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Hemicolectomy for patients with appendiceal neuroendocrine tumours 1-2cm in size: a retrospective, Europe-wide, pooled, cohort study

Cédric Nesti, Konstantin Bräutigam, Marta Benavent, Laura Bernal, Hessa Boharoon, Johan Botling, Antonin Bouroumeau, Iva Brcic, Maximilian Brunner, Guillaume Cadiot, Maria Camara, Emanuel Christ, Thomas Clerici, Ashley K. Clift, Hamish Clouston, Lorenzo Cobianchi, Jarosław B. Ćwikła, Kosmas Daskalakis, Andrea Frilling, Rocio Garcia-Carbonero, Simona Grozinsky-Glasberg, Jorge Hernando, Valérie Hervieu, Johannes Hofland, Pernille Holmager, Frediano Inzani, Henning Jann, Paula Jimenez-Fonseca, Enes Kaçmaz, Daniel Kaemmerer, Gregory Kaltsas, Branislav Klimacek, Ulrich Knigge, Agnieszka Kolasińska-Ćwikła, Walter Kolb, Beata Kos-Kudła, Catarina Alisa Kunze, Stefania Landolfi, Stefano La Rosa, Carlos López López, Kerstin Lorenz, Maurice Matter, Peter Mazal, Claudia Mestre-Alagarda, Patricia Morales del Burgo, Els J. M. Nieveen van Dijkum, Kira Oleinikov, Lorenzo A. Orci, Francesco Panzuto, Marianne Pavel, Marine Perrier, Henrik Mikael Reims, Guido Rindi, Anja Rinke, Maria Rinzivillo, Xavier Sagaert, Ilker Satiroglu, Andreas Selberherr, Alexander R. Siebenhüner, Margot E. T. Tesselaar, Michael J. Thalhammer, Espen Thiis-Evensen, Christos Toumpanakis, Timon Vandamme, José G. van den Berg, Alessandro Vanoli, Marie-Louise F. van Velthuysen, Chris Verslype, Stephan A. Vorburger, Alessandro Lugli, John Ramage, Marcel Zwahlen, PhD, Aurel Perren*, and Reto M. Kaderli*

* Shared authorship.

Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland (C Nesti MD; R M Kaderli MD); **Institute of Pathology, University of Bern, Bern, Switzerland** (K Bräutigam MD; Prof A Perren MD; Prof A Lugli MD); **Department of Medical Oncology, University Hospital Virgen del Rocío, Instituto de Biomedicina De Sevilla (IBIS), Seville, Spain** (M Benavent MD; L Bernal MD); **Neuroendocrine Tumour Unit - ENETS Centre of Excellence, Royal Free Hospital London, London, UK** (H Boharoon MD; Prof C Toumpanakis MD); **Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden** (J Botling MD); **Division of Clinical Pathology, Diagnostic Department, Hôpitaux Universitaires Genève, Geneva, Switzerland** (A Bouroumeau MD); **Diagnostic and Research Institute of Pathology, Medical University of Graz, Graz, Austria** (I Brcic MD); **Department of Surgery, University Hospital of Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany** (M Brunner MD); **Service d'Hépato-gastroentérologie et d'oncologie digestive, Université Reims Champagne Ardenne, CHU de Reims, Reims, France** (Prof G Cadiot MD; M Perrier MD); **Pathology Department, Hospital Universitario 12 de Octubre, Madrid, Spain** (M Camara MD); **Department of Endocrinology, Diabetology and Metabolism, ENETS Center of Excellence, University Hospital of Basel, Basel, Switzerland** (Prof E Christ MD); **Klinik für Allgemein-, Viszeral-, Endokrin- und Transplantationschirurgie, Kantonsspital St. Gallen, St. Gallen, Switzerland** (T Clerici MD; W Kolb MD); **Department of Surgery and Cancer, Imperial College London, London, UK** (A K Clift MBBS; Prof A Frilling MD); **Colorectal and Peritoneal Oncology Centre, The Christie NHS Foundation Trust, Manchester, UK** (H Clouston MD); **Department of Clinical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy** (Prof L Cobianchi MD); **Department of General Surgery, IRCCS Policlinico San Matteo Fondazione, Pavia, Italy** (Prof L Cobianchi MD); **Indywidualna Specjalistyczna Praktyka Lekarska,**

Warsaw, Poland (Prof J B Ćwikła MD); **1st Department of Propaedeutic Internal Medicine, Endocrine Unit, National and Kapodistrian University of Athens, ENETS Center of Excellence, Athens, Greece** (Prof K Daskalakis MD; Prof G Kaltsas MD); **Oncology Department, Hospital Universitario 12 de Octubre, Imas12, UCM, Madrid, Spain** (Prof R Garcia-Carbonero MD); **Neuroendocrine Tumor Unit, ENETS Center of Excellence, Department of Endocrinology and Metabolism, Hadassah Medical Organization and Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel** (Prof S Grozinsky-Glasberg MD; K Oleinikov MD); **Medical Oncology Department, Vall d´Hebron University Hospital / Vall d´Hebron Institute of Oncology (VHIO), Barcelona, Spain** (J Hernando MD); **Hospices Civils de Lyon, HEH, Lyon, France** (V Hervieu MD); **Department of Internal Medicine, Section of Endocrinology, ENETS Center of Excellence and Erasmus Cancer Institute, Erasmus MC, Rotterdam, The Netherlands** (J Hofland MD); **ENETS Neuroendocrine Tumor Centre of Excellence, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark** (P Holmager MD; Prof U Knigge MD); **Department of Endocrinology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark** (P Holmager MD; Prof U Knigge MD); **General Pathology, Department of Woman and Child Health Science and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy; Roma European NeuroEndocrine Tumor Society (ENETS) Center of Excellence** (F Inzani MD); **Hepatology and Gastroenterology, Charité University Medicine Berlin, Berlin, Germany** (H Jann MD); **Department of Medical Oncology, Hospital Universitario Central de Asturias, ISPA, Oviedo, Spain** (P Jimenez-Fonseca MD); **Department of Surgery, Amsterdam UMC location University of Amsterdam, Amsterdam, The Netherlands** (E Kaçmaz PhD; Prof E J M Nieveen van Dijkum MD); **Department of General and Visceral Surgery, Zentralklinik Bad Berka, Bad Berka, Germany** (D Kaemmerer MD); **Department of Surgery, Endocrine Surgical Unit, Uppsala University, Uppsala,**

Sweden (B Klimacek MD); **Department of Surgery, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark** (Prof U Knigge MD); **The Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland** (A Kolasińska-Ćwikła MD); **Department of Endocrinology and Neuroendocrine Neoplasms, Department of Endocrinology and Pathophysiology, Medical University of Silesia, Katowice, Poland** (Prof B Kos-Kudla MD); **Institute of Pathology, Charité–Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany** (C A Kunze MD); **Pathology Department, Vall d´Hebron University Hospital, Barcelona, Spain** (S Landolfi MD); **Institute of Pathology, Department of Laboratory Medicine and Pathology, University of Lausanne, Lausanne, Switzerland** (Prof S La Rosa MD); **Unit of Pathology, Department of Medicine and Surgery, University of Insubria, Varese, Italy** (Prof S La Rosa MD); **Medical Oncology Department, Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain** (C López López MD); **Department of Visceral, Vascular, and Endocrine Surgery, Martin-Luther University of Halle-Wittenberg, Halle, Germany** (Prof K Lorenz MD; I Satiroglu); **Department of Visceral Surgery, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland** (Prof M Matter MD); **Department of Clinical Pathology, Medical University of Vienna, General Hospital Vienna, Vienna, Austria** (Prof P Mazal MD); **Histopathology, Institute of Liver Studies, Kings College Hospital, London, UK** (C Mestre-Alagarda MD); **Department of Pathology, Hospital Universitario Central de Asturias, Oviedo, Spain** (P Morales del Burgo MD); **Division of Abdominal Surgery, Department of Surgery, Geneva University Hospitals, Geneva, Switzerland** (L A Orci MD); **Department of Medical-Surgical Sciences and Translational Medicine, Sapienza University of Rome, Rome, Italy** (F Panzuto MD); **Digestive Disease Unit, Sant'Andrea University Hospital, ENETS Center of Excellence, Rome, Italy** (F Panzuto MD; M

Rinzivillo MD); **Department of Medicine 1, Friedrich Alexander University Erlangen – Nürnberg, Erlangen, Germany** (Prof M Pavel MD); **Department of Pathology, Oslo University Hospital, Rikshospitalet, Oslo, Norway** (H M Reims MD); **Section of Anatomic Pathology, Department of Life Sciences and Public Health, Università Cattolica del Sacro Cuore; Unit of Head and Neck, Lung and Endocrine Pathology, Department of Woman and Child Health Science and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italia; Roma European NeuroEndocrine Tumor Society (ENETS) Center of Excellence** (Prof G Rindi MD); **UKGM, Marburg, Department of Gastroenterology and Endocrinology and Philipps University Marburg, Marburg, Germany** (A Rinke MD); **Translational Cell & Tissue Research, KU Leuven, Leuven, Belgium** (Prof X Sagaert MD); **Division of Visceral Surgery, Department of General Surgery, Medical University Vienna, Vienna, Austria** (A Selberherr MD); **Klinik für Medizinische Onkologie und Hämatologie, Universitätsspital Zürich und Universität Zürich, Zürich, Switzerland** (A R Siebenhüner MD); **Departement Medizinische Onkologie, Kantonsspital Schaffhausen, Schaffhausen, Switzerland** (A R Siebenhüner MD); **Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands** (Prof M E T Tesselaar MD); **Department of Surgery, Division of Visceral and Transplant Surgery, University Hospital, Medical University of Graz, Graz, Austria** (Prof M J Thalhammer MD); **Department of Gastroenterology, Oslo University Hospital, Rikshospitalet, Oslo, Norway** (E Thiis-Evensen MD); **University Hospital Antwerp, Edegem, Belgium** (T Vandamme MD); **Department of Pathology, The Netherlands Cancer Institute, Amsterdam, The Netherlands** (J G van den Berg MD); **Unit of Anatomic Pathology, Department of Molecular Medicine, University of Pavia, Pavia, Italy** (A Vanoli MD); **Unit of Anatomic Pathology, IRCCS Policlinico San Matteo Foundation, Pavia, Italy** (A Vanoli MD); **Department of Pathology, Erasmus MC, Rotterdam, The Netherlands** (M-L F van

Velthuysen MD); **Clinical Digestive Oncology, University Hospitals Leuven, Belgium** (Prof C Verslype MD); **Surgical Department, Teaching Hospitals Emmental, Burgdorf, Switzerland** (Prof S A Vorburger MD); **University of Winchester, UK** (Prof J Ramage MD); **Hampshire Hospital, UK** (Prof J Ramage MD); **Institute of Social and Preventive Medicine, University of Bern, Switzerland** (Prof M Zwahlen PhD).

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Corresponding author:

Reto Martin Kaderli, MD, FEBS

Department of Visceral Surgery and Medicine

Inselspital, Bern University Hospital, University of Bern

Freiburgstrasse

CH-3010 Bern,

Phone: +41 (0) 31 632 60 65

Email: Reto.Kaderli@insel.ch

RESEARCH IN CONTEXT

Evidence before this study: The most pertinent consensus guidelines for European countries regarding the management of appendiceal neuroendocrine tumours (aNET) 1-2cm in size were published by the European Neuroendocrine Tumor Society (ENETS). They recommend oncological right-sided hemicolectomy in cases where one or more histopathological risk factors are present (positive or unclear margins, deep mesoappendiceal invasion >3 mm, higher proliferation rate, lymphovascular invasion). Hemicolectomy is associated with higher morbidity rates and lowered quality of life. We therefore searched PubMed from inception to August 1st, 2022, using the terms “neuroendocrine tumour” and “appendix”. While several studies recently discussed potential global overtreatment by performing oncological resections for aNET 1-2cm, they are unable to inform treatment decisions due to observational design and low statistical power.

Added value of this study: This is by far the largest investigation of a homogeneous, clinically well-characterized cohort of completely resected aNET 1-2cm in size, supported by ENETS. We found that long-term overall survival was similar between patients with aNET 1-2cm that underwent appendectomy as the only measure or right-sided hemicolectomy. Residual regional lymph node metastases in those that underwent appendectomy as the only measure appeared clinically irrelevant. No patients developed novel metastases during >10 years follow-up, and there were no tumour-related deaths.

Implications of all the available evidence: The role of a systematic lymphadenectomy by right-sided hemicolectomy following complete resection of the aNET 1-2cm by appendectomy is debated, but recommended by current guidelines in the presence of histopathological “risk factors”. The results of the present European multinational cohort study provide the most

reliable evidence that right-sided hemicolectomy is not indicated in aNET 1-2cm in size, and that the potential benefits do not justify the risk of this operation. These findings should inform consensus best practice guidelines for this typically young group of patients. In view of the low incidence of the disease and the need for a long-term follow-up, a prospective, randomized trial on the present research question will likely not be practical.

ABSTRACT

Background: Awareness of a potential global overtreatment by performing oncological resections for appendiceal neuroendocrine tumours (aNET) 1-2cm is increasing, but the rarity of this situation impeded a clear recommendation hitherto. We aimed at assessing the malignant potential of aNET 1-2cm in patients with or without right-sided hemicolectomy.

Methods: This retrospective study pooled data from 40 European institutions regarding patients of any age and performance status with histopathologically confirmed aNET of size 1-2cm and complete resection of the primary tumour between January 1st 2000 and December 31st 2010. The patients either had an appendectomy only or an appendectomy with oncological right-sided hemicolectomy or ileocecal resection. Predefined primary outcomes were frequency of distant metastases and tumour-related mortality rate. Secondary outcomes included frequency of regional lymph node metastases and overall survival with or without right-sided hemicolectomy. Cox proportional hazards regression was used to estimate the relative all-cause mortality hazard associated with patients undergoing right-sided hemicolectomy compared to appendectomy alone.

Findings: Of 278 patients (110 [39.6%] men and 168 [60.4%] women) with aNET 1-2cm included in the study, 163 (58.6%) had an appendectomy and 115 (41.4%) right-sided hemicolectomy. After centralized histopathological review, the aNET was classified as a possible or probable primary tumour in two patients with distant peritoneal metastases and in two patients with distant metastases in the liver. All metastases were diagnosed synchronously with no tumour-related deaths during the follow-up. Regional lymph node metastases were found in 22 (19.6%) patients with right-sided hemicolectomy. We estimated that 12.8% (95% confidence interval 6.5 - 21.1%) of patients undergoing appendectomy likely had residual regional lymph node

metastases based on histopathological risk factors. Overall survival after a median follow-up of 13.0 years was similar between patients with appendectomy and right-sided hemicolectomy (adjusted hazard ratio .88, 95% confidence interval .36 - 2.17, P = .71).

Interpretation: This study provides evidence that right-sided hemicolectomy is not indicated following complete resection of the aNET 1-2cm by appendectomy, that regional lymph-node metastases of aNET are clinically irrelevant, and that an additional postoperative exclusion of metastases and histopathological evaluation of risk factors is not supported by the presented results.

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INTRODUCTION

Appendiceal neuroendocrine tumours (aNET) are often diagnosed incidentally on histopathological examination and occur in 1.5% of all appendectomies with an annual incidence rate of 0.15 – 0.6 per 100,000.[1,2] The most pertinent consensus guidelines for the management of aNET were published in 2016 by the European Neuroendocrine Tumor Society (ENETS).[2] Simple appendectomy and oncological right-sided hemicolectomy are undebated surgical procedures for aNET <1cm and >2cm, respectively, but the treatment of aNET 1-2cm, accounting for 5-25% of all aNET, is challenging. The ENETS guidelines recommend oncological right-sided hemicolectomy in cases where one or more histopathological features are present: positive or unclear margins, deep mesoappendiceal invasion >3 mm, higher proliferation rate (WHO grade 2 [G2]), vascular (V1) and/or lymph vessel (L1) invasion. These factors have been associated with the presence of lymph node metastases,[3-6] but the prognostic implications of the latter are unknown.[7] Based on several recent retrospective studies,[3,8-14] there is growing awareness that there may be overtreatment in this intermediate-risk group. This is important as hemicolectomy is associated with short-term morbidity rates of 2% and impaired health-related quality of life.[1,6]

The ability of existing literature to reliably inform treatment guidelines is limited by several factors. First, the short follow-up (maximum 5 years) of many studies precludes understanding of long-term safety of either surgical approach, which is compounded by small sample size (less than 15 patients).[8,10] Second, data on follow-up,[9] risk factors [9,10,13,14] and aNET diameter [9,12,13] were missing or inconsistently reported. Third, aNET 1-2 cm were combined with the biologically different goblet cell adenocarcinomas (formerly goblet cell carcinoid), high grade or anaplastic

carcinoid tumours [10-13] and aNET <1cm [3,11,14] in the statistical analyses, making inference regarding the intermediate-risk tumour group difficult.

By pooling data from 40 European institutions with >10 years of follow-up, this study seeks to robustly quantify the malignant potential of aNET 1-2cm in size, and evaluate the appropriateness of the two typically used treatment approaches.

METHODS

Study Design and Participants

We conducted a multicentre, international, retrospective cohort study of patients of any age and performance status with histopathologically confirmed aNET 1-2cm that underwent complete resection of the primary tumour between January 1st 2000 and December 31st 2010.

The ENETS office invited all 56 ENETS centres of excellence to participate in the present study and the study was presented in two ENETS advisory board meetings 2019 and 2020. Twenty four further European institutions were approached by personal contacts. Of the 54 institutions that agreed to participate, we included 40 institutions in 15 European countries (Austria, Belgium, Denmark, France, Germany, Greece, Israel, Italy, Netherlands, Norway, Poland, Spain, Sweden, Switzerland, and United Kingdom). Fourteen institutions were excluded for various reasons (**appendix p 1 and p2**).

This multicentre study was approved by the ethics commission of the canton Bern, Switzerland (KEKBE 2019-01135) and at each participating centre per their institutional guidelines. Only anonymized data were shared with the coordinating institution Inselspital Bern, University of Bern, Switzerland. No written informed consent was necessary. The study is registered with ClinicalTrials.gov, NCT03852693.

Procedures

Demographic, clinical, pathologic, treatment, and outcome data were extracted from electronic medical records at each institution either by C.N. during an on-site visit or by local investigators with expertise in the treatment of NET. Missing follow-up data were completed by contacting the family doctor and/or the patients directly. Standardized data collection templates were used.

Study data were collected and centrally managed by C.N. using REDCap electronic data capture tools hosted at CTU Bern, University of Bern.[15,16]

Patients were summarized in two subgroups based on surgical approach: (1) Simple appendectomy or appendectomy during another primary surgery (subsequently named appendectomy), and (2) appendectomy with oncological right-sided hemicolectomy or ileocecal resection in one or two stages (subsequently named right-sided hemicolectomy).

All available tissue blocks with missing histopathological risk factors defined by the ENETS guidelines were reviewed locally by an experienced NET pathologist. In case of deceased or metastatic patients, all tissue blocks available were reviewed by A.P. at the Institute of Pathology, University of Bern by using the 2019 World Health Organization (WHO) classification of gastrointestinal tumours to confirm the diagnosis of the primary tumour and the metastasis and collect all relevant pathological information. If the aNET was confirmed, the likelihood of the metastasis originating from the aNET as primary tumour was classified as unlikely (metastasis of a histopathologically different primary NET/neuroendocrine carcinoma; main tumour mass of the primary NET in the ileum), possible (no tissue block available) or probable (histopathological serosal perforation of the aNET with concomitant peritoneal spreading; image guided and clinical diagnosis of metastases with carcinoid syndrome, while no tissue blocks were available).

Outcomes

Predefined primary outcomes were the frequency of distant metastases and tumour-related mortality rate subsequent to complete resection of aNETs 1-2cm in size. Secondary outcomes were the frequency of patients with regional lymph node metastases in aNETs 1-2cm treated with right-sided hemicolectomy and the association of regional lymph node metastases with the

histopathological risk factors according to the ENETS guidelines. Based on a statistical adjustment for the latter histopathological risk factors, the frequency of patients with regional lymph node metastases at the time of diagnosis was estimated for aNET 1-2cm treated with appendectomy. Additionally, overall survival was assessed for patients with or without right-sided hemicolectomy.

Statistical Analysis

We provide descriptive information of the entire patient population and separately for those with appendectomy and those with right-sided hemicolectomy. Crude comparisons between the two subgroups are done with t-tests for continuous characteristics and chi-square tests for categorical characteristics. For the survival analysis, observation time started at the date of primary surgery and ended at the date of death or last date the patient was known to be alive. Kaplan-Meier methodology was used to estimate 5-, 10-, 15- and 20-year overall survival after primary surgery. Cox proportional hazards regression was used to estimate the relative all-cause mortality hazard associated with patients undergoing right-sided hemicolectomy compared to appendectomy alone. In order to account for differences in patient and tumour characteristics, we used multivariable Cox regression where we included age, sex, American Society of Anaesthesiologists (ASA) score and histopathological risk factors. This was done using hazard ratios (HRs) and 95% confidence intervals (CIs). The proportional hazards assumption was assessed via visual inspection of whether the curves are reasonably parallel in the so-called "log-log" plots, i.e. the plot of the ln{-ln(survival)} curves for patient group versus ln(analysis time).

Among the subgroup that underwent right-sided hemicolectomy, we compared the percentage of patients with and without lymph node metastases stratified by histopathological risk factors.

As patients not undergoing completion right-sided hemicolectomy after appendectomy may have residual, undetected regional lymph node metastases, we sought to estimate this indirectly. We fitted a logistic regression model (considering tumour location, grade, resection margin, lymphovascular invasion and mesoappendix infiltration) in this subgroup for having a positive lymph node, and used the coefficients of this logistic regression model to estimate the proportion of patients having undetected regional lymph node metastases in the subgroup with appendectomy only. We used the bootstrap method to obtain a 95% CI for this estimate.[17] A p value of less than .05 was considered statistically significant. We did all analyses using Stata (version 17).

Role of the Funding Source

The funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report. All authors agreed with the decision to submit for publication.

RESULTS

Of 13 patients with reported metastases, four were excluded (ileal NET with infiltration in the appendix [two patients], goblet cell adenocarcinoma [one patient] and aNET larger than 2cm [one patient]). In all, 278 patients with aNET 1-2cm that underwent complete resection of the primary tumour between January 1st 2000 and December 31st 2010 were included in the study (**figure 1**). We identified 163 (58.6%) patients with appendectomy and 115 (41.4%) with right-sided hemicolectomy (including one patient with ileocecal resection). There were no significant differences in the two subgroups in terms of age (P = .90), sex (P = .11) and ASA score (P = .62). We did not collect data on race/ethnicity. Histopathological features differed significantly only in terms of tumour location (P = .0026) and resection margin (P = .0001) with more tumours at the base and more positive resection margins in patients with right-sided hemicolectomy (14.8 vs. 6.7% and 13.0 vs. 0.6%, respectively) (**table 1)**. In all, 52 (18.7%) patients showed serosal perforation of the aNET in histopathological examination. All patients had a clinical follow-up, while a follow-up with computed tomography (CT) or magnetic resonance imaging (MRI) was performed in 156 (56.1%) patients (75/163 [46.0%] patients with appendectomy and 81/115 [70.4%] with right-sided hemicolectomy). After 10 years or more, 42 (15.1%) patients had a follow-up with CT or MRI (19/163 [11.7%] patients with appendectomy and 23/115 [20.0%] with right-sided hemicolectomy).

In the histopathological review of the nine patients with metastatic disease (four patients with appendectomy and five patients with right-sided hemicolectomy), the aNET 1-2cm was classified as unlikely to be the origin of metastases in five patients, possible in one patient, and probable in three patients (**table 2**). Of the latter four patients, metastases were diagnosed synchronously

198 with the aNET 1-2cm. Two patients had a histopathological serosal perforation and peritoneal
199 spreading. Distant peritoneal metastases were successfully treated without recurrence by
200 electrocoagulation and oncological right-sided hemicolectomy, respectively. In one patient, a
201 liver metastasis was successfully treated by radiofrequency ablation, followed by Peptide
202 Receptor Radionuclide Therapy (PRRT), without previous biopsy. In one patient with bilobar liver
203 metastases and a lymph node metastasis in the transverse mesocolon, new regional and distant
204 metastases occurred despite three doses of PRRT, followed by selective internal radiation
205 therapy (SIRT). No tissue samples were available. The patient is alive after a follow-up of 11 years.
206 In both patients with liver metastases, the only histopathological risk factor according to the
207 ENETS guidelines was lymphovascular invasion of the primary tumour.
208 Overall, tumour-related death was attributed to the aNET 1-2cm by the local treating institution
209 in two patients. However, our central histopathological review suggested that their metastases
210 were likely unrelated to the aNET 1-2cm (one patient had a poorly differentiated small-cell
211 neuroendocrine carcinoma without any known metastases of a well differentiated NET and
212 another had a main tumour mass in the ileum thought to be the primary).
213
214 Regional lymph node metastases were found in 22 (19.6%) patients with right-sided
215 hemicolectomy (in three patients with right-sided hemicolectomy no lymph nodes were
216 evaluated). Regarding the histopathological risk factors defined by the ENETS guidelines, their
217 occurrence was significantly associated with the resection margin only (P = .023; **appendix p 3**)
218 with a higher proportion of patients with R0 resection margin in patients without lymph node
219 metastases (87.8 vs. 63.6%).

Since no lymph nodes were retrieved in patients with appendectomy only, the presence of lymph node metastases was estimated in this group. **Appendix p 3** shows the logistic regression model fitted for having regional lymph node metastases in patients with right-sided hemicolectomy. Based on the coefficients of this model, we estimated that 12.8% (95% CI 6.5 - 21.1%) of patients undergoing appendectomy likely had undetected residual regional lymph node metastases at the time of diagnosis.

The median follow-up was 13.0 years (interquartile range, 11.0 – 15.6 years). In 163 patients with appendectomy only, 20 deaths were recorded in 20 years resulting in estimates of overall survival after 5, 10, 15 and 20 years of 95.6% (95% CI 90.9-97.9%), 91.6% (95% CI 85.9-95.0%), 87.1% (95% CI 80.1-91.8%) and 80.4% (95% CI 69.5-87.8%). In 115 patients with right-sided hemicolectomy, 13 deaths were recorded in 20 years resulting estimates of overall survival after 5, 10, 15 and 20 years of 93.9% (95% CI 87.6-97.0%), 91.2% (95% CI 84.2-95.2%), 87.4% (95% CI 79.1-92.6%) and 87.4% (95% CI 79.1-92.6%). Kaplan-Meier estimates of overall survival were similar between patients with appendectomy and right-sided hemicolectomy (HR .88, 95% CI .44 - 1.75, P = .71; **figure 2**) with reasonably parallel lines in the "log-log" plots. They were also similar in multivariable cox regression analysis including histopathological risk factors (tumour location, tumour grade, resection margin, lymphovascular invasion and mesoappendix infiltration) (adjusted HR .88, 95% CI .41 - 1.89, P = .75) and including both histopathological risk factors and patient characteristics (age, sex and ASA score) (adjusted HR .88, 95% CI .36 - 2.17, P = .79). There was no surgical mortality.

Patients with incidental appendectomy performed during primary surgery for another indication and those with appendectomy as a consequence of primary oncological right-sided hemicolectomy or ileocecal resection might have had advanced tumours of different entities, leading to a bias in the overall survival. After excluding these patients (41 [25.2%] patients with appendectomy and 22 [19.1%] patients with right-sided hemicolectomy), Kaplan-Meier estimates of overall survival were still similar between patients with appendectomy and right-sided hemicolectomy (HR .81, 95% CI .19 - 3.41, P = .78; **figure 3**) with 5 (4.1%) deaths reported after appendectomy and 3 (3.2%) deaths reported after right-sided hemicolectomy. They were also similar in multivariable cox regression analysis for the latter two groups of patients including histopathological risk factors (tumour location, tumour grade, resection margin, lymphovascular invasion and mesoappendix infiltration) (adjusted HR 1.19, 95% CI .21 - 6.90, P = .84) and including both histopathological risk factors and patient characteristics (age, sex and ASA score) (adjusted HR .67, 95% CI .02 - 18.07, P = .81).

DISCUSSION

The aim of this Europe-wide retrospective ENETS study was to quantify the malignant potential of aNET 1-2cm. The summarized results include two main statements: first, regional lymph node metastases of aNET 1-2cm are clinically not relevant and not associated with reduced tumour-specific survival; second, right-sided hemicolectomy has no benefit on long-term survival following complete resection of the primary tumour by appendectomy.

These two statements with practical implication need further discussion. Brighi et al. found a difference in disease-specific survival of 78 vs. 141 months in patients with aNET and regional lymph node metastases compared to those without nodal involvement, although this difference was not statistically significant.[3] However, histopathological slides have not been reviewed and it is unclear how many of these patients had aNET >2cm. Also, no patient developed relapse during follow-up in this study, irrespective of appendectomy with or without hemicolectomy. Other studies,[10,12-14] as well as our own results, do not show survival differences depending on presence or absence of lymph node metastases. We found regional lymph node metastases in 19.6% of patients with right-sided hemicolectomy, a similar range as previously reported.[1,4,12,18] Corrected for the histopathological risk factors defined in the ENETS guidelines, we would expect residual lymph node metastases in 12.8% of the patients with appendectomy in the present study population. Nevertheless, the overall survival after a median follow-up of 13 years was similar with or without resection of regional lymph nodes, and no tumour relapse or tumour-related death occurred. Consequently, completion right-sided hemicolectomy following the ENETS guidelines in aNET 1-2cm would lead to overtreatment with unnecessary morbidity. Since lymph node metastases seem clinically irrelevant, this finding might be extrapolable to aNET >2cm.

Additionally, a recent study found a lowered health-related quality of life due to impaired social functioning and development of diarrhea after oncological right-sided hemicolectomy in aNET patients.[6]

Importantly, no patient with aNET 1-2cm developed metachronous distant metastasis during >10 years of follow-up. Distant metastases reported at time of appendectomy turned out to be most frequently metastases of concomitant ileal NET in centralized histopathological review. Interestingly, the only distant metastases clearly related to aNET 1-2cm were peritoneal metastases, and they were associated with serosal perforation of the primary tumour. Even this feature, which is associated with NET induced death in pancreatic and ileal NET, was controlled by loco-ablative techniques in one patient and by performing right-sided hemicolectomy in the second patient.

The risk for further distant metastases in aNET 1-2cm is very low. In the present study we only found two patients with synchronous distant metastases in the liver, leading to a risk for distant metastases other than peritoneal metastases of 0.7%. Importantly, the diagnosis could not be confirmed histopathologically due to missing tissue samples in both patients.

At this point the question about strengths and limitations of our study arises: the strengths include a well characterized cohort of 278 patients with aNET 1-2cm, standardized data collection by on-site visits of C.N. or dedicated local investigators with expertise in the treatment of NET, and the long median follow-up. The vast majority of available relative survival data are based on cancer registries, such as the Surveillance, Epidemiology, and End Results (SEER) program [12-14,19] or the National Cancer Data Base (NCDB),[10] suffering from coding issues in the presence of combined ileal and aNET and from nomenclature changes, as goblet cell adenocarcinomas used

to be classified as NET in earlier days. This is an important issue with regard to the results of our centralized histopathological review: In 13 patients with the external diagnosis of aNET 1-2cm with metastases, four were reclassified to a different primary tumour or a size >2cm, and in another five the metastases were judged as unlikely from the aNET, accounting for 69.2% of all metastasized patients. Another strength is that long-term overall survival rates up to 10 years are rarely described,[11,12,19] but are of utmost importance in this tumour of young patients. The appendectomy is a standardized procedure. Therefore, the results of the present study are generalizable to non-specialised institutions around the world.

The study also has limitations: first, the observational nature with the need to retrospectively compare patients with appendectomy and right-sided hemicolectomy; second, not all aNET have been reviewed histopathologically and not all histopathological risk factors could be obtained; third, all patients had a clinical follow-up, but only few patients had a follow-up by CT or MRI after 10 years or more; fourth, despite the important support of ENETS, the Europe-wide participation of institutions and the inclusion of patients over a period of 11 years, the study group is relatively small given by the low incidence of the disease. The approximate incidence rate for aNET independent of size is 0.15-0.6/100,000/year.[2]

The results of the present European multinational cohort study provide the most reliable evidence that right-sided hemicolectomy is not indicated in aNET 1-2cm in size, that the potential benefits do not justify the risk of this operation, and that an additional postoperative exclusion of metastases by a further medical imaging and histopathological evaluation of risk factors is not supported by the presented results and may therefore not be necessary. These findings should inform consensus best practice guidelines for this typically young group of patients.

Contributors: AP and RMK contributed equally to this work. CN and RMK had full access to all the data and verified the data in the study. CN and RMK take responsibility for the integrity of the data and accuracy of the data analysis.

Concept and design: RMK, AP, MZ.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: RMK, CN, AP, MZ.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: MZ.

Obtained funding: RMK, AP, MZ.

Administrative, technical, or material support: AP, RMK.

Supervision: AP, RMK.

All authors had access to all the data reported in the study. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Data sharing: The de-identified individual-level patient data, data dictionary, and protocol for this study can be provided to researchers upon written request 24–36 months after publication of this article. Please send enquiries to the corresponding author. A detailed proposal for how the data will be used is required and we will assess applications on a case-by-case basis, and only for the purpose of individual participant data meta-analysis. A data access agreement must be signed for these data to be released.

Conflict of Interest: MB reports, outside the submitted work, funding from Novartis, Pfizer and Ipsen, payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing or

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REFERENCES

1. Pawa N, Clift AK, Osmani H, et al. Surgical Management of Patients with Neuroendocrine Neoplasms of the Appendix: Appendectomy or More. *Neuroendocrinology* 2018; **106**(3): 242-51.
2. Pape UF, Niederle B, Costa F, et al. ENETS Consensus Guidelines for Neuroendocrine Neoplasms of the Appendix (Excluding Goblet Cell Carcinomas). *Neuroendocrinology* 2016; **103**(2): 144-52. doi: 10.1159/000443165. Epub 2016 Jan 5.
3. Brighi N, La Rosa S, Rossi G, et al. Morphological Factors Related to Nodal Metastases in Neuroendocrine Tumors of the Appendix: A Multicentric Retrospective Study. *Ann Surg* 2020; **271**(3): 527-33.
4. Holmager P, Willemoe GL, Nielsen K, et al. Neuroendocrine neoplasms of the appendix: Characterization of 335 patients referred to the Copenhagen NET Center of Excellence. *Eur J Surg Oncol* 2021; **47**(6): 1357-63.
5. Boxberger N, Redlich A, Boger C, et al. Neuroendocrine tumors of the appendix in children and adolescents. *Pediatr Blood Cancer* 2013; **60**(1): 65-70.
6. Alexandraki KI, Kaltsas G, Grozinsky-Glasberg S, et al. The effect of prophylactic surgery in survival and HRQoL in appendiceal NEN. *Endocrine* 2020; **70**(1): 178-86.
7. Grozinsky-Glasberg S, Alexandraki KI, Barak D, et al. Current size criteria for the management of neuroendocrine tumors of the appendix: are they valid? Clinical experience and review of the literature. *Neuroendocrinology* 2013; **98**(1): 31-7.
8. de Lambert G, Lardy H, Martelli H, Orbach D, Gauthier F, Guerin F. Surgical Management of Neuroendocrine Tumors of the Appendix in Children and Adolescents: A Retrospective French Multicenter Study of 114 Cases. *Pediatr Blood Cancer* 2016; **63**(4): 598-603.

9. Henderson L, Fehily C, Folaranmi S, et al. Management and outcome of neuroendocrine tumours of the appendix-a two centre UK experience. *J Pediatr Surg* 2014; **49**(10): 1513-7.
10. Nussbaum DP, Speicher PJ, Gulack BC, et al. Management of 1- to 2-cm Carcinoid Tumors of the Appendix: Using the National Cancer Data Base to Address Controversies in General Surgery. *J Am Coll Surg* 2015; **220**(5): 894-903.
11. Steffen T, Ebinger SM, Warschkow R, Luthi C, Schmied BM, Clerici T. Long-Term Survival is not Impaired After the Complete Resection of Neuroendocrine Tumors of the Appendix. *World J Surg* 2015; **39**(11): 2670-6.
12. Groth SS, Virnig BA, Al-Refaie WB, Jarosek SL, Jensen EH, Tuttle TM. Appendiceal carcinoid tumors: Predictors of lymph node metastasis and the impact of right hemicolectomy on survival. *J Surg Oncol* 2011; **103**(1): 39-45.
13. Mehrvarz Sarshekeh A, Advani S, Halperin DM, et al. Regional lymph node involvement and outcomes in appendiceal neuroendocrine tumors: a SEER database analysis. *Oncotarget* 2017; **8**(59): 99541-51.
14. Mosquera C, Fitzgerald TL, Vora H, Grzybowski M. Novel nomogram combining depth of invasion and size can accurately predict the risk for regional nodal metastases for appendiceal neuroendocrine tumors (A-NET). *J Surg Oncol* 2017; **116**(6): 651-7.
15. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform* 2019; **95**: 103208.
16. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42**(2): 377-81.

17. Efron B. Nonparametric standard errors and confidence intervals. *Canadian Journal of Statistics* 1981; **9**(2): 139-58.
18. Rault-Petit B, Do Cao C, Guyetant S, et al. Current Management and Predictive Factors of Lymph Node Metastasis of Appendix Neuroendocrine Tumors: A National Study from the French Group of Endocrine Tumors (GTE). *Ann Surg* 2019; **270**(1): 165-71.
19. Mullen JT, Savarese DM. Carcinoid tumors of the appendix: a population-based study. *J Surg Oncol* 2011; **104**(1): 41-4.

FIGURE LEGENDS

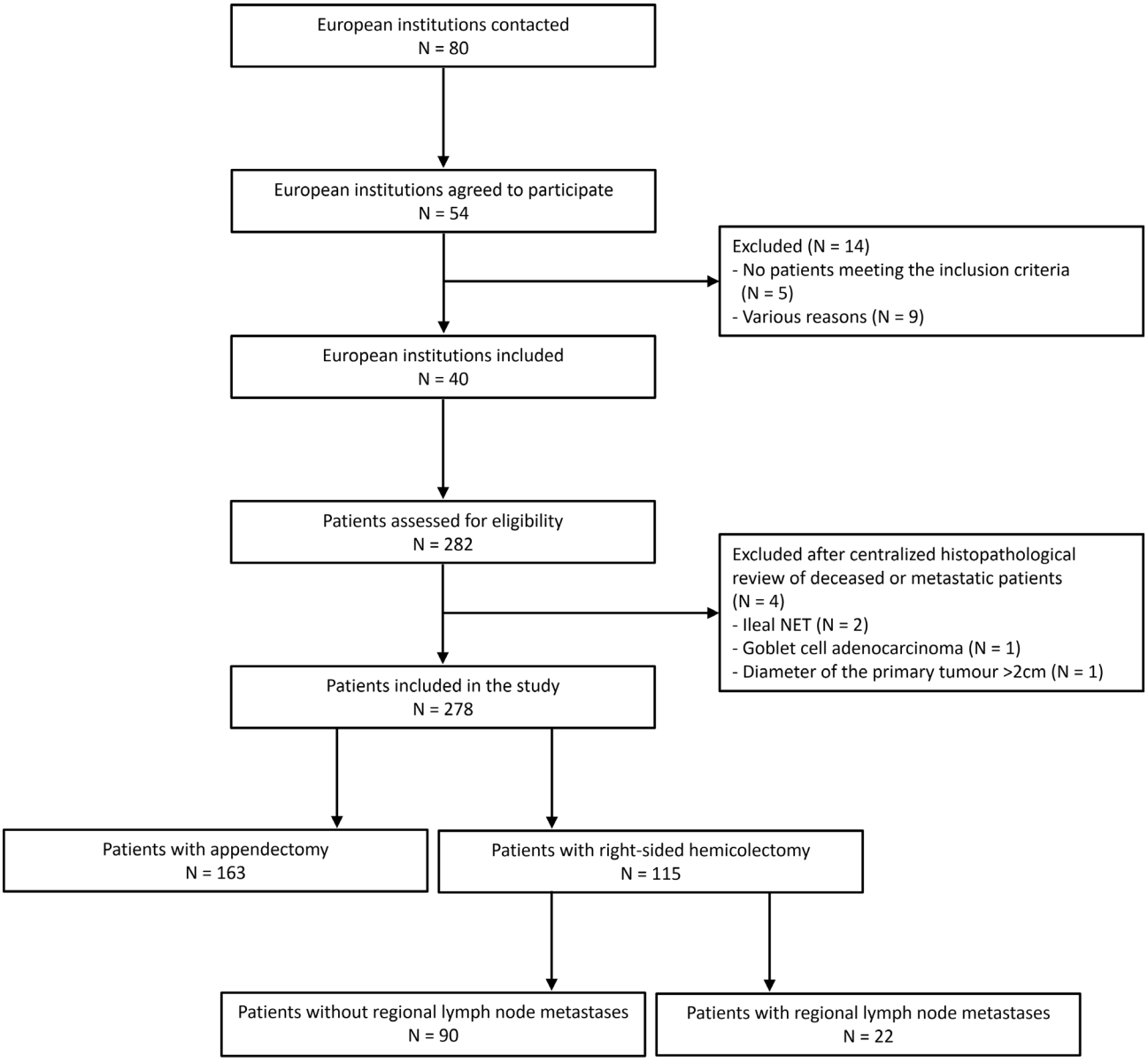
Figure 1. Study flow chart.

Figure 2. Kaplan-Meier estimates of overall survival for patients treated with appendectomy vs. right-sided hemicolectomy.

Figure 3. Kaplan-Meier estimates of overall survival for patients treated with appendectomy vs. right-sided hemicolectomy excluding patients with advanced tumours of different entities.

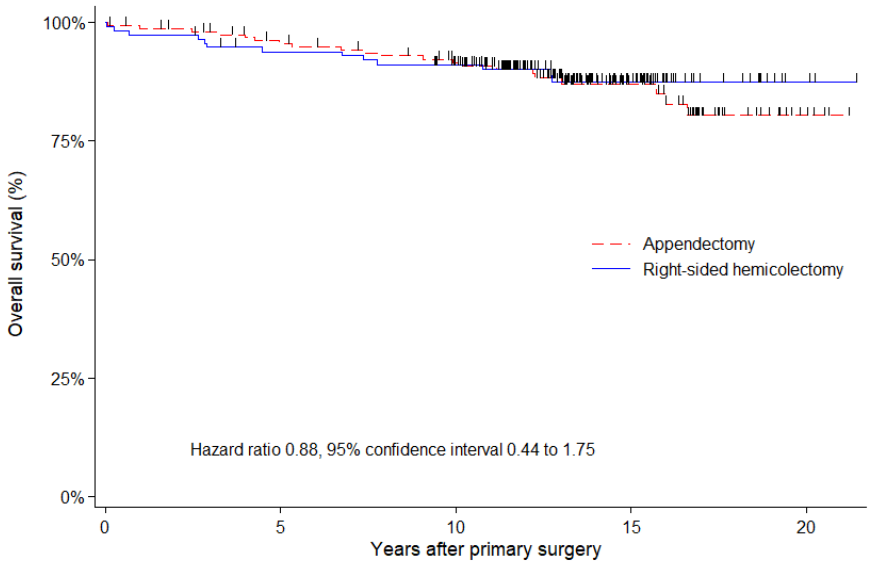
FIGURES

Figure 1.



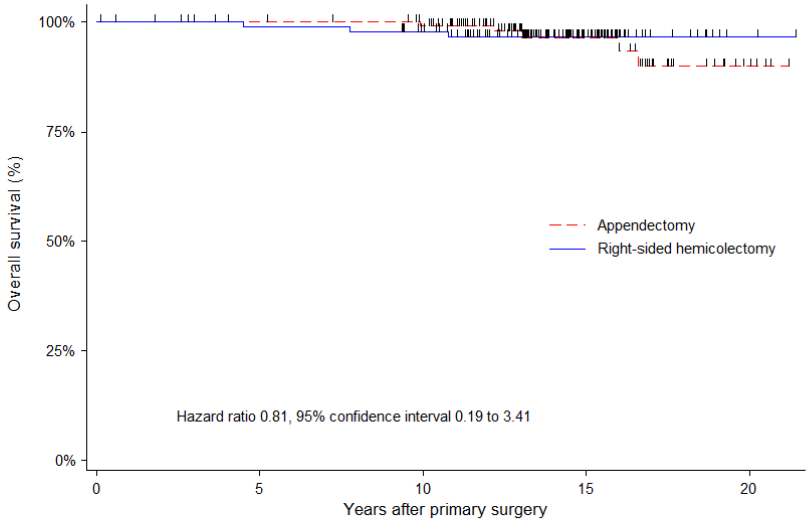
Abbreviation: NET, neuroendocrine tumour.

Figure 2.



Number at risk (number censored)					
Appendectomy	163 (0)	147 (9)	134 (16)	50 (95)	4 (141)
Right-sided hemicolectomy	115 (0)	105 (3)	96 (9)	38 (65)	3 (101)

Figure 3.



Number at risk (number censored)					
Appendectomy	122 (0)	115 (7)	109 (12)	41 (78)	4 (116)
Right-sided hemicolectomy	93 (0)	91 (1)	85 (6)	35 (56)	2 (89)

TABLES

Table 1. Patient Characteristics

	Overall (N = 278)	Appendectomy (N = 163)	Right-sided hemicolectomy (N = 115)	P Value
Age at initial surgery, mean (SD), y	36.0 (18.2)	36.2 (18.4)	35.9 (17.9)	.90
Sex, No. (%)				
Male	110 (39.6)	71 (43.6)	39 (33.9)	.11
Female	168 (60.4)	92 (56.4)	76 (66.1)	
ASA score, No. (%)				
I	147 (52.9)	82 (50.3)	65 (56.5)	.62
II	36 (13.0)	21 (12.9)	15 (13.0)	
III	18 (6.5)	11 (6.8)	7 (6.1)	
IV	1 (0.4)	1 (0.6)	0 (0.0)	
V	1 (0.4)	0 (0.0)	1 (0.9)	
Not available	75 (27.0)	48 (29.5)	27 (23.5)	
Histopathological features, No. (%)				
Tumour location				
Tip/middle	227 (81.7)	144 (88.3)	83 (72.2)	.0026
Base	28 (10.1)	11 (6.7)	17 (14.8)	
Not available	23 (8.3)	8 (4.9)	15 (13.0)	
Tumour grade				
Grade 1	235 (84.5)	142 (87.1)	93 (80.9)	.36
Grade 2	25 (9.0)	12 (7.4)	13 (11.3)	
Not available	18 (6.5)	9 (5.5)	9 (7.8)	
Resection margin				
R0	252 (90.6)	156 (95.7)	96 (83.5)	.0001
R1	16 (5.8)	1 (0.6)	15 (13.0)	
Not available	10 (3.6)	6 (3.7)	4 (3.5)	
Lymphovascular invasion				
Yes	61 (21.9)	28 (17.2)	33 (28.7)	.073
No	191 (68.7)	119 (73.0)	72 (62.6)	
Not available	26 (9.4)	16 (9.8)	10 (8.7)	
Mesoappendix infiltration				
≤3mm	80 (28.8)	42 (25.8)	38 (33.0)	.10
>3mm	28 (10.1)	13 (8.0)	15 (13.0)	
Not available	170 (61.2)	108 (66.3)	62 (53.9)	
Tumour size				
1.0-1.5mm	221 (79.5)	135 (82.8)	86 (74.8)	.10
1.6-2.0mm	57 (20.5)	28 (17.2)	29 (25.2)	

Abbreviations: ASA, American Society of Anaesthesiologists.

Table 2. Histopathological review of deceased or metastatic patients

Patient no.	Likelihood of metastases due to a NET 1-2cm[a]	Time point of diagnosis[b]	Tumour-related death[c]	Histopathological review
1	Unlikely	Follow-up	Yes	Liver metastasis of poorly differentiated small-cell NEC
2	Unlikely	Initially	Yes	Diffuse infiltration of the ileum most probably due to ileal NET (main tumour mass in ileum)
3	Unlikely	Follow-up	No	Additional ileal NET found in follow-up
4	Unlikely	Initially	No	Primary tumour most probably ileal NET
5	Unlikely	Follow-up	No	Metastasis in the renal hilum due to colon NET
6	Possible	Initially	No	Liver metastasis diagnosed by (68)Gallium-DOTATATE PET-CT and successfully ablated with subsequent PRRT without previous biopsy
7	Probable	Initially	No	Distant peritoneal metastases
8	Probable	Initially	No	Distant peritoneal metastases
9	Probable	Initially	No	Concomitant metastases in liver and transverse mesocolon with the clinical diagnosis of a carcinoid syndrome and without second primary tumour

[a]The likelihood of the aNET as primary tumour for diagnosed metastases was classified as unlikely, possible or probable based on the centralized histopathological review.

[b]Time point at which metastases were diagnosed the first time (at initial presentation or in the follow-up).

[c]Diagnosis by the local treating institution (before centralized histopathological review).

Abbreviations: NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; PRRT, Peptide Receptor Radionuclide Therapy.