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Original Article

Current practice in proton therapy delivery in adult cancer patients across Europe

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ABSTRACT

Background and purpose: Major differences exist among proton therapy (PT) centres regarding PT delivery in adult cancer patient. To obtain insight into current practice in Europe, we performed a survey among European PT centres.

Materials and methods: We designed electronic questionnaires for eight tumour sites, focusing on four main topics: 1) indications and patient selection methods; 2) reimbursement; 3) on-going or planned studies, 4) annual number of patients treated with PT.

Results: Of 22 centres, 19 (86%) responded. In total, 4233 adult patients are currently treated across Europe annually, of which 46% consists of patients with central nervous system tumours (CNS), 15% head and neck cancer (HNC), 15% prostate, 9% breast, 5% lung, 5% gastrointestinal, 4% lymphoma, 0.3% gynaecological cancers. CNS are treated in all participating centres (n = 19) using PT, HNC in 16 centres, lymphoma in 10 centres, gastrointestinal in 10 centres, breast in 7 centres, prostate in 6 centres, lung in 6 centres, and gynaecological cancers in 3 centres. Reimbursement is provided by national health care systems for the majority of commonly treated tumour sites. Approximately 74% of centres enrol patients for prospective data registration programs. Phase II-III trials are less frequent, due to reimbursement and funding problems. Reasons for not treating certain tumour types with PT are lack of evidence (30%), reimbursement issues (29%) and/or technical limitations (20%).

Conclusion: Across European PT centres, CNS tumours and HNC are the most frequently treated tumour types. Most centres use indication protocols. Lack of evidence for PT and reimbursement issues are the most reported reasons for not treating specific tumour types with PT.

Abbreviations: PT, proton therapy; EPTN, European Particle Therapy Network; INSPIRE, INfraStructure in Proton International Research; CNS, central nervous system; HNC, head and neck cancer, GI, gastrointestinal; PTCOG, Particle Therapy Co-Operation Group.

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Compared to paediatric patients, indications for proton therapy (PT) for adult patients are less acknowledged [1]. Although radiation of intra-ocular tumours and chordoma/chondrosarcoma of the skull base are currently regarded as standard indications for adult patients in virtually all countries, there are major differences regarding patient selection for PT across European countries and even between centres in the same country [2–4]. This is especially true for adult patients who would normally be treated with photon therapy but may benefit from PT because of more favourable dose distributions.

Currently, there are approximately 100 PT centres in operation world-wide, most of which started in the last decade [5]. Despite this rapid increase in the number of PT facilities, PT capacity remains limited in relation to the total number of patients treated with radiotherapy. In addition to limited capacity, reimbursement and technical capabilities also play an important role in which patients are considered eligible for PT. Moreover, reimbursement issues are an important challenge in patients' access to PT [6–8]. It is not clear if reimbursement across Europe is determined by insurance companies or to what extent reimbursement agreements with health-care providers exist on a national and/or institutional level. In addition to potential reimbursement restrictions, technical limitations for moving targets, and lack of evidence derived from clinical trials, may affect acceptance of treating patients with PT [8–11].

Several radiation therapy societies have published recommendations on how to select patients for PT [12–15]. However, it is still unknown to what extent these recommendations are adopted in routine daily practise across Europe.

Because the number of clinical PT centres in Europe has increased substantially, with a foreseen number of facilities of just under 50 by 2025 (Damien C. Weber, personal communication), task force groups and international projects such as the European Particle Therapy Network (EPTN) and INfraStructure in Proton International REsearch (INSPIRE) seek to provide and increase the collaboration between European centres, and to enhance evidence-based particle therapy at a European level. Dedicated work packages have been established for prospective data registration and clinical trials for particle therapy (EPTN – work package 1) and patient selection methods (INSPIRE – work package 8) within the framework of these collaborations [16–18]. The aim should ultimately be to arrive at a more uniform approach across Europe.

The purpose of this study is to explore the different selection methods applied in the European PT centres and to obtain more insight in current daily practice in Europe.

Materials and methods

Anonymous online questionnaires were composed for eight different tumour sites, including central nervous system (CNS) tumours, head and neck (HNC) cancer, breast cancer, prostate cancer, lung cancer, lymphoma, gastrointestinal (GI) tumours (including oesophageal, gastric, pancreatic, liver, rectal and anal cancer) and gynaecological tumours (including cervical, endometrial, vulvar, and vaginal cancer).

The questionnaires consisted of 135 questions (on average, 17 questions per tumour site) regarding the application of PT for adult patients, including 24 multiple choice questions, 34 checkbox questions, 67 open questions and 10 matrix questions (GI and gynaecological tumours that included multiple tumour sites). Open questions were used to obtain additional information on the closed questions to allow centres to add comments or information on a topic, other than included in the closed questions.

We focused on four main topics, including: (1) indications and patient selection methods; (2) reimbursement; (3) clinical and preclinical on-going or planned studies; and (4) the number of patients treated with PT per year.

The questionnaire was developed as a web-based application within a free software tool: Google forms (https://www.google.com/forms). Eight links were provided for each tumour site separately, to enable the survey to be completed by different personnel from a centre. Using this web-based system, participants could enter data or select appropriate answers from a list of predefined answers. The questionnaire was first evaluated by colleagues with expertise in radiotherapy of a given tumour site and based on their comments, adjustments were made accordingly before distributing the questionnaires across the PT centres.

The questionnaire was composed in such a way that, based on the responses to previous questions, only relevant questions regarding a particular tumour site were presented. For instance, if adult patients with specific malignancies were not treated with PT at a certain centre, all corresponding questions were automatically skipped. Centres that did not treat patients with a certain tumour site were only asked for their reasons not to treat that particular tumour site with PT. Therefore, the time required to complete the questionnaire depended on the number of tumour sites treated at the PT centre and took an average of 5–10 min to complete per site.

E-mails were sent to the European PT centres that are active within EPTN or mentioned at the website of Particle Therapy Co-Operation Group (PTCOG). In June 2020, the first electronic invitation was sent to all 22 European PT centres in thirteen different countries. Centres treating intra-ocular tumours only were not included into the study. First and second reminders were sent in September 2020 and January 2021, respectively. The survey was closed in March 2021. Number of patients treated with PT in 2020 were obtained from participating centres in June 2021. Collected data were evaluated per centre and statistics were performed for all centres together.

Statistical analysis

Descriptive statistics for continuous variables were given as n (%), mean, standard deviation (SD), minimum (min), maximum (max), 1st (Q25) and 3rd (Q75) quartiles. Categorical variables were given as percentages. Check box question results were given as % of responses indicating what % of the total responses were in each category (these %s will sum to 100%) and % of centres indicating what % of centres mentioned each category (these %s will sum to >100% if at least one centre chose more than one response). Comparison of centres were performed using Mann-Whitney *U* test. All statistical tests were two-sided and a *p*-value of $\leq$0.05 was considered statistically significant. Analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows, version 21.0 (SPSS Inc., Chicago, ILL, USA).

Results

Responses were obtained from 19 out of 22 centres (86%) from all 13 countries where PT is available (Table 1). All participating centres used PT to treat adult cancer patients for at least one of eight tumor site investigated. The estimated total number of adult patients treated with PT in 2020 in the participating centres was 4233 with an average of 223 (SD: 209, Q25–Q75: 113–238, min–max: 20–950) patients per centre (Fig. 1). Some centres were still in the ramp up phase at the time of the survey. There was a wide variation between centres in terms of number of patients per tumour site treated with PT.

Patients with CNS tumours (46%), HNC (15%), prostate cancer (15%), and breast cancer (9%) constituted the majority of the

patients treated with PT, while patients with gynaecological tumours were rarely treated with PT (Fig. 1).

For tumour sites including different tumour subgroups (CNS, GI, and gynaecological cancers), the number of patients treated and the number of treating centres are presented per tumour subgroup in Table 2. Of all patients with CNS tumours treated with PT, 40% were patients with low grade glioma or base of skull tumours. These patients were treated in all participating centres. Of the GI cancer patients treated with PT, 59% were patients with oesophageal cancer.

Major variability existed regarding the number of tumour sites treated in the participating centres. On average, the PT centres treated patients with 4 different tumours sites ranging from 1 to 8 tumour sites per centre (Fig. 1). CNS are treated in all participating centres (n = 19) using PT, HNC in 16 centres, lymphoma in 10 centres, gastrointestinal in 10 centres, breast in 7 centres, prostate in 6 centres, lung in 6 centres, and gynaecological cancers in 3 centres (Fig. 1).

Table 1
Number of centres invited and participated in the study per country.

Countries	Invited centres (n)	Participating centres (n)	Participation rate
Austria	1	1	100%
Belgium	1	1	100%
Czech Republic	1	1	100%
Denmark	1	1	100%
England	1	1	100%
France	3	3	100%
Germany	4	3	75%
Italy	2	1	50%
Poland	1	1	100%
Spain	2	1	50%
Sweden	1	1	100%
Switzerland	1	1	100%
The Netherlands	3	3	100%
Total	22	19	86%

Of the 13 participating countries, 7 (54%) countries (Belgium, Denmark, France, Germany, Sweden, the Netherlands, and United Kingdom) had a national indication protocol for patient selection for at least one tumour site, whereas other countries (Austria, Czech Republic, Italy, Poland, Spain and Switzerland; 46%) relied on institutional indication protocols for the tumour sites treated in those countries.

Table 2
Number of centres treating subgroups of the tumour sites and number of adult patients treated with PT in 2020. Of 19 centres participated, CNS tumours treated in 19, GI cancers in 11 and gynaecological in 3 centres.

Tumour sites	Subgroups	Patients n (%)	N of centres treating that tumour site
CNS tumours	Low-grade glioma	405 (21)	19
	Base of skull tumours	371 (19)	19
	Meningioma	339 (17)	18
	Benign tumours	211 (11)	16
	Craniospinal axis (CSA)	225 (12)	13
	Germinoma/non-germinoma	77 (4)	11
	High-grade glioma	183 (9)	7
	Other	153 (8)	6
	Total	*1965 (100)*	*19*
GI cancers	Oesophageal cancer	116 (59)	9
	Pancreatic cancer	46 (23)	5
	Anal cancer	14 (7)	4
	Liver cancer	13 (7)	4
	Rectal cancer	7 (4)	4
	Gastric cancer	2 (1)	1
	Total	*198 (100)*	*10*
Gynaecological cancers	Endometrial cancer	5 (38)	2
	Cervical cancer	5 (38)	2
	Vulvar cancer	3 (23)	1
	Vaginal cancer	0	0
	Total	*13 (100)*	*3*

Centres	Gantry (n)	Treatment start	Number of patients treated in 2020										N of tumor sites treated in that centre
			CNS	HNC	Prostate	Breast	Lung	GI	Lymphoma	GYN	Total (n)	Total (%)	
Centre_1	3	2012	110	50	500	150	30	50	60		950	22%	7
Centre_2	2	2018	100	120		60	80	50	10		420	10%	6
Centre_3	4	2013	308	50	30			11	15		414	10%	5
Centre_4	2	2014	300	10							310	7%	2
Centre_5	4	2011	170	90				2			262	6%	3
Centre_6	1	2019	41	15		40	90	23	5		214	5%	6
Centre_7	2	2018	72	30		86	10		2		200	5%	5
Centre_8	4	2015	153	6	13			13	10	2	197	5%	6
Centre_9	1	2014	70	10	80		10	20	5		195	5%	6
Centre_10	2	2015	115	38		2			39		194	5%	4
Centre_11	3	2019	69	61		39		3			172	4%	4
Centre_12	2(3)*	2016	60	80	10			10		2	162	4%	5
Centre_13	3	1984-2018	90	32					15		137	3%	3
Centre_14	2	2011, 2016	88	40							128	3%	2
Centre_15	1	2020	40	15	5	4	5	16	3	9	97	2%	8
Centre_16	3	2018	79								79	2%	1
Centre_17	1	1991, 2016	60								60	1%	1
Centre_18	1	2020	20	2							22	1%	2
Centre_19	1	2018	20								20	0%	1
Total (n)	*43*		1965	649	638	381	225	198	164	13	4233		
Total (%)			46%	15%	15%	9%	5%	5%	4%	0%		100%	
% of centras treating that tumor site			100%	84%	32%	37%	32%	53%	53%	16%			

Fig. 1. Treatment starting year of the centres and number of treatment rooms, tumour types treated with PT and average number of patients treated each centre in 2020. Grey cells represent tumour sites that are not treated with PT in that centre. *Two fixed beam rooms, from 2022 one gantry and two fixed beam rooms.

Forty-seven percent of the centres that were treating CNS tumours had a national indication protocol, while for other commonly treated tumour sites this was 31% for HNC, 60% for lymphoma, 57% for breast cancer, 56% for oesophageal cancer, 50% for lung cancer, and 17% for prostate cancer. Most of the centres did not have a protocol for tumour sites that were rarely treated with PT such as GI (except for oesophageal) and gynaecological cancers. The numbers of centres that have national or institutional protocols per tumour site, or do not use such protocols are listed in Fig. 2.

While selecting patients for PT, photon vs. proton plan comparison was 'always' performed in 8 (42%) centres and 'depending on case' in 14 (74%) centres for at least one tumour site. When plan comparisons were made, the difference in normal tissue complication probability (ΔNTCP) was evaluated after plan comparison for HNC in 6 centres, lymphoma in 4, breast cancer in 4, lung cancer in 3, and oesophageal cancer in 3 centres. For the other tumour sites, plan comparisons were only used to evaluate ΔDose between photon and proton plans (Fig. 2). Furthermore, seven centres (from Denmark, France, Germany, Italy and in the Netherlands) stated that they used the model-based approach to select patient for PT for at least one tumour site including HNC, breast, lymphoma, lung and oesophageal cancer.

Other frequently mentioned general factors selecting patients for PT were younger age, good performance status, good prognosis, reirradiation, oligorecurrences, unacceptable OAR doses with photon therapy, suitable tumour location and size, curative intent, and genetic syndromes with higher radiosensitivity. Tumour-site specific factors used for selecting patients for PT were summarized in Table 3.

Treatment costs were covered by national care for CNS tumours (89%), HNC (81%), breast (86%), lymphoma (60%), lung (67%), and oesophageal cancer (67%) in most of the centres treating these tumour sites. However, for prostate cancer reimbursement was mostly dependent on health insurance companies' policies (50%) (Fig. 3). There was no reimbursement, i.e., patients had to pay treatment costs themselves for gynaecological cancers in 60% of the centres treating these tumour types (Fig. 2).

Currently, 14 (74%) centres used observational studies for PT for at least one of tumour site to evaluate the added value of PT (Fig. 2). In total, 41 phase II and III studies were reported to be on-going or planned in 10 centres, mostly for CNS tumours, HNC, prostate cancer and lymphoma. Most of these studies were conducted in centres from Denmark, Germany, Sweden, and France (Appendix A, Table A1). On the other hand, the most frequently reported reasons for not conducting studies were 'no reimbursement' (29%), 'no funding' (24%), 'technical limitations' (21%) and 'problems with patient referral and enrolment' (16%) (Fig. 2).

The most frequently reported reasons for not treating certain tumour types with PT was lack of evidence for the therapeutic gain of protons over photons (30%), followed by reimbursement issues (29%), technical limitations (20%), and lack of patient referral (13%). Interestingly, few centres reported limited treatment capacity as a factor (3%). For lymphoma and lung cancer, technical limitations were the dominant factor, whereas a lack of evidence was the most frequently mentioned reason for not treating breast and prostate cancer patients (Fig. 3).

Discussion

The survey presented in this paper revealed various policies and methods for the application of PT in adult patients across European centres. Of the 22 centres invited, 19 (86%) completed the survey. In addition, each of the 13 countries that provide PT was represented by at least one centre.

To our knowledge, there is no study comparing the patients' access to PT in Europe and other part of the world. However, a rough estimation can be obtained about it, using the data regarding the number of patients treated with PT annually, which was provided by several PT centres to the PTCOG central database. Based on that, including both adult and paediatric patients, a total of 22,012 patients were treated in 92 PT centres worldwide during 2020. Fifty-eight percent of these patients were treated in PT centres located in North America, 33% in Europe and 9% in Asia [19].

In 2017, Weber et al. reported on the variability of technical capabilities between PT centres [20]. Although they did not

	CNS	HNC	Lymphoma	Breast	Lung	Prostate	Esophageal	Pancreatic	Liver	Rectal	Anal	Gastric	Cervical	Endometrial	Vulvar	Vaginal	Total
1) Do you treat adult patients with proton therapy in your centre?																	
Yes	19	16	10	7	6	6	9	5	4	4	4	1	2	2	1	0	32%
No	0	3	9	12	13	13	10	14	15	15	15	18	17	17	18	19	68%
2) If 'Yes' to Q1, do you have indication protocols to select patients for proton therapy in your centre?																	
National	9	5	6	4	3	1	5	1	0	2	1	0	0	1	0	0	40%
Institutional	8	9	4	2	2	4	4	4	3	1	2	1	2	1	1	0	50%
No	2	2	0	1	1	1	0	0	1	1	1	0	0	0	0	0	10%
3) If 'Yes' to Q1, do you perform photon vs. proton plan comparison to select patients for proton therapy in your centre?																	
Always	5	4	3	2	3	0	2	1	1	0	0	0	0	0	0	0	22%
Depends on case	7	8	4	4	2	1	4	2	0	2	0	1	1	2	1	0	41%
No	7	4	3	1	1	5	3	2	3	2	4	0	1	0	0	0	38%
4) If 'Yes' to Q3, how is the plan comparison used for decision-making in your centre?																	
ΔNTCP	0	6	4	4	3	0	3	1	1	0	0	0	0	0	0	0	37%
ΔDose	12	6	3	2	2	1	3	2	0	2	0	1	1	2	1	0	63%
5) If 'Yes' to Q1, are the treatment costs of proton therapy reimbursed?																	
National care covers	17	13	6	6	4	2	6	2	2	2	2	0	1	0	0	0	66%
Up to insurance company	2	3	3	0	2	3	2	2	1	1	1	0	0	1	0	0	22%
Patients have to pay	0	0	1	1	0	1	1	1	1	1	1	1	1	1	1	0	13%
*6) Are there any clinical/preclinical studies conducted/planned for proton therapy in your centre?**																	
Observational	13	10	7	4	4	5	6	5	4	3	4	2	2	1	1	0	51%
Phase II interventional	2	4	3	1	2	1	1	0	2	1	1	0	0	0	0	0	13%
Phase III interventional	2	2	1	2	1	1	1	0	0	0	0	0	0	0	0	0	7%
No	4	2	1	1	0	0	3	5	5	6	5	8	0	1	0	0	29%
*7) If 'No' to Q6, what are the main reasons?**																	
No Reimbursement	1	2	0	2	0	0	1	1	1	1	1	1	0	0	0	0	29%
No Funding	0	2	0	1	0	0	1	1	1	1	1	1	0	0	0	0	24%
Technical limitations	1	1	0	0	0	0	1	1	1	1	1	1	0	0	0	0	21%
Patient referral/enrolment	0	0	1	1	0	0	0	0	0	0	0	0	1	1	1	1	16%
No dedicated facility/staff	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5%
Logistic limitations	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3%
Too time consuming	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3%

Fig. 2. Number of centres that treat adult cancer patients with PT (1), use indication protocols (2), perform plan comparison (3), evaluate ΔNTCP or ΔDose after plan comparison (4), receive reimbursement for PT (5), conducted or planned studies for PT (6), reasons for not conduction a study for PT (7) per tumour site. *Check-box questions, for which >1 options could have been chosen by centres.

Table 3
Tumour-site specific factors considered while selecting patients for PT.

Tumour site	Factors
CNS tumours	Good neurocognitive function Molecular type and histology Good prognosis Tumour close to critical structures such as the brain stem
HNC	Good immobilization capacity of the patient during long treatment time Locally advanced HNC with primary tumour close to skull base Tumours of nasopharynx, salivary gland, and paranasal sinus tumours Unilateral tumours Dose reduction to the brain
Lymphoma	Supradiaphragmatic localisation (mediastinal, HNC, axillary, precardiac) Gender (female) Cardiovascular risk factors
Lung cancer	Non-small cell lung cancer Maximal tumour motion <2 cm
Breast cancer	Cardiovascular risk factors Left-sided tumours Internal mammary chain RT Accelerated partial breast RT
Prostate cancer	Difficult anatomic situations (such as bowel loops) Comorbidities (such as colitis ulcerosa) Patient preference
GI cancers	Technical feasibility Reproducibility of tissues
Gynaecological cancers	Pelvic side wall recurrences of cervical cancer Para-aortic RT Oligorecurrences

specifically focus on the treatment of adult patients, some data were available for these patients. In line with that study, we also found that CNS and HNC are still the most frequently treated tumour sites in adult patients. However, we found an increase in the number of centres that are now treating breast cancer, lymphoma, oesophageal and lung cancer patients, which emphasizes the technological developments in tumour motion monitoring and moving target irradiation with PT [21–23]. A similar trend was also observed in PT centres located in the USA, based on the results of the annual surveys conducted by National Association of Proton Therapy [24].

Currently, compared with the findings of Weber et al. [20], more centres use written indication protocols (66% vs. 90%) or enrol patients in clinical trials (53% vs. 71%), even though most of these studies were observational studies. Interestingly, the average number of patients treated annually per centre was reported as 221 (40–557) by Weber et al., including both paediatric and adult cases in 15 centres included in that report, whereas it is now 223 (20–950) including only adult patients in our study, indicating an increase in applying PT for adult patients during the last 5 years.

In the centres participating in this survey, two main strategies were mentioned for using PT in adult patients: (1) decreasing side effects, and (2) dose escalation. However, applying PT for dose escalation was quite rare and was used particularly in clinical trial settings in some tumour sites. Patients were mostly selected for PT to decrease the risk of radiation-induced side effects, either in the primary or in the re-irradiation setting. In line with recommendations by some RT societies, younger patients with good performance status, favourable prognosis and tumours close to the critical structures were the most reported factors (Table 3) that were used for selecting patients for PT [12–15]. Although younger patients are expected to benefit most from PT due to longer life expectancy, there are also claims that geriatric patients may benefit, as this more vulnerable group of patients receive mostly lower RT doses due to concerns about side-effects [25].

The model-based approach is considered a more individualized methodology to select patients for PT, which is currently an accepted method in the Netherlands in addition to standard indications, like for paediatric and adult CNS patients [26]. With this approach, patients qualify for PT if ΔDose based on the photon vs. proton plan comparison translates into a putatively clinically significant ΔNCTP [27]. In the current survey, centres from four other countries including Denmark, France, Germany, and Italy also reported using a model-based approach to select patient for PT for at least one tumour site such as HNC, lymphoma, breast cancer, lung cancer and oesophageal cancer. In Italy, a model-based strategy is under development in in-silico studies, in order to support future clinical decision-making selecting patients which may benefit from PT. The installation of a PT single room with gantry would allow to apply the investigated approach in the clinical routine.

In the literature, general recommendations for patient selection and patient-specific decision support systems have been proposed [28–31], such as the Proton Priority System. This system uses a weighted sum of 7 domains including diagnosis, anatomic site, stage, performance status/comorbidities, age, urgency, and protocol participation [28]. Others use simulation tools that integrate a wide range of side effects (NTCPs and second primary cancer induction probabilities), tumour control probability (TCP), cost effectiveness and quality-adjusted life years to guide the allocation of patient treatment slots [28–31]. However, none of the participating centres reported using such tools for patient selection. Still, 63% of the centres reported that they performed photon vs. proton plan comparisons to select patients for PT. Of these, two thirds evaluated ΔDose rather than ΔNTCP. This might be explained by the lack of high quality NTCP-models for several tumour types [32]. The model-based approach has been adopted in the Netherlands, Denmark, France, Germany, Italy, and Spain for a number of tumour sites including GI, breast and HNC. Furthermore, a web-based software tool, ReCompare (REmote COMparison of PARticlE and photon treatment plans), was developed by researchers from Germany to facilitate remote treatment plan exchange between photon and PT centres for comparison and patient selection [33]. In addition, in a recent report from the PT Clinical Trial Strategy Group of the United Kingdom, it was promoted to design and participate in PT clinical trials, to advance quality assurance, methodology, interpretation of the results and the consistency of reporting of clinical trials for PT [34].

A notable finding of the current study was that reimbursement was provided by national health care systems for the majority of

	CNS	HNC	Lymphoma	GI	Breast	Prostate	Lung	Gynaecology	Total
Lack of evidence	0	1	2	4	6	8	6	5	30%
No Reimbursement	0	1	3	4	5	5	5	8	29%
Technical limitations	0	1	5	1	4	1	6	3	20%
No patient referral	0	0	1	2	3	3	3	2	13%
Treatment capacity	0	0	2	0	1	0	0	0	3%
Other	0	0	1	1	0	1	1	1	5%

Fig. 3. Reasons for non-treating adult patients with PT based on tumour sites.

commonly treated tumour sites. Reimbursement rates were higher among countries with a national indication protocol for PT. Reimbursement was also provided by the national care system for exceptional cases in some countries, after being carefully selected by a tumour board. A transparent reimbursement system was accepted in the Dutch national indication protocol, where first a national agreement is reached among the members of the Netherlands Society for Radiation Oncology for every indication, followed by a formal approval by the Health Care Institute, which guarantees reimbursement by the payers [27]. Another practical solution for patient selection was developed in the Czech Republic with the care givers for prostate cancer patients. Patients with low to intermediate risk prostate cancer are treated with extreme hypofractionated schedule of 5 fraction 7.25 Gy each, which enabled lower costs with PT than a conventionally fractionated photon therapy [35].

Our study has some limitations. First, even though there was at least one representing centre from each country, this survey might not directly reflect the practice in that country as a whole, as differences may exist between centres within a country. This disclaimer is somewhat mitigated by the high national percentage response rate, as all but 2 countries had a centre response rate of 100% (Table 1) and numbers of those countries not responding were low. Second, some of the centres were still in their ramp-up phase, which may not reflect the future practice of these centres when they are in operation with full capacity. Third, some of the open questions were left blank, especially when only one representative from a centre had to complete the survey for many different tumour sites.

The most important reason for not treating specific tumour sites with PT was lack of evidence from clinical trials. Formal phase II or III interventional studies are conducted less frequently, mostly due to reimbursement and funding problems. Some centres, especially from the Netherlands, mentioned methodological reasons not to conduct randomised controlled trials, e.g., lack of generalizability and dependence of continuous technological improvements and prefer using a model-based clinical evaluation based on well-structured prospective data registration programs [17]. We would recommend that each patient is at least registered in a (national) prospective data registry program. Because the majority of PT centres globally are located outside Europe (and thus also most clinical studies), collaborations between PT centres both within and outside Europe are warranted [36].

Conclusion

In Europe, a wide range of tumour sites are treated with PT, of which CNS and HNC tumours are the most frequently treated in adult patients. Most centres use national or institutional guidelines for selecting patients for PT and these are usually covered by national health care systems. It is encouraging to see that most patients treated with PT are included in prospective data registration programs and/or are included in clinical trials, as this will provide important information on the added value of PT in the future.

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Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.12.004.

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