specific treatment*: both very low ⊕○○○, downgraded because of risk of bias and imprecision].

Group **Outcome** **Author, year**	**total number of patients**	**study effect per outcome**
PICO 7, subgroup 1: Cancer registries and quality indicators		
***Overall survival (OS)* – 4 observational studies (230,354 patients)**		
Jakobsen et al., 2013 **[108]**	38,661	*Overall survival – lung cancer registry with quality indicators with moderate effect:* all lung cancers -1-year OS: 1) 2003: 1-year OS 36.6% 2) 2011: 1-year OS 42.7% -2-year OS: 1) 2003: 2-year OS 19.8% 2) 2010: 2-year OS 24.3%
Jakobsen et al., 2016 **[203]**	52,435	*Overall survival – lung cancer registry with quality indicators with moderate effect:* all lung cancers: -1-year OS: 1) 2000-2004: 1-year OS 33% (95% CI 32%–34%) 2) 2010-2012: 1-year OS 43% (95% CI 42%–44%); p<0.0001
Khakwani et al., 2013 **[249]**	120,745	*Overall survival – lung cancer registry with quality indicators with trivial effect* (HR<1.0: implementation of cancer registry and quality indicators correlating with higher OS over time)*:* NSCLC -OS:

		1% annual improvement in OS over the study period; adjusted HR 0.99, 95% CI 0.98-0.99
Khakwani et al., 2014 **[250]**	18,513	*Overall survival – lung cancer registry with quality indicators with trivial effect:* SCLC -median OS: 1) 2004/2005: median OS 179 days 2) 2011: median OS 190 days; p=n.s.
***Mortality* – 1 observational study (38,661 lung cancer patients)**		
Jakobsen et al., 2013 **[108]**	38,661	*30-day mortality – lung cancer registry with quality indicators with large effect:* all lung cancers -30-day survival: 1) 2003: 30-day survival in surgical resected pts. 93.7% 2) 2012: 30-day survival in surgical resected pts. 99.0%
***Accuracy of staging* – 2 observational studies (70,948 lung cancer patients)**		
Jakobsen et al., 2016 **[203]**	52,435	Accuracy of staging – *lung cancer registry with quality indicators with large effect* (OR>1.0: implementation of cancer registry and quality indicators correlating with higher accuracy of staging over time)*:* all lung cancers 1) 2000-2004: complete staging 10,378/18,805 pts (55.2%); OR 1.0 (reference) 2) 2010-2012: complete staging 12,083/13,592 pts (88.9%); OR 6.5, 95% CI 6.12-6.91; p<0.0001
Khakwani et al., 2014 **[250]**	18,513	Accuracy of staging – *lung cancer registry with quality indicators with large effect* (OR>1.0: implementation of cancer registry and quality indicators correlating with higher accuracy of staging over time)*:* SCLC 1) 2004/2005: stage present in 1,457/1,867 pts. (78.0%); OR 1.0 (reference) 2) 2011: stage present in 3,303/3,499 pts. (94.4%); OR 4,74, 95% CI 3,96-5,68); p<0.001
***Pathological confirmation* – 1 observational study (at least 140,000 patients)**		
Beckett et al., 2012 **[248]**	over 140,000	*Pathological confirmation – lung cancer registry with quality indicators with moderate effect:* all lung cancers 1) 2005: pathological confirmation rate 64% 2) 2009 75.6% (IQR 71-85%)
***Receipt of curative treatment* – 3 observational studies (at least 231,096 patients)**		
Beckett et al., 2012 **[248]**	over 140,000	*xReceipt of curative treatment – lung cancer registry with quality indicators with small effect:* all lung cancers

		1) 2005: surgical resection rate in NSCLC pts. 14% 2) 2009: surgical resection rate in NSCLC pts. 18.3%
Jakobsen et al., 2013 **[108]**	38,661	*Receipt of curative treatment – lung cancer registry with quality indicators with small effect:* all lung cancers 1) 2008: surgical resection rate 18.7% 2) 2012: surgical resection rate 19.8%
Jakobsen et al., 2016 **[203]**	52,435	*Receipt of curative treatment – lung cancer registry with quality indicators with small effect* (OR>1.0: implementation of cancer registry and quality indicators correlating with higher resection rates over time)*:* all lung cancers 1) 2000-2004: surgical resection in 2,271/18,805 pts (12.1%); OR 1.0 (reference) 2) 2010-2012: surgical resection 2,216/13,592 pts (16.3%); OR 1.42, 95% CI 1.33-1.51; p<0.0001
***Receipt of any tumour-specific treatment* – 2 observational studies (at least 178,661 patients)**		
Beckett et al., 2012 **[248]**	over 140,000	*Receipt of any tumour-specific treatment – lung cancer registry with quality indicators with large effect:* all lung cancers 1) 2005: any tumour-specific treatment rate 43% 2) 2009: any tumour-specific treatment rate 59.1%
Jakobsen et al., 2013 **[108]**	38,661	*Receipt of any tumour-specific treatment – lung cancer registry with quality indicators with large effect:* all lung cancers 1) 2000: any tumour-specific treatment rate approx. 60% 2) 2012: any tumour-specific treatment rate 85%

Table 75: Effect results of studies ineligible for meta-analysis sorted by outcomes regarding PICO 7, subgroup 1 (cancer registries and quality indicators)

The GRADE evidence profile relating to subgroup 1 in PICO 7 (Cancer registries and quality indicator systems) is presented in ***Table 76***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cancer registries and quality indicators	no cancer registries and quality indicators	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
4 [108, 203, 249, 250]	observational studies	not serious	serious [a]	serious [b]	serious [c]	none	We detected 2 studies with large effects (52,435 patients) and 2 studies with trivial effects (139,258 patients).				⊕◯◯◯ VERY LOW	CRITICAL
30-day mortality												
1 [108]	observational studies	not serious	not serious	not serious	not serious	none	We detected 1 study with a large effect (38,661 pts.)				⊕⊕◯◯ LOW	CRITICAL
Accuracy of staging												
2 [108, 250]	observational studies	not serious	not serious	serious [b]	not serious	none	We detected 2 studies with a large effect (50,910 patients).				⊕◯◯◯ VERY LOW	CRITICAL
Pathological confirmation												
1 [248]	observational studies	serious [d]	not serious	not serious	not serious	none	We detectd 1 study with a moderate effect (over 140,000 pts.)				⊕◯◯◯ VERY LOW	CRITICAL
Receipt of curative treatment												
3 [108, 203, 248]	observational studies	serious [e]	not serious	not serious	serious [c]	none	We detected 3 studies with a small effect (over 231,096 pts.).				⊕◯◯◯ VERY LOW	CRITICAL
Receipt of any tumour-specific treatment												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cancer registries and quality indicators	no cancer registries and quality indicators	Relative (95% CI)	Absolute (95% CI)		
2 [108, 248]	observational studies	serious [d]	not serious	not serious	serious [c]	none	We detected 2 studies with a large effect (over 178,661 pts.).				⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

Explanations:

a. 2 studies favoured the intervention, 2 without certain effect

b. Studies explored different patient populations in 2 distinct health care systems.

c. A pooled effect was not calculable and also not estimable.

d. Flawed measurement of both exposure and outcome. Potential failure to adequately control confounding.

e. In 1 study flawed measurement of both exposure and outcome. Potential failure to adequately control confounding.

Table 76: GRADE evidence profile for PICO 7, subgroup 1 (Cancer registries and quality indicator systems)

2) PICO 7, subgroup 2: All lung cancer, all stages, application of specialized lung cancer services (vs. no application)

Only three observational studies by *Wolfson et al.* and *Shulman et al.* from the United States of America as well as by *Adizie et al.* from the United Kingdom investigated the prognostic value of specialized lung cancer services (296,548 lung cancer patients in a total 472,089 cancer patients) [251-253].

In both US-based studies, a large effect was detected with improved ***overall survival*** in patients treated in National Cancer Institute Comprehensive Cancer Centers (21,265 lung cancer patients) when compared to a more than eightfold larger patient cohort treated outside these specialised services (185,319 lung cancer patients; *Shulman et al.* calculated survival only in 174,319 out of their 252,392 patients omitting patients in network programs or programs of unknown type; adjusted HR 0.83, 95% CI 0.80-0.86; *Wolfson et al.:* adjusted HR 1.4, 95% CI 1.3-1.6) [251, 252]. Analogously, when applying an eleven-item composite score to assess the quality of 129 UK lung cancer services (ten items on structural and one on processual quality prompted by a survey), the lung cancer services in the highest scoring group (tripartite division: 0-4, 5-7, and 8-11 points) had better *one-year overall survival* after multivariate regression analysis (organisational score 0-4: reference, organisational score 5-7: HR 1.89, 95% CI 0.99-3.61, organisational score 8-11: HR 2.30, 95% CI 1.04-5.08), also by a large effect [253]. Due to differing patient populations a meta-analysis was not clinically meaningful (see effect results in ***Table 77***).

[quality of evidence for *overall survival* very low ⊕◯◯◯, downgraded because of indirectness]

Adizie et al. explored also ***receipt of curative treatment*** displaying a large effect favouring the intervention (organisational score 0-4: reference, organisational score 5-7: OR 1.13, 95% CI 0.92-1.40, organisational score 8-11: OR 1.62, 95% CI 1.26-2.09) (effect results in ***Table 77***) [253].

[quality of evidence for *curative treatment rate:* low ⊕⊕◯◯]

Group Outcome	total number of patients	study effect per outcome

Author, year		
PICO 7, subgroup 2: Specialized lung cancer services		
***Overall survival (OS)* – 5 observational studies (296,548 lung cancer patients)**		
Adizie et al., 2019 **[253]**	33,312	*Overall survival – specialised lung cancer service with large effect* (HR<1.0: implementation of specialized lung cancer services correlating with higher OS)*:* -less specialized lung cancer services (organisational score 0-4) vs. specialized lung cancer services (organisational score>4): 1) organisational score 0-4: HR 1.0 reference 2) organisational score 5-7: HR 0.53, 95% CI 0.28-1.01 3) organisational score 8-11: HR 0.43, 95% CI 0.20-0.96
Shulman et al., 2018 **[252]**	252,392	*Overall survival – specialised lung cancer service with large effect* (HR<1.0: implementation of specialized lung cancer services correlating with higher OS) 1) no-NCI-CCC: HR 1,0 (reference) 2) NCI-CCC: adjusted HR 0.83, 95% CI 0.80-0.86
Wolfson et al., 2015 **[251]**	10,844	*Overall survival – specialised lung cancer service with large effect* (HR<1.0: implementation of specialized lung cancer services correlating with higher OS)*:* 1) no-NCI-CCC: adjusted HR 1.0 (reference) 2) NCI-CCC: adjusted HR 0.7, 95% CI 0.6-0.8
***Receipt of curative treatment* – 1 observational study (33,312 lung cancer patients)**		
Adizie et al., 2019 **[253]**	33,312	*Receipt of curative treatment – specialised lung cancer service with large effect* (OR>1.0: implementation of specialized lung cancer services correlating with higher receipt of curative treatment)*:* -less specialized lung cancer services (organisational score 0-4) vs. specialized lung cancer services (organisational score>4): 1) organisational score 0-4: OR 1.0 reference 2) organisational score 5-7: OR 1.13, 95% CI 0.92-1.40 3) organisational score 8-11: OR 1.62, 95% CI 1.26-2.09

Table 77: Effect results of studies ineligible for meta-analysis sorted by outcomes regarding PICO 7, subgroup 2 (implementation of specialized lung cancer services; NCI-CCC: National Cancer Institute Comprehensive Cancer Centers)

The GRADE evidence profile relating to subgroup 2 in PICO 7 (Specialized lung cancer services) is presented in ***Table 78***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cancer registries and quality indicators	no cancer registries and quality indicators	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
4 [108, 203, 249, 250]	observational studies	not serious	serious [a]	serious [b]	serious [c]	none	We detected 2 studies with large effects (52,435 patients) and 2 studies with trivial effects (139,258 patients).				⊕◯◯◯ VERY LOW	CRITICAL
30-day mortality												
1 [108]	observational studies	not serious	not serious	not serious	not serious	none	We detected 1 study with a large effect (38,661 pts.)				⊕⊕◯◯ LOW	CRITICAL
Accuracy of staging												
2 [108, 250]	observational studies	not serious	not serious	serious [b]	not serious	none	We detected 2 studies with a large effect (50,910 patients).				⊕◯◯◯ VERY LOW	CRITICAL
Pathological confirmation												
1 [248]	observational studies	serious [d]	not serious	not serious	not serious	none	We detectd 1 study with a moderate effect (over 140,000 pts.)				⊕◯◯◯ VERY LOW	CRITICAL
Receipt of curative treatment												
3 [108, 203, 248]	observational studies	serious [e]	not serious	not serious	serious [c]	none	We detected 3 studies with a small effect.				⊕◯◯◯ VERY LOW	CRITICAL
Receipt of any tumour-specific treatment												
2 [108, 248]	observational studies	serious [d]	not serious	not serious	serious [c]	none	We detected 1 study with a large effect (38,661 pts.) and 1 study ith a moderate effect (over 140,000 pts.).				⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

Explanations:

a. 2 studies favoured the intervention, 2 without certain effect
b. Studies explored different patient populations in 2 distinct health care systems.
c. A pooled effect was not calculable and also not estimable.
d. Flawed measurement of both exposure and outcome. Potential failure to adequately control confounding.
e. In 1 study flawed measurement of both exposure and outcome. Potential failure to adequately control confounding.

Table 78: GRADE evidence profile for PICO 7, subgroup 2 (Specialized lung cancer services)

3) PICO 7, subgroup 3: All lung cancer, all stages, application of individual quality improvement measures (vs. no application)

The systematic evidence search retrieved two observational studies (14,958 patients) from the United Kingdom [254] and the United States of America [255].

Overall survival was determined in one large regional study in Scotland (1,898 unselected lung cancer patients) on the effect of quality improvement interventions in comparison to historical cohorts. The Scottish study demonstrated an improved *overall survival* following the improvement measures after adjustment for other prognostic factors (adjusted HR 0.80, 95% CI 0.70-0.90) [254].

[quality of evidence for *overall survival*: very low ⊕○○○, downgraded because of risk of bias].

30-day, 60-day and ***90-day mortality*** showed small effects in *Faris et al.* (2,566 patients; 30-day mortality: OR 0.85, 95% CI 0.58-1.23, 60-day mortality: OR 0.74, 95%-CI 0.54-1.01, and 90-day mortality: OR 0.82, 95% CI 0.62-1.09)[255].

[quality of evidence for *30-day-, 60-day- and 90-day mortality*: very low ⊕○○○, downgraded because of risk of bias and imprecision].

Accuracy of staging was significantly increased as a result of quality improvement initiatives in the British study by *Erridge et al.* [254] and the US-study by *Faris et al.* [255] and (pooled effect: OR 1.470, 95% CI 1.104-1.957; forest plot in ***Figure 18***)

[quality of evidence for *accuracy of staging*: very low ⊕○○○, downgraded because of serious risk of bias and inconsistency]

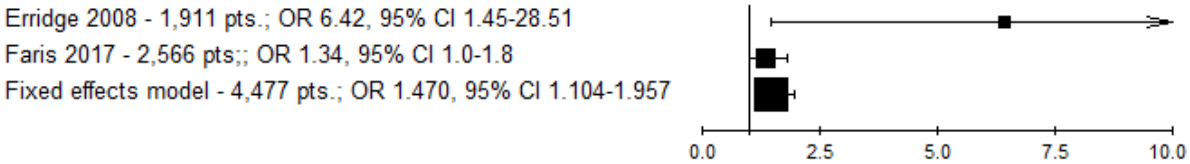


Figure 18: Forest plot with HR and 95% CI for effect of implementation of individual quality improvement measures on accuracy of staging based on meta-analysis in two eligible observational studies (4,477 patients; I^2 76%; OR>1.0: implementation of individual quality improvement measures correlating with higher accuracy of staging) [254, 255]

Erridge et al. revealed similar ***pathological confirmation*** rates after implementation of the quality improvement measure (OR 1,19, 95% CI 0,97-1,47) [254]. [quality of evidence for *pathological confirmation*: very low ⊕○○○, downgraded because of serious risk of bias and imprecision]

The implemented quality improvement measure by *Erridge et al.* (1,898 patients) resulted in similar ***rates of curative treatment*** (OR 1.04, 95% CI 0.77-1.40), but higher ***rates of any tumour-specific treatment*** (OR 1.31, 95% CI 1.05-1.63) [254].

[quality of evidence for *receipt of curative treatment*: very low ⊕○○○, downgraded because of risk of bias and imprecision].

[quality of evidence for *receipt of any tumour-specific treatment*: very low ⊕○○○, downgraded because of risk of bias].

The GRADE evidence profile relating to subgroup 3 in PICO 7 (Individual quality improvement measures) is presented in ***Table 79***.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	individual quality improvement measures	no individual quality improvement measures	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
1 [254]	observational studies	serious [a]	not serious	not serious	not serious	none	-/1027 [b]	-/994 [b]	**HR 0.80** (0.70 to 0.90)	**-- per 1.000** (from -- to --) [b]	⨁◯◯◯ VERY LOW	CRITICAL
30-day mortality												
1 [255]	observational studies	serious [a]	not serious	not serious	serious [c]	none	52/1270 (4.1%)	62/1296 (4.8%)	**OR 0.85** (0.58 to 1.23)	**8 more per 1.000** (from 9 fewer to 32 more)	⨁◯◯◯ VERY LOW	CRITICAL
60-day mortality												
1 [255]	observational studies	serious [a]	not serious	not serious	serious [c]	none	73/1270 (5.7%)	99/1296 (7.6%)	**OR 0.74** (0.54 to 1.01)	**25 more per 1.000** (from 1 fewer to 57 more)	⨁◯◯◯ VERY LOW	CRITICAL
90-day mortality												
1 [255]	observational studies	serious [a]	not serious	not serious	serious [c]	none	98/1270 (7.7%)	120/1296 (9.3%)	**OR 0.82** (0.62 to 1.09)	**18 more per 1.000** (from 7 fewer to 49 more)	⨁◯◯◯ VERY LOW	CRITICAL
Accuracy of staging												
2 [254, 255]	observational studies	serious [d]	serious [e]	not serious	not serious	none	2163/2254 (96.0%)	2101/2223 (94.5%)	**OR 1.47** (1.10 to 1.96)	**17 more per 1.000** (from 5 more to 26 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	individual quality improvement measures	no individual quality improvement measures	Relative (95% CI)	Absolute (95% CI)		
Pathological confirmation												
1 [254]	observational studies	serious [a]	not serious	not serious	serious [c]	none	713/971 (73.4%)	709/925 (76.6%)	**OR 0.84** (0.68 to 1.03)	**33 fewer per 1.000** (from 76 fewer to 5 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Receipt of curative treatment												
1 [254]	observational studies	serious [a]	not serious	not serious	serious [c]	none	99/984 (10.1%)	90/927 (9.7%)	**OR 1.04** (0.77 to 1.40)	**3 more per 1.000** (from 21 fewer to 34 more)	⊕◯◯◯ VERY LOW	CRITICAL
Receipt of any tumour-specific treatment												
1 [254]	observational studies	serious [a]	not serious	not serious	not serious	none	800/984 (81.3%)	712/927 (76.8%)	**OR 1.31** (1.05 to 1.63)	**45 more per 1.000** (from 9 more to 76 more)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio; **OR:** Odds ratio

Explanations:

a. Failure to adequately control confounding.
b. Study did not provide numbers of events.
c. The 95% CI includes the potential for benefit; however, cannot exclude the possibility of no benefit.
d. Failure to adequately control confounding in both studies.
e. High heterogeneity (I^2= 76%, CIs without overlap) among studies suspected.

Table 79: GRADE evidence profile for PICO 7, subgroup 3 (Individual quality improvement measures)

4) PICO 7, subgroup 4: All lung cancer, all stages, application of audits/quality indicator systems (no application)

Three studies, one from the United Kingdom [256], one from the Netherlands [257], and one from the USA [258] addressed the implementation of audits/quality indicator systems.

In the British single-centre study in surgically treated lung cancer patients, *Hagan et al.* successfully applied a full audit cycle, with a large effect on ***30-day mortality*** after the intervention (OR 2.08, 95% CI 0.37-11.62) (202 patients) [256]. Likewise, *Ten Berge et al.* reported on the results from 2012-2015 of the on-going Dutch Lung Surgery Audit with a small effect on *30-day mortality* (OR 1.46, 95% CI 0.96-2.22) and a trivial effect on *morbidity* (severe complications) (OR 0.86, 95% CI 0.71-1.04) after lung operation within the given time period (19,557 patients) [257]. In their US single-centre study, *Cerfolio et al.* showed a small effect on *30-day mortality* rates (OR 1.36, 95% CI 0.52-3.56) and large effects on ***major morbidity*** (OR 2.2, 95% CI 1.53–3.55) and ***overall morbidity*** *rates* (OR 1.7, 95% CI 1.14-2.70) when critical quality indicators in the peri-operative setting of NSCLC patients were fulfilled (778 patients) [258].

[quality of evidence for *mortality*: very low ⊕◯◯◯, downgraded because of risk of bias].

[quality of evidence for *morbidity:* very low ⊕◯◯◯, downgraded because of risk of bias]

The GRADE evidence profile relating to subgroup 4 in PICO 7 (Audit/quality indicator system) is presented in ***Table 80***.

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
30-day mortality									
3 [256-258]	observational studies	serious [a]	not serious	serious [b]	serious [c,d]	none	We detected 1 study (202 pts.) with a large effect and 2 studies with small effects (4,537 pts-).	⊕◯◯◯ VERY LOW	CRITICAL
Morbidity									
2 [257, 258]	observational studies	serious [e]	serious [f]	serious [b]	serious [c,d]	none	We detected 1 study with a large effect (778 pts.) and 1 study with a trivial effect (19,557 pts.).	⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval

Explanations:

a. Failure to adequately control confounding in 2 studies.
b. Applied audit/quality indicator systems were different across studies.
c. Calculation of a pooled effect was not meaningful.
d. Small sample size of 1 study raises concerns about potential imprecision.
e. Failure to adequately control confounding in 1 study.
f. Overall morbidity rate was improved in Cerfolio 2011 after implementation, whereas major morbidity rate was similar. Ten Berge 2018 revealed no certain effect.

Table 80: GRADE evidence profile for PICO 7, subgroup 4 (Audit/quality indicator system)

C. PICO 7: GRADE evidence to decision framework

Table 81 depicts the GRADE evidence to decision framework relating to PICO 7 based upon on the GRADE evidence profiles as well as additional considerations by the task force panel.

PICO 7: In patients with lung cancer (or those suspected of having lung cancer), should quality improvement measures be applied in lung cancer care rather than no application of these methods in lung cancer care?	
POPULATION:	all lung cancer types, all stages and all treatment modalities
INTERVENTION:	a) cancer registries and quality indicators; b) specialized lung cancer services; c) individual quality improvement measures; d) audits/quality indicator systems
COMPARISON:	no quality improvement measure
MAIN OUTCOMES:	Overall survival; Mortality; Accuracy of staging ; Pathological confirmation; Receipt of curative treatment ; Receipt of any tumour-specific treatment;
SETTING:	Both outpatient and inpatient
PERSPECTIVE:	Clinical recommendations – population perspective
BACKGROUND:	Structured quality improved measures may help to enhance and harmonize quality of lung cancer care.
CONFLICT OF INTERESTS:	N/A

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Quality improvement measures for lung cancer care bear the potential to positively impact on patient outcomes. Nevertheless, their place value has rarely been assessed on a systematic basis.	The implementation of quality improvement measures is considered as an essential topic in lung cancer care by the task force., Likewise, it is a key priority topic for ERS as well as ELF and the Patient Advisory Group

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Our systematic review revealed the following desirable effects of quality improvement measures (see related PICO 7 evidence tables, subgroups 1-4 for details): a) Cancer registries and quality indicators: The implementations resulted in improvement of overall survival, mortality, accuracy of staging, pathological confirmation, receipt of curative therapy, and receipt of any tumour-specific therapy. b) Specialized lung cancer services: Three studies demonstrated improved overall survival in more specialized lung cancer services. One study also proved higher rates of receipt of any tumour-specific treatments. c) Quality improvement measures: Overall survival, 30-day, 60-day, 90-day mortality, accuracy of staging, and receipt of any tumour-specific treatment were positively affected. Pathological confirmationas well as receipt of curative treatments did not show any certain effect. d) Audits/quality indicator systems: Three studies could demonstrate better 30-day mortality. One study detected in addition lower morbidity rates, while one study revealed only a trivial effect.	The task force considers the following additional desirable effects of MDT implementation to be likely: -higher satisfaction of patients and medical professionals

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	a) Cancer registries and quality indicators: none of the evaluated studies indicated any harms. b) Specialized lung cancer services: none of the evaluated studies indicated any harms. c) Quality improvement measures: none of the evaluated studies indicated any harms. d) Audits/ quality indicator systems: none of the evaluated studies indicated any harms.	As task force panel, we are concerned about the following additional undesirable effects of MDT implementation: -lack of standardisation and validation

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall quality of the evidence was graded as very low (see related PICO 7 evidence tables, subgroups 1-4 for details)	None

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	We did not perform a systematic literature search specifically on patient values relating to quality improvement measures. Our present PICO-focussed systematic evidence search and assessment did not retrieve any related pieces of evidence.	Quality improvement measures are a key priority of patients as confirmed by patient and ELF representatives in our task force panel.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Our systematic evidence assessment resulted in moderate desirable effects and small undesirable effects.	Weighing desirable and undesirable effects based on our systematic evidence assessment, our task force panel discussions and clinical experience, we see benefits in quality improvement measures in principle. Yet, we are cautious about the named potential undesirable effects.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	We did not perform a systematic literature search specifically on required resources relating to quality improvement measures. Our present PICO-focussed systematic evidence search and assessment did not retrieve any related pieces of evidence.	We estimate at least moderate costs to implement quality improvement measures alongside the lung cancer care continuum.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	not applicable	Required resources are depending on multiple factors, especially staff, IT hardware and network coordination/linkage.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	We did not perform a systematic literature search specifically on cost effectiveness relating to quality improvement measures. Our present PICO-focussed systematic evidence search and assessment did not retrieve any related pieces of evidence.	Despite increased short-term costs to implement quality improvement measures as well as ongoing costs for maintaining them, we assume mid- and long-term savings due to reduction of mis-, over- and undertreatment. Yet, cost-effectiveness analyses are missing taking into account variation on the local and national care level as well as among different health care systems.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	We did not perform a systematic literature search specifically on equity relating to quality improvement measures. Our present PICO-focussed systematic evidence search and assessment did not retrieve any related pieces of evidence.	Implementation of quality improvement measures within lung cancer services may help to reduce inequalities of care provision. Conversely, appropriate implementation is not expected to create inequality.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	We did not perform a systematic literature search specifically on acceptability to key stakeholders relating to quality improvement measures. Our present PICO-focussed systematic evidence search and assessment did not retrieve any related pieces of evidence.	Quality improvement measures are already well-accepted by patients, medical professionals and healthcare providers alike. However, the above mentioned potential undesirable effects need to be acknowledged.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes	We did not perform a systematic literature search specifically on feasibility of implementing quality improvement measures.	If sufficient resources are made available, we assume that quality improvement measures are feasible to be implemented.

○ Varies ○ Don't know	Our present PICO-focussed systematic evidence search and assessment did not retrieve any related pieces of evidence.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest utilizing national clinical lung cancer registries involving quality indicators to provide feedback for future lung cancer guidelines and to inform lung cancer services [conditional recommendation for the intervention; very low overall quality of evidence].

We suggest referring lung cancer patients to services with ready access (*) to multiple lung cancer specialist facilities (**) [conditional recommendation for the intervention; very low overall quality of evidence].

(*) ready access: reasonable proximity and timeliness

(**) lung cancer specialist facilities include functional diagnostics, imaging, endoscopy, pathology/molecular biology, thoracic surgery, radiotherapy, systemic treatments, and palliative care as well as multidisciplinary teams

We suggest developing and implementing specific quality improvement measures (***) to improve quality of lung cancer care where required and when superordinate guidance is missing [conditional recommendation, very low overall quality of evidence].

(***) i.e. clinical pathways

We suggest the implementation of an internal and/or external evaluation system (****) for lung cancer services [conditional recommendation; very low overall quality of evidence].

(****) different terms are used beside evaluation system: i.e. internal/external audit system, certification system, quality indicator systems

Justification

We are confident that all four types of quality improvement measures bear the potential to optimize lung cancer processes and to improve patient-relevant outcomes. The limited body of evidence with a very low level of confidence in the effect estimates led to a conditional recommendation.

Subgroup considerations

None

Implementation considerations

Quality improvement initiatives based on the explored measures are essential for achieving and maintaining an adequate, state-of-the-art management of lung cancer patients. Precious resources may be economised by collaborations on regional, national and international levels.

Monitoring and evaluation

The impact as well as the expended resources of quality improvement measures need to be assessed on a regular basis. The cost-effectiveness analyses may prompt to optimize or to suspend certain quality improvement measures.

Research priorities

Peer-review visits or benchmarking approaches may be utilized.

Table 81: GRADE evidence to decision framework relating to PICO 7

PICO question 8: In patients with lung cancer (or those suspected of having lung cancer), should patient decision tools be involved in the decision-making and -sharing process rather than not involving them?

A. PICO 8: General summary of the Evidence

Two systematic reviews on patient decision tools were the only applicable pieces of evidence selected for the qualitative synthesis out of the 357 retrieved abstracts (PRISMA flow diagram: ***online supplement A***) within the scope of this search question [259, 260], a recently published systematic review did not add further evidence within the given scope [261]. The work by *Austin et al.* included studies on the impact of tools for shared decision making in patients with various cancer types but also serious non-malignant diseases [259], out of which one randomized controlled trials with inclusion of lung cancer patients was extracted [262]. *Spiegle et al.* systematically reviewed articles with similar scope but with a focus on cancerous diseases only [260], comprising four additional randomized controlled trials applicable for this PICO [263-266]. The range of publication years spanned more than a decade (1999-2013). Three studies derived from Australia [263-265], one each from Italy [266] and the USA [262].

None of the five randomized controlled trials enrolled exclusively lung cancer patients, all were composed of heterogeneous populations. The number of lung cancer patients (233 patients) and all study patients (1,355 patients) included ranged from 7-109 patients and 60-629 patients, respectively [262-266]. The three Australian studies included lung cancer patient of all histologies, stages and therapies [263-265], while the Italian and the US-study focussed on chemotherapy and stage IV patients, respectively [262, 266].

All five randomized controlled trials applied different aids as mostly unblinded interventions to foster patient involvement in the decision-making process (web-based communication aid [262], verbal information from an oncologist with or without two booklets and videotape on chemo-/radiotherapy [266], question prompt list [265], cancer consultation preparation package [265], question prompt sheet with or without question-asking coaching session [263]). Three studies randomized into one interventional arm and one control arm [263-265], while one two trial had two interventional and one control study groups [262]. The remaining study explored three interventional arms without a control group [266].

Individual studies, their main characteristics, and assessments of respective limitations per outcome are depicted in ***online supplement C***. A priori, all outcomes were considered either critical or important related to this PICO (***online supplement A***). *Patient satisfaction* was the only addressed outcome parameter in all five randomized controlled trials. Studies used different Likert scales to measure patient satisfaction with 3 [266], 23 [262] and 25-items [263-265], respectively.

No evidence was found relating to *overall survival, progression-free survival, disease-free survival, mortality, morbidity, staging, pathological confirmation, other treatment outcome, receipt of any active tumour-specific treatments (versus palliative care only), performance status* and *other patient reported outcome measures (PROMs).*

B. PICO 8: Summary, rating of the quality of evidence and GRADE evidence profile – All lung cancer, all stages, involvement of patient decision tools (vs. no involvement of patient decision tools)

Despite the substantial heterogeneity across the body of evidence relating to varying lung cancer populations as well as different interventional tools and patient satisfaction measures, a subgrouping of distinct subgroups or pooling of results was not meaningful.

Patient satisfaction was the only addressed outcome parameter in all five studies. No separate results were reported specifically for lung cancer patients in any of the studies. The largest randomized controlled trial by *Meropol et al.* (109 lung cancer patients, 629 cancer patients) showed a small effect relating to better patient satisfaction in the two interventional group compared to a regular visit regarding making treatment decisions ($p=0.003$), result of treatment decision ($p<0.001$), physician communication format ($p=0.026$) as well as discussions on supportive services ($p=0.029$) and quality of life concerns ($p=0.042$) [262]. The

remaining four studies demonstrated only trivial effects of patient decision tools on patient satisfaction, but no significant differences between the control and interventional arms [263-266]. Detailed results are provided in ***Table 82***.

[quality of evidence for patient satisfaction: very low ⊕◯◯◯, downgraded because of serious risk of bias, indirectness, inconsistency and imprecision].

Group **Outcome** **Author, year**	**total number of lung cancer patients**	**study effect per outcome**
PICO 8: All lung cancer types, all stages, all treatment modalities, patient decision tool		
***Patient satisfaction* – 5 randomized controlled trials (233 lung cancer patients)**		
Brown et al., 1999	7	*Patient satisfaction – patient decision tool with trivial effect:* median patient satisfaction score 108.0 (IQR 100-109) vs. 107 (IQR 97-113.5), p=0.705
Butow et al., 2004	29	*Patient satisfaction – patient decision tool with trivial effect:*satisfaction high, but not significantly different in nonparametric Mann-Whitney tests in intervention and control group; no result figures stated
Clayton et al., 2007	35	*Patient satisfaction – patient decision tool with trivial effect:* mean patient satisfaction score 110.1 vs. 110.3, 95% CI for difference -3.4-2.9, p=n.s.
De Lorenzo et al., 2004	53	*Patient satisfaction – patient decision tool with trivial effect:* no group specific results stated, only generally related to information given by oncologist: the more time spent by oncologist, the more satisfactory the quality of oral information was perceived by pts.
Meropol et al., 2013	109	*Patient satisfaction – patient decision tool with small effect:* better patient satisfaction in the two interventional group compared to a regular visit regarding making treatment decisions (p=0.003), result of treatment decision (p<0.001), physician communication format (p=0.026) as well as discussions on supportive services (p=0.029) and quality of life concerns (p=0.042)

Table 82: Effect results of studies ineligible for meta-analyses on patient satisfaction for PICO 8 (all lung cancer types, all stages, all treatment modalities, patient decision tools)

The GRADE evidence profile relating to PICO 8 (All lung cancer types, all stages, all treatment modalities, patient decision tools) is presented in ***Table 83***.

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Patient satisfaction (measure by..., range of possible scores x-x; higher = better/worse)									
5 [262-266]	randomised trials	serious [a]	serious [b]	serious [c]	serious [d]	none	We detected 1 study with a small effect (109 pts.) and 4 studies with trivial effect (124 pts.).[e]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations:

a. Potential lack of allocation concealment in Brown 1999, lack of blinding in Brown 1999, De Lorenzo 2004 and Meropol 2013, incomplete accounting of patients and outcome events in Butow 2004 and De Lorenzo 2004 (no result figures stated)
b. Positive effect of intervention on patient satisfaction in Meropol et al. vs. no certain effect in 4 other RCTs
c. RCTs use different interventional tools and outcome measures in mixed cancer cohorts without specific results for lung cancer patients
d. A pooled effect was incalculable and also barely estimable.
e. This is based on our individual four-stage evaluation scheme (see online supplement section A)

Table 83: GRADE evidence profile for PICO 8 (All lung cancer types, all stages, all treatment modalities, patient decision tools)

C. PICO 8: GRADE evidence to decision framework

Table 84 depicts the GRADE evidence to decision framework relating to PICO 8 based upon on the GRADE evidence profiles as well as additional considerations by the task force panel.

PICO 8: In patients with lung cancer (or those suspected of having lung cancer), should patient decision tools be involved in the decision-making and -sharing process rather than not involving them?	
POPULATION:	All lung cancer types, all stages, all treatment modalities
INTERVENTION:	patient decision tools
COMPARISON:	no patient decision tools
MAIN OUTCOMES:	Patient satisfaction;
SETTING:	Both outpatient and inpatient
PERSPECTIVE:	Clinical recommendations – population perspective
BACKGROUND:	Provision of patient information and obtainment of patient consent are fundamental ethical and legal requirements within the medical profession. However, the immanent knowledge gap in the physician-patient relationship may impose a barrier in communication and decision-making.
CONFLICT OF INTERESTS:	N/A

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	A pan-European survey project run by ELF in 2015 which addressed patients, caretakers and national patient organisations revealed the need for improvement of patient-professional communication towards shared-decision making. https://europeanlunginfo.org/lung-cancer/research-and-news/report-on-consultation-lung-cancer-patient-priorities-report	Provision of patient information and obtainment of patient consent are fundamental ethical and legal requirements within the medical profession. However, the immanent knowledge gap in the physician-patient relationship may impose a barrier in communication and decision-making. The improvement of shared-decision making is considered as an essential topic in lung cancer care by us, Likewise, it is a key priority topic for ERS as well as ELF and the Patient Advisory Group

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Our systematic review revealed the following desirable effects of patient decision tools (see related PICO 8 evidence table for details): -improved patient satisfaction with a patient decision tool in mixed cancer in 1 study, while 4 other studies showed only trivial effects.	From the clinical experience of the TF members, the following additional desirable effects of patient decision tools might be likely: -more structured communication -better provision of essential information tailored to patient needs -reduction of medical professional-patient knowledge gap -improved shared-decision making -helps certain populations to better communicate/express their desires/decisions A recent systematic review recently demonstrated substantial benefits of patient decision tools in malignancies other than lung cancer [267].

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	No harms were detected by our systematic review (see related PICO 8 evidence table for details).	From their clinical experience, the TF members are concerned about the following additional undesirable effects of patient decision tools: -one patient decision tool solution may not satisfy all patient needs -lack of standardisation and validation -risk of misunderstanding of certain pieces of information by patients, i.e. statistics

Certainty of evidence

What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall quality of the evidence was graded as very low (see related PICO 8 evidence table for details)	We assume that the favourable effects of patient decision tools on patient-reported outcomes detected in other cancer entities can also be applied to lung cancer patients.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	We did not perform a systematic literature search specifically on patient values relating to patient decision tools Our systematic review on other outcomes did not retrieve any related pieces of evidence.	Improvement of shared-decision making is a key priority of patients as confirmed by patient and ELF representatives in our task force panel, therefor well-designed patient decision tools are highly appreciated. During development, a patient-focus should be set on: -usage of lay language instead of academic language -more illustrative presentation of information, i.e. easy-to-understand flowcharts and diagrams -statistics need to be explained in a simple way as often not well understood by patients and caretakers Patients have a key interest in shared-decision making and more structured communication with medical professionals according to a pan-European survey project run by ELF in 2015 which addressed patients, caretakers and national patient organisations. https://europeanlunginfo.org/lung-cancer/research-and-news/report-on-consultation-lung-cancer-patient-priorities-report

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Our systematic evidence assessment resulted in small desirable effects and varying undesirable effects.	Weighing desirable and undesirable effects based on our systematic evidence assessment, our task force panel discussions and clinical experience, we favour the implementation of patient decision tools to facilitate shared-decision making in lung cancer care in principle. Yet, we see potential problems in the application of these tools by certain populations as well as potential risks going along with lack of standardisation and validation.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	We did not perform a systematic literature search specifically on required resources relating to patient decision tools. Our systematic review did not retrieve any related pieces of evidence.	We assume at least moderate costs to design, implement and maintain patient decision tools in lung cancer care depending amongst other on the technical developmental stage of the tools.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● No included studies	not applicable	Required resources for development and implementation depend on the extent of the patient decision tool, especially on the degree of digitalisation. Multiple, uncoordinated initiatives on various levels, different nations and cancer entities bear the risk of waste of human and financial resources, instead, joint adventures seem necessary.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	We did not perform a systematic literature search specifically on cost effectiveness relating to patient decision tools. Our systematic review did not retrieve any related pieces of evidence.	Improvements of patient satisfaction as a result of implementing decision tools is so far rarely taken into account into cost-effectiveness-calculations, yet seem highly important to us and thereby to probably favour the intervention.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	We did not perform a systematic literature search specifically on equity relating to patient decision tools. Our systematic review did not retrieve any related pieces of evidence.	The immanent knowledge gap in the physician-patient relationship may impose a barrier in communication and decision-making. In general, patient decision tools may facilitate informed consent discussions, nevertheless, their impact may be limited by factors such as age, educational and cultural background as well as language barriers, but also the readiness to receive and recognise messages in a disease as deadly as lung cancer. The application of patient decision tools may be difficult for certain populations (i.e. elderly, non-native speakers, persons with reading difficulties)

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not perform a systematic literature search specifically on acceptability to key stakeholders relating to patient decision tools. Our systematic review revealed good acceptance in principle of the applied patient decision tools in all 5 studies.	If well-designed, we are convinced that patient decision tools will be accepted by patients, medical professionals and healthcare authorities,

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	We did not perform a systematic literature search specifically on feasibility of implementing patient decision tools. In our systematic review, none of the 5 studies reported problems implementing patient decision tools.	If sufficient resources are provided, we expect patient decision tools to be designed, implemented and maintained well.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		**Varies**	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

In patients with lung cancer, we suggest using patient decision tools as a measure to improve patient involvement in shared decision making. (Conditional recommendation, Very low certainty of evidence)

Justification

Patient decision tools may improve patient satisfaction and facilitate disease understanding. The limited body of evidence with a very low level of confidence in the effect estimates led to a conditional recommendation.

Subgroup considerations

The impact of patient decision tools may be limited by factors such as age, educational and cultural background as well as language barrier and certain impairments.

Implementation considerations

Forces should be joint on regional, national and even international levels where patient organizations like the European Lung Foundation promote creation and translation of tools. Open access depositories for patient decision tools are preferable.

Monitoring and evaluation

Need assessments among lung cancer patients and patient organizations may help to develop better patient-tailored decision tools.

Research priorities

Modern learning theory approaches should be considered.

Table 84: GRADE evidence to decision framework relating to PICO 8

References

1. Murray PV, O'Brien ME, Sayer R, Cooke N, Knowles G, Miller AC, Varney V, Rowell NP, Padhani AR, MacVicar D, Norton A, Ashley S, Smith IE. The pathway study: results of a pilot feasibility study in patients suspected of having lung carcinoma investigated in a conventional chest clinic setting compared to a centralised two-stop pathway. *Lung Cancer* 2003: 42(3): 283-290.
2. Abdel-Rahman O. Impact of Timeliness of Surgical Treatment on the Outcomes of Patients with Non-metastatic Non-small Cell Lung Cancer: Findings From the PLCO Trial. *World J Surg* 2019: 43(11): 2927-2933.
3. Porta M, Gallen M, Malats N, Planas J. Influence of "diagnostic delay" upon cancer survival: an analysis of five tumour sites. *J Epidemiol Community Health* 1991: 45(3): 225-230.
4. Robinson E, Mohilever J, Zidan J, Sapir D. Delay in diagnosis of cancer. Possible effects on the stage of disease and survival. *Cancer* 1984: 54(7): 1454-1460.
5. Yang KY, Chen YM, Huang MH, Perng RP. Revisit of primary malignant neoplasms of the trachea: clinical characteristics and survival analysis. *Jpn J Clin Oncol* 1997: 27(5): 305-309.
6. Abrao FC, de Abreu I, Rocha RO, Munhoz FD, Rodrigues JHG, Batista BN. Interaction between treatment delivery delay and stage on the mortality from non-small cell lung cancer. *J* 2018: 10(5): 2813-2819.
7. Alanen V, Koivunen JP. Association of diagnostic delays to survival in lung cancer: single center experience. *Acta Oncol* 2019: 1-6.
8. Annakkaya AN, Arbak P, Balbay O, Bilgin C, Erbas M, Bulut I. Effect of symptom-to-treatment interval on prognosis in lung cancer. *Tumori* 2007: 93(1): 61-67.
9. Bhandari S, Pham D, Pinkston C, Oechsli M, Kloecker G. Timing of treatment in small-cell lung cancer. *Med Oncol* 2019: 36(6): 47.
10. Bozcuk H, Martin C. Does treatment delay affect survival in non-small cell lung cancer? A retrospective analysis from a single UK centre. *Lung Cancer* 2001: 34(2): 243-252.
11. Bryant AS, Cerfolio RJ. Differences in outcomes between younger and older patients with non-small cell lung cancer. *Ann Thorac Surg* 2008: 85(5): 1735-1739; discussion 1739.
12. Buccheri G, Ferrigno D. Lung cancer: clinical presentation and specialist referral time. *European Respiratory Journal* 2004: 24(6): 898-904.
13. Canizares Carretero MA, Rivo Vazquez JE, Blanco Ramos M, Toscano Novella A, Garcia Fontan EM, Purrinos Hermida MJ. [Influence of delay of surgery on the survival of patients with bronchogenic carcinoma]. *Arch Bronconeumol* 2007: 43(3): 165-170.
14. Coughlin S, Plourde M, Guidolin K, Fortin D, Frechette E, Malthaner R, Inculet R. Is it safe to wait? The effect of surgical wait time on survival in patients with non-small cell lung cancer. *Can J Surg* 2015: 58(6): 414-418.
15. Di Girolamo C, Walters S, Gildea C, Benitez Majano S, Rachet B, Morris M. Can we assess Cancer Waiting Time targets with cancer survival? A population-based study of individually linked data from the National Cancer Waiting Times monitoring dataset in England, 2009-2013. *PLoS ONE* 2018: 13(8): e0201288.
16. Diaconescu R, Lafond C, Whittom R. Treatment delays in non-small cell lung cancer and their prognostic implications. *J Thorac Oncol* 2011: 6(7): 1254-1259.
17. Forrest LF, Adams J, Rubin G, White M. The role of receipt and timeliness of treatment in socioeconomic inequalities in lung cancer survival: population-based, data-linkage study. *Thorax* 2015: 70(2): 138-145.
18. Gomez DR, Liao KP, Swisher SG, Blumenschein GR, Erasmus JJ, Jr., Buchholz TA, Giordano SH, Smith BD. Time to treatment as a quality metric in lung cancer: Staging studies, time to treatment, and patient survival. *Radiother Oncol* 2015: 115(2): 257-263.
19. Gonzalez-Barcala FJ, Falagan JA, Garcia-Prim JM, Valdes L, Carreira JM, Puga A, Martin-Lancharro P, Garcia-Sanz MT, Anton-Sanmartin D, Canive-Gomez JC, Pose-Reino A, Lopez-Lopez R. Timeliness of care and prognosis in patients with lung cancer. *Ir J Med Sci* 2014: 183(3): 383-390.

20. Gonzalez-Barcala FJ, Garcia-Prim JM, Alvarez-Dobano JM, Moldes-Rodriguez M, Garcia-Sanz MT, Pose-Reino A, Valdes-Cuadrado L. Effect of delays on survival in patients with lung cancer. *Clin Transl Oncol* 2010: 12(12): 836-842.
21. Gould MK, Ghaus SJ, Olsson JK, Schultz EM. Timeliness of care in veterans with non-small cell lung cancer. *Chest* 2008: 133(5): 1167-1173.
22. Hansen HC, Janssen S, Thieme C, Perlov A, Schild SE, Rades D. Potential Impact of the Interval Between Imaging and Whole-brain Radiotherapy in Patients With Relatively Favorable Survival Prognoses. *Anticancer Res* 2019: 39(3): 1343-1346.
23. Kanarek NF, Hooker CM, Mathieu L, Tsai HL, Rudin CM, Herman JG, Brock MV. Survival after community diagnosis of early-stage non-small cell lung cancer. *Am J Med* 2014: 127(5): 443-449.
24. Kashiwabara K, Koshi S, Itonaga K, Nakahara O, Tanaka M, Toyonaga M. Outcome in patients with lung cancer found on lung cancer mass screening roentgenograms, but who did not subsequently consult a doctor. *Lung Cancer* 2003: 40(1): 67-72.
25. Kasymjanova G, Small D, Cohen V, Jagoe RT, Batist G, Sateren W, Ernst P, Pepe C, Sakr L, Agulnik J. Lung cancer care trajectory at a Canadian centre: an evaluation of how wait times affect clinical outcomes. *Curr* 2017: 24(5): 302-309.
26. Labbe C, Anderson M, Simard S, Tremblay L, Laberge F, Vaillancourt R, Lacasse Y. Wait times for diagnosis and treatment of lung cancer: a single-centre experience. *Curr* 2017: 24(6): 367-373.
27. Montero C, Rosales M, Otero I, Blanco M, Rodriguez G, Peterga S, Pita S, Verea H. [Lung cancer in the health care area of A Coruna (Spain): incidence, clinical approach and survival]. *Arch Bronconeumol* 2003: 39(5): 209-216.
28. Myrdal G, Lambe M, Hillerdal G, Lamberg K, Agustsson T, Stahle E. Effect of delays on prognosis in patients with non-small cell lung cancer. *Thorax* 2004: 59(1): 45-49.
29. Neal RD, Allgar VL, Ali N, Leese B, Heywood P, Proctor G, Evans J. Stage, survival and delays in lung, colorectal, prostate and ovarian cancer: comparison between diagnostic routes. *Br J Gen Pract* 2007: 57(536): 212-219.
30. Pita-Fernandez S, Montero-Martinez C, Pertega-Diaz S, Verea-Hernando H. Relationship between delayed diagnosis and the degree of invasion and survival in lung cancer. *J Clin Epidemiol* 2003: 56(9): 820-825.
31. Radzikowska E, Roszkowski-Sliz K, Chabowski M, Glaz P. Influence of delays in diagnosis and treatment on survival in small cell lung cancer patients. *Adv Exp Med Biol* 2013: 788: 355-362.
32. Radzikowska E, Roszkowski-Sliz K, Glaz P. The impact of timeliness of care on survival in non-small cell lung cancer patients. *Pneumonol Alergol Pol* 2012: 80(5): 422-429.
33. Salomaa ER, Sallinen S, Hiekkanen H, Liippo K. Delays in the diagnosis and treatment of lung cancer. *Chest* 2005: 128(4): 2282-2288.
34. Shin DW, Cho J, Kim SY, Guallar E, Hwang SS, Cho B, Oh JH, Jung KW, Seo HG, Park JH. Delay to curative surgery greater than 12 weeks is associated with increased mortality in patients with colorectal and breast cancer but not lung or thyroid cancer. *Ann Surg Oncol* 2013: 20(8): 2468-2476.
35. Vinod SK, Chandra A, Berthelsen A, Descallar J. Does timeliness of care in Non-Small Cell Lung Cancer impact on survival? *Lung Cancer* 2017: 112: 16-24.
36. Yorio JT, Xie Y, Yan J, Gerber DE. Lung cancer diagnostic and treatment intervals in the United States: a health care disparity? *J Thorac Oncol* 2009: 4(11): 1322-1330.
37. Zivkovic D. Effect of delays on survival in patients with lung carcinoma in Montenegro. *Acta Clin* 2014: 53(4): 390-398.
38. Samson P, Patel A, Garrett T, Crabtree T, Kreisel D, Krupnick AS, Patterson GA, Broderick S, Meyers BF, Puri V. Effects of Delayed Surgical Resection on Short-Term and Long-Term Outcomes in Clinical Stage I Non-Small Cell Lung Cancer. *Ann Thorac Surg* 2015: 99(6): 1906-1912; discussion 1913.
39. Nadpara P, Madhavan SS, Tworek C. Guideline-concordant timely lung cancer care and prognosis among elderly patients in the United States: A population-based study. *Cancer epidemiol* 2015: 39(6): 1136-1144.

40. Redaniel MT, Martin RM, Ridd MJ, Wade J, Jeffreys M. Diagnostic intervals and its association with breast, prostate, lung and colorectal cancer survival in England: historical cohort study using the Clinical Practice Research Datalink. *PLoS ONE* 2015: 10(5): e0126608.
41. Anggondowati T, Ganti AK, Islam KMM. Impact of time-to-treatment on overall survival of non-small cell lung cancer patients-an analysis of the national cancer database. *Transl* 2020: 9(4): 1202-1211.
42. Arici S, Sakin A, Cekin R, Secmeler S, Yasar N, Cihan S. Does the Waiting Period for Genetic Tests Affect the Prognosis in Chemotherapy-Treated de novo Metastatic Non-Small Cell Lung Cancer Patients without a Driver Mutation? *Oncol Res Treat* 2020: 1-7.
43. Booth CM, Shepherd FA, Peng Y, Darling G, Li G, Kong W, Biagi JJ, Mackillop WJ. Time to adjuvant chemotherapy and survival in non-small cell lung cancer: a population-based study. *Cancer* 2013: 119(6): 1243-1250.
44. Bullard JT, Eberth JM, Arrington AK, Adams SA, Cheng X, Salloum RG. Timeliness of Treatment Initiation and Associated Survival Following Diagnosis of Non-Small-Cell Lung Cancer in South Carolina. *South Med J* 2017: 110(2): 107-113.
45. Bütof R, Kirchner K, Appold S, Löck S, Rolle A, Höffken G, Krause M, Baumann M. Potential clinical predictors of outcome after postoperative radiotherapy of non-small cell lung cancer. *Strahlenther Onkol* 2014: 190(3): 263-269.
46. Huang CS, Hsu PK, Chen CK, Yeh YC, Shih CC, Huang BS. Delayed surgery after histologic or radiologic-diagnosed clinical stage I lung adenocarcinoma. *J* 2020: 12(3): 615-625.
47. Sheinson D, Wong WB, Wu N, Mansfield AS. Impact of delaying initiation of anaplastic lymphoma kinase inhibitor treatment on survival in patients with advanced non-small-cell lung cancer. *Lung Cancer* 2020: 143: 86-92.
48. Tsai CH, Kung PT, Kuo WY, Tsai WC. Effect of time interval from diagnosis to treatment for non-small cell lung cancer on survival: a national cohort study in Taiwan. *BMJ Open* 2020: 10(4): e034351.
49. Cone EB, Marchese M, Paciotti M, Nguyen DD, Nabi J, Cole AP, Molina G, Molina RL, Minami CA, Mucci LA, Kibel AS, Trinh QD. Assessment of Time-to-Treatment Initiation and Survival in a Cohort of Patients With Common Cancers. *JAMA netw* 2020: 3(12): e2030072.
50. Aragoneses FG, Moreno N, Leon P, Fontan EG, Folque E, Bronchogenic Carcinoma Cooperative Group of the Spanish Society of P, Thoracic S. Influence of delays on survival in the surgical treatment of bronchogenic carcinoma. *Lung Cancer* 2002: 36(1): 59-63.
51. Cushman TR, Jones B, Akhavan D, Rusthoven CG, Verma V, Salgia R, Sedrak M, Massarelli E, Welsh JW, Amini A. The Effects of Time to Treatment Initiation for Patients With Non-small-cell Lung Cancer in the United States. *Clin Lung Cancer* 2020: 18.
52. Gao SJ, Corso CD, Wang EH, Blasberg JD, Detterbeck FC, Boffa DJ, Decker RH, Kim AW. Timing of Surgery after Neoadjuvant Chemoradiation in Locally Advanced Non-Small Cell Lung Cancer. *J Thorac Oncol* 2017: 12(2): 314-322.
53. Khorana AA, Tullio K, Elson P, Pennell NA, Grobmyer SR, Kalady MF, Raymond D, Abraham J, Klein EA, Walsh RM, Monteleone EE, Wei W, Hobbs B, Bolwell BJ. Time to initial cancer treatment in the United States and association with survival over time: An observational study. *PLoS ONE* 2019: 14(3): e0213209.
54. Liu Y, Zhai X, Li J, Li Z, Ma D, Wang Z. Is there an optimal time to initiate adjuvant chemotherapy to predict benefit of survival in non-small cell lung cancer? *Chin* 2017: 29(3): 263-271.
55. Ramsden K, Laskin J, Ho C. Adjuvant Chemotherapy in Resected Stage II Non-small Cell Lung Cancer: Evaluating the Impact of Dose Intensity and Time to Treatment. *Clinical Oncology (Royal College of Radiologists)* 2015: 27(7): 394-400.
56. Salazar MC, Rosen JE, Wang Z, Arnold BN, Thomas DC, Herbst RS, Kim AW, Detterbeck FC, Blasberg JD, Boffa DJ. Association of Delayed Adjuvant Chemotherapy With Survival After Lung Cancer Surgery. *JAMA Oncol* 2017: 3(5): 610-619.
57. Samson P, Crabtree TD, Robinson CG, Morgensztern D, Broderick S, Krupnick AS, Kreisel D, Patterson GA, Meyers B, Puri V. Defining the Ideal Time Interval Between Planned Induction Therapy and Surgery for Stage IIIA Non-Small Cell Lung Cancer. *Ann Thorac Surg* 2017: 103(4): 1070-1075.

58. Wah W, Stirling RG, Ahern S, Earnest A. Influence of timeliness and receipt of first treatment on geographic variation in non-small cell lung cancer mortality. *Int J Cancer* 2020: 12.
59. Würschmidt F, Bünemann H, Ehnert M, Heilmann HP. Is the time interval between surgery and radiotherapy important in operable nonsmall cell lung cancer? A retrospective analysis of 340 cases. *Int J Radiat Oncol Biol Phys* 1997: 39(3): 553-559.
60. Yang CJ, Wang H, Kumar A, Wang X, Hartwig MG, D'Amico TA, Berry MF. Impact of Timing of Lobectomy on Survival for Clinical Stage IA Lung Squamous Cell Carcinoma. *Chest* 2017: 152(6): 1239-1250.
61. Bhandari S, Kumar R, Pham D, Gaskins J, Kloecker G. Treatment Timing in Small Cell Lung Cancer, a National Cancer Database Analysis. *Am J Clin Oncol* 2020: 43(5): 362-365.
62. Loh LC, Chan LY, Tan RY, Govindaraju S, Ratnavelu K, Kumar S, Raman S, Vijayasingham P, Thayaparan T. Effect of time delay on survival in patients with non-small cell lung cancer--a Malaysian study. *Asia Pac J Public Health* 2006: 18(1): 69-71.
63. Quarterman RL, McMillan A, Ratcliffe MB, Block MI. Effect of preoperative delay on prognosis for patients with early stage non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2003: 125(1): 108-113; discussion 113-104.
64. Torring ML, Frydenberg M, Hansen RP, Olesen F, Vedsted P. Evidence of increasing mortality with longer diagnostic intervals for five common cancers: a cohort study in primary care. *Eur J Cancer* 2013: 49(9): 2187-2198.
65. Wang L, Correa CR, Hayman JA, Zhao L, Cease K, Brenner D, Arenberg D, Curtis J, Kalemkerian GP, Kong FM. Time to treatment in patients with stage III non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2009: 74(3): 790-795.
66. Comber H, Cronin DP, Deady S, Lorcain PO, Riordan P. Delays in treatment in the cancer services: impact on cancer stage and survival. *Ir Med J* 2005: 98(8): 238-239.
67. Yun YH, Kim YA, Min YH, Park S, Won YJ, Kim DY, Choi IJ, Kim YW, Park SJ, Kim JH, Lee DH, Yoon SJ, Jeong SY, Noh DY, Heo DS. The influence of hospital volume and surgical treatment delay on long-term survival after cancer surgery. *Ann Oncol* 2012: 23(10): 2731-2737.
68. Samson P, Patel A, Crabtree TD, Morgensztern D, Robinson CG, Colditz GA, Waqar S, Kreisel D, Krupnick AS, Patterson GA, Broderick S, Meyers BF, Puri V. Multidisciplinary Treatment for Stage IIIA Non-Small Cell Lung Cancer: Does Institution Type Matter? *Ann Thorac Surg* 2015: 100(5): 1773-1779.
69. Weller D, Vedsted P, Rubin G, Walter FM, Emery J, Scott S, Campbell C, Andersen RS, Hamilton W, Olesen F, Rose P, Nafees S, Van Rijswijk E, Hiom S, Muth C, Beyer M, Neal RD. The Aarhus statement: improving design and reporting of studies on early cancer diagnosis. *Br J Cancer* 2012: 106(7): 1262-1267.
70. Boland JM, Maleszewski JJ, Wampfler JA, Voss JS, Kipp BR, Yang P, Yi ES. Pulmonary Invasive Mucinous Adenocarcinoma and Mixed Invasive Mucinous/Non-Mucinous Adenocarcinoma- A Clinicopathological and Molecular Genetic Study with Survival Analysis. *Hum Pathol* 2017: 17.
71. Nadpara PA, Madhavan SS, Tworek C, Sambamoorthi U, Hendryx M, Almubarak M. Guideline-concordant lung cancer care and associated health outcomes among elderly patients in the United States. *J Geriatr Oncol* 2015: 6(2): 101-110.
72. Malalasekera A, Nahm S, Blinman PL, Kao SC, Dhillon HM, Vardy JL. How long is too long? A scoping review of health system delays in lung cancer. *European Respiratory Review* 2018: 27(149): 180045.
73. Gravier FE, Smondack P, Prieur G, Medrinal C, Combret Y, Muir JF, Baste JM, Cuvelier A, Boujibar F, Bonnevie T. Effects of exercise training in people with non-small cell lung cancer before lung resection: a systematic review and meta-analysis. *Thorax* 2022: 77(5): 486-496.
74. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 1985: 312(25): 1604-1608.
75. Bilfinger TV, Albano D, Perwaiz M, Keresztes R, Nemesure B. Survival Outcomes Among Lung Cancer Patients Treated Using a Multidisciplinary Team Approach. *Clin Lung Cancer* 2018: 19(4): 346-351.
76. Bowen EF, Anderson JR, Roddie ME. Improving surgical resection rates in lung cancer without a two stop service. *Thorax* 2003: 58(4): 368.

77. Boxer MM, Vinod SK, Shafiq J, Duggan KJ. Do multidisciplinary team meetings make a difference in the management of lung cancer? *Cancer* 2011: 117(22): 5112-5120.
78. Bydder S, Nowak A, Marion K, Phillips M, Atun R. The impact of case discussion at a multidisciplinary team meeting on the treatment and survival of patients with inoperable non-small cell lung cancer. *Intern Med J* 2009: 39(12): 838-841.
79. Dillman RO, Chico SD. Cancer patient survival improvement is correlated with the opening of a community cancer center: comparisons with intramural and extramural benchmarks. *J Oncol Pract* 2005: 1(3): 84-92.
80. Fergusson RJ, Thomson CS, Brewster DH, Brown PH, Milroy R, Scottish Cancer Trials Lung G, Scottish Cancer Therapy N. Lung cancer: the importance of seeing a respiratory physician. *European Respiratory Journal* 2003: 21(4): 606-610.
81. Forrest LM, McMillan DC, McArdle CS, Dunlop DJ. An evaluation of the impact of a multidisciplinary team, in a single centre, on treatment and survival in patients with inoperable non-small-cell lung cancer. *Br J Cancer* 2005: 93(9): 977-978.
82. Freeman RK, Van Woerkom JM, Vyverberg A, Ascioti AJ. The effect of a multidisciplinary thoracic malignancy conference on the treatment of patients with lung cancer. *European Journal of Cardio-Thoracic Surgery* 2010: 38(1): 1-5.
83. Friedman EL, Kruklitis RJ, Patson BJ, Sopka DM, Weiss MJ. Effectiveness of a thoracic multidisciplinary clinic in the treatment of stage III non-small-cell lung cancer. *J Multidiscip Healthc* 2016: 9: 267-274.
84. Hung HY, Tseng YH, Chao HS, Chiu CH, Hsu WH, Hsu HS, Wu YC, Chou TY, Chen CK, Lan KL, Chen YW, Wu YH, Chen YM. Multidisciplinary team discussion results in survival benefit for patients with stage III non-small-cell lung cancer. *PLoS ONE* 2020: 15(10): e0236503.
85. Keating NL, Landrum MB, Lamont EB, Bozeman SR, Shulman LN, McNeil BJ. Tumor boards and the quality of cancer care. *J Natl Cancer Inst* 2013: 105(2): 113-121.
86. Kehl KL, Landrum MB, Kahn KL, Gray SW, Chen AB, Keating NL. Tumor board participation among physicians caring for patients with lung or colorectal cancer. *J Oncol Pract* 2015: 11(3): e267-278.
87. Lau KK, Rathinam S, Waller DA, Peake MD. The effects of increased provision of thoracic surgical specialists on the variation in lung cancer resection rate in England. *J Thorac Oncol* 2013: 8(1): 68-72.
88. Martin-Ucar AE, Waller DA, Atkins JL, Swinson D, O'Byrne KJ, Peake MD. The beneficial effects of specialist thoracic surgery on the resection rate for non-small-cell lung cancer. *Lung Cancer* 2004: 46(2): 227-232.
89. Mitchell PL, Thursfield VJ, Ball DL, Richardson GE, Irving LB, Torn-Broers Y, Giles GG, Wright GM. Lung cancer in Victoria: are we making progress? *Med J Aust* 2013: 199(10): 674-679.
90. Nemesure B, Albano D, Bilfinger T. Lung cancer recurrence and mortality outcomes over a 10-year period using a multidisciplinary team approach. *Cancer epidemiol* 2020: 68: 101804.
91. Nwaejike N, Elbur E, Malagon I, Dodman N, Hewitt K, Fontaine E, Krysiak P, Jones M, Shah R, Rammohan KS. Is there a role for the high-risk multidisciplinary team meeting in thoracic surgery? *Interact Cardiovasc Thorac Surg* 2016: 22(4): 397-400.
92. Pan CC, Kung PT, Wang YH, Chang YC, Wang ST, Tsai WC. Effects of multidisciplinary team care on the survival of patients with different stages of non-small cell lung cancer: a national cohort study. *PLoS ONE* 2015: 10(5): e0126547.
93. Riedel RF, Wang X, McCormack M, Toloza E, Montana GS, Schreiber G, Kelley MJ. Impact of a multidisciplinary thoracic oncology clinic on the timeliness of care. *J Thorac Oncol* 2006: 1(7): 692-696.
94. Rogers MJ, Matheson L, Garrard B, Maher B, Cowdery S, Luo W, Reed M, Riches S, Pitson G, Ashley DM. Comparison of outcomes for cancer patients discussed and not discussed at a multidisciplinary meeting. *Public Health* 2017: 149: 74-80.
95. Stevens W, Stevens G, Kolbe J, Cox B. Management of stages I and II non-small-cell lung cancer in a New Zealand study: divergence from international practice and recommendations. *Intern Med J* 2008: 38(10): 758-768.

96. Stewart I, Leary A, Khakwani A, Borthwick D, Tod A, Hubbard R, Beckett P, Tata LJ. Do working practices of cancer nurse specialists improve clinical outcomes? Retrospective cohort analysis from the English National Lung Cancer Audit. *Int J Nurs Stud* 2020: 103718.
97. Stone E, Rankin N, Kerr S, Fong K, Currow DC, Phillips J, Connon T, Zhang L, Shaw T. Does presentation at multidisciplinary team meetings improve lung cancer survival? Findings from a consecutive cohort study. *Lung Cancer* 2018: 124: 199-204.
98. Tamburini N, Maniscalco P, Mazzara S, Maietti E, Santini A, Calia N, Stefanelli A, Frassoldati A, Santi I, Rinaldi R, Nigim F, Righi R, Pedrazzi S, Cavallesco G. Multidisciplinary management improves survival at 1 year after surgical treatment for non-small-cell lung cancer: a propensity score-matched study. *European Journal of Cardio-Thoracic Surgery* 2018: 53(6): 1199-1204.
99. Russell GK, Jimenez S, Martin L, Stanley R, Peake MD, Woolhouse I. A multicentre randomised controlled trial of reciprocal lung cancer peer review and supported quality improvement: results from the improving lung cancer outcomes project. *Br J Cancer* 2014: 110(8): 1936-1942.
100. Powell HA, Baldwin DR. Multidisciplinary team management in thoracic oncology: more than just a concept? *Eur Respir J* 2014: 43(6): 1776-1786.
101. Ke KM, Blazeby JM, Strong S, Carroll FE, Ness AR, Hollingworth W. Are multidisciplinary teams in secondary care cost-effective? A systematic review of the literature. *Cost Eff Resour Alloc* 2013: 11(1): 7.
102. De Ieso PB, Coward JI, Letsa I, Schick U, Nandhabalan M, Frentzas S, Gore ME. A study of the decision outcomes and financial costs of multidisciplinary team meetings (MDMs) in oncology. *Br J Cancer* 2013: 109(9): 2295-2300.
103. Ahmed HZ, Liu Y, O'Connell K, Ahmed MZ, Cassidy RJ, Gillespie TW, Patel P, Pillai RN, Behera M, Steuer CE, Owonikoko TK, Ramalingam SS, Curran WJ, Higgins KA. Guideline-concordant Care Improves Overall Survival for Locally Advanced Non-Small-cell Lung Carcinoma Patients: A National Cancer Database Analysis. *Clin Lung Cancer* 2017: 18(6): 706-718.
104. Allen JW, Farooq A, O'Brien TF, Osarogiagbon RU. Quality of surgical resection for nonsmall cell lung cancer in a US metropolitan area. *Cancer* 2011: 117(1): 134-142.
105. Boxer MM, Duggan KJ, Descallar J, Vinod SK. Do patients discussed at a lung cancer multidisciplinary team meeting receive guideline-recommended treatment? *Asia Pac J Clin Oncol* 2016: 12(1): 52-60.
106. Casebeer A, Antol DD, DeClue RW, Hopson S, Li Y, Khoury R, Michael T, Sehman M, Parikh A, Stemkowski S, Bunce M. The Relationship Between Guideline-Recommended Initiation of Therapy, Outcomes, and Cost for Patients with Metastatic Non-Small Cell Lung Cancer. *J Manag Care Spec Pharm* 2018: 24(6): 554-564.
107. Elegbede AA, Gibson AJ, Fu H, Dean ML, Ezeife DA, Lau H, Cheung WY, Bebb DG. Real-World Adherence to Guideline-Recommended Treatment for Small Cell Lung Cancer. *American Journal of Clinical Oncology* 2020: 43(4): 236-242.
108. Jakobsen E, Green A, Oesterlind K, Rasmussen TR, Iachina M, Palshof T. Nationwide quality improvement in lung cancer care: the role of the Danish Lung Cancer Group and Registry. *J Thorac Oncol* 2013: 8(10): 1238-1247.
109. Mainz J, Hansen AM, Palshof T, Bartels PD. National quality measurement using clinical indicators: the Danish National Indicator Project. *J Surg Oncol* 2009: 99(8): 500-504.
110. McCarthy M, Datta P, Khachatryan A, Coleman MP, Rachet B. eWould compliance with cancer care standards improve survival for breast, colorectal and lung cancers? *J Epidemiol Community Health* 2008: 62(7): 650-654.
111. Neubauer MA, Hoverman JR, Kolodziej M, Reisman L, Gruschkus SK, Hoang S, Alva AA, McArthur M, Forsyth M, Rothermel T, Beveridge RA. Cost effectiveness of evidence-based treatment guidelines for the treatment of non-small-cell lung cancer in the community setting. *Journal of oncology practice/American Society of Clinical Oncology* 2010: 6(1): 12-18.
112. Novoa N, Jimenez MF, Aranda JL, Rodriguez M, Ramos J, Gomez Hernandez MT, Varela G. Effect of implementing the European guidelines for functional evaluation before lung resection on cardiorespiratory morbidity and 30-day mortality in lung cancer patients: a case-control study on a matched series of patients. *European Journal of Cardio-Thoracic Surgery* 2014: 45(4): e89-93; discussion e93.

113. Odell DD, Feinglass J, Engelhardt K, Papastefan S, Meyerson SL, Bharat A, DeCamp MM, Bilimoria KY. Evaluation of adherence to the Commission on Cancer lung cancer quality measures. *J Thorac Cardiovasc Surg* 2019: 157(3): 1219-1235.
114. Osarogiagbon RU, Ray MA, Faris NR, Smeltzer MP, Fehnel C, Houston-Harris C, Signore RS, McHugh LM, Levy P, Wiggins L, Sachdev V, Robbins ET. Prognostic Value of National Comprehensive Cancer Network Lung Cancer Resection Quality Criteria. *Ann Thorac Surg* 2017: 103(5): 1557-1565.
115. Samson P, Crabtree T, Broderick S, Kreisel D, Krupnick AS, Patterson GA, Meyers B, Puri V. Quality Measures in Clinical Stage I Non-Small Cell Lung Cancer: Improved Performance Is Associated With Improved Survival. *Ann Thorac Surg* 2017: 103(1): 303-311.
116. Yue D, Gong L, You J, Su Y, Zhang Z, Zhang Z, Gu F, Wang M, Wang C. Survival analysis of patients with non-small cell lung cancer who underwent surgical resection following 4 lung cancer resection guidelines. *BMC Cancer* 2014: 14: 422.
117. Blum TG, Rich A, Baldwin D, Beckett P, De Ruysscher D, Faivre-Finn C, Gaga M, Gamarra F, Grigoriu B, Hansen NC, Hubbard R, Huber RM, Jakobsen E, Jovanovic D, Konsoulova A, Kollmeier J, Massard G, McPhelim J, Meert AP, Milroy R, Paesmans M, Peake M, Putora PM, Scherpereel A, Schonfeld N, Sitter H, Skaug K, Spiro S, Strand TE, Tarright S, Thomas M, van Schil PE, Vansteenkiste JF, Wiewrodt R, Sculier JP. The European initiative for quality management in lung cancer care. *Eur Respir J* 2014: 43(5): 1254-1277.
118. Fervers B, Burgers JS, Haugh MC, Brouwers M, Browman G, Cluzeau F, Philip T. Predictors of high quality clinical practice guidelines: examples in oncology. *Int J Qual Health Care* 2005: 17(2): 123-132.
119. Commission; E. Aid Delivery Methods. Volume 1. Project Cycle Management Guidelines. European Commission, Brussels, 2004.
120. Nuckols TK, Lim Y-W, Wynn BO, Mattke S, Maclean CH, Harber P, Brook RH, Wallace P, Garland RH, Asch S. Rigorous Development does not Ensure that Guidelines are Acceptable to a Panel of Knowledgeable Providers. *Journal of General Internal Medicine* 2008: 23(1): 37-44.
121. Shaneyfelt TM, Mayo-Smith MF, Rothwangl J. Are Guidelines Following Guidelines? *Jama* 1999: 281(20): 1900.
122. Perrier L, Mrklas K, Lavis JN, Straus SE. Interventions encouraging the use of systematic reviews by health policymakers and managers: A systematic review. *Implementation Science* 2011: 6(1): 43.
123. Murthy L, Shepperd S, Clarke MJ, Garner SE, Lavis JN, Perrier L, Roberts NW, Straus SE. Interventions to improve the use of systematic reviews in decision-making by health system managers, policy makers and clinicians. *Cochrane Database Syst Rev* 2012(9): CD009401.
124. Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, Whitty P, Eccles MP, Matowe L, Shirran L, Wensing M, Dijkstra R, Donaldson C. Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health Technol Assess* 2004: 8(6): iii-iv, 1-72.
125. Jørgensen AW, Hilden J, Gøtzsche PC. Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review. *Bmj* 2006: 333(7572): 782.
126. Fang P, He W, Gomez D, Hoffman KE, Smith BD, Giordano SH, Jagsi R, Smith GL. Racial disparities in guideline-concordant cancer care and mortality in the United States. *Adv Radiat Oncol* 2018: 3(3): 221-229.
127. Bach PB, Cramer LD, Schrag D, Downey RJ, Gelfand SE, Begg CB. The influence of hospital volume on survival after resection for lung cancer. *N Engl J Med* 2001: 345(3): 181-188.
128. Baum P, Diers J, Haag J, Klotz L, Eichhorn F, Eichhorn M, Wiegering A, Winter H. Nationwide effect of high procedure volume in lung cancer surgery on in-house mortality in Germany. *Lung Cancer* 2020: 149: 78-83.
129. Begg CB, Cramer LD, Hoskins WJ, Brennan MF. Impact of hospital volume on operative mortality for major cancer surgery. *Jama* 1998: 280(20): 1747-1751.
130. Bernard A, Cottenet J, Mariet AS, Quantin C, Pages PB. Is an activity volume threshold really realistic for lung cancer resection? *J* 2018: 10(10): 5685-5694.
131. Bernard A, Pages PB, Mariet AS, Pforr A, Cottenet J, Quantin C. [Evaluation of surgical practice in the treatment of lung cancer in France from the PMSI national database]. *Rev Mal Respir* 2019: 36(1): 31-38.

132. Bilimoria KY, Bentrem DJ, Feinglass JM, Stewart AK, Winchester DP, Talamonti MS, Ko CY. Directing surgical quality improvement initiatives: comparison of perioperative mortality and long-term survival for cancer surgery. *Journal of Clinical Oncology* 2008: 26(28): 4626-4633.
133. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. *N Engl J Med* 2003: 349(22): 2117-2127.
134. Birkmeyer JD, Sun Y, Goldfaden A, Birkmeyer NJ, Stukel TA. Volume and process of care in high-risk cancer surgery. *Cancer* 2006: 106(11): 2476-2481.
135. Birkmeyer JD, Sun Y, Wong SL, Stukel TA. Hospital volume and late survival after cancer surgery. *Ann Surg* 2007: 245(5): 777-783.
136. Burgers JA, Damhuis RA. 30-day mortality after the start of systemic anticancer therapy for lung cancer: is it really a useful performance indicator? *ERJ open res* 2018: 4(4).
137. Chang CM, Huang KY, Hsu TW, Su YC, Yang WZ, Chen TC, Chou P, Lee CC. Multivariate analyses to assess the effects of surgeon and hospital volume on cancer survival rates: a nationwide population-based study in Taiwan. *PLoS ONE* 2012: 7(7): e40590.
138. Cheung MC, Hamilton K, Sherman R, Byrne MM, Nguyen DM, Franceschi D, Koniaris LG. Impact of teaching facility status and high-volume centers on outcomes for lung cancer resection: an examination of 13,469 surgical patients. *Ann Surg Oncol* 2009: 16(1): 3-13.
139. Committee for Scientific A, Kazui T, Osada H, Fujita H. An attempt to analyze the relation between hospital surgical volume and clinical outcome. *Gen Thorac Cardiovasc Surg* 2007: 55(12): 483-492.
140. Damhuis RA, Maat AP, Plaisier PW. Performance indicators for lung cancer surgery in the Netherlands. *European Journal of Cardio-Thoracic Surgery* 2015: 47(5): 897-903; discussion 903-894.
141. Eaton BR, Pugh SL, Bradley JD, Masters G, Kavadi VS, Narayan S, Nedzi L, Robinson C, Wynn RB, Koprowski C, Johnson DW, Meng J, Curran WJ, Jr. Institutional Enrollment and Survival Among NSCLC Patients Receiving Chemoradiation: NRG Oncology Radiation Therapy Oncology Group (RTOG) 0617. *J Natl Cancer Inst* 2016: 108(9).
142. Falcoz PE, Puyraveau M, Rivera C, Bernard A, Massard G, Mauny F, Dahan M, Thomas PA, Epithor G. The impact of hospital and surgeon volume on the 30-day mortality of lung cancer surgery: A nation-based reappraisal. *J Thorac Cardiovasc Surg* 2014: 148(3): 841-848; discussion 848.
143. Finlayson EV, Goodney PP, Birkmeyer JD. Hospital volume and operative mortality in cancer surgery: a national study. *Arch Surg* 2003: 138(7): 721-725; discussion 726.
144. Freixinet JL, Julia-Serda G, Rodriguez PM, Santana NB, de Castro FR, Fiuza MD, Lopez-Encuentra A, Bronchogenic Carcinoma Cooperative Group of the Spanish Society of P, Thoracic Surgery G-S. Hospital volume: operative morbidity, mortality and survival in thoracotomy for lung cancer. A Spanish multicenter study of 2994 cases. *European Journal of Cardio-Thoracic Surgery* 2006: 29(1): 20-25.
145. Gansler T, Fedewa SA, Flanders D, Virgo KS, Ward EM. "Lumping" vs "splitting" in oncologic pathology: association with cancer center type and case volume. *J Registry Manag* 2012: 39(2): 43-52.
146. Goyal G, Kommalapati A, Bartley AC, Gunderson TM, Adjei AA, Go RS. Association between hospital volume and mortality of patients with metastatic non-small cell lung cancer. *Lung Cancer* 2018: 122: 214-219.
147. Hadaya J, Dobaria V, Aguayo E, Mandelbaum A, Sanaiha Y, Revels SL, Benharash P. Impact of Hospital Volume on Outcomes of Elective Pneumonectomy in the United States. *Ann Thorac Surg* 2020: 110(6): 1874-1881.
148. Hannan EL, Radzyner M, Rubin D, Dougherty J, Brennan MF. The influence of hospital and surgeon volume on in-hospital mortality for colectomy, gastrectomy, and lung lobectomy in patients with cancer. *Surgery* 2002: 131(1): 6-15.
149. Harrison S, Tangel V, Wu X, Christos P, Gaber-Baylis L, Turnbull Z, Port J, Altorki N, Stiles B. Are minimum volume standards appropriate for lung and esophageal surgery? *J Thorac Cardiovasc Surg* 2018: 155(6): 2683-2694.e2681.
150. Hiraishi Y, Jo T, Michihata N, Hasegawa W, Sakamoto Y, Urushiyama H, Matsui H, Fushimi K, Nagase T, Yasunaga H, Yamauchi Y. Hospital Volume and Mortality following Diagnostic Bronchoscopy in Lung Cancer Patients: Data from a National Inpatient Database in Japan. *Respiration* 2019: 97(3): 264-272.

151. Hoffmann H, Passlick B, Ukena D, Wesselmann S. [Surgical Therapy for Lung Cancer: Why it Should be Performed in High Volume Centres]. *Zentralbl Chir* 2019: 144(1): 62-70.
152. Hollenbeck BK, Hong J, Zaojun Y, Birkmeyer JD. Misclassification of hospital volume with Surveillance, Epidemiology, and End Results Medicare data. *Surg Innov* 2007: 14(3): 192-198.
153. Ioka A, Tsukuma H, Ajiki W, Oshima A. Hospital procedure volume and survival of cancer patients in Osaka, Japan: a population-based study with latest cases. *Jpn J Clin Oncol* 2007: 37(7): 544-553.
154. Kim SY, Park JH, Kim SG, Woo HK, Park JH, Kim Y, Park EC. Disparities in utilization of high-volume hospitals for cancer surgery: results of a Korean population-based study. *Ann Surg Oncol* 2010: 17(11): 2806-2815.
155. Kozower BD, Stukenborg GJ. The relationship between hospital lung cancer resection volume and patient mortality risk. *Ann Surg* 2011: 254(6): 1032-1037.
156. Learn PA, Bach PB. A decade of mortality reductions in major oncologic surgery: the impact of centralization and quality improvement. *Med Care* 2010: 48(12): 1041-1049.
157. Lee JS, Scott CB, Komaki R, Ettinger DS, Sause WT. Impact of institutional experience on survival outcome of patients undergoing combined chemoradiation therapy for inoperable non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2002: 52(2): 362-370.
158. Li WW, Visser O, Ubbink DT, Klomp HM, Kloek JJ, de Mol BA. The influence of provider characteristics on resection rates and survival in patients with localized non-small cell lung cancer. *Lung Cancer* 2008: 60(3): 441-451.
159. Lien YC, Huang MT, Lin HC. Association between surgeon and hospital volume and in-hospital fatalities after lung cancer resections: the experience of an Asian country. *Ann Thorac Surg* 2007: 83(5): 1837-1843.
160. Little AG, Rusch VW, Bonner JA, Gaspar LE, Green MR, Webb WR, Stewart AK. Patterns of surgical care of lung cancer patients. *Ann Thorac Surg* 2005: 80(6): 2051-2056; discussion 2056.
161. Luchtenborg M, Riaz SP, Coupland VH, Lim E, Jakobsen E, Krasnik M, Page R, Lind MJ, Peake MD, Moller H. High procedure volume is strongly associated with improved survival after lung cancer surgery. *Journal of Clinical Oncology* 2013: 31(25): 3141-3146.
162. Moller H, Riaz SP, Holmberg L, Jakobsen E, Lagergren J, Page R, Peake MD, Pearce N, Purushotham A, Sullivan R, Vedsted P, Luchtenborg M. High lung cancer surgical procedure volume is associated with shorter length of stay and lower risks of re-admission and death: National cohort analysis in England. *Eur J Cancer* 2016: 64: 32-43.
163. Moore CB, Cox ML, Mulvihill MS, Klapper J, D'Amico TA, Hartwig MG. Challenging 30-day mortality as a site-specific quality metric in non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2019: 28.
164. Mulvihill MS, Cox ML, Becerra DC, Watson JA, Voigt SL, Yerokun BA, Speicher PJ, D'Amico TA, Tong B, Hartwig MG. Higher Utilization of Surgery Confers Superior Survival in Stage I Non-Small Cell Lung Cancer. *Ann Thorac Surg* 2018: 27.
165. Khuri SF, Daley J, Henderson W, Hur K, Hossain M, Soybel D, Kizer KW, Aust JB, Bell RH, Jr., Chong V, Demakis J, Fabri PJ, Gibbs JO, Grover F, Hammermeister K, McDonald G, Passaro E, Jr., Phillips L, Scamman F, Spencer J, Stremple JF. Relation of surgical volume to outcome in eight common operations: results from the VA National Surgical Quality Improvement Program. *Ann Surg* 1999: 230(3): 414-429; discussion 429-432.
166. Kommalapati A, Tella SH, Appiah AK, Smith L, Ganti AK. Association Between Treatment Facility Volume, Therapy Types, and Overall Survival in Patients With Stage IIIA Non-Small Cell Lung Cancer. *Journal of the National Comprehensive Cancer Network* 2019: 17(3): 229-236.
167. Kunisawa S, Yamashita K, Ikai H, Otsubo T, Imanaka Y. Survival analyses of postoperative lung cancer patients: an investigation using Japanese administrative data. *Springerplus* 2014: 3: 217.
168. Nagayasu T, Sato S, Yamamoto H, Yamasaki N, Tsuchiya T, Matsumoto K, Miyazaki T, Endo S, Tanaka F, Yokomise H, Okumura M. The impact of certification of general thoracic surgeons on lung cancer mortality: a survey by The Japanese Association for Thoracic Surgery. *European Journal of Cardio-Thoracic Surgery* 2016: 49(5): e134-140.

169. Nathan H, Atoria CL, Bach PB, Elkin EB. Hospital volume, complications, and cost of cancer surgery in the elderly. *Journal of Clinical Oncology* 2015: 33(1): 107-114.
170. Okawa S, Tabuchi T, Morishima T, Koyama S, Taniyama Y, Miyashiro I. Hospital volume and postoperative 5-year survival for five different cancer sites: A population-based study in Japan. *Cancer Sci* 2020: 111(3): 985-993.
171. Osada H, Yamakoshi E. Hospital volume and surgical outcomes of lung cancer in Japan. *Gen Thorac Cardiovasc Surg* 2007: 55(9): 360-365.
172. Ost DE, Ernst A, Lei X, Feller-Kopman D, Eapen GA, Kovitz KL, Herth FJ, Simoff M, Registry AQB. Diagnostic yield of endobronchial ultrasound-guided transbronchial needle aspiration: results of the AQuIRE Bronchoscopy Registry. *Chest* 2011: 140(6): 1557-1566.
173. Otake H, Yasunaga H, Horiguchi H, Matsutani N, Matsuda S, Ohe K. Impact of hospital volume on chest tube duration, length of stay, and mortality after lobectomy. *Ann Thorac Surg* 2011: 92(3): 1069-1074.
174. Pages PB, Cottenet J, Mariet AS, Bernard A, Quantin C. In-hospital mortality following lung cancer resection: nationwide administrative database. *European Respiratory Journal* 2016: 47(6): 1809-1817.
175. Pezzi CM, Mallin K, Mendez AS, Greer Gay E, Putnam JB, Jr. Ninety-day mortality after resection for lung cancer is nearly double 30-day mortality. *J Thorac Cardiovasc Surg* 2014: 148(5): 2269-2277.
176. Romano PS, Mark DH. Patient and hospital characteristics related to in-hospital mortality after lung cancer resection. *Chest* 1992: 101(5): 1332-1337.
177. Sakata R, Kuwano H, Yokomise H. Hospital volume and outcomes of cardiothoracic surgery in Japan: 2005-2009 national survey. *Gen Thorac Cardiovasc Surg* 2012: 60(10): 625-638.
178. Schillemans V, Vrijens F, De Gendt C, Robays J, Silversmit G, Verleye L, Camberlin C, Dubois C, Stordeur S, Wauters I, Van Meerbeeck JP, Van Eycken E, De Leyn P. Association between surgical volume and post-operative mortality and survival after surgical resection in lung cancer in Belgium: A population-based study. *Eur J Surg Oncol* 2019: 16.
179. Sheetz KH, Chhabra KR, Smith ME, Dimick JB, Nathan H. Association of Discretionary Hospital Volume Standards for High-risk Cancer Surgery With Patient Outcomes and Access, 2005-2016. *JAMA Surg* 2019: 14.
180. Simunovic M, Rempel E, Theriault ME, Coates A, Whelan T, Holowaty E, Langer B, Levine M. Influence of hospital characteristics on operative death and survival of patients after major cancer surgery in Ontario. *Can J Surg* 2006: 49(4): 251-258.
181. Sioris T, Sihvo E, Sankila R, Salo J. Effect of surgical volume and hospital type on outcome in non-small cell lung cancer surgery: a Finnish population-based study. *Lung Cancer* 2008: 59(1): 119-125.
182. Soares M, Toffart AC, Timsit JF, Burghi G, Irrazabal C, Pattison N, Tobar E, Almeida BF, Silva UV, Azevedo LC, Rabbat A, Lamer C, Parrot A, Souza-Dantas VC, Wallet F, Blot F, Bourdin G, Piras C, Delemazure J, Durand M, Tejera D, Salluh JI, Azoulay E, Lung Cancer in Critical Care Study I. Intensive care in patients with lung cancer: a multinational study. *Ann Oncol* 2014: 25(9): 1829-1835.
183. Strand TE, Rostad H, Damhuis RA, Norstein J. Risk factors for 30-day mortality after resection of lung cancer and prediction of their magnitude. *Thorax* 2007: 62(11): 991-997.
184. Thai AA, Stuart E, Te Marvelde L, Milne RL, Knight S, Whitfield K, Mitchell P. Hospital lung surgery volume and patient outcomes. *Lung Cancer* 2019: 129: 22-27.
185. Tchouta LN, Park HS, Boffa DJ, Blasberg JD, Detterbeck FC, Kim AW. Hospital Volume and Outcomes of Robot-Assisted Lobectomies. *Chest* 2017: 151(2): 329-339.
186. Urbach DR, Bell CM, Austin PC. Differences in operative mortality between high- and low-volume hospitals in Ontario for 5 major surgical procedures: estimating the number of lives potentially saved through regionalization. *Cmaj* 2003: 168(11): 1409-1414.
187. Urbach DR, Baxter NN. Does it matter what a hospital is "high volume" for? Specificity of hospital volume-outcome associations for surgical procedures: analysis of administrative data. *Qual Saf Health Care* 2004: 13(5): 379-383.

188. von Itzstein MS, Lu R, Kernstine KH, Halm EA, Wang S, Xie Y, Gerber DE. Closing the gap: Contribution of surgical best practices to outcome differences between high- and low-volume centers for lung cancer resection. *Cancer Med* 2020: 21.
189. Wouters MW, Siesling S, Jansen-Landheer ML, Elferink MA, Belderbos J, Coebergh JW, Schramel FM. Variation in treatment and outcome in patients with non-small cell lung cancer by region, hospital type and volume in the Netherlands. *Eur J Surg Oncol* 2010: 36 Suppl 1: S83-92.
190. Bendzsak AM, Baxter NN, Darling GE, Austin PC, Urbach DR. Regionalization and Outcomes of Lung Cancer Surgery in Ontario, Canada. *Journal of Clinical Oncology* 2017: 35(24): 2772-2780.
191. Birkmeyer NJ, Goodney PP, Stukel TA, Hillner BE, Birkmeyer JD. Do cancer centers designated by the National Cancer Institute have better surgical outcomes? *Cancer* 2005: 103(3): 435-441.
192. Boffa DJ, Mallin K, Herrin J, Resio B, Salazar MC, Palis B, Facktor M, McCabe R, Nelson H, Shulman LN. Survival After Cancer Treatment at Top-Ranked US Cancer Hospitals vs Affiliates of Top-Ranked Cancer Hospitals. *JAMA netw* 2020: 3(5): e203942.
193. Ellis MC, Diggs BS, Vetto JT, Schipper PH. Intraoperative oncologic staging and outcomes for lung cancer resection vary by surgeon specialty. *Ann Thorac Surg* 2011: 92(6): 1958-1963; discussion 1963-1954.
194. Farjah F, Flum DR, Varghese TK, Jr., Symons RG, Wood DE. Surgeon specialty and long-term survival after pulmonary resection for lung cancer. *Ann Thorac Surg* 2009: 87(4): 995-1004; discussion 1005-1006.
195. Goodney PP, Lucas FL, Stukel TA, Birkmeyer JD. Surgeon specialty and operative mortality with lung resection. *Ann Surg* 2005: 241(1): 179-184.
196. Meguid RA, Brooke BS, Chang DC, Sherwood JT, Brock MV, Yang SC. Are surgical outcomes for lung cancer resections improved at teaching hospitals? *Ann Thorac Surg* 2008: 85(3): 1015-1024; discussion 1024-1015.
197. Silvestri GA, Handy J, Lackland D, Corley E, Reed CE. Specialists achieve better outcomes than generalists for lung cancer surgery. *Chest* 1998: 114(3): 675-680.
198. Smith CB, Wolf A, Mhango G, Wisnivesky JP. Impact of Surgeon Volume on Outcomes of Older Stage I Lung Cancer Patients Treated via Video-assisted Thoracoscopic Surgery. *Semin Thorac Cardiovasc Surg* 2017: 29(2): 223-230.
199. Treasure T, Utley M, Bailey A. Assessment of whether in-hospital mortality for lobectomy is a useful standard for the quality of lung cancer surgery: retrospective study. *BMJ* 2003: 327(7406): 73.
200. von Meyenfeldt EM, Gooiker GA, van Gijn W, Post PN, van de Velde CJ, Tollenaar RA, Klomp HM, Wouters MW. The relationship between volume or surgeon specialty and outcome in the surgical treatment of lung cancer: a systematic review and meta-analysis. *J Thorac Oncol* 2012: 7(7): 1170-1178.
201. Tieu B, Schipper P. Specialty matters in the treatment of lung cancer. *Semin Thorac Cardiovasc Surg* 2012: 24(2): 99-105.
202. Ely S, Jiang SF, Patel AR, Ashiku SK, Velotta JB. Regionalization of Lung Cancer SurgeryImproves Outcomes in an Integrated Healthcare System. *Ann Thorac Surg* 2020: 14.
203. Jakobsen E, Rasmussen TR, Green A. Mortality and survival of lung cancer in Denmark: Results from the Danish Lung Cancer Group 2000-2012. *Acta Oncol* 2016: 55 Suppl 2: 2-9.
204. Erridge SC, Murray B, Williams L, Brewster D, Black R, Price A, Murray N, Sheehan F. Improved survival from lung cancer in British Columbia compared to Scotland-are different treatment rates the whole story? *Lung Cancer* 2009: 64(3): 358-366.
205. Imperatori A, Harrison RN, Leitch DN, Rovera F, Lepore G, Dionigi G, Sutton P, Dominioni L. Lung cancer in Teesside (UK) and Varese (Italy): a comparison of management and survival. *Thorax* 2006: 61(3): 232-239.
206. Khakwani A, Rich AL, Tata LJ, Powell HA, Stanley RA, Baldwin DR, Hubbard RB. The pathological confirmation rate of lung cancer in England using the NLCA database. *Lung Cancer* 2013: 79(2): 125-131.
207. Fischer-Valuck BW, Boggs H, Katz S, Durci M, Acharya S, Rosen LR. Comparison of stereotactic body radiation therapy for biopsy-proven versus radiographically diagnosed early-stage non-small lung cancer: a single-institution experience. *Tumori* 2015: 101(3): 287-293.
208. Fujii O, Demizu Y, Hashimoto N, Takagi M, Terashima K, Mima M, Jin D, Nagano F, Katsui K, Okimoto T, Iwata H, Niwa Y, Yamashita T, Akagi T, Daimon T, Sasaki R, Hishikawa Y, Abe M, Murakami M, Fuwa N.

Particle therapy for clinically diagnosed stage I lung cancer: comparison with pathologically proven non-small cell lung cancer. *Acta Oncol* 2015: 54(3): 315-321.
209. Haidar YM, Rahn DA, 3rd, Nath S, Song W, Bazhenova L, Makani S, Fuster MM, Sandhu AP. Comparison of outcomes following stereotactic body radiotherapy for non-small cell lung cancer in patients with and without pathological confirmation. *Therap* 2014: 8(1): 3-12.
210. Takeda A, Kunieda E, Sanuki N, Aoki Y, Oku Y, Handa H. Stereotactic body radiotherapy (SBRT) for solitary pulmonary nodules clinically diagnosed as lung cancer with no pathological confirmation: comparison with non-small-cell lung cancer. *Lung Cancer* 2012: 77(1): 77-82.
211. Reck M, Rabe KF. Precision Diagnosis and Treatment for Advanced Non-Small-Cell Lung Cancer. *N Engl J Med* 2017: 377(9): 849-861.
212. European Medicines Agency. Medicines. 2019 [cited 10.07.2022]; Available from: https://www.ema.europa.eu/en/medicines
213. WHO Classification of Tumours Editorial Board. Thoracic Tumours. 5th ed. International Agency for Research on Cancer, Lyon, France, 2021.
214. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. International Agency for Research on Cancer, Lyon, 2015.
215. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, Beer DG, Powell CA, Riely GJ, Van Schil PE, Garg K, Austin JH, Asamura H, Rusch VW, Hirsch FR, Scagliotti G, Mitsudomi T, Huber RM, Ishikawa Y, Jett J, Sanchez-Cespedes M, Sculier JP, Takahashi T, Tsuboi M, Vansteenkiste J, Wistuba I, Yang PC, Aberle D, Brambilla C, Flieder D, Franklin W, Gazdar A, Gould M, Hasleton P, Henderson D, Johnson B, Johnson D, Kerr K, Kuriyama K, Lee JS, Miller VA, Petersen I, Roggli V, Rosell R, Saijo N, Thunnissen E, Tsao M, Yankelewitz D. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol* 2011: 6(2): 244-285.
216. Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, Rind D, Montori VM, Brito JP, Norris S, Elbarbary M, Post P, Nasser M, Shukla V, Jaeschke R, Brozek J, Djulbegovic B, Guyatt G. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013: 66(7): 726-735.
217. Guyatt GH, Alonso-Coello P, Schunemann HJ, Djulbegovic B, Nothacker M, Lange S, Murad MH, Akl EA. Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. *J Clin Epidemiol* 2016: 80: 3-7.
218. Badr H, Smith CB, Goldstein NE, Gomez JE, Redd WH. Dyadic psychosocial intervention for advanced lung cancer patients and their family caregivers: results of a randomized pilot trial. *Cancer* 2015: 121(1): 150-158.
219. Bakitas M, Lyons KD, Hegel MT, Balan S, Brokaw FC, Seville J, Hull JG, Li Z, Tosteson TD, Byock IR, Ahles TA. Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. *Jama* 2009: 302(7): 741-749.
220. Bakitas MA, Tosteson TD, Li Z, Lyons KD, Hull JG, Li Z, Dionne-Odom JN, Frost J, Dragnev KH, Hegel MT, Azuero A, Ahles TA. Early Versus Delayed Initiation of Concurrent Palliative Oncology Care: Patient Outcomes in the ENABLE III Randomized Controlled Trial. *J Clin Oncol* 2015: 33(13): 1438-1445.
221. Brumley R, Enguidanos S, Jamison P, Seitz R, Morgenstern N, Saito S, McIlwane J, Hillary K, Gonzalez J. Increased satisfaction with care and lower costs: results of a randomized trial of in-home palliative care. *J Am Geriatr Soc* 2007: 55(7): 993-1000.
222. Cheville AL, Kollasch J, Vandenberg J, Shen T, Grothey A, Gamble G, Basford JR. A home-based exercise program to improve function, fatigue, and sleep quality in patients with Stage IV lung and colorectal cancer: a randomized controlled trial. *J Pain Symptom Manage* 2013: 45(5): 811-821.
223. Franciosi V, Maglietta G, Degli Esposti C, Caruso G, Cavanna L, Berte R, Bacchini G, Bocchi L, Piva E, Monfredo M, Scafuri V, Di Cesare P, Melotti B, Sequino M, Rimanti A, Binovi C, Ghisoni F, Caminiti C. Early palliative care and quality of life of advanced cancer patients-a multicenter randomized clinical trial. *Ann* 2019: 14.

224. Gade G, Venohr I, Conner D, McGrady K, Beane J, Richardson RH, Williams MP, Liberson M, Blum M, Della Penna R. Impact of an inpatient palliative care team: a randomized control trial. *J Palliat Med* 2008: 11(2): 180-190.
225. Greer JA, Pirl WF, Jackson VA, Muzikansky A, Lennes IT, Heist RS, Gallagher ER, Temel JS. Effect of early palliative care on chemotherapy use and end-of-life care in patients with metastatic non-small-cell lung cancer. *J Clin Oncol* 2012: 30(4): 394-400.
226. Groenvold M, Petersen MA, Damkier A, Neergaard MA, Nielsen JB, Pedersen L, Sjogren P, Stromgren AS, Vejlgaard TB, Gluud C, Lindschou J, Fayers P, Higginson IJ, Johnsen AT. Randomised clinical trial of early specialist palliative care plus standard care versus standard care alone in patients with advanced cancer: The Danish Palliative Care Trial. *Palliat Med* 2017: 31(9): 814-824.
227. Higginson IJ, Bausewein C, Reilly CC, Gao W, Gysels M, Dzingina M, McCrone P, Booth S, Jolley CJ, Moxham J. An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. *Lancet Respir Med* 2014: 2(12): 979-987.
228. McCorkle R, Jeon S, Ercolano E, Lazenby M, Reid A, Davies M, Viveiros D, Gettinger S. An Advanced Practice Nurse Coordinated Multidisciplinary Intervention for Patients with Late-Stage Cancer: A Cluster Randomized Trial. *Journal of Palliative Medicine* 2015: 18(11): 962-969.
229. Meyers FJ, Carducci M, Loscalzo MJ, Linder J, Greasby T, Beckett LA. Effects of a problem-solving intervention (COPE) on quality of life for patients with advanced cancer on clinical trials and their caregivers: simultaneous care educational intervention (SCEI): linking palliation and clinical trials. *J Palliat Med* 2011: 14(4): 465-473.
230. Nipp RD, Temel B, Fuh CX, Kay P, Landay S, Lage D, Franco-Garcia E, Scott E, Stevens E, O'Malley T, Mohile S, Dale W, Traeger L, Jackson V, Greer JA, El-Jawahri A, Temel JS. Pilot Randomized Trial of a Transdisciplinary Geriatric and Palliative Care Intervention for Older Adults With Cancer. *Journal of the National Comprehensive Cancer Network* 2020: 18(5): 591-598.
231. Pantilat SZ, O'Riordan DL, Dibble SL, Landefeld CS. Hospital-based palliative medicine consultation: a randomized controlled trial. *Arch Intern Med* 2010: 170(22): 2038-2040.
232. Rabow MW, Dibble SL, Pantilat SZ, McPhee SJ. The comprehensive care team: a controlled trial of outpatient palliative medicine consultation. *Arch Intern Med* 2004: 164(1): 83-91.
233. Steinhauser KE, Alexander SC, Byock IR, George LK, Olsen MK, Tulsky JA. Do preparation and life completion discussions improve functioning and quality of life in seriously ill patients? Pilot randomized control trial. *Journal of Palliative Medicine* 2008: 11(9): 1234-1240.
234. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, Dahlin CM, Blinderman CD, Jacobsen J, Pirl WF, Billings JA, Lynch TJ. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010: 363(8): 733-742.
235. Temel JS, Greer JA, El-Jawahri A, Pirl WF, Park ER, Jackson VA, Back AL, Kamdar M, Jacobsen J, Chittenden EH, Rinaldi SP, Gallagher ER, Eusebio JR, Li Z, Muzikansky A, Ryan DP. Effects of Early Integrated Palliative Care in Patients With Lung and GI Cancer: A Randomized Clinical Trial. *Journal of Clinical Oncology* 2017: 35(8): 834-841.
236. Temel JS, Sloan J, Zemla T, Greer JA, Jackson VA, El-Jawahri A, Kamdar M, Kamal A, Blinderman CD, Strand J, Zylla D, Daugherty C, Furqan M, Obel J, Razaq M, Roeland EJ, Loprinzi C. Multisite, Randomized Trial of Early Integrated Palliative and Oncology Care in Patients with Advanced Lung and Gastrointestinal Cancer: Alliance A221303. *Journal of Palliative Medicine* 2020: 07.
237. Vanbutsele G, Pardon K, Van Belle S, Surmont V, De Laat M, Colman R, Eecloo K, Cocquyt V, Geboes K, Deliens L. Effect of early and systematic integration of palliative care in patients with advanced cancer: a randomised controlled trial. *Lancet Oncol* 2018: 19(3): 394-404.
238. Wagner EH, Ludman EJ, Aiello Bowles EJ, Penfold R, Reid RJ, Rutter CM, Chubak J, McCorkle R. Nurse navigators in early cancer care: a randomized, controlled trial. *J Clin Oncol* 2014: 32(1): 12-18.
239. Zhuang H, Ma Y, Wang L, Zhang H. Effect of early palliative care on quality of life in patients with non-small-cell lung cancer. *Curr* 2018: 25(1): e54-e58.

240. Zimmermann C, Swami N, Krzyzanowska M, Hannon B, Leighl N, Oza A, Moore M, Rydall A, Rodin G, Tannock I, Donner A, Lo C. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *Lancet* 2014: 383(9930): 1721-1730.
241. Ferrell B, Sun V, Hurria A, Cristea M, Raz DJ, Kim JY, Reckamp K, Williams AC, Borneman T, Uman G, Koczywas M. Interdisciplinary Palliative Care for Patients With Lung Cancer. *J Pain Symptom Manage* 2015: 50(6): 758-767.
242. Nguyen HQ, Ruel N, Macias M, Borneman T, Alian M, Becher M, Lee K, Ferrell B. Translation and Evaluation of a Lung Cancer, Palliative Care Intervention for Community Practice. *J Pain Symptom Manage* 2018: 02.
243. King JD, Eickhoff J, Traynor A, Campbell TC. Integrated Onco-Palliative Care Associated With Prolonged Survival Compared to Standard Care for Patients With Advanced Lung Cancer: A Retrospective Review. *J Pain Symptom Manage* 2016: 51(6): 1027-1032.
244. Lafitte C, Etienne-Mastroianni B, Fournel C, Natoli L, Foucaut AM, Girard N. Implementation of optimized supportive care and hospital needs along the management of patients with advanced lung cancer. *Lung Cancer* 2018: 124: 143-147.
245. Lammers A, Slatore CG, Fromme EK, Vranas KC, Sullivan DR. Association of Early Palliative Care With Chemotherapy Intensity in Patients With Advanced Stage Lung Cancer: A National Cohort Study. *J Thorac Oncol* 2019: 14(2): 176-183.
246. Nieder C, Tollali T, Haukland E, Reigstad A, Flatoy LR, Engljahringer K. Impact of early palliative interventions on the outcomes of care for patients with non-small cell lung cancer. *Support Care Cancer* 2016: 24(10): 4385-4391.
247. Sullivan DR, Chan B, Lapidus JA, Ganzini L, Hansen L, Carney PA, Fromme EK, Marino M, Golden SE, Vranas KC, Slatore CG. Association of Early Palliative Care Use With Survival and Place of Death Among Patients With Advanced Lung Cancer Receiving Care in the Veterans Health Administration. *JAMA Oncol* 2019: 19.
248. Beckett P, Woolhouse I, Stanley R, Peake MD. Exploring variations in lung cancer care across the UK--the 'story so far' for the National Lung Cancer Audit. *Clin Med* 2012: 12(1): 14-18.
249. Khakwani A, Rich AL, Powell HA, Tata LJ, Stanley RA, Baldwin DR, Duffy JP, Hubbard RB. Lung cancer survival in England: trends in non-small-cell lung cancer survival over the duration of the National Lung Cancer Audit. *Br J Cancer* 2013: 109(8): 2058-2065.
250. Khakwani A, Rich AL, Tata LJ, Powell HA, Stanley RA, Baldwin DR, Hubbard RB. Small-cell lung cancer in England: trends in survival and chemotherapy using the National Lung Cancer Audit. *PLoS ONE* 2014: 9(2): e89426.
251. Wolfson JA, Sun CL, Wyatt LP, Hurria A, Bhatia S. Impact of care at comprehensive cancer centers on outcome: Results from a population-based study. *Cancer* 2015: 121(21): 3885-3893.
252. Shulman LN, Palis BE, McCabe R, Mallin K, Loomis A, Winchester D, McKellar D. Survival As a Quality Metric of Cancer Care: Use of the National Cancer Data Base to Assess Hospital Performance. *Journal of oncology practice/American Society of Clinical Oncology* 2018: 14(1): e59-e72.
253. Adizie JB, Khakwani A, Beckett P, Hubbard R, Navani N, Harden SV, Woolhouse I. Impact of organisation and specialist service delivery on lung cancer outcomes. *Thorax* 2019: 74(6): 546-550.
254. Erridge SC, Murray B, Price A, Ironside J, Little F, Mackean M, Walker W, Brewster DH, Black R, Fergusson RJ, South-East Scotland Cancer Network Lung Cancer T. Improved treatment and survival for lung cancer patients in South-East Scotland. *J Thorac Oncol* 2008: 3(5): 491-498.
255. Faris NR, Smeltzer MP, Lu F, Fehnel CL, Chakraborty N, Houston-Harris CL, Robbins ET, Signore RS, McHugh LM, Wolf BA, Wiggins L, Levy P, Sachdev V, Osarogiagbon RU. Evolution in the Surgical Care of Patients With Non-Small Cell Lung Cancer in the Mid-South Quality of Surgical Resection Cohort. *Semin Thorac Cardiovasc Surg* 2017: 29(1): 91-101.
256. Hagan ME, Williams ST, Socci L, Malik M, Internullo E, Martin-Ucar AE. Completing the audit cycle improves surgical standards in lung cancer. Why do some patients still not receive the best care? *J Thorac Oncol* 2013: 8(6): 779-782.

257. Ten Berge M, Beck N, Heineman DJ, Damhuis R, Steup WH, van Huijstee PJ, Eerenberg JP, Veen E, Maat A, Versteegh M, van Brakel T, Schreurs WH, Wouters MW. Dutch Lung Surgery Audit: A National Audit Comprising Lung and Thoracic Surgery Patients. *Ann Thorac Surg* 2018: 106(2): 390-397.
258. Cerfolio RJ, Bryant AS. Optimal care of patients with non-small cell lung cancer reduces perioperative morbidity. *J Thorac Cardiovasc Surg* 2011: 141(1): 22-33.
259. Austin CA, Mohottige D, Sudore RL, Smith AK, Hanson LC. Tools to Promote Shared Decision Making in Serious Illness: A Systematic Review. *JAMA Intern Med* 2015: 175(7): 1213-1221.
260. Spiegle G, Al-Sukhni E, Schmocker S, Gagliardi AR, Victor JC, Baxter NN, Kennedy ED. Patient decision aids for cancer treatment: are there any alternatives? *Cancer* 2013: 119(1): 189-200.
261. Spronk I, Meijers MC, Heins MJ, Francke AL, Elwyn G, van Lindert A, van Dulmen S, van Vliet LM. Availability and effectiveness of decision aids for supporting shared decision making in patients with advanced colorectal and lung cancer: Results from a systematic review. *Eur J Cancer Care (Engl)* 2019: 28(3): e13079.
262. Meropol NJ, Egleston BL, Buzaglo JS, Balshem A, Benson AB, 3rd, Cegala DJ, Cohen RB, Collins M, Diefenbach MA, Miller SM, Fleisher L, Millard JL, Ross EA, Schulman KA, Silver A, Slater E, Solarino N, Sulmasy DP, Trinastic J, Weinfurt KP. A Web-based communication aid for patients with cancer: the CONNECT Study. *Cancer* 2013: 119(7): 1437-1445.
263. Brown R, Butow PN, Boyer MJ, Tattersall MH. Promoting patient participation in the cancer consultation: evaluation of a prompt sheet and coaching in question-asking. *Br J Cancer* 1999: 80(1-2): 242-248.
264. Butow P, Devine R, Boyer M, Pendlebury S, Jackson M, Tattersall MH. Cancer consultation preparation package: changing patients but not physicians is not enough. *J Clin Oncol* 2004: 22(21): 4401-4409.
265. Clayton JM, Butow PN, Tattersall MH, Devine RJ, Simpson JM, Aggarwal G, Clark KJ, Currow DC, Elliott LM, Lacey J, Lee PG, Noel MA. Randomized controlled trial of a prompt list to help advanced cancer patients and their caregivers to ask questions about prognosis and end-of-life care. *J Clin Oncol* 2007: 25(6): 715-723.
266. De Lorenzo F, Ballatori E, Di Costanzo F, Giacalone A, Ruggeri B, Tirelli U. Improving information to Italian cancer patients: results of a randomized study. *Ann Oncol* 2004: 15(5): 721-725.
267. McAlpine K, Lewis KB, Trevena LJ, Stacey D. What Is the Effectiveness of Patient Decision Aids for Cancer-Related Decisions? A Systematic Review Subanalysis. *JCO Clin Cancer Inform* 2018: 2: 1-13.