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Original Article

Patterns of proton therapy use in pediatric cancer management in 2016: An international survey

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ABSTRACT

Purpose: To facilitate the initiation of observational studies on late effects of proton therapy in pediatric patients, we report on current patterns of proton therapy use worldwide in patients aged less than 22 years.

Materials & methods: Fifty-four proton centers treating pediatric patients in 2016 in 11 countries were invited to respond to a survey about the number of patients treated during that year by age group, intent of treatment, delivery technique and tumor types.

Results: Among the 40 participating centers (participation rate: 74%), a total of 1,860 patients were treated in 2016 (North America: 1205, Europe: 432, Asia: 223). The numbers of patients per center ranged from 1 to 206 (median: 29). Twenty-four percent of the patients were <5 years of age, and 50% <10 years. More than 30 pediatric tumor types were identified, mainly treated with curative intent: 48% were CNS, 25% extra-cranial sarcomas, 7% neuroblastoma, and 5% hematopoietic tumors. About half of the patients

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were treated with pencil beam scanning. Treatment patterns were broadly similar across the three continents.

Conclusion: To our knowledge, this survey provides the first worldwide assessment of proton therapy use for pediatric cancer management. Since previous estimates in the United States and Europe, CNS tumors remain the cancer types most commonly treated with protons in 2016. However, the proportion of extracranial tumors is growing worldwide. The typically low numbers of patients treated in each center indicate the need for international research collaborations to assess long-term outcomes of proton therapy in pediatric patients.

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Several national guidelines consider proton therapy an optimal radiation modality for treating pediatric tumors and reducing treatment toxicities [1–6]. Compared with photons, protons have better physical properties providing clear dosimetric advantages to improve treatment conformality and lower doses to surrounding normal tissues [7–9]. This could have considerable clinical benefits to reduce treatment toxicities while maintaining or improving cure rates, especially when treating young patients with a tumor located close to critical normal tissues, such as the brain stem, eyes and spinal cord. Over the past decade, an expanding number of clinical outcome studies on proton therapy has been provided [9]. However, little data on late effects is yet available. Few phase-II [10,11] and, to our knowledge, no phase-III [12], randomized controlled trials have been conducted to compare clinical outcomes of proton vs. photon therapy in the pediatric setting. Observational data on late effects also remain sparse due to small sample sizes in single-institution studies and limited follow-up capturing long-term outcomes [13–16]. Despite the limited information on late effects, the demonstrated dosimetric advantages of protons have led to increasing use of this technique. Since 2012, the number of proton centers has increased from 34 to 61 worldwide [17]. By 2025, 132 centers are planned to be operating in 31 countries, and the numbers of patients treated with protons are expected to rapidly increase in the next coming years. Assessing the long-term clinical benefits and toxicities of proton therapy is thus critically needed.

In addition to the United States (U.S.) Pediatric Proton Consortium Registry which currently involves 13 centers across the country [18], an International Pediatric Proton Therapy Consortium has been proposed to build cooperation across institutions and initiate international collaborative studies evaluating long-term effects [19]. As a first step of this initiative, we conducted a patterns of care survey to estimate the number of pediatric patients treated with protons in 2016 and describe the clinical indications and delivery techniques used worldwide.

Materials & methods

The survey was conducted between July 2017 and June 2018 in all proton centers treating pediatric patients in 2016 worldwide. A total of 61 centers operating in 16 countries were identified through the Particle Therapy Co-Operative Group (PTCOG) website [17]. After exclusion of eye proton therapy ($n = 5$) and adult cancer ($n = 1$) centers and another one that stopped treating patients before 2016, 54 centers located in 11 countries were eligible for the survey. We invited all eligible centers to participate.

The questionnaire was adapted from the U.S. 2010–2012 survey [20] to collect information about the number of patients <22 years of age treated in 2016 at each center, by age group (<1, 1 to <5, 5 to < 10, 10 to < 15, and 15 to <22 years), intent of treatment (curative, palliative), delivery modality (primary or boost irradiation) and technique (passive scattering, uniform scanning, or pencil beam scanning), tumor types or non-malignant diseases (e.g. arteriovenous malformation), and patients' country of residency. The survey did not request any personal identifying information, and was exempt from IRB review per 45 CFR 46 and NIH Policy by the NCI Office of Human Research Protections Program. The questionnaire was sent to key contacts identified through multiple sources including the PTCOG website, national cancer organizations, authors of peer-reviewed publications or the center's website. The survey was closed on June 25, 2018. Descriptive statistics were computed with SAS 9.4 (SAS Institute Inc., Cary, NC, United States). Percentage ranges across centers are provided only among those with ≥10 patients, while other statistics include all participating centers.

Results

Number of treated patients

A total of 40 centers participated in the survey, including 20 in North America, nine in Europe and 11 in Asia (Table 1). Among the 54 eligible centers treating pediatric patients in 2016, the participation rate was 74% overall. The non-participating centers did not respond ($n = 12$) or declined ($n = 2$) the invitation. In the 40 participating centers, 1860 patients <22 years of age were treated with protons in 2016: 1205 in North America, 432 in Europe and 223 in Asia. Ten (25%) centers treated <10 patients, while 19 (48%) treated ≥30 patients and 7 (18%) ≥100 patients. Six out of the seven centers treating ≥100 patients were located in North America. In centers that started treating patients before 2016, the median number of patients per center was 29 ($n = 36$, range: 1 to 206) overall, 68 ($n = 16$, range: 1 to 206) in North America, 31 ($n = 9$, range: 2 to 171) in Europe and 12 ($n = 11$, range: 2 to 62) in Asia. By center, no association was observed between the number of patients in 2016 and the center's first year of operation (Fig. 1).

Intent of treatment, delivery modality, and technique

The intent of treatment was curative in 98% of patients in all continents (range across centers: 86 to 100%). Information on this question was available for 1788/1860 patients treated in 38/40 centers. Protons were used as boost irradiation in 2% of patients (range across centers: 0 to 20%). Pencil beam scanning was available in 25 (63%) centers, passive scattering in 16 (40%), and uniform scanning beam in ten (25%); 11 (28%) centers having ≥2 techniques available. Pencil beam scanning was used in 13 (65%) centers located in North America, seven (78%) in Europe, and five (45%) in Asia. A total of 950 (51%) of the pediatric patients were treated with pencil beam scanning (Table 2).

Patient age

Overall, 923 (50%) patients were <10 years old, and 446 (24%) were < 5 years. The proportion of pediatric patients <10 years was slightly higher in Europe (58%) and Asia (61%) than in the U. S. (44%) (Fig. A1). In all continents, the proportion of children <10 years was lower in centers that opened most recently: 47%

Table 1
Numbers of operating and participating centers in the survey, numbers of patients <22 years of age treated in 2016 and proportion of those patients living outside the treatment country, by continent and country.

	Operating centers in 2016*	Participating centers		Pediatric patients treated in 2016	
	N	*N*	(% of operating)	*N*	(% from foreign countries)
Overall	**54**	**40**	**(74)**	**1860**	**(24)**
North America	**23**	**20**	**(87)**	**1205**	**(22)**
United States	23	20	(87)	1205	(22)
Europe	**12**	**9**	**(75)**	**432**	**(29)**†
Czech Rep.	1	1	(100)	31	(58)
France	2	2	(100)	92	(9)
Germany	4	3	(75)	205	(35)
Italy	2	1	(50)	32	(–)
Poland	1	0	(0)	–	(–)
Sweden	1	1	(100)	25	(4)
Switzerland	1	1	(100)	47	(34)
Asia	**19**	**11**	**(58)**	**223**	**(27)**‡
China	2	0	(0)	–	(–)
Japan	11	9	(82)	104	(27)
Russia	3	0	(0)	–	(–)
South Korea	2	2	(100)	119	(–)
Taiwan	1	0	(0)	–	(–)

–: missing data.
* Excluding eye proton centers and centers treating only adults.
† Information missing in 1 out of the 9 participating centers ‡information missing in 2 out of the 9 participating centers

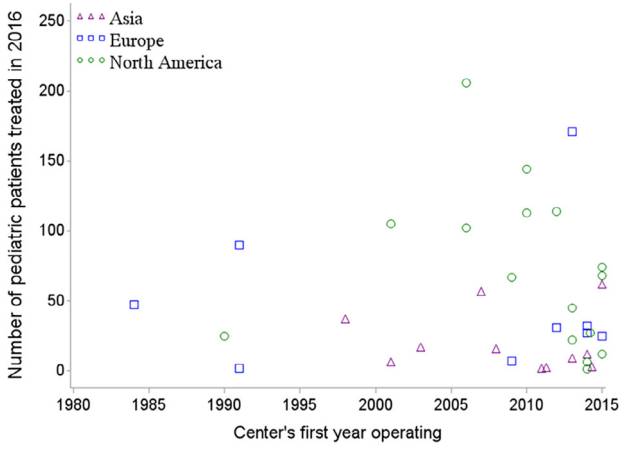

Fig. 1. Number of pediatric patients treated in 2016 in 40 proton therapy centers according to the centers' first year operating.

(range across centers: 33% to 68%) in the 28 centers that opened in 2005–2015 compared to 64% (range across centers: 53% to 95%) in the eight centers that opened <2005 (Fig. A2).

Types of pediatric diseases treated

Forty-eight percent of the patients were treated for CNS tumors, with medulloblastoma, ependymoma, low-grade glioma, and craniopharyngioma being the most frequent tumor types (Table 3). An additional 14% of patients were treated for other head and neck tumors. Extra-cranial sarcomas accounted for 25% of the patients, with similar frequencies in all continents. In Europe and Asia, the proportion of head and neck tumors treated was higher in centers that opened more recently than in the centers that have been opened longer (Fig. A3). The opposite trend was observed in North America where the proportion of head and neck tumors decreased, but the proportion of hematopoietic tumors increased, with the center's first year operating. Medulloblastoma, rhabdomyosarcoma, Hodgkin lymphoma (in North America), neuroblastoma (in North America and Asia), ependymoma and Ewing sarcoma were treated in >70% to 100% of centers, while other tumor types were treated in fewer centers (Fig. 2).

Discussion

This first survey of worldwide patterns of proton therapy use for pediatric cancer management included 40 centers located in 11 countries. With a participation rate of 74%, we estimate that between 2000 and 2500 pediatric patients were treated with pro-

Table 2
Number (%) of patients <22 years of age according to the proton therapy delivery technique by continent and country.

	Passive scattering beam	Uniform scanning beam	Pencil beam scanning	Unknown
Overall	**625 (33.6)**	**271 (14.6)**	**947 (51.0)**	**14 (0.8)**
North America	**397 (32.9)**	**182 (15.1)**	**614 (51.0)**	**12 (1.0)**
United States	397 (32.9)	182 (15.1)	614 (51.0)	12 (1.0)
Europe	**117 (27.1)**	**41 (9.5)**	**274 (63.4)**	**0 (0)**
Czech Rep.	0 (0)	0 (0)	31 (100.0)	0 (0)
France	90 (97.8)	0 (0)	2 (2.2)	0 (0)
Germany	27 (13.2)	41 (20)	137 (66.8)	0 (0)
Italy	0 (0)	0 (0)	32 (100.0)	0 (0)
Sweden	0 (0)	0 (0)	25 (100.0)	0 (0)
Switzerland	0 (0)	0 (0)	47 (100.0)	0 (0)
Asia	**111 (49.8)**	**48 (21.5)**	**62 (27.8)**	**2 (0.9)**
Japan	79 (76.0)	0 (0)	23 (22.1)	2 (1.9)
South Korea	32 (26.9)	48 (40.3)	39 (32.8)	0 (0)

Table 3
Number (%) of tumor types among patients <22 years of age treated with protons by continent and country.

	All countries	North America	Europe	Asia
Overall	**1860 (100.0)**	**1205 (100.0)**	**432 (100.0)**	**223 (100.0)**
Cns tumors	**890 (47.8)**	**562 (46.6)**	**246 (56.9)**	**82 (36.8)**
Medulloblastoma	233 (12.5)	149 (12.4)	59 (13.7)	25 (11.2)
Ependymoma	208 (11.2)	131 (10.9)	62 (14.4)	15 (6.7)
Glioma, low grade*	131 (7.0)	93 (7.7)	25 (5.8)	13 (5.8)
Craniopharyngioma	101 (5.4)	61 (5.1)	34 (7.9)	6 (2.7)
Glioma, high grade†	57 (3.1)	30 (2.5)	17 (3.9)	10 (4.5)
Atypical teratoid rhabdoid tumor	50 (2.7)	28 (2.3)	19 (4.4)	3 (1.3)
Supratentorial primitive neuroectodermal tumors	20 (1.1)	11 (0.9)	6 (1.4)	3 (1.3)
Pineoblastoma	19 (1.0)	11 (0.9)	7 (1.6)	1 (0.4)
Meningioma	17 (0.9)	14 (1.2)	2 (0.5)	1 (0.4)
Pituitary adenoma	11 (0.6)	5 (0.4)	6 (1.4)	0 (0)
Choroid plexus carcinoma	5 (0.3)	2 (0.2)	3 (0.7)	0 (0)
Pineal parenchymal tumor	4 (0.2)	4 (0.3)	0 (0)	0 (0)
Other CNS tumors	34 (1.8)	23 (1.9)	6 (1.4)	5 (2.2)
Other head & neck diseases	**252 (13.5)**	**162 (13.4)**	**60 (13.9)**	**30 (13.5)**
Skull base chordoma/chondrosarcoma	42 (2.3)	25 (2.1)	16 (3.7)	1 (0.4)
Intracranial pure germinoma (intracranial)	90 (4.8)	52 (4.3)	19 (4.4)	19 (8.5)
Non-germinomatous germ cell tumor (intracranial)	31 (1.7)	25 (2.1)	3 (0.7)	3 (1.3)
Nasopharyngeal carcinoma	22 (1.2)	15 (1.2)	5 (1.2)	2 (0.9)
Retinoblastoma	17 (0.9)	8 (0.7)	6 (1.4)	3 (1.3)
Salivary gland tumors	13 (0.7)	12 (1.0)	1 (0.2)	0 (0)
Arteriovenous malformation	8 (0.4)	5 (0.4)	3 (0.7)	0 (0)
Hemangioma	1 (0.1)	1 (0.1)	0 (0)	0 (0)
Uveal melanoma	3 (0.2)	2 (0.2)	0 (0)	1 (0.4)
Other intracranial non-CNS tumors	25 (1.3)	17 (1.4)	7 (1.6)	1 (0.4)
Neuroblastoma & other peripheral nervous cell tumors	**124 (6.7)**	**67 (5.6)**	**16 (3.7)**	**41 (18.4)**
Neuroblastoma	111 (6.0)	57 (4.7)	13 (3.0)	41 (18.4)
Vestibular schwannoma	7 (0.4)	5 (0.4)	2 (0.5)	0 (0)
Esthesioneuroblastoma	6 (0.3)	5 (0.4)	1 (0.2)	0 (0)
Bone & soft tissues sarcoma (extra-cranial)	**467 (25.1)**	**307 (25.5)**	**104 (24.1)**	**56 (25.1)**
Rhabdomyosarcoma	253 (13.6)	162 (13.4)	52 (12)	39 (17.5)
Ewing sarcoma	128 (6.9)	91 (7.6)	27 (6.3)	10 (4.5)
Osteosarcoma	12 (0.6)	8 (0.7)	2 (0.5)	2 (0.9)
Non-skull base chordoma/chondrosarcoma	10 (0.5)	5 (0.4)	3 (0.7)	2 (0.9)
Desmoid tumor	8 (0.4)	5 (0.4)	3 (0.7)	0 (0)
Other or unknown sites/histology	56 (3.0)	36 (3.0)	17 (3.9)	3 (1.3)
Urogenital neoplasia	**9 (0.5)**	**7 (0.6)**	**1 (0.2)**	**1 (0.4)**
Wilms tumor	7 (0.4)	6 (0.5)	0 (0)	1 (0.4)
Non-CNS germ cell tumor	2 (0.1)	1 (0.1)	1 (0.2)	0 (0)
Hematopoietic tumors	**94 (5.1)**	**86 (7.1)**	**2 (0.5)**	**6 (2.7)**
Hodgkin Lymphoma	80 (4.3)	77 (6.4)	1 (0.2)	2 (0.9)
Non-Hodgkin Lymphoma	10 (0.5)	6 (0.5)	1 (0.2)	3 (1.3)
Leukemia	3 (0.2)	2 (0.2)	0 (0)	1 (0.4)
Other or unknown sites/histology	1 (0.1)	1 (0.1)	0 (0)	0 (0)
Other/unspecified tumors	**24 (1.3)**	**14 (1.2)**	**3 (0.7)**	**7 (3.1)**

CNS: central nervous system.
* Including astrocytoma, oligodendroglioma & optic pathway glioma.
† Including glioblastoma multiforme.

tons in 2016. Pediatric cancers represented an estimated 10% of all proton therapy patients treated in 2016 [17]. In countries where information was available regarding the total number of pediatric patients receiving radiotherapy, the percentage of them treated with protons (either as primary treatment or boost irradiation) was 10% in France [21] and Japan [22], 15% in the U.S. [20], and 33% in Sweden (Dr. Petra Witt Nyström, emailed personal communication, 2018 June 18). In the U.S., we estimate that, for some aggressive tumor types (e.g. rhabdomyosarcoma, medulloblastoma, and ependymoma), protons are currently used to treat up to 50–70% of all pediatric patients receiving radiotherapy (Table 4).

Our data suggest that the number of patients aged <15 years treated with protons has doubled in the U.S. between 2012 [20] and 2016. This trend reflects the substantial increase in the number of centers treating pediatric patients in the U.S., from nine in 2012 to 23 in 2016, and increased acceptance of proton therapy's role in pediatric oncology. In Europe, the number of patients aged <18 years has increased even more rapidly, by 50% since 2014 when 7 centers were in operation [23] (vs. 12 centers in 2016).

The number of pediatric patients varies widely across centers, with 25% of centers treating less than 10 patients per year and 18% of centers treating ≥100 patients per year currently. The annual number of patients per center was often much lower in Asia (median: 12) and in Europe (median: 31) compared to North America (median: 68), but with a wide range between the centers. Several factors may influence the pediatric volume in proton centers. These include the technical capability (type of proton facility, technique of proton delivery, number of gantries) and the local organization of pediatric care, especially the presence and work time of pediatric radiation oncologists and anesthetists. The lower median number of treated patients per center in Asia and Europe may also reflect a lower propensity of pediatric medical or radiation oncologists to refer their patients to or use protons in those regions, a more limited access and referral capabilities to proton centers (including travel burden for the families), barriers for collaboration between referral pediatric oncology departments and proton centers, and/or lower financial incentives or pressure for proton therapy use in countries with national health insurance

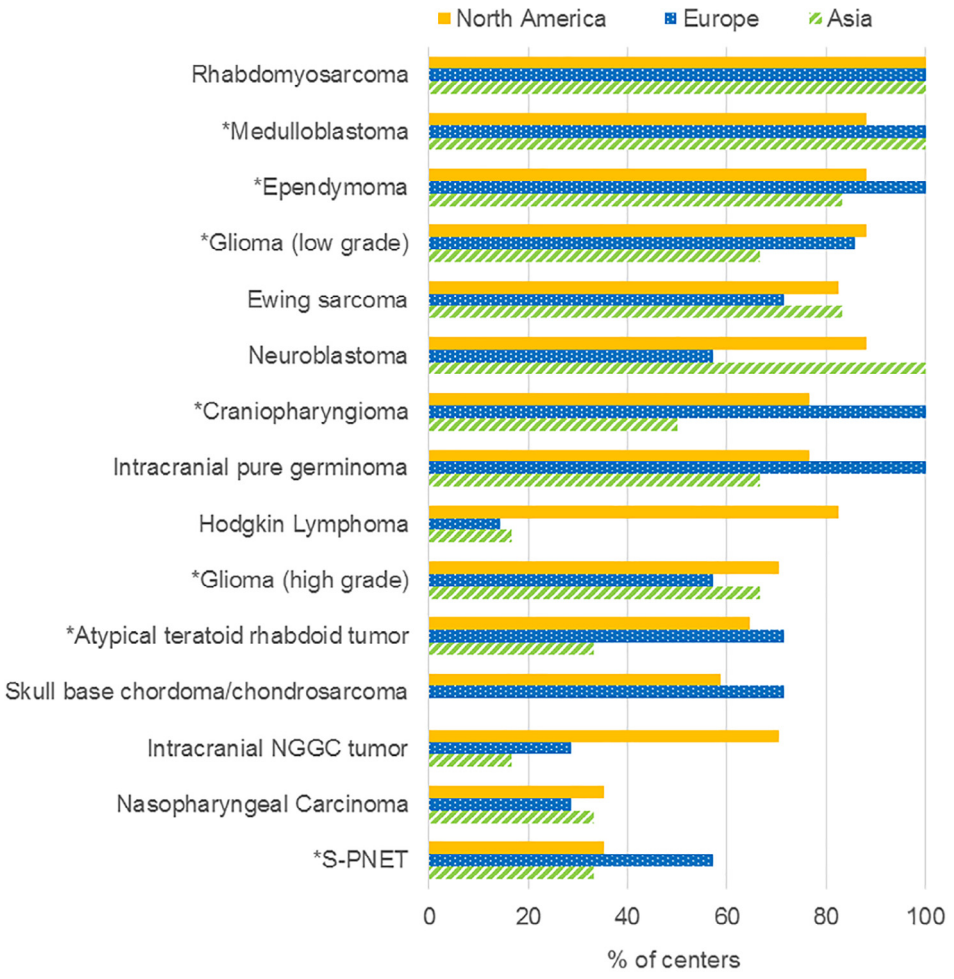

Fig. 2. Proportion of proton centers treating each of the 15 most frequent tumor types in pediatric patients by continent.
S-PNET: Supratentorial primitive neuroectodermal tumors; NGGC: non-germinomatous germ cell: *Tumors of the central nervous system. NB: Data are restricted to centers that treated ≥10 pediatric patients (North America: $n = 17$; Europe: $n = 7$; Asia: $n = 6$). The tumor types are sorted by descending order of total numbers of patients treated for each diagnosis in all countries.

schemes, although all these issues also arise in the U.S. The number of patients referred from foreign countries, however, did not vary between the continents (Table 1), and the number of patients treated in 2016 was not clearly related to the centers' first operating year (Fig. 1).

The variable pediatric volume across radiotherapy centers raises the question of whether there is sufficient expertise and experience in specific clinical indications to ensure an acceptable level of quality of care. This might be especially true in the specific context of modern precision therapies for pediatric cancer management, because these involve high technical complexity and unique considerations of treating a child with radiation, especially in terms of late effects. This issue has real implications, as systematic reviews from both Europe [24] and the U.S. [25] have demonstrated better survival among children with brain tumors and sarcomas treated at high volume centers. To address this, some countries, such as Denmark, the Netherlands, and Sweden actively use centralized medical systems to concentrate pediatric cancer patients in high volume proton/photon centers with pediatric radiotherapy expertise. In North America and Germany, some proton centers serve a similar role and concentrate a large number of pediatric patients. Nonetheless, volume activity requirements need to be considered in relation to accessibility of care, and the optimal balance between the two is definitely not obvious, especially in large countries. Selected academic medical centers thus offer

Table 4
Estimated proportion of patients <22 years of age treated with protons for a malignant disease among all patients receiving radiotherapy in 2016 in the United States.

	Projected number of U.S. patients treated with protons	Proportion of all patients receiving radiotherapy
Rhabdomyosarcoma	145	54%
Medulloblastoma	134	50%
Ependymoma*	118	68%
Ewing Sarcoma	82	53%
Neuroblastoma	51	30%
Hodgkin lymphoma	69	18%
Atypical teratoid rhabdoid tumor	25	62%
Nasopharyngeal carcinoma	13	46%
Primitive Neuroectodermal tumors	10	17%

U.S.: United States.
NB: Numbers of U.S. patients treated with protons were projected after deducting the 22% of patients referred from abroad to be treated in a U.S. proton center, and assuming similar patterns of proton use in the 20 participating and the 3 non-participating centers in the 2016 survey. The numbers of all patients receiving radiotherapy were estimated based on 2014–2015 SEER data on cancer incidence and radiation treatment (released on April 2018).
* Ependymoma cases include malignant and non-malignant subependymomas and myxopapillary ependymomas.

additional training in pediatric radiation oncology targeting the whole radiation oncology community with a focus on the technical specifics of proton therapy. As more and more proton centers come online, credentialing criteria or standards potentially including a minimal pediatric volume activity requirement may be established in addition to training for centers and physicians intending on treating children.

In our survey, a very wide variety of pediatric tumor types were treated with protons. More than 30 tumor types were identified, the ten most frequent accounting for 75% of patients (Table 3). Since previous surveys carried out in the U.S. [20] and in Europe [23], CNS tumors remain the most commonly treated tumor types in 2016. However, with a wider variety of tumors treated, the increased technical capability of large "gantry-based" systems, and advanced treatment planning techniques to improve sparing of organ at risks, the proportion of all proton-treated cancers that are CNS tumors declined in the U.S. from 62% in 2010 to 55% in 2012 [20], and 48% in 2016 (considering CNS histologies of the International Classification of Childhood Cancers as listed in Table 3). In Europe, the median proportion across centers of extracranial tumors increased from 17% in 2014 [23] to 27% in 2016, as well as the proportion of medulloblastoma which became one of the two leading indications for pediatric proton therapy in 2016 (Table 3).

Our findings regarding tumor types broadly reflect national guidelines and informal priorities for clinical indications for proton therapy in pediatrics [1–6]. General consensus was observed across centers to consider many pediatric tumors, including but not limited to rhabdomyosarcoma, medulloblastoma, ependymoma, low-grade glioma, craniopharyngioma, intracranial germ-cell tumor and Ewing sarcoma, as appropriate clinical indications for proton therapy, with >70% of centers treating those tumor types in 2016 (Fig. 2). There was emerging consensus across centers in North America and Asia to treat patients with neuroblastoma, but less clarity in Europe. We estimate that one in three patients treated with radiotherapy for neuroblastoma in the U.S. currently receives protons (Table 4). The most notable differences between the continents was for skull base chordoma/chondrosarcoma (60–70% of centers in North America and Europe treating this tumor type vs. 0% in Asia) and Hodgkin lymphoma (>80% of centers in North America treating this tumor vs. 15% in Asia and Europe). These indications (and variation) in the application of proton therapy are largely consistent with the conclusions of an international expert consensus panel convened in 2016 [8].

Different proton delivery techniques were used across the countries in 2016. In the U.S. and Europe, pencil beam scanning was available at most centers (20/29 centers) and used to treat more than half of proton-treated patients (Table 2). In Asia, fewer centers (5/11 centers) used this technique, and half of the patients were treated with passive scattering and one-fifth with uniform scanning beam. The different dose distribution of each technique may have important implications in terms of tumor control and toxicity rates. Better proximal and distal dose conformality with pencil beam scanning may reduce doses to surrounding normal tissues, but passive scattered techniques provide more robust dose distribution currently for moving targets. Moreover, aperture-based passive scattering techniques result in a tighter radiation penumbra and thus reduce dose lateral to the target compared to pencil beam scanning that does not use apertures [26]. In contrast, the whole-body secondary neutron dose is increased with the use of apertures. The effect of proton delivery techniques on normal tissue exposures and toxicity risks thus remains controversial. The high potential for neutrons to induce chromosomal aberrations and DNA damages [27,28] and the variations in proton and neutron dose distribution with different proton beam quality, incidence and collimation techniques [26,29,30] may substantially affect the risk of late effects. Simulation studies have predicted reduced risks of second malignancies with pencil beam scanning [26], but those results should be interpreted cautiously and as illustrative only of the various physical dose distributions with different radiotherapy techniques as long as large uncertainties remain on the biological effects of neutron doses [27,28].

The present survey has two main limitations. First, despite our efforts to reach all centers, the survey did not reach 100% participation rate in all countries, with 14 out of the 54 non-adult centers not responding to the questionnaire. However, it is possible that some of the non-respondents did not treat pediatric patients in 2016. Second, the survey collected no individual data to avoid requiring ethical agreements for each center and increase the participation rate, which prevented us from assessing the relationship between individual characteristics and identifying specific tumor types for which protons were used as boost irradiation or re-irradiation.

Nonetheless, the survey highlights important considerations for patient care. First, evidence suggests that pediatric proton therapy is still concentrated among relatively few centers, which has implications for training and workforce expertise distribution. Second, proton therapy represents a sizable financial investment. In planning a facility, design and staffing should incorporate age-specific considerations encompassing anesthesia, play therapists, and pediatric nursing, since it is likely children will represent a non-negligible proportion of their patient base. Third, during the continuing expansion of proton therapy use worldwide, pediatric medical and radiation oncologists need means for cooperation to share experience and expertise. The Pediatric Proton Consortium Registry presents one platform for this sharing but it is constrained by financial limitations and is currently only active in the U.S. [18]. Across oncology, pediatric solid tumors are rare. Collaboration on an international scale is necessary to improve evidence on the long-term benefits of protons compared to conformal photon therapy, both in terms of tumor control and long-term toxicities [9,19]. While access to proton therapy remains limited in most countries, for the more consensual indications but especially for the many indications that remain debated, now is the ideal time to launch international collaborations to provide a high level of evidence (provided that methods and duration of follow-up are adequate) by comparing patient groups with similar clinical characteristics. Unfortunately, the current regulatory climate makes multi-site, multi-national research collaboration on clinical pediatric studies a challenge. Moreover, funding to coordinate high-quality, long-term clinical outcome studies needed for a comparative analysis of proton therapy has typically been viewed as low-priority in North America, Europe, and Asia. Until clinical evidence on long-term outcomes of proton therapy is available, decisions to refer pediatric patients to this treatment modality will continue to be based on dosimetric model comparisons, single institution experience, and/or expert recommendation, without a full knowledge on the possible late effects.

In conclusion, approximately 2000 to 2500 patients <22 years of age were treated with protons worldwide in 2016, mainly CNS tumors and axial sarcomas managed with curative intent but there was a wide variety of pediatric tumor types treated. Despite the limited data on late effects quantifying the value of protons compared to modern photon therapy techniques in pediatrics, a high consensus was observed across centers to consider rhabdomyosarcoma, medulloblastoma, ependymoma, low-grade glioma, craniopharyngioma, intracranial germ-cell tumor, neuroblastoma and Ewing sarcoma as clinical indications for proton therapy, but only mild to low agreement remains for other tumor types. While the numbers of proton centers and clinical indications, especially for extra-cranial tumors, are rapidly increasing worldwide, there is urgent need and current opportunities to build international,

observational studies on the late effects of protons and photons in pediatric patients. Assessing the long-term outcomes of proton therapy as well as of modern conformal photon techniques for tumor types that are currently considered both standard and non-standard indications for one or another technique in pediatrics is needed to provide evidence-based guidelines on which to base future treatment recommendations.

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Declaration of interest

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Appendix A. Supplementary data

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