Contemporary paediatric radiation oncology

Tom Boterberg,[1] Cathy Dunlea,[2] Semi Harrabi,[3] Geert Janssens,[4,5] Anne Laprie,[6] Gillian Whitfield,[7] Mark Gaze ,[8] on behalf of the SIOP-Europe Radiation Oncology Working Group

[1]Department of Radiotherapy, University of Ghent, Ghent, Belgium
[2]Department of Radiotherapy, University College London Hospitals NHS Foundation Trust, London, UK
[3]Department of Radiotherapy, University Hospital Heidelberg, Heidelberg, Baden-Württemberg, Germany
[4]Department of Paediatric Oncology, Princess Maxima Center for Pediatric Oncology, Utrecht, The Netherlands
[5]Department of Radiotherapy, University Medical Centre, Utrecht, The Netherlands
[6]Department of Radiotherapy, Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France
[7]Department of Radiotherapy, Christie Hospital, Manchester, UK
[8]Department of Oncology, University College London Hospitals NHS Foundation Trust, London, UK

Correspondence to
Dr Mark Gaze, Oncology, University College London Hospitals NHS Foundation Trust, London, London, UK; mgaze@nhs.net

Received 6 December 2021
Accepted 3 July 2022

To cite: Boterberg T, Dunlea C, Harrabi S, *et al*. *Arch Dis Child* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/archdischild-2021-323059

ABSTRACT

Treatment with ionising radiation is a valuable component of treatment schedules for a many children and young people with cancer. While some form of radiotherapy has been in use for over 100 years, a series of innovations has revolutionised paediatric radiation oncology. Mostly, high-energy X-ray photons are used, but proton beam radiotherapy is increasingly offered, especially in children and young people. This is to reduce the radiation exposure of healthy normal tissues and so the likelihood of adverse effects. Other methods of radiotherapy delivery include brachytherapy and molecular radiotherapy. The most appropriate treatment technique should be selected for every child. Advances in computers and imaging, developments in the technology of radiation delivery and a better understanding of pathology and molecular biology of cancer, coupled with parallel improvements in surgery and systemic therapy, have led to a transformation of practice in recent decades. Initially an empirical art form, radiotherapy for children has become a technically advanced, evidence-based cornerstone of increasingly personalised cancer medicine with solid scientific foundations. Late sequelae of treatment—the adverse effects once accepted as the cost of cure—have been significantly reduced in parallel with increased survival rates. The delivery of radiotherapy to children and young people requires a specialised multiprofessional team including radiation oncologists, therapeutic radiographers, play specialists and physicists among others. This article reviews the types of radiotherapy now available and outlines the pathway of the child through treatment. It aims to demonstrate to paediatricians how contemporary paediatric radiation oncology differs from past practice.

INTRODUCTION

The incidence of cancer in children and young people

Although only about 1% of the total cancer burden, malignant disease in children and young people is relevant. The worldwide cancer incidence rate in those aged 0–19 years is 157 per million, with significant variation by age, sex and geography.[1] This equates to over 279 000 diagnoses worldwide annually. In developed countries, 80% of children survive their cancer,[2] but neoplasms are the principal cause of death by disease beyond 1 year of age in the EU, and accounted for 25% of total deaths in those aged 1–15 years in England and Wales in 2018.

The varied use of radiotherapy in children and young people

Radiotherapy, or treatment with ionising radiation, comprises part, along with surgery and chemotherapy, of many multimodality cancer treatment protocols. Overall, around one-third of paediatric oncology patients receive radiotherapy, although the utilisation rate varies, depending on the tumour type and its risk category[3] (table 1), and has fluctuated, but typically reduced, over time.[4]

Deciding when to use radiotherapy

Radiation oncologists are core members of the paediatric oncology multidisciplinary team. Paediatric oncologists, paediatric radiation oncologists and paediatric surgeons with appropriate subspecialisation for the tumour site, guided by pathologists, radiologists and nuclear medicine physicians, discuss and agree in the diagnostic and treatment multidisciplinary team meeting on the most appropriate treatment plan for patients with newly diagnosed or relapsed disease and following response assessment.[5] Many different factors are considered for risk group assignment, which will determine the treatment plan in newly diagnosed patients. For some diseases, a definitive decision on whether or not radiotherapy is needed cannot be made at the time of diagnosis but depends on response assessment after initial systemic therapy.

THE TYPES OF RADIOTHERAPY

The art of radiotherapy is to get an adequate dose of radiation into the tumour bed while keeping exposure of healthy normal tissues as low as reasonably achievable.[6] The planning target volume (PTV) is the three-dimensional region identified as containing the cancer within the body, at which the therapeutic dose of radiation is aimed. Radiation can be delivered in a number of distinct ways (figure 1), and it is important to choose the optimal technique for each patient.

Simple external beam radiotherapy techniques

Most radiotherapy worldwide is delivered with high-energy X-rays or photons from a linear accelerator. This can be used in very simple forms for palliative treatments.

Conformal radiotherapy

For curative radiotherapy, an adequate dose is needed, and it is desirable to shape the high-dose volume to the area that needs to be irradiated while sparing surrounding tissues through which the radiation passes. A degree of shaping can be achieved with 'conformal radiotherapy', in which the volume to be treated is covered by a number of beams, shaped to the target through the use of multileaf collimators (MLCs), aimed from different

Table 1 To demonstrate the varied use of radiotherapy in different diseases and changes in use over time

Utilisation rate		Examples
Very high 80%–100%		High-grade glioma Germinoma Medulloblastoma
Intermediate 10%–80%	Depending on risk group assigned at diagnosis	Neuroblastoma Rhabdomyosarcoma
Intermediate 10%–80%	Depending on response to induction chemotherapy	Wilms tumour Ewing sarcoma Hodgkin lymphoma
Very low 0%–10%		Hepatoblastoma Extracranial germ cell tumour Non-Hodgkin lymphoma
Formerly frequent	Now very rarely used in frontline therapy as a result of improved systemic therapy	Acute lymphoblastic leukaemia Retinoblastoma

directions that overlap at the target. The shaping to the target, or 'conformity', is not generally optimal, as some tissues outside the target volume will receive a high dose.

Intensity modulated radiotherapy

Intensity modulated radiotherapy (IMRT), which has become more widely available over the last two decades, achieves a superior degree of shaping to the high-dose volume, including concavities. The target is irradiated with several overlapping beams, but the intensity varies across the width of the beam. This is achieved by the MLC leaves moving into the beam for part of the beam on time, allowing for more conformal shaping.

A rotational technique where the beams enter over a full 360° arc, so called intensity modulated arc therapy (IMAT) (figure 2A-C), is one form of IMRT.[7] Different radiotherapy equipment manufacturers offer various techniques for IMAT delivery. Typically, with IMAT, the linear accelerator rotates around a stable patient, but an alternative system combines longitudinal couch movement during rotation of the radiation source, resulting in a helical delivery of radiation.

If available, a form of IMRT is often preferable to conformal radiotherapy for a curative treatment.

Stereotactic radiotherapy

Stereotactic treatment may take the form of a single procedure, called stereotactic radiosurgery (SRS), or fractionated stereotactic radiotherapy (table 2). These are forms of high precision

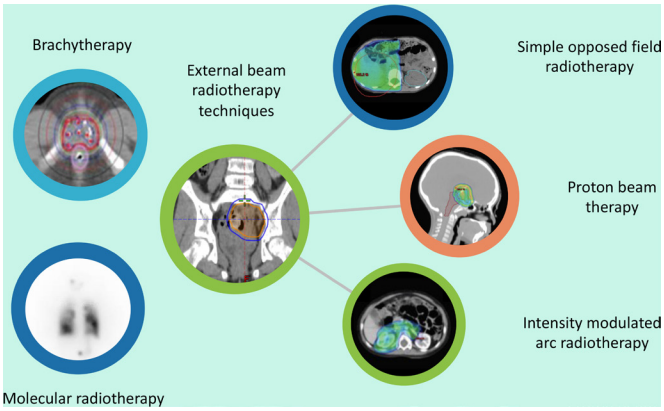

Figure 1 The principal categories of different radiotherapy techniques.

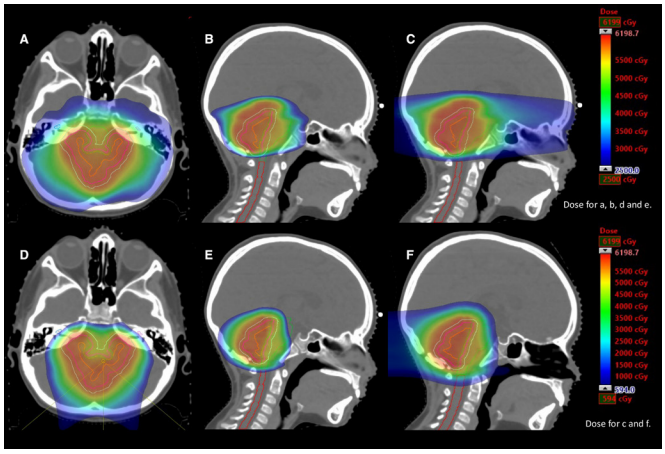

Figure 2 The difference in absorbed dose between intensity modulated arc therapy with photons (upper panel) and proton beam therapy (lower panel) radiotherapy plans for a 7-year-old boy following complete resection of a posterior fossa ependymoma. (A) Axial and (B) sagittal dose distributions with colour wash indicating all tissues receiving more than 25 Gy (42% of prescribed dose) and (C) sagittal low dose distribution showing tissues receiving more than 5.94 Gy (10% of prescribed dose) – photon treatment. (D–F) Corresponding images with proton treatment, clearly indicating a much more favourable sparing of tissues outside the clinical target volume (red line).

treatment for small, well-defined targets, in either the body or the brain, where a high dose is desired to the target, with much lower dose only a few millimetres away. Targets are localised with a high degree of accuracy, typically within 1 mm for intracranial lesions, by using increased image guidance and, for cranial locations, by the patient being in a more rigid than usual immobilisation device. Irradiation is by multiple beams or arcs entering from many different directions in three dimensions. Once again, there are different techniques for SRS and SFRT delivery: a multipurpose high-specification linear accelerator may be used, or a dedicated machine emitting a very large number of beams all focused on one point.

Image-guided radiotherapy (IGRT)

All modern equipment is fitted with devices for IGRT, which visualises the target in the treatment room and facilitates compensation for either *INTRA*-fractional changes (such as respiratory motion, bowel movement and bladder filling) or *INTER*-fractional differences (such as positional ('setup') variability, weight loss and tumour shrinkage).

Most image guidance uses either plain X-rays, or 'cone beam' CT, which is of a much lower quality than diagnostic CT, but also a much lower radiation dose. More sophisticated image guidance integrated into radiotherapy treatment equipment, such as the MRI linear accelerator, is undergoing clinical evaluation in a number of centres.[8]

Adaptive radiotherapy

The radiotherapy plan is based on the size and shape of the tumour, and size and shape of the patient at the time of treatment preparation. Adaptive radiotherapy recognises that the tumour or patient size and shape may change over the 2–6 weeks of treatment. Changes to the plan may be required as the course of treatment progresses.

Table 2 Different forms of stereotactic treatment and their indications

	Fractionated stereotactic radiotherapy	Radiosurgery
How it is delivered	Treatment divided into a number of smaller, equal-sized, administrations over a period of time	A single large dose given on one occasion
Typical applications	Extracranial metastatic lesions skull base chordoma or chondrosarcoma (where proton therapy is not available) benign, non-infiltrative tumours (in young patients to limit the irradiated volume)	Brain metastases vestibular schwannomas small meningiomas arteriovenous malformations (a benign condition)

Total body irradiation (TBI)

In some circumstances, principally as conditioning for bone marrow transplantation for leukaemia and some benign haematological conditions, there is no distinct target to be treated, or specific normal tissue to be spared; rather the whole body is treated more or less uniformly.[9] TBI has been shown in a recent, large randomised trial to offer significant survival benefits over other conditioning regimens for acute lymphoblastic leukaemia.[10] While there have been attempts to reduce its late visceral toxicity by introducing total marrow and lymphoid irradiation techniques, these remain experimental.[11]

Proton beam therapy

Good radiotherapy requires optimal tumour coverage with sparing of healthy tissue. Especially in young patients who will become long-term survivors, the reduction of late sequelae is essential. For radiosensitive normal tissues—'organs at risk' (OAR)—the probability for impairment increases with the amount of dose absorbed.[12] Proton beam radiotherapy (PBT) has a great potential to reduce the burden of treatment-related toxicity, in particular for patients with brain tumours (figure 2D–F).[13] Due to distinct physical properties, PBT is a highly conformal treatment technique. The resulting steep dose gradients allow for an excellent target coverage even in close vicinity to critical normal tissues (figure 3).

There is increasing evidence that the postulated advantages of PBT translate into improved clinical outcome. Children with medulloblastoma treated with PBT have less neurocognitive impairment.[14] Although the number of proton facilities worldwide is increasing, and the use of PBT for paediatric patients is becoming more common, access to such facilities is still restricted. International research collaboration to further investigate and understand the effects and side effects of PBT is essential.

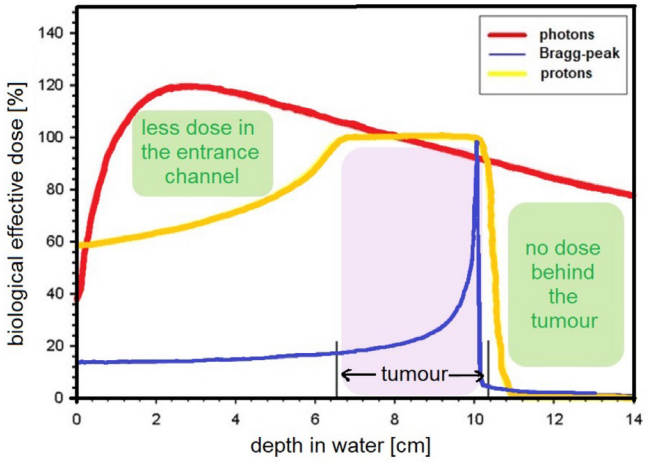

Figure 3 This shows a typical inverse dose depth profile of protons (yellow) as a result of multiple superimposed Bragg-peaks (blue) of different energies with reduced dose deposition in the entrance channel and steep dose gradient at the distal end allowing for highly conformal treatment. A photon curve (red) is shown for comparison. For simplicity, this diagram represents a beam from a single direction, although in practice, a number of beams coming from different directions will be used. In this way, the dose to the tumour will be significantly greater than the dose to surrounding normal tissues.

Brachytherapy

Brachytherapy is the insertion of sealed radioactive sources into a body cavity such as the vagina or uterus,[15] or percutaneously into the tumour, for example, transperineally into the prostate.[16] To be suitable for brachytherapy, tumours need to be small, localised, and accessible to implantation. The main benefits are as an alternative or an adjunct to surgery, allowing preservation of the organ and normal function, and a reduction of dose to nearby healthy normal tissues. Contemporary practice is for the insertion of treatment catheters that are subsequently after-loaded with the radioactive source. Brachytherapy is given over a much shorter overall time than a conventionally fractionated course of external beam radiotherapy.

Molecular radiotherapy

Molecular radiotherapy, or radionuclide therapy, is the use of systemically administered radiopharmaceuticals.[17] The most established example is the use of radioactive iodine in differentiated thyroid cancer. This is a simple oral administration under conditions of thyroid-stimulating hormone (TSH) stimulation, with the aim of either ablating the thyroid remnant after surgery, or treating nodal or distant metastatic disease. Children are more likely to have advanced disease at presentation, but their outlook with this treatment is excellent.[18] Neuroblastoma is another important paediatric indication for molecular radiotherapy. Iodine-131 labelled meta-iodobenzylguanidine (mIBG) therapy has been available for over 30 years but is now increasingly being evaluated in clinical trials aimed at optimising its use.[19]

THE RADIOTHERAPY PATHWAY

Information and consent

Radiotherapy is often associated with parental fears and anxiety.[20] A number of interventions have been shown to be helpful, of which adequate provision of information is one.[21] As for surgery or chemotherapy delivery, a clear explanation of the procedure, with an honest but sympathetically delivered account of the likely short-term and possible long-term consequences of treatment is essential. Possible adverse effects should be set in the context of the benefit of treatment and supported by written information. Ideally, formal written consent should not be sought until a second or subsequent consultation, which therefore allows time for the family to process the information given and to ask further questions.[22]

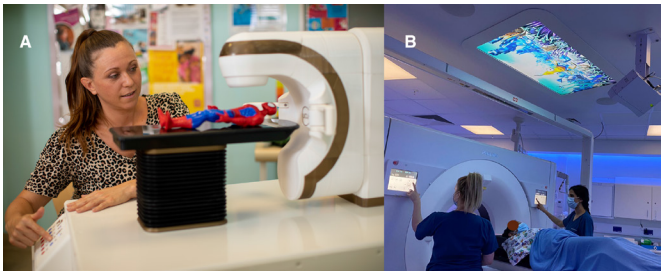

Figure 4 (A) Play specialist explaining radiotherapy treatment using a model linear accelerator and a doll. (B) Image projected onto the ceiling to distract a young person during radiotherapy planning. Images provided by University College London Hospitals.

Immobilisation and anaesthesia

To deliver the radiation dose reproducibly day after day to a tumour volume with small margins and to spare any surrounding OAR, the child's positioning for treatment must have minimal variability. Two aspects are important: first, the child must cooperate willingly with treatment or be anaesthetised, and second, immobilisation devices may be used.

The expertise and knowledge of play specialists to explain the radiotherapy pathway, including immobilisation procedures, can enhance the parent's confidence in the process and encourage children to remain calm (figure 4). The use of play therapy, in combination with distraction methods, such as introducing a visual media stream or music during treatment delivery, improves children's tolerance for immobilisation if required and their ability to hold still for treatment delivery.[23] For infants and toddlers, usually less than three or 4 years old, general anaesthesia may be required.[24]

The type of immobilisation device used depends on the treatment site and technique. Examples of the most common equipment used include vacuum bags and thermoplastic shells (figure 5). Although the personalised immobilisation devices are used for the entire treatment course, permanent or semipermanent skin marks may also be used to aid set-up reproducibility.

Surface-guided radiotherapy, which captures a patient's body contour to reproduce positioning for treatment, may enable open-face masks and eliminate the necessity for permanent skin marks.[25]

Scanning for target volume delineation

Target volume definition for radiotherapy has drastically changed in the last two decades. A CT scan performed with the patient immobilised in the treatment position is required. The use of intravenous contrast media may increase visibility of the tumour, vasculature and normal organs. Coregistration ('fusion') of other types of imaging in the treatment planning systems is often helpful to increase soft-tissue definition, for example, in brain, pelvic or extremity tumours, or to show the initial tumour site before surgery or chemotherapy.

MRI fusion is mandatory for planning in many cases. Preoperative and postoperative/postchemotherapy preradiotherapy MRI scans are performed. For brain tumours, the use of three-dimensional volumetric sequences allows a better distortion management as well as the most accurate registration with the planning CT scan.[26 27]

For abdominal tumours, MRI may be useful, but CT is often preferred preoperatively by surgeons for vascular analysis. Image fusion with preoperative, postchemotherapy imaging helps defining the target volumes post-operatively taking into account the movement of organs after surgery.[28]

The accuracy of target volume definition in Hodgkin lymphoma is improved if the diagnostic fluoro-deoxy-glucose positron emission tomography CT has been performed in radiotherapy treatment position.[29]

Figure 5 (A) The thermoplastic raw material with three fixation points attached before it has been warmed and moulded to a patient's head. (B) A moulded head and shoulders immobilisation device with five-point fixation being decorated to make it appealing to a child. Images provided by University College London Hospitals.

Target volume delineation and outlining of OAR

Adequate delineation of the target volume is critical as highly precise techniques are less forgiving for even small errors than the wide field techniques of the past. Inadequate delineation may be accompanied by geographical misses and inferior local control. Equally important is the correct outlining of OAR since inaccuracies in their delineation may lead to increased toxicity.

Specific terminology has been developed for target volume definition in radiotherapy. The gross tumour volume (GTV) is the extent of the tumour as visible on diagnostic imaging. Following surgery, often a 'virtual GTV' has to be defined based on the preoperative size and location of the tumour. The GTV is then extended to form a clinical target volume (CTV) by taking into account possible microscopic spread or possibly invaded areas like adjacent lymph nodes for certain disease types. Typically, an isotropic expansion of a 5 mm up to 2 cm is used, depending on the characteristics of the tumour. In addition, surgical and pathology reports can be used to further define the CTV. This GTV-to-CTV margin can be cropped at natural barriers to spread such as bone or tentorium, or apparently uninvolved normal organs. An additional 'internal margin' may be added to create an internal target volume (ITV), taking into account tumour and/or organ motion as can be assessed by four-dimensional CT. To compensate for patient positional ('set-up') uncertainty and other possible small deviations in machine stability, a margin will be added to the CTV/ITV to produce a PTV. For OAR a similar margin can be added to form a planning risk volume.

Dose prescription

The prescribed total dose is highly disease specific and usually ranges between 10 and 70 Gy. Even for one disease type, the prescribed dose may vary to an extent depending on the stage and other risk factors. Except for SRS, low-dose TBI and some palliative treatments, this total dose is delivered in divided doses over the course of days or weeks ('fractionated'). In paediatric radiotherapy, the fraction size is usually limited to 1.8 Gy or less, since increasing fraction size is accompanied by increasing late toxicity. Standard fractionation is one fraction daily, 5 days per week.

Hypofractionation is the use of a higher dose per fraction to a lower total dose. This type of treatment is typically not given daily, but every 2 or 3 days. It is usually used for limited metastatic disease or to give an additional boost to a limited volume

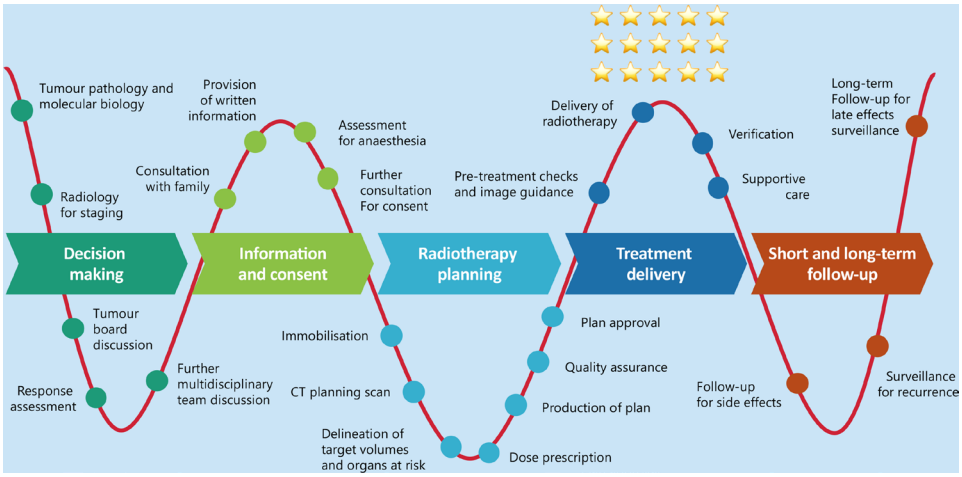

Figure 6 The treatment pathway. A flow diagram to show some of the more important steps in the typical radiotherapy pathway.

of residual disease. So far, it is mostly used in adults, but there is growing interest for paediatric application.

In hyperfractionation, two (or very rarely three) fractions a day are given. A typical example is TBI. Hyperfractionated accelerated radiotherapy uses a lower dose per fraction in a shortened total treatment time. Less late toxicity can be expected due to the lower fraction dose, but practical issues such as twice daily anaesthesia may preclude its use.

Plan generation and dosimetry

A radiotherapy plan is generated by a dosimetrist, or radiotherapy physicist, in consultation with the radiation oncologist. Although ideally the target should be given the prescribed dose while the OAR are minimally irradiated, very often a compromise between optimal target coverage and allowing some dose to OAR is needed. The International Commission on Radiation Units guidelines detail how to assess adequate target coverage and for OAR dose constraints have been developed, all of which should be verified before a plan can be signed as acceptable by the radiation oncologist.[30]

Quality assurance (QA)

QA) in radiotherapy concerns delineation, planning, patient position verification, dosimetry and machine QA.

It is considered good practice having a colleague review target volume delineation.[31] This process can be prospective review by external experts, which is becoming standard in clinical trials, and will provide timely feedback to the treating clinician. Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials is a project from the International Society of Paediatric Oncology-Europe in partnership with the European Organisation for Research and Treatment of Cancer to facilitate prospective QA across participating paediatric trials in Europe.[32]

Machine QA is performed by the radiation physicist and secures the optimal functioning of the equipment in all its aspects. Critical items are checked daily, while less critical or variable items will be monitored less frequently. Part of the maintenance is also performed by the provider.

Treatment delivery

Radiotherapy is an iterative process (figure 6). Prior to treatment delivery, the patient should be positioned exactly as during the preparatory CT simulation. IGRT is used to verify and adjust the patient's position. Once the optimal position has been confirmed, treatment commences. Depending on the complexity, this may take from just a few minutes to 45 min.

Supportive care

Patients are reviewed during treatment as prompt intervention may reduce acute toxicities such as nausea and vomiting, anorexia and weight loss, diarrhoea, skin reactions, mucositis and myelosuppression.

Additionally, a multidisciplinary team should be available to deal with emotional, psychological, social, financial and educational issues. In most cases where multimodality treatment is given, this will be in place already, but for those rare children with isolated radiotherapy alone treatments, referral to this supportive care team may be necessary.

Follow-up and late effects

Follow-up may be needed to detect local or metastatic relapse. In children who are considered to be cured, follow-up for long-term complications is important. Radiotherapy late effects can never be totally avoided. A multidisciplinary team dealing with late effects follow-up should consist of appropriate specialists in at least paediatric and radiation oncology, endocrinology, psychology, education, ophthalmology and audiology.[33]

CONCLUSIONS

- Paediatric radiation oncologists are a central part of the multidisciplinary team for children and young people's cancer.
- They work with a team of radiographers, physicists, play specialists and anaesthetists to deliver carefully selected, complex treatments for about one-third of children with malignant disease.
- Technical advances have allowed increasingly curative treatments to be delivered with fewer late effects than previously.
- Treatments are increasingly personalised and evidence based, with children treated wherever possible within clinical trials.

Twitter Mark Gaze @MarkGaze

Acknowledgements We would like thank the Radiotherapy Department of University College London Hospitals for providing some images, as indicated.

Contributors All authors are members of the European Society for Paediatric Oncology (SIOP Europe) Radiation Oncology Working Group's Steering Committee (https://siope.eu/siop-europe-radiation-oncology-working-group/). The concept for this Review came from MG and was developed and refined by all the authors

together. All authors contributed sections to the draft manuscript, which was then reviewed and modified by all authors. All authors approved the final submitted version of the manuscript, and all authors made equal contributions.

Funding MG is supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre and by the Radiation Research Unit at the Cancer Research UK City of London Centre Award (C7893/A28990).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study. Not applicable.

ORCID iD
Mark Gaze http://orcid.org/0000-0002-8344-7902

REFERENCES

1 Steliarova-Foucher E, Colombet M, Ries LAG, *et al*. International incidence of childhood cancer, 2001–10: a population-based registry study. *Lancet Oncol* 2017;18:719–31.
2 Public Health England. Children, teenagers and young adults UK cancer statistics report 2021. Available: http://www.ncin.org.uk/cancer_type_and_topic_specific_work/cancer_type_ specific_work/cancer_in_children_teenagers_and_young_adults/ [Accessed 28 Feb 2021].
3 Bishr MK, Zaghloul MS, Elmaraghi C, *et al*. The radiotherapy utilization rate in pediatric tumors: an analysis of 13,305 patients. *Radiother Oncol* 2021;154:220–6.
4 Jairam V, Roberts KB, Yu JB. Historical trends in the use of radiation therapy for pediatric cancers: 1973-2008. *Int J Radiat Oncol Biol Phys* 2013;85:e151–5.
5 Janssens GO, Timmermann B, Laprie A, *et al*. Recommendations for the organisation of care in paediatric radiation oncology across Europe: a SIOPE–ESTRO–PROS–CCI-Europe collaborative project in the framework of the JARC. *Eur J Cancer* 2019;114:47–54.
6 The Radiotherapy Board (made up of the Society and College of Radiographers, Institute of Physics and Engineering in Medicine and the Royal College of Radiologists). Ionising radiation (medical exposure) regulations: implications for clinical practice in radiotherapy. London: the Royal College of radiologists, 2020. Available: https://www.rcr.ac.uk/sites/default/files/guidance-on-irmer-implications-for-clinical-practice-in-radiotherapy.pdf [Accessed 18 May 2021].
7 Gains JE, Stacey C, Rosenberg I, *et al*. Intensity-Modulated Arc therapy to improve radiation dose delivery in the treatment of abdominal neuroblastoma. *Future Oncol* 2013;9:439–49.
8 de Mol van Otterloo SR, Christodouleas JP, Blezer ELA, *et al*. The momentum study: an international Registry for the evidence-based introduction of MR-Guided adaptive therapy. *Front Oncol* 2020;10:1328.
9 Hoeben BAW, Pazos M, Albert MH, *et al*. Towards homogenization of total body irradiation practices in pediatric patients across SIOPE affiliated centers. A survey by the SIOPE radiation oncology Working group. *Radiother Oncol* 2021;155:113–9.
10 Peters C, Dalle J-H, Locatelli F, *et al*. Total body irradiation or chemotherapy conditioning in childhood all: a multinational, randomized, Noninferiority phase III study. *JCO* 2021;39:295–307.
11 Wong JYC, Filippi AR, Scorsetti M, *et al*. Total marrow and total lymphoid irradiation in bone marrow transplantation for acute leukaemia. *Lancet Oncol* 2020;21:e477–87.
12 Bentzen SM, Constine LS, Deasy JO, *et al*. Quantitative analyses of normal tissue effects in the clinic (QUANTEC): an introduction to the scientific issues. *Int J Radiat Oncol Biol Phys* 2010;76:S3–9.
13 Harrabi SB, Bougatf N, Mohr A, *et al*. Dosimetric advantages of proton therapy over conventional radiotherapy with photons in young patients and adults with low-grade glioma. *Strahlenther Onkol* 2016;192:759–69.
14 Kahalley LS, Peterson R, Ris MD, *et al*. Superior intellectual outcomes after proton radiotherapy compared with photon radiotherapy for pediatric medulloblastoma. *JCO* 2020;38:454–61.
15 Minard-Colin V, Walterhouse D, Bisogno G, *et al*. Localized vaginal/uterine rhabdomyosarcoma-results of a pooled analysis from four international cooperative groups. *Pediatr Blood Cancer* 2018;65:e27096.
16 Chargari C, Haie-Meder C, Guérin F, *et al*. Brachytherapy combined with surgery for conservative treatment of children with bladder neck and/or prostate rhabdomyosarcoma. *Int J Radiat Oncol Biol Phys* 2017;98:352–9.
17 Aldridge MD, Peet C, Wan S, *et al*. Paediatric molecular radiotherapy: challenges and opportunities. *Clin Oncol* 2021;33:80–91.
18 Lee KA, Sharabiani MTA, Tumino D, *et al*. Differentiated thyroid cancer in children: a UK multicentre review and review of the literature. *Clin Oncol* 2019;31:385–90.
19 Wilson JS, Gains JE, Moroz V, *et al*. A systematic review of 131I-meta iodobenzylguanidine molecular radiotherapy for neuroblastoma. *Eur J Cancer* 2014;50:801–15.
20 Hovén E, Anclair M, Samuelsson U, *et al*. The influence of pediatric cancer diagnosis and illness complication factors on parental distress. *J Pediatr Hematol Oncol* 2008;30:807–14.
21 Skoutari A, Chounta E, Skenteris N, *et al*. Oncologic children undergoing radiotherapy: ways to alleviate the psychological burden: a review. *Rev Recent Clin Trials* 2021;16:166–72.
22 The Royal College of Radiologists,, Society and College of Radiographers,, Institute of Physics and Engineering in Medicine, Children's Cancer and Leukaemia Group. Good practice guide for paediatric radiotherapy, second edition. London, the Royal College of radiologists, 2018. Available: https://www.rcr.ac.uk/publication/good-practice-guide-paediatric-radiotherapy-second-edition [Accessed 8 May 2021].
23 Hiniker SM, Bush K, Fowler T, *et al*. Initial clinical outcomes of audiovisual-assisted therapeutic ambience in radiation therapy (AVATAR). *Pract Radiat Oncol* 2017;7:311–8.
24 Ntoukas SM, Ritchie T, Awrey S, *et al*. Minimizing general anesthetic use in pediatric radiation therapy. *Pract Radiat Oncol* 2020;10:e159–65.
25 Freislederer P, Kügele M, Öllers M, *et al*. Correction to: recent advances in surface guided radiation therapy. *Radiat Oncol* 2020;15:244.
26 Paulson ES, Crijns SPM, Keller BM, *et al*. Consensus opinion on MRI simulation for external beam radiation treatment planning. *Radiother Oncol* 2016;121:187–92.
27 van der Heide UA, Frantzen-Steneker M, Astreinidou E, *et al*. Mri basics for radiation oncologists. *Clin Transl Radiat Oncol* 2019;18:74–9.
28 Janssens GO, Melchior P, Mul J, *et al*. The SIOP-Renal tumour Study Group consensus statement on flank target volume delineation for highly conformal radiotherapy. *Lancet Child Adolesc Health* 2020;4:846–52.
29 Metwally H, Courbon F, David I, *et al*. Coregistration of Prechemotherapy PET-CT for Planning Pediatric Hodgkin's Disease Radiotherapy Significantly Diminishes Interobserver Variability of Clinical Target Volume Definition. *Int J Radiat Oncol Biol Phys* 2011;80:793–9.
30 International Commission on radiation units and measurements: radiation therapy. Available: https://www.icru.org/current-activities-of-icru/radiation-therapy/ [Accessed 18 May 2021].
31 The Royal College of Radiologists. *Radiotherapy target volume definition and peer review – rcr guidance*. London: The Royal College of Radiologists, 2017. https://www.rcr.ac.uk/system/files/publication/field_publication_files/bfco172_peer_review_outlining.pdf
32 Kelly SM, Effeney R, Gaze MN, *et al*. QUARTET: a SIOP Europe project for quality and excellence in radiotherapy and imaging for children and adolescents with cancer. *Eur J Cancer* 2022;172:209–20.
33 Skinner R, Wallace WHB, Levitt GA, eds. *Therapy based long term follow up: Practice Statement. United Kingdom Children's Cancer Study Group*. Second ed, 2005. https://www.cclg.org.uk/write/MediaUploads/Member%20area/Treatment%20guidelines/LTFU-full.pdf