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Original Research

Radiotherapy practice for paediatric brain tumours across Europe and quality assurance initiatives: Current situation, international survey and future perspectives

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Abstract ***Aim:*** The aim of the study is to analyse radiotherapy quality assurance (RTQA) processes in the treatment of paediatric central nervous system (CNS) tumours across Europe. ***Methods:*** The RTQA aspects of major past and current European trials for paediatric CNS tumours were reviewed based on study protocols and publications. A survey among radiation oncologists and paediatric oncologists about the practices of RTQA in paediatric CNS tumours across European countries was also performed.
Results: Several (inter)national initiatives to implement RTQA are being developed across Europe, with an apparent paradigm shift from retrospective to prospective RTQA. Experts from 21 of 29 contacted countries responded to the survey. National consensus guidelines for paediatric CNS tumours are available in 10 of 21 countries. Twenty-one of 33 experts

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believe that the level of involvement of paediatric radiation oncologists in the meetings and activities of the national paediatric oncology societies is adequate. Central storage of radiotherapy data is available in France, Germany and Denmark. RTQA programmes for paediatric brain tumours are available in 7 countries. Twelve of 21 experts believe that there is a well-established national referral network for the radiation treatment of paediatric patients in their respective countries.

Conclusion: As a result of the review and survey, the following measures are proposed: (1) developing international RT guidelines for paediatric CNS tumours, (2) improving the collaboration between paediatric oncologists and paediatric radiation oncologists, (3) building a central storage system for RT data, (4) implementing international prospective RTQA platforms and (5) promoting European referral networks to reduce inequality.

1. Introduction

The improved survival rates of paediatric patients with central nervous system (CNS) tumours over recent decades are accompanied by a growing concern about long-term sequelae and the quality of life of the survivors [1]. Radiotherapy (RT) continues to be a cornerstone in the curative treatment of paediatric brain tumours, next to surgery and to a somewhat lesser extent chemotherapy. However, the potential severe long-term sequelae of CNS irradiation are well known [2]. Improved diagnostic imaging and more advanced RT techniques and equipment, for example, intensity-modulated RT and particle therapy, are tackling this issue, at the price of growing complexity and the need for highly specialised centres [3,4]. Through increasingly conformal RT, the dose is better targeted to the tumour, minimising the dose to normal brain structures outside the planning target volume and hence reducing the risk of long-term side-effects [5].

A clear description of the RT procedures, including equipment, patient positioning and simulation, volume selection and definitions, dose–volume constraints, treatment planning and verification, is needed to achieve treatment compliance and uniformity between institutions. In this complex technical setting, quality assurance (QA) programmes are essential because data demonstrate that deviations in RT can result in increased morbidity and mortality [6,7].

The implementation of radiotherapy quality assurance (RTQA) systems is, however, far from universally achieved. Defining accurately the current practices of radiation oncologists and the existing RT resources at a supranational level is a major challenge. Lievens *et al.* recently drew an accurate picture in adult oncology, but not without difficulty and only in the frame of a long-term cooperative project (Health Economics in Radiation Oncology [HERO]) [8,9]. A similar paediatric-specific project is currently being carried out by Demoor-Goldschmidt *et al.* [10], with the first results highlighting the difficulties in obtaining accurate and complete data.

To analyse RTQA processes in the treatment of paediatric CNS tumours in Europe, we reviewed the RTQA aspects of past and current European collaborative trials, and we performed an international survey of radiation and paediatric oncologists on RTQA practices in Europe.

2. Past and present

2.1. Status of RTQA in paediatric CNS tumours in Europe

2.1.1. Materials and methods

A literature review to assess and summarise the current situation of RTQA in paediatric brain tumours across Europe was performed. In addition, RTQA aspects of relevant trials in the available study protocols and publications were reviewed, and the European Organisation for Research and Treatment of Cancer (EORTC) RTQA levels were assessed [11]. Since 2006, RTQA requirements for sites participating in EORTC trials have been classified into five different levels. General credentialing (level 1) helps to ensure delivery of RT of minimum acceptable quality across all sites and consists of a facility questionnaire and external reference dosimetry audit. Protocol-specific institutional tests (levels 2–5) help verify that external beam RT planning and delivery is congruent with the study guidelines: level 2 includes dummy runs; level 3, limited individual case review; level 4, extensive individual case review and level 5, complex dosimetry checks.

2.1.2. Results

A paradigm shift from retrospective to prospective RTQA is observed over recent years. Although in older studies, if any QA was performed at all, retrospective assessments were the norm [7,12,13], the more recent trials for paediatric brain tumours predominantly

Table 1
RTQA aspects in recent clinical trial protocols for paediatric CNS tumours.

Clinical trial	Study start	Study end	Tumour type	RTQA	Level of control	Retrospective vs prospective	EORTC RTQA level	Required compliance	Publication of RTQA aspects	Conclusion(s) of RTQA publication
Completed trials										
HIT-SIOP PNET-3 [12,14]	March 1992	January 2000	MB (M0-M1)	Yes	International	Retrospective	Level 3	UNK	Separately from the primary publication (1 year later)	RT duration (<50 days) impacts EFS
HIT-SIOP PNET-4 [15,16]	January 2001	December 2006	MB (SR)	Yes	National	Prospective for some national groups; retrospective (within 1 year) for all patients	Level 4	Mandatory for CSI; Optional for posterior fossa/ tumour bed	QA exercise (dummy run) before study opening (in some countries)	Ambiguities in draft protocol, areas of interclinician variability. Protocol revised and improved.
HART Milan [17]	1998	2007	MB (MTX)	Yes	Local (only one institution administering RT)	Retrospective	UNK (not specified)	NA	Within primary publication (not detailed)	'RT at the same institution following the local technical guidelines and quality control process'
French M-SFOP 98 [18]	December 1998	October 2001	MB (SR)	Yes	National	Prospective for CSI, retrospective for tumour bed boost	Level 4	Mandatory	Within primary publication (somewhat detailed) and following preexisting national guidelines	Prospective RT review is feasible and useful (no isolated frontal relapse occurred compared with seven in the previous report)
SFOP HR [19]	January 1993	June 1999	MB (HR)	Yes	National	Retrospective	Level 4	Mandatory	Within primary publication (somewhat detailed) and following preexisting national guidelines	EFS not statistically different for patients with no or one major deviation or for patients with more than one
LGG 2004 [20]	April 2004	April 2012	LGG	No[a]	National	Retrospective	None	Mandatory (not clearly specified)	No mention in primary publication	NA
SIOP CNS GCT II (NCT01424839)	October 2011	June 2018	IGCT	No[a]	National	Retrospective	None	Mandatory (not clearly specified)	NA	NA
Ongoing trials										
HIT-SIOP PNET-5 (NCT02066220)	June 2014	Open	MB (SR)	Yes	National + international	Prospective	Level 4	Mandatory for CSI, boost and any	NA	NA

								relapse		
SIOP-EP-II (NCT02265770)	April 2015	Open	EP	Yes	for countries participating in QUARTET National	Retrospective (within 4 months)	Level 4	Mandatory (although not clearly specified)	NA	NA

ATRT, atypical teratoid rhabdoid tumour; CNS, central nervous system; CSI, craniospinal irradiation; EFS, event-free survival; EORTC, European Organisation for Research and Treatment of Cancer; EP, ependymoma; HART, hyperfractionated accelerated radiotherapy; HR, high risk; IGCT, intracranial germ cell tumour; LGG, low grade glioma; MB, medulloblastoma; MTX, metastatic disease; NA, not applicable; QUARTET, QUAlity and excellence in RadioTherapy and imaging for children and adolescents with cancer across Europe in clinical Trials; RT, radiotherapy; RTQA, radiotherapy quality assurance; SR, standard risk; stPNET, supratentorial primitive neuroectodermal tumour; UNK, unknown.
Treatment strategies for infants are not included (as they do not include RT).
[a] Only data collection.

include prospective RTQA programmes (Table 1). An example of this paradigm shift is given by the HIT-SIOP PNET trials. In PNET-3, the RTQA review (EORTC RTQA level 3) was performed retrospectively and published one year after the trial's primary publication [12,14]. In PNET-4, however, RTQA was performed prospectively by some national groups and retrospectively within one year for all patients [15]. RTQA was considered mandatory to participate in the trial for craniospinal irradiation (CSI; EORTC RTQA level 4). Furthermore, a QA exercise (dummy run, level 2) was performed in the United Kingdom (UK) centres before the opening of PNET-4, in which ambiguities in the draft protocol and areas of interclinician variability in target volume delineation were found. Consequently, the protocol was revised and improved before the opening of the trial [16]. In the ongoing PNET-5 trial (NCT02066220), an amendment has been submitted to have RTQA performed prospectively and mandatory for both CSI and the boost.

These examples of RTQA, although effective in the clinical trial setting, leave patients treated outside that context ('real-world' patients) behind. There is guidance in some countries which recommends that RT target volume and organ at risk delineation should not be left to one individual but should be peer-reviewed by an experienced colleague before planning and treatment [21]. There is also specific paediatric guidance in this regard [22].

Problems may arise when single-centre treatment protocols or clinical trials carried out in few highly specialised centres are transferred to wider real-world settings [23]. One example of this was the generalisation of the hyperfractionated accelerated RT (HART)–intensive chemotherapy strategy [17] for metastatic medulloblastoma from a single institution in Milan to a wider international setting. The results (3-year overall survival [OS] of 56% [24]) were far below those of the original publication (3-year OS of 77%). One of the reasons given by the authors for not being able to replicate the original trial results was the differences in treatment delivery, which RTQA measures could have helped to reduce. Furthermore, severe cases of neurotoxicity, which were not reported in the original publication, were found in the UK cohort for complex, multifactorial reasons [25]. The reported cases of myelitis and other grade 3–4 CNS toxicities seemed to associate with the overlapping of the upper cervical spine within posterior fossa boost volumes in conjunction with neurotoxicity associated with thiotepa. As a result of these real-world studies, the HART-intensive chemotherapy strategy was abandoned in the UK and internationally [24,25].

More recently, a European platform for RTQA in paediatric oncology, named QUARTET (QUAlity and excellence in RadioTherapy and imaging for children and adolescents with cancer across Europe in clinical Trials), has been developed [26]. QUARTET will support the implementation of RTQA programmes in several trials

(e.g. SIOP PNET-5, SIOP-EP-II). Although currently it only includes patients participating in clinical trials, one of the aims of QUARTET is to eventually expand to patients treated outside trials as well [27].

2.2. Survey on practices across Europe of paediatric oncologists and radiation oncologists involved in the treatment of brain tumours

2.2.1. Materials and methods

One reference paediatric radiation oncologist and/or one reference paediatric oncologist of 29 countries (27 European countries plus Israel and Turkey) involved in the treatment of CNS tumours were contacted in February 2018 by email and invited to complete an online 12-item questionnaire (Supplementary Material 1). Possible participants were found through networking/suggestion by international leaders in the field.

The answers provided as 'free text' were used to reconcile conflicting responses between experts from the same country. If not possible, a distinction was made depending on the best suited expertise for each question: the reply of the radiation oncologists was given preference for questions 3, 4, 5, 8 and 9; the reply of the paediatric oncologists was given preference for questions 1, 2, 7 and 10 and questions 6, 11 and 12 did not require this distinction.

To compare the number of RT centres between countries, the total number was divided by the population of each country. Population data were obtained from the Central Bureau of Statistics for Israel and from Eurostat for the other countries [28,29].

2.2.2. Results

Forty-eight experts (20 radiation oncologists and 28 paediatric oncologists) from 29 countries were contacted; 33 experts responded: 18 of 20 (90%) radiation oncologists and 15 of 28 (54%) paediatric oncologists from 21 countries participated in the survey (Fig. 1). The outcome of the survey generated the following answers:

(Q1) The median number of centres per country treating paediatric patients with cancer is 6.2 (range 0.6–11.9) per 10 million inhabitants.
(Q2) The median number of centres treating paediatric patients with CNS tumours is 4.8 (range 0.6–11.9) per 10 million inhabitants.
(Q3) The number of RT departments that treat paediatric patients with CNS tumours varies across countries, with a median of 3.7 (range 0.6–10.7) per 10 million inhabitants (Fig. 2).
(Q4) There is a well-established referral network for the RT treatment of paediatric patients in 12 of 21 (57%) countries (Fig. 3).
(Q5) Four of 21 countries (France, Germany, the Netherlands, the UK) have a national paediatric RT society.
(Q6) Involvement of radiation oncologists in meetings of the respective national paediatric oncology societies is considered '(somewhat) sufficient' by 64% (21/33) of

Fig. 1. Participation according to country.

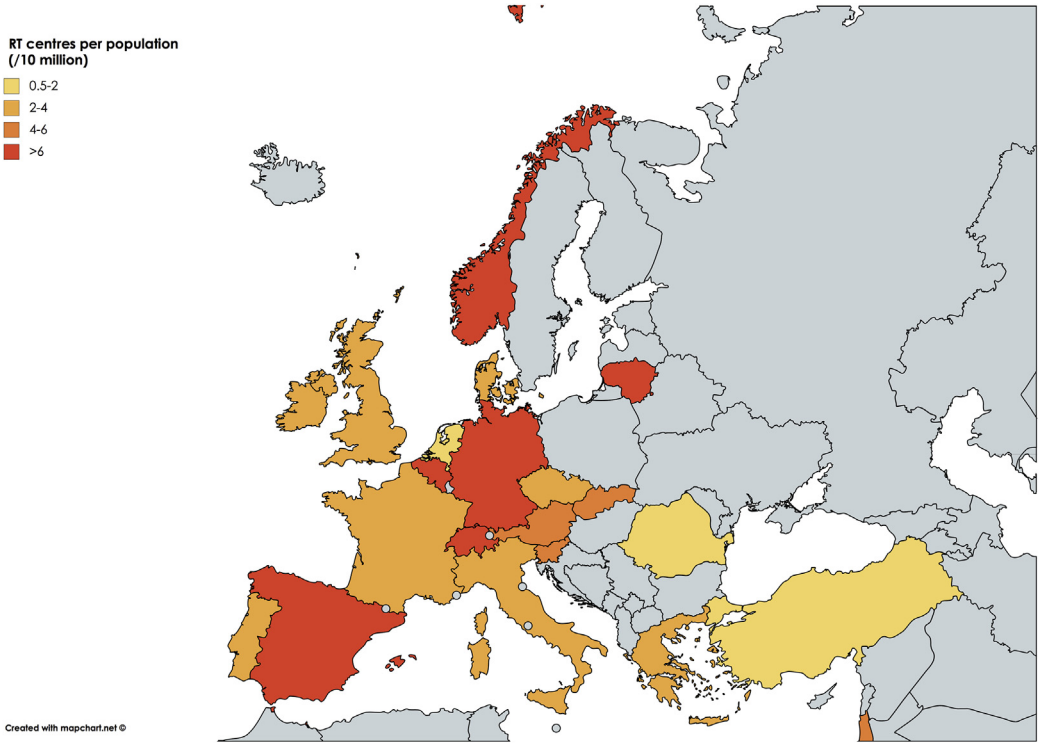

Fig. 2. Radiotherapy centres treating paediatric CNS tumours per country population (number per 10 million inhabitants). (Survey question #3). RT, radiotherapy.

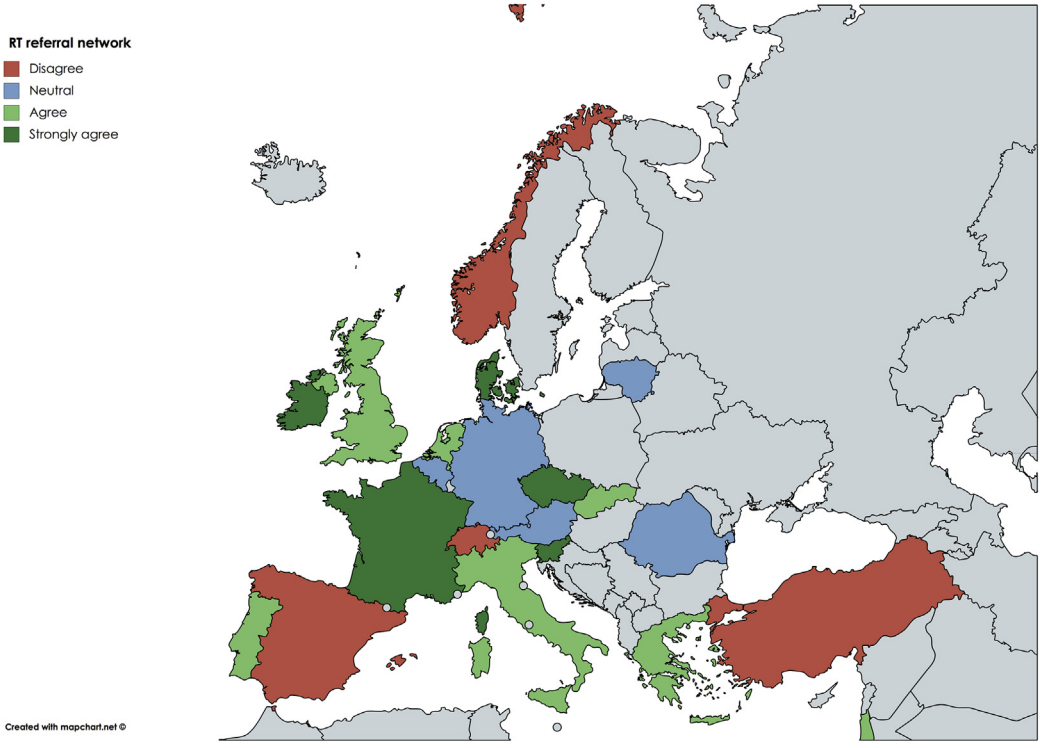

Fig. 3. Existence of a well-established national referral network for the radiotherapy treatment of paediatric patients: Map showing responses by country. (Survey question #4). Of note: In case of disagreement, the opinion of the radiation oncologist is highlighted in the map. No respondents 'strongly disagreed' with the statement.

participants, and '(somewhat) insufficient' by 30% (10/33) (Fig. 4). The proportion of participants considering the involvement 'insufficient' is higher among radiation oncologists (33%; 6/18) than among paediatric oncologists (7%; 1/15).

(Q7) National consensus guidelines for the treatment of paediatric CNS tumours exist in 48% (10/21) of the countries.

(Q8) National RTQA programmes for the treatment of paediatric CNS tumours are in place in 33% (7/21) of the participating European countries. These programmes are very heterogeneous, ranging from peer review of selected cases to well-established, comprehensive systems.

(Q9) Three countries (14%; 3/21) have a central storage system for RT data in place. In all of them (Denmark, France and Germany), the complete digital imaging and communications in medicine (DICOM)-RT plans are collected as part of the data.

(Q10) In all participating countries, paediatric patients with CNS tumours have access to a particle therapy facility, either nationally or abroad, and are supported by the public health system. In 8 of 21 countries, proton facilities are available within their own borders [30].

(Q11) Most participants (85%; 28/33) (strongly) agreed that all paediatric patients with CNS tumours are granted equal access to quality RT in their respective countries. Five respondents showed concerns that this might not be the case all over their country (Israel, Italy, Spain, Switzerland, Turkey) because of differences in geographical distribution and in the level of experience among RT centres.

(Q12) Nearly all (91%; 30/33) consulted experts believe that the patients would benefit to a considerable or to a great degree from a European RTQA guideline for paediatric brain tumours.

The full tabulated breakdowns of responses can be found in Supplementary Material 2.

3. Discussion: Future

The review and survey we have performed helped to identify the following areas of improvement.

3.1. Standardisation of treatment: guidelines

Clinical guidelines are an affordable and straightforward approach towards standardisation of treatments, especially for the management of rare diseases, such as paediatric malignancies. This is particularly important for patients treated outside clinical trials or for whom no clinical trials exist [31]. However, through our survey, we found out that only 48% of the participating countries have national consensus guidelines for the treatment of paediatric CNS tumours.

National and/or international guidelines can be a first step to unify strategies, facilitate QA and improve the management of children with CNS tumours. Participation in clinical trials remains a paramount treatment strategy in paediatric oncology, but still, guidelines are often needed for aspects not covered in clinical trials or time periods where these are not open.

Moreover, almost all (91%) consulted experts believe that the patients would benefit from a European RTQA guideline for paediatric brain tumours. There seems to be an increasing awareness of the necessity for a common effort across European CNS tumour specialists to ensure high-quality RT treatment. In that line, the European society of paediatric oncology (SIOPE) Brain Tumour Group has recently published a consensus guideline on craniospinal target volume delineation for high-precision RT, which has the potential to improve the consistency of craniospinal delineation [32].

Looking at similar experiences in adult oncology, several international, disease-specific RT guidelines exist for adult cancers, based on published level 1 or 2 evidence and/or expert consensus, detailing delineation and dose recommendations (e.g. for glioblastoma [33,34]). While level 1 or 2 evidence is not always available, especially in a paediatric and rare disease context, consensus is presumably reachable by the international neuro-oncology community. In parallel, regular audit procedures should be implemented at a local, national and international level to ensure the centres comply with the directives of the guidelines. This could raise the

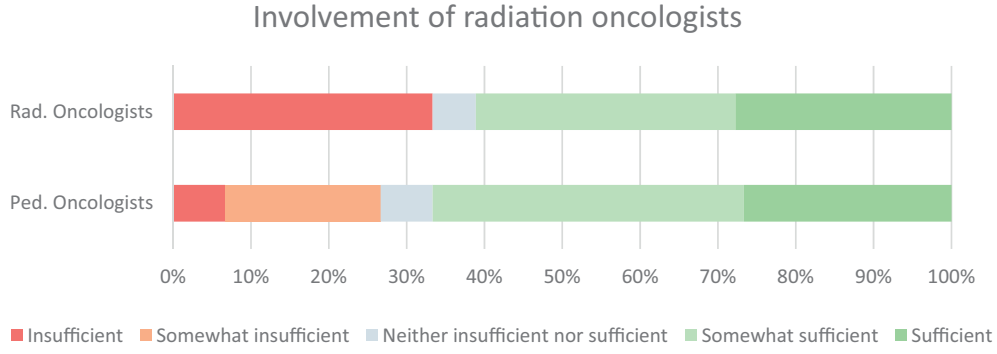

Fig. 4. Opinion about the level of involvement of paediatric radiation oncologists in the meetings and activities of their national paediatric oncology societies. (Survey question #6).

standards for RT treatment beyond clinical trial protocol provisions.

3.2. Multidisciplinary work: collaboration between paediatric specialists and professional organisations

The importance of multidisciplinary tumour boards for paediatric tumours has already been reported [35]. Beyond this, close collaboration between paediatric oncologists, neurosurgeons and radiation oncologists is critical for providing quality care and for enabling the development of new RTQA initiatives. However, about one-third (30%) of the consulted experts believe that the level of involvement of paediatric radiation oncologists in the meetings and activities of the national paediatric oncology societies is inadequate. In fact, the discontent seems higher among radiation oncologists, with 33% of them considering said involvement to be insufficient. These numbers leave room for improvement.

Only one-fifth (19%) of the participating countries have a national paediatric RT group. There is a need to involve all the paediatric radiation oncology groups or societies to share experiences and recommendations at a supranational level. This is particularly relevant in smaller countries, where the number of specialists is low, and it may not be practical or useful to have a national group. Recently, the SIOPE Radiotherapy Working Group has been created, which will benefit all national organisations.

One of the aspects that this new group could tackle is the training and certification of paediatric radiation oncologists. In the same line of pushing childhood CNS cancer care towards excellence, this remains an area of concern that could benefit from international agreement [22,36].

Although this goes beyond the European scope of this work, it is important to recognise the advanced status of QA practices in North America, with vast experience in central reviews, educational sessions, benchmarking of complex techniques and dummy runs, online planning atlases and so on [37–39]. Despite the differences with the European health system landscape, we ought to benefit from the North American experience and lessons learnt.

3.3. Central storage of RT data

An important step towards the implementation of RTQA systems is central storage of RT data, done in 3 of 21 European countries according to our survey (in the meantime, a fourth country—Belgium—has started central storage as well). An optimal storage should include the full planning and the final report, with the complete DICOM-RT plan and any auxiliary imaging used to define the target(s); all treatment deviations should be documented and stored as well. An affordable first approach for this storage could be the use of national cancer registries, which is already being done by some countries (e.g. Belgium and the Netherlands). A shared database has the additional advantage of facilitating the link with other clinical and translational data (long-term follow-up, biobanking, pathology reports, tumour genomics and so on) while maintaining compliance with local data protection regulations, such as the new General Data Protection Regulation in Europe [40].

International storage has additional advantages. Pan-European platforms allow including all types of paediatric patients with brain tumours, regardless of their inclusion in clinical trials, as seen with the SIOPE-diffuse intrinsic pontine glioma (DIPG) registry [41]. This would help to amplify our knowledge with real-world data and eventually reduce the gap between the outcome of patients enrolled within and outside clinical trials.

3.4. RTQA programmes

According to our survey, only 7 of 21 European countries have RTQA programmes in place for the treatment of paediatric brain tumours. In addition, the existing programmes are heterogeneous with respect to the levels of RTQA [11], or in some cases, part of international trials with mandatory RTQA.

In our opinion, the ultimate aim is to have a prospective RTQA system in which each new RT plan is reviewed by an international expert panel before the treatment is applied, which is challenging in clinical practice because of time constraints and financial difficulties. This is especially the case in children with brain tumours in which the clinical situation may not allow delays in the start of the treatment or for tumours in which a late onset of RT reduces survival [42]. Prospective review is being currently implemented in some trials (e.g. SIOP PNET-5). Until QUARTET can be extended across all types of CNS tumours and to patients treated outside clinical trials [27], the standards and practices could be improved by a systematic continuous retrospective review.

3.5. Equal access to RT for paediatric patients with CNS tumours across Europe

At a national level, no differences were reported in the access to RT treatment in our survey for most (85%) of the participating countries. At a European level, inequality prevails according to previous studies, with a well-known inequality of outcomes for paediatric patients with cancer [43,44]. One of the reasons could be the imbalance in RT resources, with a wide range of levels of access to best-care facilities and specialists across countries [10]. In fact, according to our survey, there is wide variability in the number of RT centres that treat paediatric patients with CNS tumours, with some

countries having 20 times more centres per million inhabitants than others. These numbers are reflecting the differences in national healthcare policies and/or the socio-economic status. However, more important than the number of centres per million inhabitants is the number of patients treated per centre, given the growing complexity of paediatric RT. Although the minimum or optimal number of patients per centre is not established, centres treating a higher number of paediatric cancers will benefit from their experience in providing best care.

The factors leading to inequality across European countries extend beyond the distribution of resources, with insufficient networking being an important part of the equation. According to the survey, only 57% of the experts believe that there is a well-established national referral network for radiation treatment in their respective countries. Existing national and European referral networks for RT for paediatric brain tumours should be expanded and new ones created. The recently launched European Reference Network for Paediatric Oncology (ERN PaedCan) [45] could be an appropriate framework to start implementing referral pathways for RT in paediatric brain tumours and promoting RTQA initiatives.

The weaknesses of our study need to be acknowledged. The review of RTQA aspects in past and current European trials is not exhaustive; however, our purpose was to highlight some relevant examples to expose the ongoing paradigm shift towards prospective RTQA. In addition, not all European countries responded to the international survey. Nonetheless, the inclusion of 21 participating countries from all European regions allows the drawing of a reasonably comprehensive European perspective. The limited number of participating experts responds to the purpose of selectively involving highly specialised, reference paediatric oncologists and radiation oncologists treating CNS tumours.

In conclusion, an ongoing audit of our medical practice is desirable in all aspects of paediatric oncology, but QA has become increasingly important in RT for CNS tumours as this aspect of treatment becomes ever more technical and complex. Childhood cancers are rare compared with adult tumours, with children accounting for only about 1% of all RT patients. Within this small number, there is an increasing diversity of diseases and subgroups requiring individualised treatment. This means that even experienced clinicians in large centres see only a limited number of any one type of treatment. RTQA allows expertise to be spread from more experienced to less experienced centres, for the benefit of patients, for example, through real-time review of contours and dosimetry. Several positive initiatives, both national and international, are being undertaken to implement RTQA in the treatment of paediatric patients across Europe, and there is still room for improvement. Creating a European RTQA guideline for paediatric CNS tumours, improving collaboration between paediatric radiation oncologists and other specialists, building a European central storage system for RT data, implementing international RTQA platforms and promoting European referral networks to reduce inequality are measures that will hopefully contribute to improve the still dismal overall outcome of paediatric patients with CNS tumours and reduce long-term toxicities.

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Conflict of interest statement

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.03.018.

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