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Patients' needs in proton therapy: A survey among ten European facilities

G.C. Mazzola [a,b,1], L. Bergamaschi [a,b,1], C. Pedone [a,b,*], M.G. Vincini [a], M. Pepa [a,3], M. Zaffaroni [a], S. Volpe [a,b], B. Rombi [c], J. Doyen [d], P. Fossati [e], K. Haustermans [f], M. Høyer [g], J.A. Langendijk [h], R. Matute [i], E. Orlandi [j], H. Rylander [k], E.G.C. Troost [l,m,n], R. Orecchia [a], D. Alterio [a,2], B.A. Jereczek-Fossa [a,b,2]

[a] Division of Radiation Oncology, IEO, European Institute of Oncology, IRCCS, Milan, Italy
[b] Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy
[c] Proton Therapy Center, Trento, Italy
[d] Centre Antoine Lacassagne, Nice, France
[e] MedAustron Ion Therapy Center, Wiener Neustadt, Austria
[f] PARTICLE Proton Therapy Center, Leuven, Belgium
[g] Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark
[h] University Medical Center Groningen, Groningen, The Netherlands
[i] Centro de Protonterapia Quironsalud, Madrid, Spain
[j] CNAO National Center for Oncological Hadrontherapy, Pavia, Italy
[k] The Skandion Clinic, Uppsala, Sweden
[l] Faculty of Medicine and University Hospital Carl Gustav Carus, Department of Radiotherapy and Radiation Oncology, Dresden, Germany
[m] OncoRay - National Center for Radiation Research in Oncology: Faculty of Medicine and University Hospital Carl Gustav Carus, Dresden; Helmholtz-Zentrum Dresden-Rossendorf, Dresden, Germany
[n] Institute of Radiooncology - OncoRay, Helmholtz-Zentrum Dresden-Rossendorf, Dresden, Germany

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ABSTRACT

Aims: The number of Proton Therapy (PT) facilities is still limited worldwide, and the access to treatment could be characterized by patients' logistic and economic challenges. Aim of the present survey is to assess the support provided to patients undergoing PT across Europe.

Methods: Through a personnel contact, an online questionnaire (62 multiple-choice and open-ended questions) via Microsoft Forms was administered to 10 European PT centers. The questionnaire consisted of 62 questions divided into 6 sections: i) personal data; ii) general information on clinical activity; iii) fractionation, concurrent systemic treatments and technical aspects of PT facility; iv) indication to PT and reimbursement policies; v) economic and/ or logistic support to patients vi) participants agreement on statements related to the possible limitation of access to PT. A qualitative analysis was performed and reported.

Results: From March to May 2022 all ten involved centers filled the survey. Nine centers treat from 100 to 500 patients per year. Paediatric patients accounted for 10–30%, 30–50% and 50–70% of the entire cohort for 7, 2 and 1 center, respectively. The most frequent tumours treated in adult population were brain tumours, sarcomas and head and neck carcinomas; in all centers, the mean duration of PT is longer than 3 weeks. In 80% of cases, the treatment reimbursement for PT is supplied by the respective country's Health National System (HNS). HNS also provides economic support to patients in 70% of centers, while logistic and meal support is provided in 20% and 40% of centers, respectively. PT facilities offer economic and/or logistic support in 90% of the cases. Logistic support for parents of pediatric patients is provided by HNS only in one-third of centers. Overall, 70% of respondents agree that geographic challenges could limit a patient's access to proton facilities and 60% believe that additional support should be given to patients referred for PT care.

* Corresponding author at: Division of Radiation Oncology, IEO, European Institute of Oncology, IRCCS, Milan, Italy.
E-mail address: cristiana.pedone@unimi.it (C. Pedone).

[1] Co-first authors.
[2] Co-last authors.
[3] Dr. Pepa was with the European Institute of Oncology (IEO) IRCCS, Milan, Italy at the time of the study but has moved to the National Center for Oncological Hadrontherapy (CNAO), Pavia, Italy since.

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Conclusions: Relevant differences exist among European countries in supporting patients referred to PT in their logistic and economic challenges. Further efforts should be made by HNSs and PT facilities to reduce the risk of inequities in access to cancer care with protons.

Introduction

Proton therapy (PT) represents one of the most recent and promising external beam radiation treatment techniques. Physical characteristics of proton beams allow reaching a more conformed dose to target volumes achieving advantages both in terms of higher dose to target volumes and better sparing of surrounding healthy tissues. On the other hand, compared to modern photon-based approaches (eg Intensity Modulated Radiotherapy and Stereotactic Body Radiotherapy), PT has some disadvantages such as higher dosimetric uncertainty, higher costs, and longer time required for the entire treatment process and the still limited number of facilities worldwide. Thanks to data provided by scientific literature, the indication to PT in the field of malignant cancers is rapidly increasing, and the number of candidates to PT is consequently growing [5,12]. For prostate cancer, Amini et al. reported the percentage of patients treated with PT increased between 2004 and 2013 from 2.7% to 5.6% of all external beam treatments [1]. Similarly, according to the US national cancer database, the proportion of pediatric patients (age 0–21) treated with PT increased from 1.9% to 17.5% between 2004 and 2013 [15].

Nevertheless, PT remains a resource-limited approach due to the low number of facilities currently available worldwide. The main limiting factor is represented by the high set-up cost of construction and maintenance of the PT centers [4]. Therefore, access to PT care can be burdened by logistic and economic discomfort. This aspect could produce inequality in access to PT among patients candidates for this approach. As an example, a cross-sectional study showed that Black patients were less likely to receive PT than their White counterparts, and these disparities were greatest for those cancers in which PT was the recommended radiation therapy modality [13]. Authors, therefore, concluded that many efforts should be applied to improve equity in access to PT facilities across different countries. In the Nordic European regions, two facilities centralized PT care. Ohlsson-Nevo et al. reported the results of a workshop on patients' perspectives in this context [14]. Among different analyzed factors, it has been highlighted that access to PT facilities could imply for patients to be treated away from home. Therefore, issues regarding daily transportation and/or logistic accommodation can lead to a potential risk of patient distress.

In this scenario, the present survey aimed to investigate the different policies to support logistic and/or economic issues for patients candidate to PT across different European centers.

Materials and methods

Following personal contact (no specific selection criteria – we chose preferably one center/nation with the exception for two Italian PT facilities), an online questionnaire was administered via Microsoft Forms to Medical Directors of 10PT centers in Europe in May 2022. Microsoft Forms (https://forms.office.com), a free online software tool, was used to develop the questionnaire: an email with a direct link to the online survey was sent to each participant.

The questionnaire consisted of a total of 62 questions divided into six sections: i) personal data and informed consent obtained from participants to the survey (questions from 1 to 6); ii) general information about the clinical activity of the PT facility (questions from 7 to 16); iii) fractionation, concurrent systemic treatments and technical aspects of PT facility (questions from 17 to 33); iv) indication to PT and reimbursement policies (questions from 34 to 39); v) provided (if any) economic and/ or logistic support to patients referred to PT (questions from 40 to 55) vi) participants agreement on statements related to the possible limitation of access to PT due to patients' geographical and/or economic discomfort (questions from 56 to 62). A list of questions has been reported in Supplementary Material (**Table S1**).

Twenty-three questions had only closed answers (pre-defined drop-down menu) while 17 had closed and open answers aiming to provide additional information and/or comments. Six questions allowed multiple choice answers.

Cost coverage for patients' accommodation, logistics and meals was investigated. For the pediatric population, support to parents (in terms of housing) was also considered. Support to patients' needs was considered as provided by the Health National System (HNS), private health insurance or PT facilities.

Collected data were centrally analyzed at the European Institute of Oncology (Coordinator Center – European Institute of Oncology, Milan, Italy). A qualitative analysis was performed and reported.

Results

All invited agreed to participate. From March to the end of May 2022 ten Radiation Oncologist from nine European Countries (Belgium - center n.1, Italy - centers n.2 and 3, France - center n.4, Nederland – center n. 5, Denmark - center n. 6, Germany - center n. 7, Austria - center n. 8, Sweden - center n. 9, Spain - center n. 10) filled the questionnaire. All of the respondents gave their consent to the use of data for scientific purposes.

A list of answers has been reported in **Table S1**.

General information

Nine centers declared treating from 100 to 500 patients/year (one center treated < 100 patients).

All centers treat pediatric patients, and this population accounts for 10–30%, 30–50% and 50–70% of the entire patient population in 7, 2 and 1 centers, respectively. Regarding the three mostly treated oncologic diseases among the pediatric population in each center, the most frequent are medulloblastomas (80% of responders), sarcomas (60%), ependymomas (60%) and brain tumors (50%).

With regards the three most often adult oncologic diseases treated with PT in each center, the most frequent are brain tumors (70% of responders), sarcomas (60%), head and neck (HN) cancers (50%), and chordomas (40%).

Benign diseases are also managed in 6 of the participating centers. The most frequent lesions are arteriovenous malformations in 2 centers, while other 3 centers provided for a miscellaneous case-mix (recurrent pleomorphic adenomas, meningiomas and pituitary adenomas).

Fractionation, concurrent treatments and technical aspects

Hypofractionated PT (dose fraction > 3 Gy/fr RBE – relative biological effectiveness) is used for selected malignant and benign tumors (prostate cancers, reirradiation, pancreatic and rectal cancers, hepatocarcinomas, chordomas and arteriovenous malformations) in 40% of the participating centers.

In all centers, PT can be performed concurrently with systemic chemotherapy, while immunotherapy and target therapies are associated with PT in only 3 and 4 centers, respectively.

A mixed beam approach (photon-based and PT) is proposed in 60% of the centers for a variety of clinical conditions (medulloblastomas, chordoma/chondrosarcomas, ependymomas, paranasal and nasopharyngeal tumors, sarcomas and head and neck tumors requiring bilateral

neck irradiation, salivary glands tumors). Reirradiation is performed by all centers in a proportion ranging from < 5% to 20% of cases.

From a technical point of view, motion tracking is available in 5 centers, strategies such as Deep Inspiration Breath Hold (DIBH) and gating are done for eye, thoracic and abdominal moving targets (such as Hodgkin lymphomas and thymomas, hepatocarcinomas and pancreatic tumors).

Indication to PT and reimbursement policies

The majority of PT centers (80%) performed comparative plans between photons and protons to define indications of PT. Clinical trials are actively recruiting patients in all involved facilities. The percentage of patients enrolled in clinical trials are < 10%, 10–30%, 30–60% and > 60% in 4, 3, 1 and 2 centers, respectively. The number of active clinical trials were < 5, 5–10 and > 10 in 6, 3 and 1 center, respectively.

A multidisciplinary approach to define indication to PT is applied by the majority of centers to define indication to PT (Fig. 1).

Different policies are applied by the different centers for the reimbursement of PT. In 90% of the centers the cost of the treatment is supplied by the respective country's Health National System (HNS), defined on a regional or national basis in 4 and 5 centers, respectively. In one center a comparative dosimetric analysis is required, while in another center a compulsory insurance is available to all citizens and residents. Five centers are also allowed to treat patients with either a private health insurance, or self-payment.

Economic and logistic support for patients candidate to PT

The percentage of patients not resident in the country represents < 10%, 10–30% and 50–70% in 6, 3 and 1 center, respectively. In all centers the main duration of their treatment is longer than 3 weeks.

The most frequently used accommodation by these patients is a rented apartment (70% of the centers). In 70% and 30% of the involved centers, the HNS provide economic and logistic support for the patients' accommodation, respectively (Table 1).

In the case of regional reimbursements, rules may vary among different regions.

PT facilities offer economic and/or logistic support in 90% of the cases (Table 2).

A travel agency providing a logistic support to patients is available in 2/10 centers. In one center association of volunteers provides a support to patients in organizing travel and accommodation. In the case of pediatric patients, in three centers the HNS provide logistic support for parents (free taxi driver, financial help for housing, planning travel and book apartments).

Meal costs are supported by HNS in 40% of the cases (free lunch for paediatric patients and one parent, partial coverage of daily costs for meals). Of note in two centers, the cost is provided on a regional or provincial bases. However, patients do not receive support from any PT facilities.

Table 1
Details on economic and logistic support for the patients' accommodation provided by Health National System.

Center ID	
Economic support for the patients' accommodation	
4	Financial help for housing
5	Fixed amount or reimbursement per night
6	Full coverage for travel and accommodation
7	Daily allowance
8	Accommodation expences reimbursed for patients living further that commuting distance
9	Costs for accommodation covered by the regional health authorities.
10	Reimbursement only for national patients
Logistic support	
2	Travel costs partially covered by the health insurance
4	For patients who have to move to another city to get treatment not available in the city of origin a financial help is given for housing
6	Regional administration plans travel and books apartment

Table 2
Details of economic and/or logistic support provided by the PT facility.

Center ID	**Economic and/or logistic support provided by the Proton therapy facility**
2	Free apartments for families and single patients from local no profit organizations
3	Logistic support for paediatric cancer patients and their families
4	Financial help for housing
5	Special apartments available
6	Planning travel and book accommodation
7	Information sheet, website
8	Patient service providing support with founding and booking accommodation
10	Logistic support for some patients

Overall, the economic support provided to patients treated with PT is summarized in Table 3.

Participants' agreement on statements related to the possible limitation of access to PT results of the statement have been reported in Fig. 3

The majority of the respondents (70%) agreed (6 agree and 1 strongly agree) with the sentence "The possibility to be treated with PT in your country could be limited due to patients' geographical challenges" while 40% agreed (3 agree and 1 strongly agree) with the sentence "*The possibility to be treated with PT in your country could be limited due to patients' economic challenges*". Forty percent of respondents agreed (3 agree and 1 strongly agree) with the sentence *"Accommodation challenges could impact on patients' compliance to treatment"*.

The mean cost for patients' accommodation and meals has been estimated between 1000 and 5000 euros by half of the respondents, <

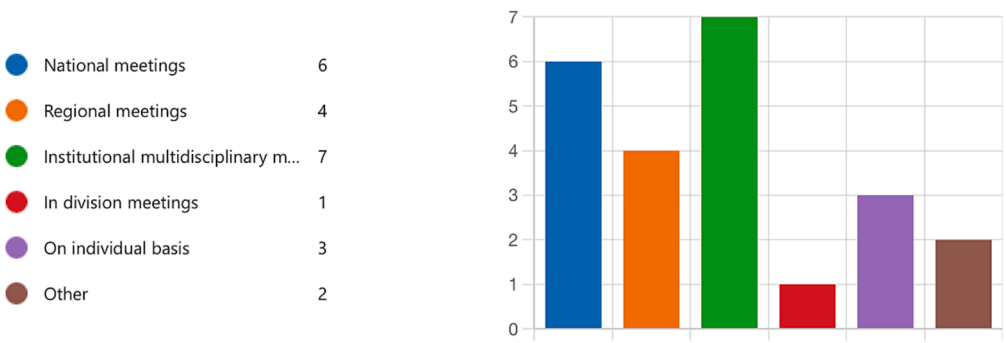

Fig. 1. Response to the question "Indication to Proton Therapy at your Institute are discussed" (multiple choice admitted).

Table 3
Details of economic and/or logistic support provided by the PT facility.

		Center ID									
		1	2	3	4	5	6	7	8	9	10
Health National System	Economic support for patients' accommodation	✗	✗	✗	✓	✓	✓	✓	✓	✓	✓
	Logistic support for patients' accommodation	✓	✗	✗	✗	✗	✓	✗	✗	✗	✗
	Logistic support for parents of pediatric patients	✗	✓	✗	✓	✗	✓	✗	✗	✗	✗
	Support for meal	✓	✓*	✗	✗	✗	✓	✗	✗	✓*	✗
PT Facilities	Economic/logistic support for patients' accommodation	✓	✓∞	✓	✓	✓	✓	✓	✓	✗	✓
	Support for meal	✗	✓*	✗	✗	✗	✗	✗	✗	✗	✗

1. Belgium; 2. Italy-1; 3. Italy-2; 4. France; 5. Netherlands; 6., Denmark; 7. Germany; 8. Austria; 9. Sweden; 10. Spain.; *Regional or Provincial support ∞Association of Volunteers.

1000 euros and > 5000 euros by the 3 and 2 remaining respondents, respectively. Sixty percent of the participants agree that patients need to be more supported in case of indication to PT both for accommodation and travel.

Discussion

Results of this survey highlight that patients candidate to PT in European countries with public health systems are only partially supported in their economic and logistic needs in the investigated centers. This finding is particularly relevant if we consider that the length of the PT treatment is longer than 3 weeks and that pediatric population represents a consistent percentage of patients. Considering that the mean cost for logistic accommodation and meals has been estimated between 1000 and 5000 euros by the majority of respondents, many of them agreed that patients should be more supported for both accommodation and travel when referred to PT. To our knowledge, this is the first survey pointing out that logistic and economic challenges could have an impact on patients' access to PT facilities in Europe because of the economic and logistic challenges faced by the patients or their families.

In recent past years, patients referred to PT are rapidly increasing [4]. In the US, the number of cases treated with PT increased from 0.4% in 2004 to 1.2% in 2018 (annual percent change [APC], 8.12%; P <.001) [12]. Of note, criteria to indicate PT among different nations remain very heterogenous and are based on different parameters such as reimbursement, literature evidence or technical aspects [6,16,20]. A recent survey showed that 4233 adult patients have been treated in 2020 in 19 European PT centers [16]. Of these, near half of them (46%) have a diagnosis of tumors of the central nervous system, while head and neck and prostate represent about 30% of the entire population. Selection criteria to indicate PT among involved centers were heterogeneous including planning comparison, patients' characteristics (young patients and good performance status), tumor site and prognosis, as well as special situations like reirradiation and genetic syndromes. Costs for most treatments were covered by HNS with only prostate and gynecological cancers requiring reimbursement by health insurance companies or patients themselves, respectively. Although the number of centers involved in the present survey is relatively low, 10 centers out of the 22 active ones in Europe (45%), the general characteristics of the analyzed population are in line with other cohorts treated with PT in Europe. Additional information provided by the present study is related to the use of concurrent systemic treatment (chemotherapy in all centers, immunotherapy in 3 centers), hypofractionation and mixed beam approach (4 centers), while reirradiation is practiced in all involved facilities.

Pediatric cancer is the most common indication for PT as concerns related to long-term side effects in surviving patients. Indeed, a scoping review revealed that PT was indicated for a majority of benign and malignant pediatric tumours, with consensus across the investigated nations (United Kingdom, USA, Canada, Nederland, Australia and New Zealand) for the following tumors: base of skull and spinal chordomas and chondrosarcomas, intracranial germ cell tumors, rhabdomyosarcoma, Ewing sarcoma, optic pathways, and other low-grade gliomas and craniopharyngiomas [20]. A large-scale analysis conducted using the American National Cancer Database (NCDB) assessed that the overall proportion of pediatric (<21 years) patients treated with PT between 2004 and 2013 increased from 1.7 to 17.5% [15]. Of note, patients with a private health insurance, higher income levels, living in metropolitan areas and with a high school degree were more likely to receive PT treatment compared to their counterparts. Interestingly, race-specific differences are often mitigated by socioeconomic and clinical factors. Moreover, despite the increased number of PT facilities in the considered period, patients treated with PT travelled significantly longer distances (200 miles) than those treated with photons ($p < 0.0001$) [15]. Therefore, the authors concluded that socioeconomic factors have a relevant impact on the use of PT also the cancer pediatric population. Data collected by the present survey highlighted that HNS offers a logistic support to parents of pediatric patients only in 30% of the cases. Therefore, this finding confirms that assistance to pediatric patients' families requires improvement.

Although the number of patients treated with PT is constantly increasing, the worldwide number of facilities remains low. Therefore,

geographical distances might create some disparities among cancer patients population. It has been shown that patients with head and neck and prostate cancers need to travel for longer distances when treated with protons compared to those treated with a photon-based approach [1,8]. About one-third (34.7%) of adults were found to live over three hours from the nearest PT center [10] in the USA. A centralized system (national network referring patients to two PT centers) has been implemented in Northern European countries. In this context, a recent workshop has shown that access to PT could imply for patients to be treated far away from home with a potential risk of inequity due to personal or practical barriers in a long-course of treatment [14]. In accordance with this finding, patients' geographical challenges represented the main issue also according to the respondents to this survey. Indeed, 70% of them believed that this aspect could represent a limitation to be treated with PT in their own countries.

Economic development represented the most important determining factor for the availability of radiation therapy facilities worldwide. This aspect is particularly evident for PT. Indeed, high inequality has been shown by Xia et al. in accessibility to PT among different countries [18]. An analysis of the National Cancer Database conducted by Nougeria et al. showed that, among patients eligible for PT in the USA, the majority (86.4%) was White, while only 13.6% was Black [12]. Therefore, Black patients were less likely to be treated with PT than their White counterparts (0.3% vs 0.5%; odds ratio [OR], 0.67; 95% CI, 0.64–0.71), and racial differences impacted the most for patients affected by a disease for which the use of PT was recommended. Authors also highlighted that these disparities increased over time (annual percent change = 0.09, P <.001). Several authors reported that, among prostate cancer patients, those treated with PT were most frequently White, younger, healthier, and living in metropolitan areas of higher-income countries [1,19], [9]. Similarly, ethnicity, high-school education and highest median household income quartile have been found to be different among head and neck cancer patients treated with PT compared to those treated with a photon-based approach [8]. Thijssen et al reported results of a national survey involving either radiation oncologists or patients aimed to identify barriers for access to PT facilities and propose intervention to overcome them [17]. Travel time represented the most important barrier for all the involved radiation oncologists and for near half of the patients. Therefore, an assistance in travel service has been proposed to minimize this issue. Other than the above-mentioned survey to the best of our knowledge, a comprehensive and detailed analysis of the current situation and barriers to access to European PT facilities is not available, yet. Results of the present survey clearly showed that strong differences exist among European countries in supporting patients candidate to PT. No data on patients' profile (ethnicity, education degree, private health insurance availability etc) have been collected by the present survey and therefore no conclusion can be carried out on eventual inequity related to this topic. Nevertheless, as respondents estimated a cost for patients' accommodation between 1000 and 5000 euros in five countries, it is reasonable to hypothesize that a certain proportion of patients (fragile elderly, people without a social/familiar caregiver network, and/or with a low social/economic status) was not able to meet economic and geographical challenges required to be treated with PT unless supported by the HNS and/or PT facilities. These findings confirm the risk of an inequity access to this modern radiation approach also among the European population. The European Society for Radiotherapy and Oncology (ESTRO) has undertaken an initiative in order to help raise awareness of the benefits of radiotherapy, improve access to radiotherapy and secure its valuable position in comprehensive, optimal cancer care [3].

Although the theoretical benefit of protons over photons is high, to date clinical evidences supporting its use are still conflicting. Promising results have been reported for several types of cancers, mainly in terms of toxicity reduction. Nevertheless, the majority of the reported data were retrieved from small cohorts of patients treated in single institution [11]. Overall, scientific evidences demonstrating the better cost/benefit ratio of protons compared to photon-based treatments are constantly increasing and many efforts are being made to democratize the use of PT. Indeed, the number of PT facilities is increasing with a relevant number of centers that are planned to be opened in the next few years. As an example, Fig. 2 reported the ratio between number of PT center over million inhabitants in the European Union (August 2022 – according to the Particle Therapy Co-Operative Group – PTCOG website https://www.ptcog.ch/), considering only active facilities (Fig. 2a) and the total number of facilities (active, under construction and in planning) (Fig. 2b).

This is due to both literature evidence on the advantages of PT over conventional radiotherapy and also the reduction of starting cost to implement a PT facility. On the other hand, it should be noted that some PT centers have also been recently dismissed. Therefore, the addition of cost-effectiveness analyses (also considering geographical issues), as well as the use of health economic metrics quantifying the disease burden (i.e. disability-adjusted life year - DALY) should be considered for the overall assessment of PT in the context of cancer care. Moreover, the prospective data collection (in the contest of clinical trials and/or tumor registries) of patients treated with PT are strongly required in order to improve the robustness of the already available scientific evidences, as well as to widen the therapeutic indication of protons. Data retrieved from controlled clinical trials would also serve to refine and make more homogeneous both clinical and dosimetric parameters available for the patients' selection process across different Institutions.

Moreover, given the current situation, collaboration among photon-based and PT facilities represents a crucial point to optimize patients' care. In a recent survey conducted in the Nederlands, logistic reasons such as a too-long lead time for a planning comparison and/or coordination for concurrent chemoradiation represented some of the major concerns among the involved radiation oncologists [17]. To overcome these barriers, the working group proposed some solutions like to improve the data exchange and reduce administrative duties. Therefore, we strongly agree that collaborative clinical networks aiming to standardize clinical and radiological data sharing with respect to the current privacy and ethical laws would help to minimize all possible inefficiencies (e.g. missing images, temporary unavailability of referred physician, time delay due to plan comparison).

A further consideration emerging from the present analysis is that standard fractionation still represents the most common schedule among, with a mean overall treatment time greater than three weeks in all involved centers. The rapid improvement of PT technologies will arguably favor both a wider use of hypofractionation and the introduction into clinical practice of some promising pre-clinical developments (like an ultra-high dose rates treatment - FLASH therapy). Kubeš et al. reported that ultra-hypofractionation has already been implemented in the Czech Republic, where patients with low to intermediate risk prostate cancer are currently treated with 5 fractions (7.25 Gy(RBE)/fraction) [7]. These aspects would have a significant impact on reducing patients' logistic discomfort by shortening the overall treatment time of PT, potentially allowing for additional patients to be treated with PT and, moreover, reducing costs by the health care system and patients [2,21].

We are aware that the major limitation of this work is the limited number of involved centers that could not be representative of the entire European scenario. Indeed, PT facilities of different European Countries did not participate in the survey (like Czech Republic and Poland) while other countries (like Croatia and Portugal) are not equipped yet with PT machines. Therefore, a more extensive survey (either in terms of involved centers and in terms of moving patients across different European Countries) is needed to achieve a comprehensive overview on the unmet patients' need when referred to a PT facility located far from their living town. Moreover, different indications to PT might translate into a different case-mix (e.g. pediatric/adult ratio). Therefore, patients' needs could also vary among the different involved PT facilities. Of note, while the support to pediatric patients and their families has been

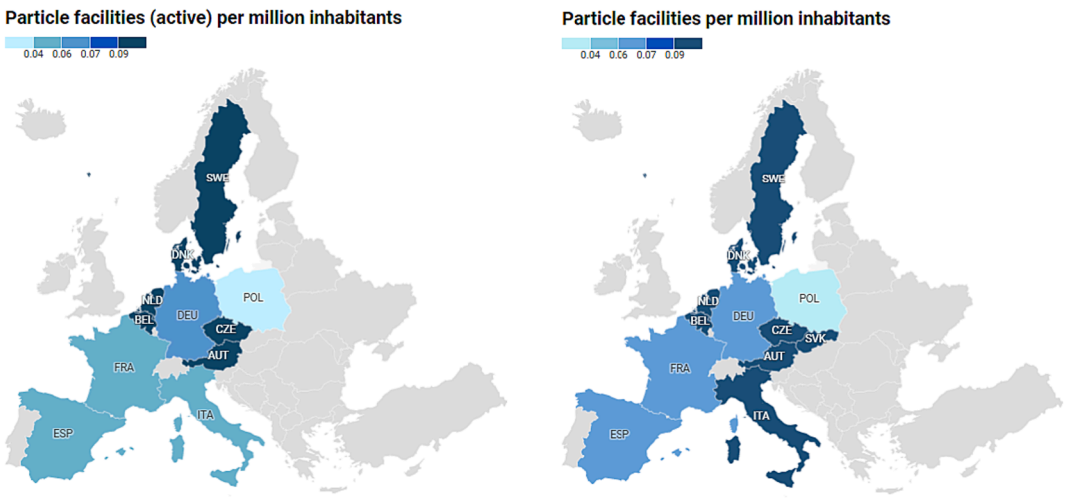

Fig. 2. Density of particle therapy facilities over million inhabitants in the European Union (august 2022) considering (left) active facilities and (2a) total facilities (active, under construction, in planning) (2b). created with https://app.datawrapper.de/.

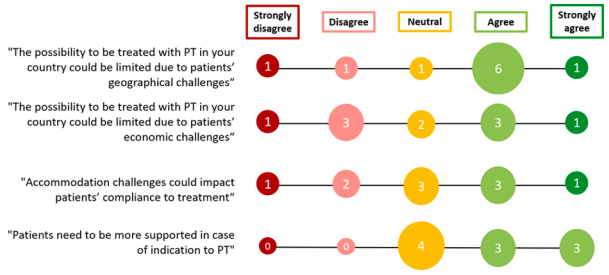

Fig. 3. Participants' agreement on statements related to the possible limitation of access to PT.

extensively reported, the present survey did not investigate the fragile population represented by elderly patients. As elders will represent an increasing proportion of cancer patients in the next few years, we believe that this topic deserves to be faced in future analysis. Finally, regional policies differ within the same nation according to the regional and provincial rules, and such heterogeneity is scarcely represented in this work.

Nevertheless, we believe that results of this survey provide the clear message that patients' discomfort (particularly logistic challenges) could represent an underestimated issue. This unmet need should be considered by both HNSs and PT facilities to minimize the risk of unethical access to PT across European countries. Moreover, this effort will constitute a benchmark for wider surveys involving additional European Centers: not only this will allow getting a fuller picture of PT indications and logistic pitfalls across Europe, but we hope would represent a starting point to improve the accessibility to this form of treatment for cancer patients across the continent.

Conclusions

Relevant differences exist among European countries in supporting patients referred to PT in their logistic and economic challenges. Further efforts should be made by HNSs and PT facilities to support patients referred to treatment in facilities located far from their city origin. Moreover, the increasing number of PT facilities being planned or already under construction will hopefully reduce the number of patients who face economic and logistic discomforts when candidate to protons.

CRediT authorship contribution statement

G.C. Mazzola: Conceptualization, Methodology, Data curation, Writing – original draft, Visualization. **L. Bergamaschi:** Conceptualization, Methodology, Data curation, Writing – original draft, Visualization. **C. Pedone:** Conceptualization, Data curation, Writing – original draft, Visualization. **M.G. Vincini:** Formal analysis, Visualization. **M. Pepa:** Methodology, Visualization. **M. Zaffaroni:** Writing – review & editing. **S. Volpe:** Writing – review & editing. **B. Rombi:** Writing – review & editing. **J. Doyen:** Writing – review & editing. **P. Fossati:** Writing – review & editing. **K. Haustermans:** Writing – review & editing. **M. Høyer:** Writing – review & editing. **J.A. Langendijk:** Writing – review & editing. **R. Matute:** Writing – review & editing. **E. Orlandi:** Writing – review & editing. **H. Rylander:** Writing – review & editing. **E. Troost:** Writing – review & editing. **R. Orecchia:** Supervision, Writing – review & editing. **D. Alterio:** Conceptualization, Methodology, Writing – original draft, Supervision. **B. Jereczek-Fossa:** Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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