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Overview

Adopting Advanced Radiotherapy Techniques in the Treatment of Paediatric Extracranial Malignancies: Challenges and Future Directions

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Abstract

Geometric uncertainties in radiotherapy are conventionally addressed by defining a safety margin around the radiotherapy target. Misappropriation of such margins could result in disease recurrence from geometric miss or unnecessary irradiation of normal tissue. Numerous quantitative organ motion studies in adults have been published, but the first paediatric-specific studies were only published in recent years. In the very near future, intensity-modulated proton beam therapy and magnetic resonance-guided radiotherapy will be clinically implemented in the UK. Such techniques offer the ability to deliver radiotherapy to the pinnacle of precision and accuracy, if geometric uncertainty relating to internal organ motion and deformation can be optimally managed. The optimal margin to account for internal organ motion in children remains largely undefined. Continuing efforts to characterise motion in children and young people is necessary to optimally define safety margins and to realise the full potential of intensity-modulated radiotherapy, magnetic resonance-guided radiotherapy and intensity-modulated proton beam therapy. This overview offers a timely review of published reports on paediatric organ motion, in anticipation of the increasing application of advanced radiotherapy techniques in paediatric radiotherapy.

Key words: IMRT; motion; MR-guided radiotherapy; paediatric; radiotherapy; respiratory

Statement of Search Strategies Used and Sources of Information

References for this review were identified by conducting a search, using PubMed and Medline, with the following words: paediatric/pediatric, radiotherapy, motion, respiratory, proton, 4DCT, MR-guided, magnetic resonance image, ultrasound. The search included meeting abstracts and was restricted to papers available in English. Further references were identified following a manual search of the reference list of included articles. Identified studies were first screened by title and/or abstract with a further full-paper screening to generate the final list of publications relevant to the scope of this review.

Introduction

A diagnosis of cancer in infants and children under 18 years of age is rare; representing <1% of all cancer cases in the UK from 2013 to 2015, although a 13% overall increase in incidence since the early 1990s has been reported [1]. About 40–50% of children diagnosed with cancer will receive radiotherapy as part of their first-line treatment [2].

The prognosis is excellent for most, with childhood cancer survival in the UK doubling over the last 40 years. Today, 80% of patients survive 5 years or more and 50% survive 10 years or more [1]. For those patients who have an excellent prognosis and in whom radiotherapy is indicated, such as Hodgkin lymphoma, radiotherapy treatment volumes need to include involved sites either in the thorax, abdomen or pelvis; in some cases, radiotherapy volumes encompass all three anatomical regions. Conversely, for patients with diagnoses of metastatic neuroblastoma and

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metastatic soft tissue sarcoma, prognosis remains comparatively poor.

All survivors of childhood cancer live with a real risk of treatment-related morbidity and mortality. The use of radiotherapy as part of the multimodal treatment of childhood cancer is risk stratified and/or response-adapted wherever possible in order to minimise the exposure of patients to irradiation and its potential late effects. Considerations for those responsible for delivering paediatric radiotherapy revolve around how best to minimise radiotherapy late effects for long-term survivors while maximising disease control and the chance of cure in those for whom prognosis remains poor.

The ability to deliver highly conformal radiotherapy on available treatment platforms is approaching the technical limits of precision. Reduced volumes of normal tissue irradiated as a result of intensity-modulated radiotherapy (IMRT) have translated into clinical benefits in several adult tumour sites [3]. For children and young people in whom radiotherapy is deemed essential, it is highly recommendable that advanced treatment delivery techniques are made available where appropriate [4]. According to the ICRU62 report, the planning treatment volume (PTV) for photon treatment techniques comprises a set-up margin and an internal margin [5], designed to take into account potential sources of geometric uncertainty in treatment delivery [6]. The conventional approach to planning for much of paediatric radiotherapy was to use parallel opposed beam arrangements. Such beam arrangements offer a buffer to changes in internal organ position during treatment that is lost when techniques with highly conformal, complex dose distributions and steep dose gradients are introduced. As a consequence, inadequate safety margins in the latter setting could result in relapse due to geographical misses. Conversely, overly generous margins could negate the potential benefits of enhanced normal tissue sparing.

In this era of ever-increasing dose conformality in radiotherapy it is of the upmost importance to develop greater understanding of the components of geometric uncertainty that are particular to children and young people. Pragmatically adopting margins derived from adult organ motion studies for all patients under 18 years is predictably suboptimal. As we look towards the establishment of intensity-modulated proton beam therapy (IMPT) and magnetic resonance-guided radiotherapy (MRGRT) services within the UK, there is a need to quantify internal organ motion for extracranial tumour sites in children and young people, and evaluate its potential impact on radiotherapy delivery to ensure delivery of the best possible dose distributions with the steepest dose gradients at normal tissue/target interfaces.

Organ Motion and its Potential Impact on Radiotherapy

The American Association of Physicists in Medicine (AAPM) Task Group 76 reports on the management of respiratory motion in radiotherapy and identifies paediatrics and young people as a key cohort in whom current scientific knowledge on respiratory motion patterns and treatment implications is absent or scarce [7]. Assessments of geometric uncertainty in children and young people for intracranial/head and neck [8–14] and extracranial [15–21] tumour sites have been reported. Extracranial sites are predominantly upper abdominal, reflecting the anatomical site of the two common paediatric extracranial malignancies requiring radiotherapy: neuroblastoma and Wilms' tumour.

Interfraction set-up uncertainties for the paediatric abdomen have been demonstrably reduced with the integration of daily low-dose (1 cGy) megavoltage cone-beam computed tomography (CBCT); reducing set-up uncertainty from 5.6, 5.2 and 5.2 mm to 1.7, 2.1 and 1.5 mm in the superior/inferior, anterior/posterior and right/left directions, respectively, compared with weekly imaging [15]. As patient set-up uncertainties reduce, it is important to adequately account for motion uncertainties, as they will represent the limiting factors in treatment accuracy [7].

Target position in the thorax and upper abdomen is affected primarily by respiratory-related organ motion (RROM), with contribution from cardiac pulsation, peristalsis and gastrointestinal filling or emptying depending on anatomical location [22–24]. In adults, intrafraction motion (organ motion and set-up error combined) has been shown to have a negative effect on photon dose distributions due to dose 'blurring' and interplay effects [7,25]. The potential degradation of the planned dosimetry will be influenced by factors such as the magnitude of motion, fractionation schedule, beam delivery (static versus dynamic) and beam-on time. Mitigating RROM is challenging due to breathing cycle and amplitude irregularities, target drift and interfraction reproducibility of organ motion that is measured days to weeks before treatment starts [7]. The interplay effect is potentially greater for IMPT and, importantly, it is not only target motion that can perturb proton therapy dose distributions, but rather motion of any tissue present in the beam path that can impact range uncertainty in proton therapy delivery [26].

As part of the multimodal treatment of childhood cancer, radiotherapy is often delivered after surgery; organ motion is measured as a surrogate for tumour bed motion in the absence of macroscopic tumour. Four studies, median 35 paediatric patients (range 10–45), have used CBCT to quantify interfraction motion of the kidneys [16,18,20]; liver [20] and diaphragm [16–18] (Table 1). These studies show that motion is greatest in the superior/inferior direction; confirming adult organ motion findings. One study, comparing 35 paediatric with 35 adult patients, showed that median kidney motion in children was statistically significantly smaller than in adults; 2.8, 2.9 mm and 5.6, 5.2 mm for median vector lengths for right and left kidney, respectively ($P < 0.05$) [16].

Intrafraction organ motion in the abdomen has been quantified using four-dimensional computed tomography and magnetic resonance imaging (4DCT and 4DMR) in a median of 20 patients (range 15–35) [19,21,27]. These studies show that intrafraction displacement occurs, in

Table 1
Published results on interfraction organ motion (in mm)

Reference	Mean age (SD/ range)	Patient number	Patients under GA	Measure of displacement	Right kidney			Left kidney			Diaphragm	Liver	Target (calcification)		
	years		(Age range)		mm			mm			mm	mm	mm		
					RL	SI	AP	RL	SI	AP	SI	SI	RL	SI	AP
[20]	4.1 (1.6)	9	9	upper pole /organ edge (max) lower organ edge (max)	1	10	1	1	8	1	nr	11 13	2	5	3
[18]	8 (1.6–17.8)	39	2	COM (mean)	0.6	0.5	0	−0.6	1.5	0	1.1	nr	nr	nr	nr
[16]	10.3 (3.1–17.8)	35	5 (3.1–7.6)	COM (mean)	−0.1	0.7	−0.4	−0.4	1	−0.9	−0.8	nr	nr	nr	nr

GA, general anaesthesia; NR, not recorded; RL, right/left; SI, superior/inferior; AP, anterior/posterior; SD, standard deviation; COM, centre of mass.
Negative integers reflect motion in left, superior and anterior directions.

order of decreasing magnitude, superior/inferior > anterior/posterior > right/left with mean superior/inferior displacements reported for the right and left kidney, liver, spleen and diaphragm; 1.9–4.7 mm, 1.4–4.8 mm, 3.2–6.8 mm, 3.0–6.9 mm and 3.6–9.6 mm, respectively, and no more than 2–3 mm anterior/posterior and right/left (Table 2).

Young children having radiotherapy often require general anaesthesia for treatment. Van Dijk *et al.* [16] reported no difference in interfraction kidney motion between five children under general anaesthesia and seven similarly aged children not under general anaesthesia (3.1–7.6 years; 3.3–7.9 years, respectively), adjusted $P > 0.007$. 4DCT and 4DMR measures of intrafraction motion are numerically smaller in patients categorised according to general anaesthesia (age ranges ≤9 versus 9–18 years) [19,21] (Table 2). Huijsken *et al.* [17] showed that intrafraction variation in diaphragm displacement was statistically significantly smaller for a subset of anaesthetised children compared with non-anaesthetised children of similar ages ($n = 7$; 2–11 years, $n = 12$; 3–10 years); 1.6 mm versus 2.4 mm, respectively, $P < 0.05$, but the mean amplitude and interfractional variation of diaphragm motion did not differ between the groups [17].

Attempts to correlate organ motion with patient variables have been made in the pursuit of a variable predictive of 'significant' organ motion in paediatric patients to avoid acquiring pretreatment 4DCT on all patients. Estimates of a population-based paediatric-specific margin would also aid radiotherapy departments without access to four-dimensional imaging, noting that a significant proportion of childhood cancers occur in low-to middle-income countries [4]. No consistently significant correlations between organ motion and patient-related variables (age, height, weight, body mass index) have been established so far [9–31]. Huijskens *et al.* showed a significant but weak correlation between age, height, weight and mean diaphragm amplitude (Spearman's $P = 0.40$, 0.45, 0.33, P value 0.007, 0.03, 0.002, respectively), suggesting that patient-related factors explain only a small proportion of the differences between patients. Interpatient variation is a persistent finding in all studies of both intra- and interfraction organ motion, suggesting that motion is patient specific, even under general anaesthesia and an individualised approach to motion assessment is required.

Individualised Motion Assessment for Paediatric Radiotherapy

Techniques to address RROM require individualised motion assessment before treatment and 4DCT is the current gold standard in adult radiotherapy planning. Methods for image acquisition and sorting, using phase- or amplitude-based binning techniques, have been previously described in detail for adults [28–30]. 4DCT still has accepted limitations, with artefacts occurring despite 4DCT image reconstruction techniques, due to variability in amplitude and frequency of breathing cycles within

Table 2
Published results on mean intrafraction organ motion (in mm) and standard deviation (SD) for superior/inferior (SI) motion when given

Reference	Age		Patient number	Patients under GA	Modality	Metric	Right kidney mean (SD)			Left kidney mean (SD)			Diaphragm mean (SD)	Liver mean (SD)	Spleen mean (SD)	GTV mean (SD)
	mean	SD (range)					RL	SI	AP	RL	SI	AP	SI	SI	SI	SI
[19]	4.1	2.1 (2–8)	11	11	4DCT	COM	0.7 (0.2)	1.9 (1.0)	0.7 (0.4)	0.7 (0.3)	1.7 (0.8)	0.9 (0.3)	5.1 (1.9)	nr	nr	nr
	12.3	nr (9–18)	9	1	4DCT	COM	1.1 (0.5)	3.9 (1.7)	1.4 (0.4)	0.9 (0.5)	3.1 (1.2)	0.9 (0.4)	9.6 (3.6)	nr	nr	nr
[27]	nr	nr (1.5–10)	15	10	4DCT	COM	0.3 (0.4)	−1.9 (1.8)	0.4 (0.8)	0.4 (1.1)	−1.4 (2.0)	0.4 (0.6)	−3.6L* (2.3)	−4.4R* (2.0)	−3.1 (2.0)	nr
[21]	3.9	nr (1–8)	17	17	4DMR	COM	0.5 (nr)	2.3 (nr)	0.8 (nr)	0.5 (nr)	1.6 (nr)	0.6 (nr)	nr	3.2 (nr)	3 (nr)	1.6 (nr)
	14.9	nr (9–20)	18	1	4DMR	COM	1	4.7	1.5	0.9	4.8	1	nr	6.8	6.9	4.7

GA, general anaesthesia; NR, not recorded; RL, right/left; AP, anterior/posterior; COM, centre of mass.
Negative integers indicate that exhale motion was more extreme than inhale.
*L, left dome of diaphragm; R, right dome of diaphragm.

patients, as shown in adults [31]. In the setting of irregular adult breathing patterns, the ability of a single 4DCT to fully characterise respiratory-related motion is potentially limited [32,33]. The stability of respiratory motion as measured on a single 4DCT in children is yet to be established. A major factor limiting adoption of 4DCT for paediatric radiotherapy planning is the associated radiation dose; 4DCT protocols are often acquired at twice the dose of standard computed tomography and dose exposure in children and young people is a prime consideration due to the risk of second malignancy induction. The adaptation of paediatric-specific imaging protocols has in the past been optimised for 3DCT-based planning and accepted a trade-off between lower dose and slightly reduced image quality. Following this rationale, published low-dose protocols can acquire 4DCT at 1.6 times the dose of 3DCT [27]. Although the clinical benefit of incorporating individualised motion information into paediatric radiotherapy planning has yet to be defined, we would argue that accepting reduced image quality, although practical when treatment portals were defined by bone anatomy alone, is contradictory if the purpose of volumetric, contrast-enhanced imaging with individualised motion assessment is to improve accuracy and precision in paediatric treatment delivery.

Individualised ICRU62 Appropriate Planning Volumes for Paediatric Radiotherapy

In adults, a common approach to motion management is to encompass the entire magnitude of motion for a particular patient within the PTV; a ‘motion encompassing technique’ [7]. 4DCT is used to determine the target position during the entire breathing cycle, which in turn defines a volume that encompasses the full extent of target excursion; the internal target volume (ITV) [5]. Including the entire magnitude of motion can be seen as a conservative approach [34]. Alternatively, the mid-ventilation (MidV) concept extracts the target’s time-averaged position and its standard deviation from 4DCT and motion is then considered a random positioning error in a probabilistic safety margin calculation [35]. MidV, with an online set-up correction strategy, has been shown to reduce PTV size by up to 30% compared with an ITV approach in adult lung radiotherapy with a reported 98% local control rate at a median follow-up of 21.9 months [36,37]. MidV has been described in planning studies in the upper abdomen despite the different tissue composition resulting in a narrower beam penumbra than is the case in lung [38,39]. Given the relatively small motion trajectory of paediatric upper abdominal organs, adopting an ITV approach is a reasonable initial step, but further work investigating MidV planning for paediatric radiotherapy should be undertaken.

Daily verification of target positioning is necessary to avoid geometric misses in treatment delivery [39]. Bone anatomy is recognised to be a poor surrogate for tumour position in the lung, abdomen and pelvis [40]. Interfraction variation in target position in many adult tumour sites is

addressed using online or offline soft tissue verification protocols. Paediatric radiotherapy in-room image guidance uses low-dose imaging protocols based on bone anatomy. Such protocols have comparatively poor soft tissue contrast limiting the ability to perform a soft tissue match and making interfraction changes in target shape challenging to address. In the absence of non-ionising image guidance, a soft tissue match will be necessary to implement motion management techniques and the associated increased imaging dose would be offset if improved localisation and reduction in irradiation of adjacent normal tissues enhances local control and reduces normal tissue toxicity. It is clear from previous reports that centres are already looking to adopt such an image-guided radiotherapy (IGRT) approach and efforts to harmonise IGRT use in paediatric radiotherapy and collate prospective data to inform protocols and evaluate outcomes should be a priority [41].

Motion management strategies are not limited to motion-encompassing approaches [7]. Advanced photon planning techniques, using non-coplanar beam arrangements have been described that reduce dose delivered to lung and breast tissue in Hodgkin lymphoma [42]. The excellent prognosis associated with Hodgkin lymphoma at all stages makes the risk reduction for radiotherapy-induced second malignancy and cardiovascular disease in survivors important [43]. Motion management strategies using inspiratory breath holding have been described in patients with mediastinal Hodgkin lymphoma. Such studies rarely include patients under the age of 18 years, although a single planning study has described the dosimetric advantage of active breathing coordinator and deep inspiration breath hold in patients aged 13–18 years with mediastinal Hodgkin lymphoma [44].

Current Status of Advanced Radiotherapy Techniques and Associated Challenges in Children and Young People

Evidence for paediatric IMRT is largely limited to non-randomised and dosimetric planning studies predominantly in intracranial and head and neck sites [45]. The use of more beams (or arc in the case of rotational IMRT), compared with conformal photon and proton therapy treatments, achieves dose distributions that conform to irregularly shaped targets and is implemented in paediatric cases where greater conformity gives target coverage that, if delivered using a conventional approach, would have exceeded normal tissue tolerance [46]. IMRT reduces the volume of normal tissue receiving a high dose, the dose region implicated in the development of many normal tissue toxicities, but comes at the price of a low-dose bath. An increased integral dose has been postulated to increase the risk of second malignancy induction, although there is a realisation that second cancers often arise in the high-dose region [46,47]. In cases where the improved high-dose conformity achieved with IMRT is substantial, the compromise of increased integral dose is considered acceptable and IMRT has demonstrably reduced grade 3 and 4 ototoxicity in medulloblastoma survivors and reduced mucositis in the treatment of childhood nasopharyngeal carcinoma [48]. In the UK, an open phase II study is investigating the role of rotational IMRT, and dose escalation from 21 to 36 Gy, in high-risk abdominal neuroblastoma, highlighting the potential role for advanced photon techniques in the abdomen for a cohort of patients where renal tolerance can be dose-limiting [49].

Stereotactic body radiotherapy (SBRT) and stereotactic radiosurgery (SRS) techniques incorporate precise immobilisation and localisation imaging allowing the use of small or minimal PTV margins. Highly conformal dose distributions with relative sparing of adjacent normal tissues enables delivery of higher biologically effective ablative doses of radiotherapy in a single or few fractions that, for some adult tumours, result in local control rates comparable with surgery. Historically, studies in children exploited the stereotactic set-up in order to apply smaller PTV margins while maintaining the benefits of fractionation on normal tissue recovery. This paradigm has been used without detriment in local control in low-grade glioma, medulloblastoma, craniopharyngioma and intracranial germ cell tumours [50–52]. Ablative strategies in children whose growing tissues are inherently more radio-sensitive to radiotherapy are evolving. The largest case series of extracranial SBRT in 14 patients with metastatic and recurrent Ewing and osteosarcoma reports its feasibility as a treatment paradigm although not without risk of grade 2 and 3 toxicity [53]. Prospective studies will be required to define treatment standards and aid patient selection for use of SBRT/SRS in children and young people.

Current estimates suggest that about 250 paediatric patients per year in the UK will receive proton therapy [54]. Proton therapy (passively scattered and intensity modulated) reduces integral dose by a factor of 2–3 compared with IMRT and IMPT has the potential to equal the dose conformity achieved by IMRT [55]. This dosimetric advantage is expected to translate into less treatment-related morbidity and second malignancy induction. Proton therapy delivery is currently associated with a number of technical and physical limitations, such as the magnitude of the lateral penumbra, uncertainties in particle range estimates and relative biological effectiveness [55]. A range uncertainty of 2.5–3.5% of depth of penetration, with an additional margin of 1–3 mm for delivery system, biological and geometric uncertainties translating into a distal and proximal CTV margin of 8 mm at a depth of 20 cm, is representative of current passive scattering proton therapy techniques [26]. The consequent dosimetric effect on skin dose and permanent alopecia in patients receiving craniospinal proton therapy for medulloblastoma has been described [56]. Such a margin exceeds, depending on anatomical location, safety margins commonly applied in photon radiotherapy. Despite the greater vulnerability of proton therapy to geometric uncertainties, kilovoltage planar imaging was up until recently the only available in-room image guidance, although kilovoltage CBCT capabilities are now commercially available on new systems. Following the opening of high energy proton therapy

centres treating children in Manchester and London, the case mix of paediatric tumours referred will undoubtedly expand beyond what is currently approved for funding [54]. Realising the maximal benefits of IMPT treatments in the presence of inter- and intrafraction organ motion in the abdomen and thorax will be challenging.

Future Directions

There is potential for magnetic resonance to positively impact the radiotherapy delivery pathway from target delineation and planning through to treatment delivery. Magnetic resonance sequences have been used to assess organ motion in adults and, more recently, in children [21] and could be substituted in place of 4DCT for individualised motion assessment without additional imaging dose. Hybrid MRGRT platforms, integrating clinical quality magnetic resonance imaging with a modern linear accelerator, are in active development [57–60]. The MRIdian system (ViewRay Inc., Oakwood Village, OH, USA) has been clinically operational since 2014 and prototype Elekta magnetic resonance linac machines, installed in two centres in the UK, will be clinically implemented this year. The delivery of real-time MRGRT is a reality and offers the opportunity to expand the integration of in-room IGRT for children and young people without additional ionising exposure risk and enable the reduction of PTV margins. To date, limited published data are available to describe MRGRT in children and initial clinical use of the Elekta MRLinac in the UK will be within the setting of a research study that specifically includes a paediatric and young patient treatment cohort (NCT02973828) [61].

Ultrasound imaging systems offer non-ionising, real-time volumetric imaging with excellent soft-tissue contrast. Platforms are in development that offer two-, three- and four-dimensional anatomical and functional imaging capabilities for inter- and intrafraction imaging [62]. Integration of ultrasound into IGRT for upper abdominal sites, primarily liver, has been described [63–65], including one paediatric paper reporting its use in a cohort of patients with neuroblastoma comparing ultrasound quantified set-up couch shifts to that of CBCT-based shifts [15]. Finding that ultrasound localisation did not correlate with CBCT shifts, the authors cited user-dependency and user-experience as potential barriers to implementing ultrasound. However, as a non-ionising imaging modality it should be a research priority for paediatric radiotherapy and proof of principle two- and three-dimensional ultrasound measurement of kidney motion is currently being investigated in a non-randomised phase II study exploring four-dimensional imaging platforms in children and young people (IRAS project ID 195329).

Conclusion

The highest incidence of cancer occurs in children younger than 5 years, falls among 5–14 year olds, but rises again in young people over the age of 15 years. Children and young people display physiological and developmental heterogeneity. This heterogeneity, together with the relative rarity of a cancer diagnosis in childhood, represents a challenge in the development of robust research strategies. Multinational clinical trials, with centralised radiotherapy quality assurance, are necessary for sufficient power to detect clinically significant results from therapeutic strategies in children and young people. Recruitment over extended periods of time is necessary such that radiotherapy guidance may no longer be deemed current when patient accrual is completed. This challenges valid interpretation of results in light of rapidly changing radiotherapy practices. This will be the greatest challenge in evaluating the exciting opportunities for additional clinical benefit to young patients made possible with emerging competing platforms and radiotherapy techniques. The impetus to develop proton beam therapy, MRGRT and stereotactic ablative body radiotherapy in the UK in a co-ordinated manner through the implementation of Cancer Research UK Advanced Radiotherapy Technologies Network (ARTNET) has been recently outlined in this journal [66]. Paediatric radiotherapy is uniquely placed, given its present centralisation, to contribute to parallel advances in children and young people. Future national and multinational studies will be important in maximising their benefits without compromising current patient outcomes. The potentially increasing complexity of treatment delivery arguably warrants further concentration of services in order to consolidate expertise in the application of these techniques.

Conflict of interest

The authors declare no conflict of interest.

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