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Original Article

The organization of care in pediatric radiotherapy across SIOP Europe affiliated centers: A multicenter survey in the framework of the 'Joint Action on Rare Cancers' project

Geert O. Janssens [a,b,*], Beate Timmermann [c], Anne Laprie [d], Henry Mandeville [e], Laetitia Padovani [f], Cyrus Chargari [g], Pamela Kearns [h], Olga Kozhaeva [i], Leila Kameric [j], Anita Kienesberger [j], Peter S.N. van Rossum [a], Tom Boterberg [k,l], Yolande Lievens [k], Gilles Vassal [m]

[a] Department of Radiation Oncology, University Medical Center, Utrecht, the Netherlands
[b] Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands
[c] Department of Particle Therapy, University Hospital Essen, West German Proton Therapy Centre Essen (WPE), West German Cancer Center (WTZ), German Cancer Consortium (DKTK), Germany
[d] Department of Radiation Oncology, Oncopole Claudius Regaud at Institut Universitaire du Cancer de Toulouse IUCT-Oncopole, Toulouse, France
[e] The Royal Marsden Hospital and Institute of Cancer Research, Sutton, United Kingdom
[f] Aix-Marseille University, Oncology-Radiotherapy-Department, CRCM Inserm UMR1068, CNRSUMR7258 AMUUM105, Assistance Publique des Hôpitaux de Marseille, Marseille, France
[g] Department of Radiation Oncology, Gustave Roussy Cancer Campus, Villejuif, France
[h] Cancer Research UK Clinical Trials Unit, National Institute for Health Research Birmingham Biomedical Research Centre, Institute of Cancer and Genomic Sciences, University of Birmingham, B15 2TT, Birmingham, United Kingdom
[i] Policy Department, European Society for Pediatric Oncology, SIOP Europe, Brussels, Belgium
[j] Childhood Cancer International - Europe, Vienna, Austria
[k] Department of Radiation Oncology, Ghent University Hospital and Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium
[l] Particle Therapy Interuniversity Center Leuven (PARTICLE), Leuven, Belgium
[m] Department of Children and Adolescent Oncology, Gustave Roussy Comprehensive Cancer Center, Paris-Saclay University, Villejuif, France

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ABSTRACT

Background/purpose: To reduce inequalities among SIOPE-affiliated countries, standard and optional levels to deliver 'Good Clinical Practice' compliant treatment in pediatric radiation oncology have been published. The aim of this project was to map the availability of pediatric radiotherapy resources across SIOPE-affiliated radiotherapy departments.

Materials/methods: An online survey with 34 questions was distributed to 246 radiotherapy departments across 35 SIOPE-affiliated countries. In addition to demographic data, 15 general items related to the organization of the radiotherapy process, and 10 radiotherapy-specific items were defined. For each of the 25 items, sum scores were calculated per center and country. Mann-Whitney U tests were used to analyze associations.

Results: Between March-June 2019, 121 departments (49 %) out of 31 countries (89 %) completed the survey. At center level, involvement of core disciplines in tumor boards (28 %), and integration of dedicated pediatric radiation therapy technologists (24 %) are limited, while rare & complex brachytherapy procedures are performed in many centers (23 %). For general and radiotherapy-specific items respectively, a relevant variation of sum scores was observed across countries ($\Delta_{general}$: ≤10 points; $\Delta_{RT\_specific}$: ≤5 points) and among centers within a country ($\Delta_{general}$: ≤9 points; $\Delta_{RT\_specific}$: ≤6 points). Sum scores for general and radiotherapy-specific items were higher in countries with a high-income ($p < 0.01$) and higher health development index ($p < 0.01$). A larger annual number of irradiated pediatric patients was associated with higher sum scores for general items ($p < 0.01$).

* Corresponding author at: Department of Radiation Oncology, University Medical Center Utrecht and Princess Maxima Center for Pediatric Oncology, Utrecht, the Netherlands.
E-mail address: g.o.r.janssens@umcutrecht.nl (G.O. Janssens).

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Conclusion: This survey demonstrates the disparities in organization of pediatric radiotherapy departments between SIOPE-affiliated countries and centers within the same country. Investment is needed to reduce inequalities in pediatric radiotherapy care.

Introduction

Despite the increased cure rates for pediatric cancers, a significant discrepancy exists in outcomes across Europe. Due to a lack of access to essential and modern components of the multidisciplinary treatment spectrum, disparities in survival rates of more than 20 % as well as in late side-effects are a reality [1–4]. To reduce these inequalities, 'European Standards of Care for Children with Cancer' have been defined, consolidating the ideal requirements for pediatric cancer units across the 'Société Internationale d'Oncologie Pédiatrique' (SIOP) Europe (SIOPE) affiliated countries [5]. These efforts have resulted in statements on the access to essential medicines, a multi-stakeholder group 'ACCELERATE' to advance investigation of new drugs, and the radiotherapy project 'QUARTET'. QUARTET is a centralized quality assurance program designed to standardize care and improve the quality of radiotherapy and imaging in international clinical trials [6–8].

In current protocols, radiotherapy is an essential treatment component, being used in roughly one third of the pediatric patients [9]. While radiotherapy for children often used a standard-treatment-for-all approach in the past, nowadays it is becoming more complex using risk-adapted strategies, the introduction of new radiotherapy modalities, a variety of radiotherapy techniques, integration of normal tissue constraints, expanding knowledge of molecular biology, and the combination of radiotherapy with new drugs. Additional capital investments and training of personnel related to these innovations potentially enhance the risk of disparities in treatment delivery between countries and between centers within the same country. For this reason, radiation, and pediatric oncologists together with the strategic partners of SIOPE recently defined 'standard' and 'optional' levels to offer Good Clinical Practice (GCP) compliant treatments in pediatric radiation oncology [10]. Within this 'Joint Action on Rare Cancers' (JARC) project, supported by the European Union and its member states, a list of items has been developed focusing on patient care, education and training, and the organization of patient-related research. In addition, more than 240 pediatric radiotherapy departments with at least one representative radiation oncologist across 35 SIOPE-affiliated countries have been mapped (https://siope.eu/about-siope/members/).

For a better understanding of the strengths and weaknesses of pediatric radiotherapy practice across the SIOPE-affiliated countries, an online survey was sent out to the pediatric radiation oncologists. The aim of the current project was to map the availability of radiotherapy resources for treating children with cancer across SIOPE that can serve as a reference for clinicians, patients, and policymakers to reduce inequalities.

Materials and methods

Between March and June 2019, a digital survey was distributed by email to (pediatric) radiation oncologists working at 246 centers across 35 SIOPE-affiliated countries. The centers were mapped in a previous part of the JARC project [10].

To document the organization of care in pediatric radiotherapy, an online survey with 34 questions and sub-questions was designed with SurveyMonkey (SurveyMonkey Inc., San Mateo, California, USA). The survey included multiple-choice, dichotomous, and open-ended questions defined by a group of expert pediatric radiation oncologists after consensual agreement and focused on daily activities related to patient care (i.e., tumor board, consultation, treatment preparation, treatment delivery, and follow-up after radiotherapy), education and training, plus research, in addition to general questions [**Supplementary file 1**]. Per center, only 1 response was required and accepted.

For data processing all questions were analyzed. However, items which turned out to be of little relevance for the quality of the organization of care were not analyzed (e.g., *Question: who prepares the child for radiotherapy? Answer: (a) parents, (b) play specialists, (c) nurses, (d) radiation therapy technologists, …*), as well as answers representing an individual opinion/situation which is not representative for the group or the department (e.g., *the level of education of the respondent*). In addition to the demographic data, 15 general items related to the organization of the radiotherapy process, and 10 radiotherapy-specific items focusing on the technical aspects were included in the final analysis.

The **general items** included: participation in, frequency and composition of tumor boards, a child-friendly environment within the radiotherapy department, the presence of educational or information tools to prepare children for radiotherapy, the availability of the radiation oncologists in case of an emergency or any urgent question, easy access to anesthesiology for treatment preparation and/or delivery, referral options for fertility preservation when indicated in the context of radiotherapy, dedicated pediatric radiation therapy technologists, the organization and involvement in late-effect outpatient clinics, access to recent pediatric radiotherapy protocols, participation in prospective clinical trials in pediatric oncology, and registration of radiotherapy and outcome data **[Supplementary file 2]**.

The evaluated **radiotherapy-specific** items included: the use of head & neck and/or body fixation when indicated, availability of 3D-treatment planning and 4D imaging, the use of intensity-modulated radiotherapy (IMRT) and stereotactic radiosurgery (SRS) when indicated, the application of cone-beam CT-scans and online position verification, as well as local access to brachytherapy and proton therapy **[Supplementary file 3]**. Per general or radiotherapy-specific item fulfilled, one point was awarded.

Sum scores were calculated for each of the 25 items and represent the proportion of responding centers meeting an item. In addition, sum scores (median and distribution) were calculated per country for both general and radiotherapy-specific items.

Mann-Whitney-U tests were used to analyze associations between the sum scores per center and socio-economic determinants of the country like the Gross National Income (GNI in 2019; scores available in 2020; https://data.oecd.org/natincome/gross-national-income.htm), Human Development Index (HDI in 2019; scores available in 2021; https://hdr.undp.org/data-center/human-development-index#/indicies/HDI), the presence of a comprehensive pediatric cancer center (defined as a hospital offering all medical disciplines for the treatment of pediatric cancer), and the number of pediatric patients treated within a radiotherapy department on annual basis. A p-value < 0.05 was considered statistically significant.

Results

Responses from 121/246 (49 %) pediatric radiotherapy departments out of 31/35 (89 %) SIOPE-affiliated countries were received. Fig. 1 demonstrates the distribution of the pediatric radiotherapy centers, including the annual number of pediatric patients irradiated per responding center. In 90/121 (74 %) participating centers, pediatric radiotherapy was integrated in a comprehensive pediatric cancer center (defined as a hospital offering all medical disciplines for the treatment of pediatric cancer). While 12/121 (10 %) of the responding centers treat >100 patients per year with radiotherapy, 61/121 (50 %) irradiate ≤ 25 cases **[Fig. 2]**.

General items, per center

As demonstrated in Fig. 3**A**, the majority (over 80 %) of the responding centers scored well on access to pediatric radiotherapy protocols, availability of anesthesia without treatment delay, referral for fertility options when indicated for radiotherapy, availability in case of emergencies, and the participation in tumor boards. However, a minority (less than 50 %) of the participating centers had radiation oncologists involved in the late effect outpatient clinics, had tumor boards involving all core disciplines (defined as pediatric oncologists, radiation oncologists, surgeons, neurosurgeons, imaging specialists, pathologists), or had dedicated pediatric radiation therapy technologists for the pediatric workflow.

Radiotherapy-specific items, per center

Fig. 3**B** demonstrates that all responding centers applied 3D radiotherapy and used head & neck fixation, when indicated. More than 90 % of the centers used cone-beam CT-scanning, which was combined with online position verification in 71 % of the centers. Advanced photon therapy techniques (IMRT) were available in 75 % of the centers. At the time of the survey, 18/121 (15 %) centers were linked to a proton therapy center while 28/121 (23 %) centers applied brachytherapy in selected pediatric cases.

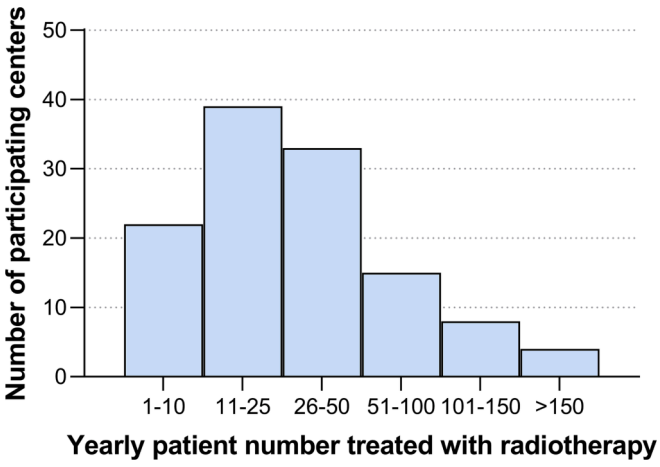

Fig. 2. Histogram with the yearly number of pediatric patients treated with radiotherapy per center in relation to the number of participating centers.

General and radiotherapy specific items, per country

The median sum scores per country for both general and radiotherapy-specific items is shown in Fig. 4. On a national level, a relevant variation (defined as: $\Delta \geq 5$ points) in sum scores for general

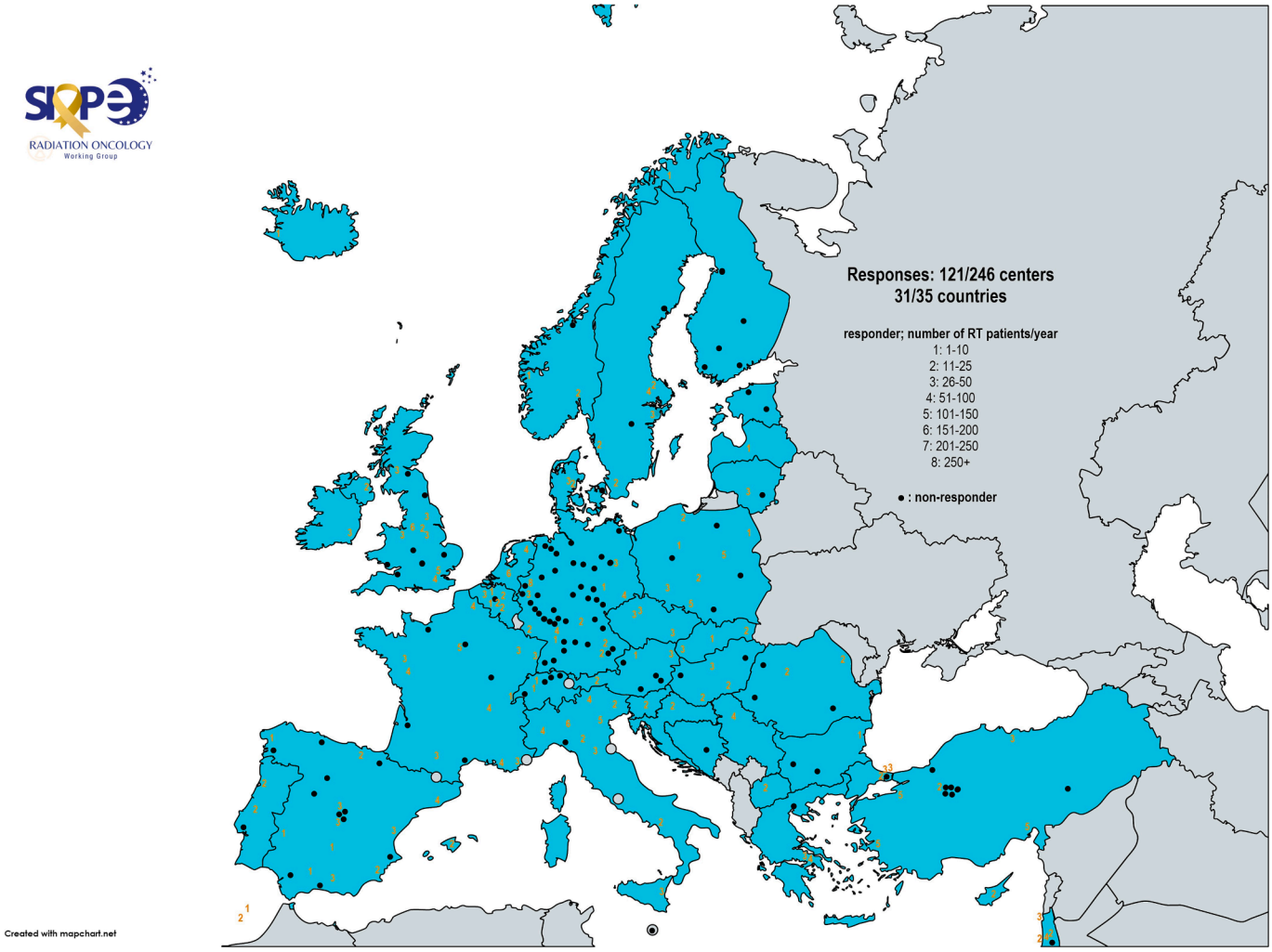

Fig. 1. The map of greater Europe with the distribution of the pediatric radiotherapy centers across SIOPE (numbers + dots), including the annual number of pediatric patients irradiated per responding center.

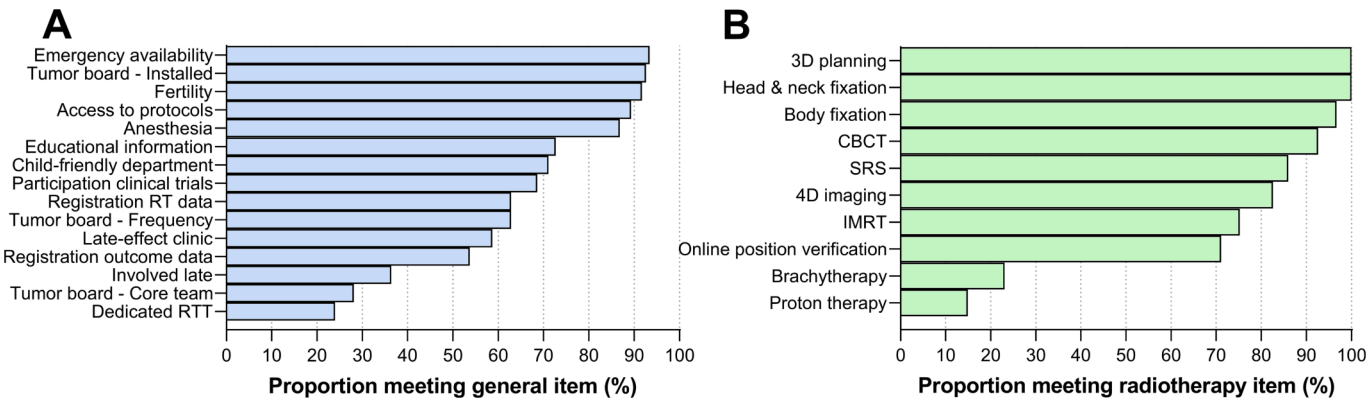

Fig. 3. Histogram with the proportion of centers meeting general (3A) and radiotherapy specific items (3B).

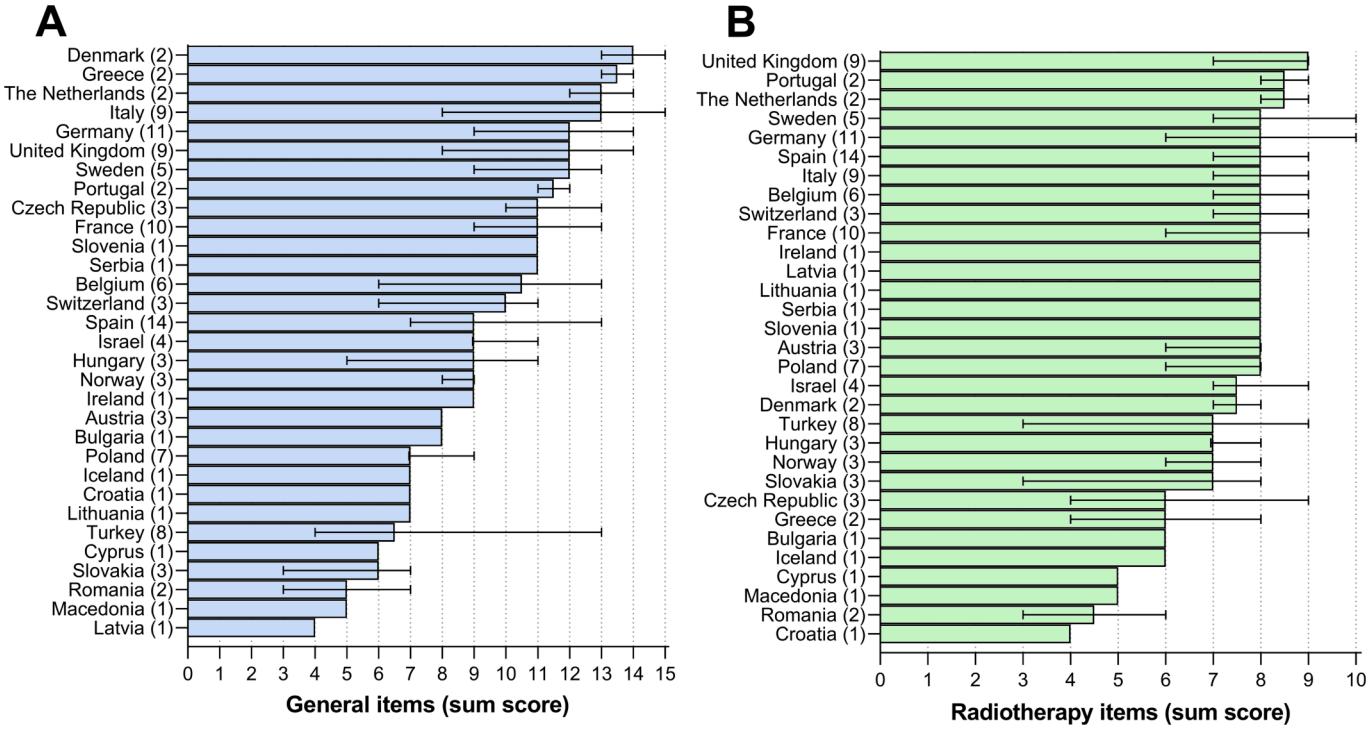

Fig. 4. Histogram ranking countries, including spread in between the national centers, based on the sum core for general (4A) and radiotherapy specific items (4B).

items was observed across centers within Turkey (Δ: 9 points); Belgium, and Italy (Δ: 7 points); Hungary, Spain, and the United Kingdom (Δ: 6 points); Germany, and Switzerland (Δ: 5 points). For radiotherapy-specific items a relevant variation was observed for radiotherapy departments within Turkey (Δ: 6 points); Slovakia, and the Czech Republic (Δ: 5 points).

Associations between demographics and sum scores per center

For both general and radiotherapy-specific items, radiotherapy departments located in high-income countries based on Gross National Income (108/121 centers), or countries with a Human Development Index ≥ 0.900 (78/121 centers) scored significantly better compared to upper-middle income countries or countries with HDI scores below 0.900 **[**Table 1**;** Fig. 5**]**. Also, a higher annual number of patients treated within a radiotherapy department was associated with better sum scores for general items but not for radiotherapy-specific items **[**Table 1**]**.

Discussion

This survey, performed in the context of the European Union 'Joint Action on Rare Cancers' project, maps the availability of pediatric radiotherapy resources across 121 centers in 31 of 35 SIOPE- affiliated countries. Differences in scores related to the quality of organization and access to modern radiotherapy tools are observed between countries but also among centers within the same country. For general items, radiotherapy departments treating a larger number of pediatric patients scored better. Centers located in upper-middle income countries or in countries with a lower human development index had a worse score for items related to the general as to the radiotherapy-specific organization of care.

Concerning the general items, over 85 % of the radiotherapy departments have access to anesthesia and pediatric protocols and can refer patients for radiotherapy-related fertility issues. Although tumor boards are implemented in over 90 % of the centers, a weekly frequency of meetings as well as the involvement of a core team of medical specialists are missing in over 70 % of centers. To further improve the scores

Table 1
Univariable associations between demographics and sum scores per center.

Demographic	n	General items (sum score)		Radiotherapy items (sum score)	
		Median [range]	*p* value	Median [range]	*p* value
GNI per capita, 2019			0.001*		0.001*
Upper-middle income	13	7.0 [3.0–13.0]		6.0 [3.0–9.0]	
High income	108	11.0 [3.0–15.0]		8.0 [3.0–9.0]	
Human Development Index (HDI), 2019			< 0.001*		0.006*
< 0.900	43	8.0 [3.0–15.0]		7.0 [3.0–9.0]	
≥ 0.900	78	11.0 [6.0–15.0]		8.0 [4.0–10.0]	
Comprehensive paediatric cancer centre			0.128		0.180
No	31	9.0 [3.0–14.0]		8.0 [4.0–9.0]	
Yes	90	11.0 [3.0–15.0]		8.0 [3.0–10.0]	
Yearly number of radiotherapy patients			< 0.001*		0.630
1–10	22	8.0 [3.0–13.0]		7.0 [3.0–9.0]	
11–25	39	9.0 [5.0–14.0]		8.0 [3.0–9.0]	
26–50	33	11.0 [5.0–15.0]		8.0 [4.0–10.0]	
51–100	15	12.0 [8.0–15.0]		8.0 [4.0–10.0]	
> 100	12	13.0 [4.0–14.0]		8.0 [3.0–10.0]	

* Statistically significant difference between groups ($p < 0.05$).

related to the general items, registration of radiotherapy data and outcome should be encouraged on a local and a national level. On a European level, standard clinical practice guidelines are under development within the context of the 'European Reference Network on Paediatric Cancer' (ERN/PaedCan) (https://paedcan.ern-net.eu/the-escp-project/) in collaboration with SIOPE [11]. In addition, educational information about radiotherapy for childhood cancer has become available via the SIOPE website and will be translated in multiple languages (https://siope.eu/Radiotherapy-for-Childhood-Cancer).

On a technical level, it is encouraging to see that 3D treatment planning and, on indication also head & neck fixation, is applied in all centers. Also, the use of cone-beam CT-scans and online position verification is already available in more than 70 % of the responding institutes, offering the opportunity to apply high-precision treatments with smaller margins towards the surrounding normal tissues. With a growing proton therapy capacity across SIOPE affiliated countries, the number of pediatric patients irradiated with protons is increasing annually but still varies between countries depending on the capacity and the ability to refer across different countries [https://ptcog.site/index.php/facilities-in-operation-public;[12]] For technical and logistical reasons, most children are still irradiated with photon therapy. Also, for this reason, within the photon therapy departments efforts should be undertaken to introduce intensity modulated arc therapy (IMAT) to further reduce the high-dose volumes in pediatric patients and exploit the benefits of modern radiotherapy delineation guidelines [13,14]. Since a clear association is observed between lower sum scores and centers located in countries with a lower GNI per capita or HDI, steering committee members from the SIOPE Radiation Oncology Working Group together with representative radiation oncologists of these countries are investigating the individual situation and needs among centers and countries. This should result in a report that can serve as a basis to negotiate missing general and/or radiotherapy-related items at institutional or national level.

Fifty percent of the responding centers irradiate less than 25 pediatric patients annually while 20 % treat between 1 and 10 patients only. The correlation between a smaller number of pediatric patients irradiated per center and a lower chance of reaching the general quality items for pediatric radiotherapy is demonstrated in the current survey. Although this survey is neither designed nor intended to demonstrate a correlation between the annual number of patients irradiated per center and outcome in survival or late toxicity, the question arises whether the same quality of care can be offered below a certain threshold [15]. For this reason, in France for example, a threshold of 12 patients per year under the age of 16 years, excluding total body irradiation and palliative treatments, has been defined by the French National Cancer Institute (INCa) leading to centralization of pediatric radiation oncology in 15 reference centers among 29 centers of pediatric oncology [16].

Historically, radiotherapy for children was mainly delivered using very simple techniques like parallel opposed fields. Nowadays, radiation oncologists are offered an increasing availability of new modalities, techniques, treatment modifications, and an increasing knowledge of late effects of radiotherapy on normal organ structure and function. These added complexities for pediatric tumors combined with a better need for the understanding of the molecular biology may further increase the already demonstrated disparities in survival and side-effects in between countries, and by extrapolation also between large and small departments within the same country [3,4]. Recently, pretreatment central radiotherapy quality control performed in Germany for non-metastatic medulloblastoma patients participating in the SIOP PNET-5 trial, demonstrated that unacceptable treatment plans for craniospinal irradiation were negatively correlated to the number of patients enrolled per institution with a cut-off of five patients [17]. Earlier, a strong correlation between the number of major target volume deviations and the risk of tumor relapse was observed in a French study with 174 medulloblastoma patients [18]. In line with the Children's Oncology Group in the United States, SIOPE introduced QUARTET in 2016, which combines the pediatric radiation oncology expertise of SIOPE with the infrastructure and experience of the European Organization for Research and Treatment of Cancer (EORTC) to deliver radiotherapy quality assurance programs for international clinical trials that include radiotherapy [8,19]. Prospective review of target volume delineation and treatment plans before onset of treatment should tackle the unacceptable deviations and reduce the risk of systematic and/or incidental errors for patients treated in clinical trials. Also, the real-time review ensures that the quality of radiotherapy meets the study objectives, and the analysis of trial outcome is credible. In addition, the QUARTET platform helps to reduce the administrative and logistical burdens of implementing national RTQA programs, promoting equal access to expertise across SIOPE-affiliated countries.

A highly selected group of pediatric patients, particularly rhabdomyosarcomas of the urogenital and head & neck area, can benefit from the ballistic advantages of brachytherapy compared to modern photon or proton therapy [20,21]. In this survey 28/121 centers offered brachytherapy. Given the large number of centers performing this approach, the rarity of good candidates, and the complexity of combining special surgical techniques with interstitial procedures, a recent survey was undertaken by the SIOPE Radiation Oncology Working Group aiming to map the indications, the estimated annual numbers, as well as the available techniques and the origin of patients per center [Janssens, *unpublished data*]. This survey demonstrates that

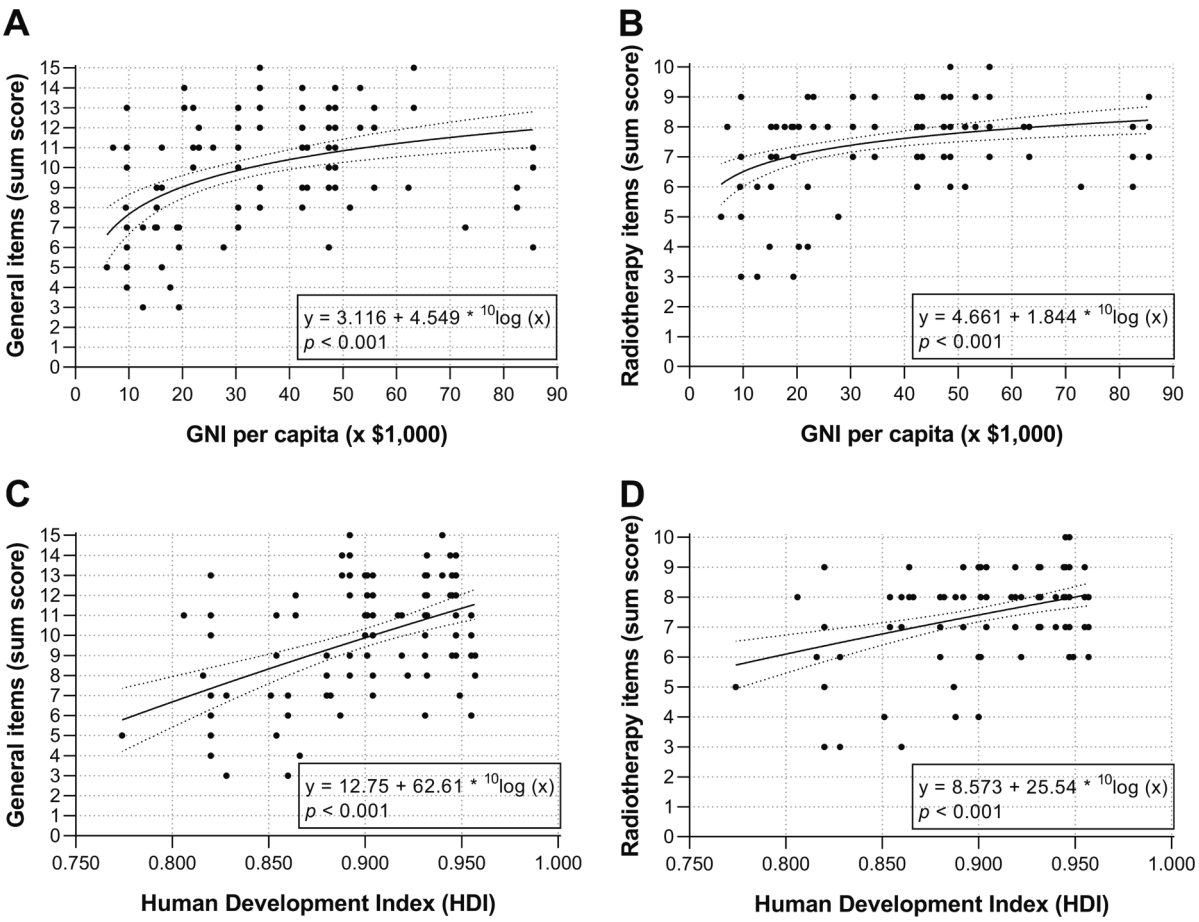

Fig. 5. Scatter plots demonstrating the relationship between responding centers (dots) located in high-income countries (based on Gross National Income per capita) or a higher Human Development Index (HDI $\geq$ 0.900) and the superior sum score for general (5A/C) and radiotherapy specific items (5B/D).

most of the centers apply brachytherapy for indications in the head & neck or urogenital region. Altogether, the respondents perform brachytherapy in an estimated number of 60–70 pediatric patients annually, often referred internationally. The survey also revealed that respondents are not well informed about the potential indications for brachytherapy. To improve awareness of the potential indications for pediatric brachytherapy, experts involved in this survey endorse the importance of a certain degree of centralization of brachytherapy across SIOPE-affiliated countries. In the meantime, Chargari et al. recently demonstrated high local control rates with acceptable late severe complication probabilities and the feasibility of an international brachytherapy referral network for selected pediatric tumors, mainly of the urogenital region [21].

This survey has a few limitations. First, although 121/246 centers across 31 out of 35 SIOPE-affiliated countries participated in the survey and all the major radiotherapy departments responded, the potential bias on the results due to the missing data from the 50 % non-responding centers is unclear. In our opinion, the observed association between income level, HDI, volume and score would likely still hold if the missing data were added, which would include more low-volume centers and centers from non-high-income countries. Secondly, the ongoing implementation of new technologies in radiotherapy and the associated radiotherapy items collected in this analysis potentially underestimates the current situation per center and per country in 2023. Radiotherapy is evolving in a continuous manner, hence each analysis will de facto only provide data of a certain time point, urging for frequent reappraisal. However, we are more concerned about the large number of centers performing the rare and highly complex brachytherapy procedures and, the fact that patients who benefit most from proton therapy often cannot be referred. In addition, a major part of the survey is not focused on technology but on the organization of care. Creating awareness of organizing weekly tumor boards with all core disciplines present is an important message.

In conclusion, this survey offers a unique insight in the level of organization of the radiotherapy departments treating pediatric patients across SIOPE-affiliated countries and confirms the disparities between countries but also among centers within the same country. SIOPE recommendations combined with local implementation of new techniques and technologies should help to decrease disparities among the affiliated countries. However, this will be a progressive endeavor, resulting in a continuously changing - and improving - landscape. Therefore, there will be the need to repeat the survey at regular basis to keep track of the organizational progress made within the field of pediatric radiation oncology.

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CRediT authorship contribution statement

Geert O. Janssens: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **Beate Timmermann:** Validation, Writing – review & editing. **Anne Laprie:** Validation, Writing – review & editing. **Henry Mandeville:** Writing – review & editing. **Laetitia Padovani:** Writing – review & editing. **Cyrus**

Chargari: Writing – review & editing. **Pamela Kearns:** Writing – review & editing. **Olga Kozhaeva:** Data curation, Writing – review & editing. **Leila Kameric:** Writing – review & editing. **Anita Kienesberger:** Writing – review & editing. **Peter S.N. van Rossum:** Formal analysis, Writing – review & editing. **Tom Boterberg:** Validation, Writing – review & editing. **Yolande Lievens:** Validation, Writing – review & editing. **Gilles Vassal:** Conceptualization, Funding acquisition, Validation, 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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2023.110075.

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