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Evolving Radiotherapy Techniques in Paediatric Oncology

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Abstract

Aims: Childhood cancer is rare and survival of childhood cancer has increased up to 80% at 5 years after diagnosis. Radiotherapy is an important element of the multimodal treatment concept. However, due to growing tissue, children are particularly sensitive to radiation-related side-effects and the induction of secondary malignancies. However, radiotherapy techniques have continuously progressed. In addition, modern treatment concepts have been improved in order to minimise long-term effects. Today, radiotherapy is used for various tumour types in childhood, such as sarcomas and tumours of the central nervous system.
Materials and methods: External beam therapy with either photons or protons and brachytherapy are predominantly used for the treatment of childhood tumours. Technical developments and features, as well as clinical outcomes, for several tumour entities are presented.
Results: The development of radiotherapy techniques, as well as risk-adapted therapy concepts, resulted in promising outcome regarding tumour control, survival and therapy-related side-effects. It is assumed that proton therapy will be increasingly used for treating children in the future. However, more data have to be collected through multi-institutional registries in order to strengthen the evidence.
Conclusion: The development of radiotherapy techniques is beneficial for children in terms of reducing dose exposure. As compared with other modern and highly conformal techniques, particularly proton therapy may achieve high survival rates and tumour control rates while decreasing the risk for side-effects. However, clinical evidence for modern radiotherapy techniques is still limited today. An optimal patient triaging with the selection of the most appropriate radiation technique for each individual patient will be an important goal for the future.

Key words: Childhood cancer; proton therapy; radiation techniques; radiation therapy

Introduction

Cancer is a rare disease in childhood [1,2]. Children at the age of 0–4 years display the highest tumour incidence. Tumours of the central nervous system (CNS) (17.2%) account for the second largest proportion following leukaemias in this age group [3]. In the last decades, survival after childhood cancer has increased considerably, with now about 80% at 5 years after diagnosis [4]. Radiotherapy is an important element in the multimodal treatment for many childhood tumours [5], offering an important opportunity when the limits of surgical possibilities have been reached. However, due to their growing tissue, children are particularly sensitive to radiation-induced adverse effects and the induction of secondary malignancies [6,7]. Therefore, new therapy concepts now focus in particular on reducing long-term sequelae, being of fundamental importance for quality of life [8]. The basic principle of radiotherapy is to tailor treatment intensity according to the individual risk profile. Continuous development of radiation techniques has offered the use of modern, precise techniques in radiotherapy, enabling improved sparing of normal tissue today. Modern imaging equipment, risk-adapted concepts and new irradiation techniques can ensure precise application of the ionising dose to the tumour-bearing tissue and increased feasibility [9]. In addition to external beam therapy with electrons, photons and protons, short distance methods, such as interstitial or intracavitary brachytherapy, can also restrict dose burden to surrounding tissue.

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All of this contributed significantly to a better protection of healthy tissue and an improved feasibility in young patients. Particularly in the treatment of solid tumours of the CNS or bones and soft tissue, radiation therapy continues to be a very important component of the multimodal therapy strategy. For other tumours, such as lymphomas, nephroblastomas or neuroblastomas, radiation therapy could be restricted to higher-risk patients.

Evolving Role of Radiotherapy for the Treatment of Childhood Malignancies

The treatment of childhood malignancies has made remarkable progress in recent decades through the further development of increasingly precise radiation techniques [10]. The current treatment standard in most centres is three-dimensional conformal photon therapy and photon-based intensity-modulated radiotherapy (IMRT). Today, imaging techniques, such as X-ray systems, computed tomography or magnetic resonance imaging, are in use to increase precision in planning and daily treatment application (image-guided radiotherapy; IGRT). Historically, before modern IGRT was introduced, treatment was applied using two-dimensional radiotherapy. Within a simulation procedure with X-rays, treatment fields relied only on the bony anatomy, as three-dimensional imaging could not be integrated in planning software and delivery [11,12]. With the advent of improved imaging modalities after the availability of modern accelerators, advanced electronics and software, three-dimensional radiotherapy and IMRT emerged and gained clinical relevance [11,13]. Planning of radiotherapy and adjustment of the radiotherapy fields to the actual tumour volume were enabled [12,13]. In addition, improved imaging and planning methods encompassed the ability to better identify and define normal tissue to be protected from high radiation doses (organs at risk; OAR) (Figure 1). In addition, it could facilitate generating and verifying dose constraints for normal tissue [11]. Particularly in children, being highly sensitive to radiotherapy due to their immature tissue [14], these technical advances are considered to be of substantial importance. In recent years, proton therapy has increasingly been used besides modern photon modalities. Unlike conventional photon therapy, proton therapy does not use high-energy electromagnetic waves, but charged particles, namely hydrogen ions (protons). These physical characteristics make protons particularly attractive for tumours requiring high doses [13] and malignancies where sparing of OARs is critical for the avoidance of late effects (Figure 2). Also, within the field of proton beam therapy, considerable developments with regard to image guidance and beam applications have been carried out. Consequently, a shift from passive scattering to active scanning techniques has evolved [15].

With regard to risk factors and risk adaptation of treatment, various parameters, such as histopathology, genetics, biology or staging, extent of surgery and radiotherapy, have been understood to affect treatment outcome. However, in particular, age at treatment has been recognised as an important factor to impact on radiotherapy-induced adverse effects (Figure 3). Young age correlates significantly with the expected risk for late effects. This fact was analysed by several investigators, in particular with regard to neurocognitive functioning and muscle and bone growth showing a higher risk of late effects in younger age [14]. In contrast to adults, the long-term documentation of late effects of children is of particular importance, as children's growth and neurocognitive development continues over years and decades after radiotherapy is completed. An extended follow-up with documentation of the degree of severity is therefore mandatory for examining the outcome [14]. As a result of introducing risk-adapted strategies, radiation doses and volumes could be reduced for many patients.

Photon-based Radiotherapy

Radiotherapy has been routinely administered in paediatric oncology since the 1930s. After orthovoltage and cobalt therapy, radiotherapy with photons has been continuously developed over the last decades. After the use of two-dimensional techniques was replaced by three-dimensional conventional techniques in the 1980s, the three-dimensional conformal technique is now treatment standard [16] and was further developed when moving to intensity modulation. Today, radiotherapy is used in childhood neuroblastoma, lymphoma, brain tumours and soft-tissue and bone sarcoma [17].

Technical Aspects of Photon-based Radiotherapy

Ionising radiation and its influence on (tumour)cells are the background for photon-based radiotherapy [18]. Traversing through the body, photons deposit energy as a result of interaction with electrons of the respective volume. However, due to the photons' properties, their peak dose deposition occurs shortly after entering the tissue and then decreases continuously until the exit of the body. Therefore, conventional radiotherapy is not ideally targeting tumours located in the depth of the body. Conventional three-dimensional radiotherapy was further developed in the 1990s and IMRT is now recognised as an advanced method of conventional radiotherapy. Compared with conventional radiotherapy, the non-uniformity of beams and the inverse treatment planning are central features of IMRT. IMRT allows improved conformity (particularly in concave volumes), better sparing of normal tissue, dose painting and dose escalation as compared with conventional photon-based radiotherapy. Today, different delivery techniques for IMRT, such as segmental and dynamic IMRT, may be used. IMRT thus has features that could make it particularly interesting for the irradiation of children. However, the effort of clinicians in planning and quality assurance is higher using IMRT and the duration of treatment per session increases. An increased total body irradiation dose in IMRT is also reported, potentially inducing the risk for secondary malignant neoplasms [16].

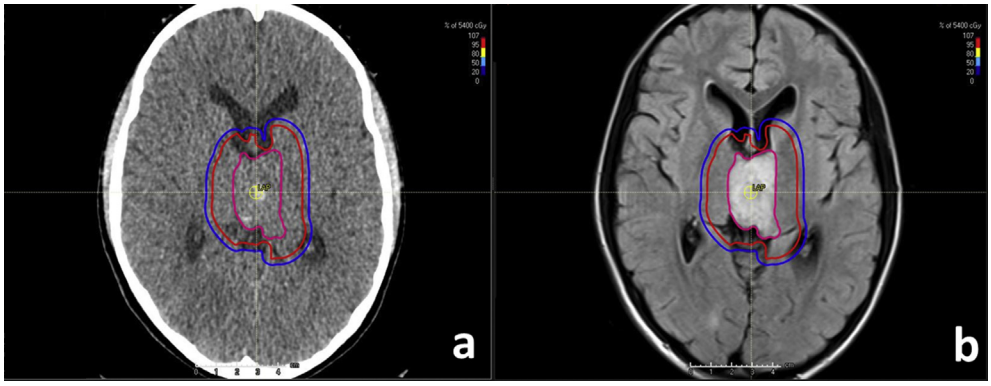

Fig 1. Planning computed tomography scan (a) fused with magnetic resonance image (b) for contouring of a patient with diffuse midline glioma (generated in RayStation®). The pink line corresponds to the gross tumour volume, the red line shows the clinical target volume and the blue line is the planning target volume.

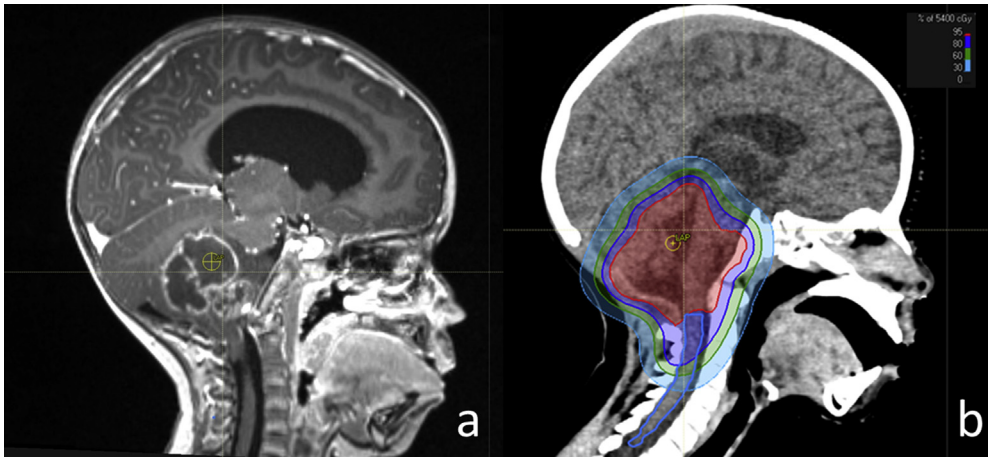

Fig 2. Diagnostic magnetic resonance image (sagittal section) (a) with corresponding pencil beam scanning proton therapy plan and dose distribution (b) for a child with ependymoma in the fourth ventricle (total dose of 54 Gy in 30 fractions, plans generated using RayStation®). Red area: region covered by 95% isodose line; dark blue area: 80% isodose; green area: 60% isodose; light blue area: 30% isodose.

Clinical Experiences of Photon-based Radiotherapy in Selected Childhood Tumour Entities

Results of photon-based radiotherapy for brain tumours, head and neck malignancies and bone and soft-tissue sarcomas (STS) are promising with regard to children. IMRT could potentially be used to achieve either higher local intensity or improved sparing of normal tissues. However, dose levels to the target were kept similar, as suggested from the multidisciplinary trials. The superiority of IMRT over conventional photon radiotherapy in terms of conformality and dose homogeneity was reported from dosimetric studies addressing different tumour sites [19,20]. IMRT can help to spare critical organs [21]. No severe acute or late toxicities were reported in a series on IMRT for various childhood tumour entities [22]. However, 10 of the 31 patients experienced local failure, although doses of radiotherapy were according to the standard and the pattern of local failure reflected the heterogeneity in the study population regarding tumour entity [22].

Outcome after IMRT for brain tumours is promising. After IMRT in childhood craniopharyngioma, progression-free survival (PFS) and overall survival (OS) after 10 years were 60.7 and 83.8%, respectively, which is similar to results after proton therapy (see below) [23]. Late toxicities appearing after IMRT were visual deficits, panhypopituitarism, hypothalamic dysfunction, cerebrovasculopathy and neurocognitive toxicity. However, the majority of complications were already present before IMRT. With regard to visual impairments, 44% of the patients experienced a resolution of deficits at last follow-up, whereas 56% had stable or worse deficits [23]. For low-grade gliomas, 8-year PFS and OS were 78.2 and 93.7% after IMRT, respectively. For patients aged 5 years or younger at the time of IMRT, PFS was significantly worse than for older patients [24]. For IMRT of the posterior fossa in childhood medulloblastoma, 5-year OS and PFS were 72 and 68.3%, respectively, and local control (LC) was promising [25]. After IMRT, transient imaging changes in eight children (15%) occurred, one of them being considered a symptomatic radionecrosis and 15% of children developed leptomeningeal recurrence [26].

Conventional radiotherapy and IMRT also resulted in favourable results for sarcomas and other entities. After IMRT or conventional radiotherapy for childhood

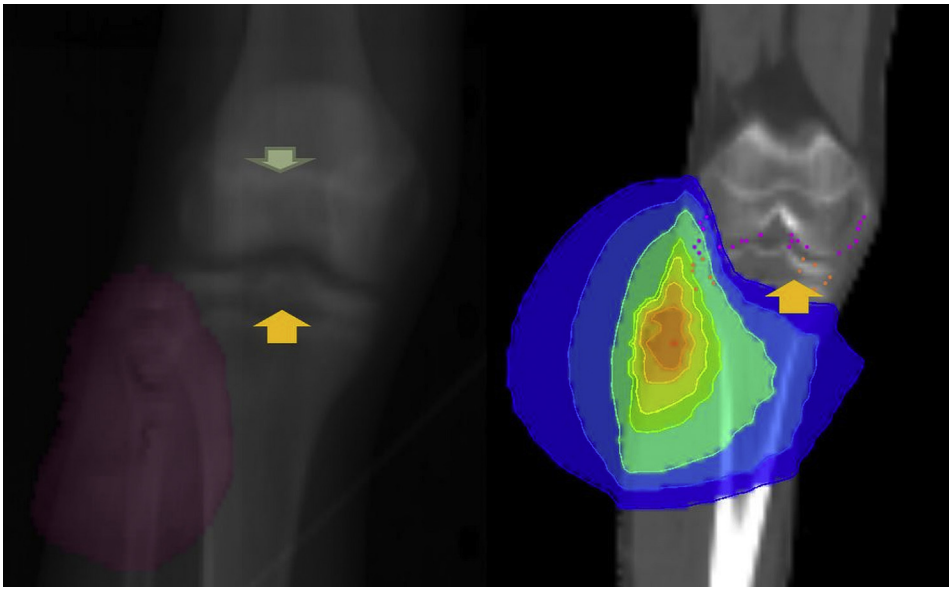

Fig 3. Dose plan from a tomotherapy treatment for a 13-year-old child with a sarcoma of the right calf achieving epiphyseal sparing to avoid growth disturbances.

rhabdomyosarcoma (RMS) of the head and neck, the 5-year survival rate was 94%. Freedom of distant metastases as well as LC rates were 89% after 5 years. High-grade toxicities and treatment interruptions were not observed [27].

In childhood nasopharyngeal carcinoma treated with simultaneous integrated boost SIB-IMRT, rates of locoregional recurrence-free survival (RFS), distant metastasis-free survival, disease-free survival and OS were 97.1, 88.2, 85.5 and 88.2% after 5 years, respectively. However, the number of patients with grade 1–2 xerostomia and ototoxicity 2 years after SIB-IMRT was 66.7 and 62.5%, respectively [28].

Proton Therapy

The potential advantage of proton therapy was first reported in 1946, when physicist Robert Wilson proposed protons for clinical use due to their special physical properties [29]. Proton therapy is a promising instrument to either, if necessary, intensify the local therapy or to reduce the risk of acute side-effects and the development of secondary tumours after tumour treatment and thus to increase the quality of life [30,31]. Although the availability and distribution of proton therapy is poor when compared with other techniques [32], sustainable progress has been made in recent years. Particularly for the treatment of tumours in the vicinity of critical organs, such as CNS tumours or in very early childhood, interest in proton therapy is growing (Figure 4). Proton therapy is therefore increasingly used in many countries [33]. At the end of 2016, about 175 000 patients worldwide had been treated with particles, about 150 000 of them with protons [34].

Technical Aspects of Proton Therapy

Due to its physical characteristics, proton therapy allows a focused and adjustable dose delivery, avoiding a larger bath of medium and low doses to the surrounding tissue. The superior dose distribution of protons is based on their energy loss (linear energy transfer) when interacting with tissue. Protons traverse tissue in a straight line. Their energy loss increases with decreasing pace of the proton, resulting in a steep fall-off of energy (Bragg Peak) when the beam stops [29,32,35]. To use proton therapy in the treatment of tumours, protons are accelerated to high energies (70–230 MeV) [35]. Depending on the proton's initial energy, the range of the proton in the tissue can be determined. Therefore, proton therapy offers the chance to precisely irradiate deep-seated tumours when needing high radiation doses or when being localised close to sensitive tissue [29].

In order to use the proton beam for clinical application, the beam is modelled to cover the individual target volumes. The beam delivery of protons is currently carried out in either traditional passive scattering or more modern active scanning mode. For scattered techniques, patient-individual hardware helping to adjust the proton beam to the tumour volume needs to be manufactured. However, in tumours with extensive distal volume, passively scattering delivery techniques may be disadvantageous regarding tissue proximal to the tumour. Active scanning techniques have been used since the mid-1990s. As scanning is based on the magnetic steering of single beamlets and the target volume is irradiated layer by layer, typically no apertures are required. Scanning techniques can achieve even more conformal coverage of target volumes in some tumours and can enable intensity-modulated proton therapy (IMPT). IMPT, which is considered to be the most conformal and modern form of proton therapy, offers the opportunity to optimise dose distribution by using computer-assisted methods that enable the best possible dose application to tumour tissue while at the same time protecting the normal tissue as much as possible. Although comparative evidence between IMPT and IMRT is still pending, it is expected that

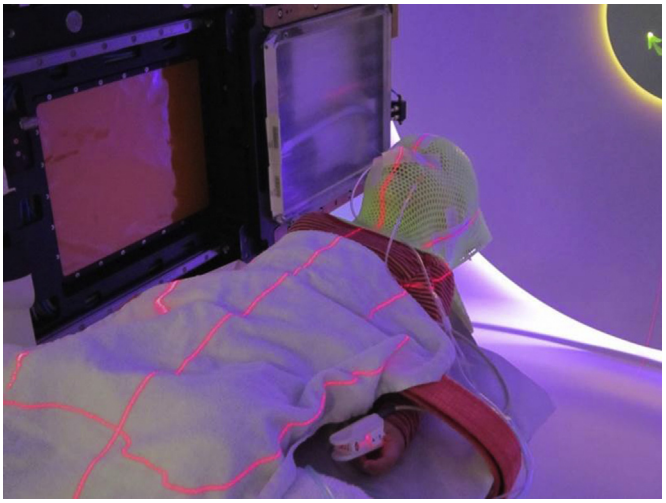

Fig 4. Positioning and immobilisation of a 16-month-old child in deep sedation treated for ependymoma in the posterior fossa with pencil beam scanning proton therapy.

IMPT will be predominantly used in the future [35]. Proton therapy can also be used for the irradiation of irregular and large target volumes, such as craniospinal irradiation (CSI). CSI plays a significant role in the management of CNS tumours such as medulloblastoma or high-risk ependymoma, atypical teratoid/rhabdoid tumours in children and germ cell tumours carrying the risk of leptomeningeal seeding. Today, CSI with protons is already considered to be the standard of care in children as it allows optimal target coverage and a reduction of dose to the OARs. Although OS and RFS were similar for children with medulloblastoma having CSI with protons or photons [36], the use of proton therapy could reduce acute toxicity as compared with photon-based CSI for patients with medulloblastoma [37]. However, CSI with protons is technically challenging and evidence is scarce [38]. Some questions remain open though. Differences in relative biological effectiveness (RBE) between photons and protons need to be investigated in order to be able to compare these techniques and to carry out optimal patient triage and treatment planning [39].

Clinical Experiences of Proton Therapy in Selected Childhood Tumour Entities

Today, proton therapy is used for the treatment of different tumour entities. In addition to CNS tumours, sarcomas of the soft tissues and bones in various localisations are candidates for proton therapy. Although large, prospective studies on children receiving proton therapy are still scarce, the results of proton therapy are promising in terms of survival, tumour control and toxicities. Current retrospective and prospective studies on the use of proton therapy for cohorts of children with intracranial ependymoma reported 3-year LC rates of 83–85%, PFS rates of 76% and OS rates of 90–95% [40,41]. For tumours of the posterior fossa, the 3-year Common Terminology Criteria for Adverse Events (CTCAE) grade 2 rate of brainstem toxicity was 5.5% [40]. Five-year LC and OS rates were 78% and 84%, respectively [42]. However, only a few publications focus on a clinical comparison of different radiotherapy techniques for treating children with ependymoma. In a study comparing treatment with IMRT and proton therapy in localised intracranial ependymoma, 3-year PFS was significantly better after proton therapy (82% versus 60% with IMRT; $P = 0.031$) and significantly less recurrences were observed (17% versus 55% with IMRT; $P = 0.005$) [43]. Also, for re-irradiation of recurrent or metastatic ependymoma, proton therapy appeared to be effective. In children who had initially received photons or protons, 3-year PFS was 28.1% after re-irradiation with proton therapy. Three-year OS after first disease progression was 78.6% [44].

For craniopharyngioma, improved sparing of OAR and high conformality were reported using protons [45]. The clinical outcome for children was promising. LC and OS rates after 3 years were 100% after proton therapy [46]. When comparing children irradiated with proton therapy or IMRT, OS, nodular failure-free survival (NFFS) and cystic failure-free survival (CFFS) after 3 years were 96, 95 and 76%, respectively, for the entire group. No significant differences between the treatment groups were reported for either OS, CFFS, NFFS or late toxicity [47]. Results regarding toxicities using proton therapy in craniopharyngioma are encouraging. In a series on 16 children treated with proton therapy, no treatment-related grade 3 toxicities occurred during treatment. The most common grade 1 adverse events during irradiation were cutaneous events and fatigue [48]. A series for treatment with proton therapy including craniopharyngioma quantified a 2-year incidence of grade 3 toxicity of 2.1%. Patients' age <5 years was one of the identified factors to increase the risk of toxicity [49].

Some studies on medulloblastomas are available. For very young children receiving proton therapy for medulloblastoma or supratentorial primitive neuroectodermal tumour, results were promising, with local failure and OS rates of 7.7 and 85.6%, respectively [50]. In a cohort of 59 children receiving CSI and boost to the tumour bed for medulloblastoma, outcome with regard to ototoxicity, reasoning index and working memory was acceptable with a cumulative incidence of hearing loss (grade 3–4 according to Pediatric Oncology Group ototoxicity scale) of 12% after 3 years and 16% after 5 years, respectively. At 5 years, PFS and OS were 80 and 83%, respectively [51], and were comparable with results after IMRT.

In childhood RMS, radiotherapy is an important treatment component [52,53] and proton therapy has been increasingly used to treat children with RMS. When comparing IMRT and conventional radiotherapy with proton therapy, proton therapy showed superior sparing of healthy tissue adjacent to the tumour for different sites [54–56]. Five-year OS of 78%, 5-year event-free survival (EFS) of 69% and 5-year LC of 81% after proton therapy of children with localised or metastatic RMS were reported [57]. For children with parameningeal RMS, results were lower, with 5-year LC of 67.5–77% [57,58] and 5-year OS of 64–73% [57–60]. Five-year PFS, Failure-free survival (FFS) and EFS were 72%. For acute $\geq$ grade 3 toxicities, results

were about 15% and for late adverse events results ranged between 0 and 18% [57,58,61]. Proton therapy was also used for Ewing sarcoma of childhood. Japanese data reported OS of 88.6, 73.1 and 56.8% after 1, 3 and 5 years, respectively [62]. Another study reported EFS, LC and OS of 60, 86 and 89% of paediatric patients after 3 years. Toxicities during proton therapy occurred mainly as mild or moderate skin reactions and serious late toxicities only occurred as haematological events. The cumulative incidence of secondary malignancy was 7% after 2 years and 15% after 3 years [63], supporting the feasibility of proton therapy.

In summary, proton therapy seems to be used for a large variety of childhood malignancies, particularly when larger volumes, young ages and high doses are concerned.

Brachytherapy

In contrast to external beam modes, such as conventional radiotherapy or proton-based radiotherapy, brachytherapy is a short distance treatment not exposing larger volumes to an ionising dose [64,65]. Although most tumours in childhood are treated using external beam radiation in a multimodal setting, brachytherapy is said to be advantageous regarding adverse events in specific cases, when the volume of radiotherapy is limited, easily accessible and well defined. Experiences are reported for brachytherapy in some STS of the head and neck or genitourinary system [66]. Brachytherapy is also applied in retinoblastomas [67,68]. However, the results of brachytherapy are difficult to compare to modern external beam modalities as many aspects of brachytherapy, such as indication, dose, volume and treatment duration, differ from those of irradiation with external sources [69]. For retinoblastoma in children, brachytherapy is often recommended for unilateral tumours located anterior to the equator. Lesions suitable for brachytherapy are typically less than 10 mm in thickness and have no virtuous seeding [70].

Technical Aspects of Brachytherapy

Brachytherapy is a form of radiation therapy where tumours are irradiated with inserted radioactive sources being deposited into or close to the tumour volume. The dose fall-off of the energy is extremely steep. This leads to the opportunity to limit the dose to normal tissue [64,65,71] and to enable a highly focal delivery of dose to the tumour volume [71]. However, as irradiated volumes and planning target volumes are relatively small compared with external beam radiation, brachytherapy is mainly useful in small tumour volumes and localised disease [64,65,71].

Radiation sources used in brachytherapy are usually available as sealed sources and might be used as needles, seeds and tubes. Energy sources such as ^{192}iridium (Ir), ^{125}iodine (I), ^{103}palladium (Pd) and ^{90}strontium/yttrium (Sr/Y) can be used [65]. For the treatment of retinoblastoma, ^{103}Pd, ^{125}I, ^{90}Sr and ^{106}ruthenium (Ru) are used [70].

Depending on the source's properties and decay, brachytherapy can be administered either temporarily or permanently [64,65]. The two major types of source implantation are either intracavitary or interstitial. Brachytherapy is applied as either low-dose, medium-dose or high-dose treatment [65]. However, high-dose rate remote afterloading with ^{192}Ir is predominantly used today.

Clinical Experiences of Brachytherapy in Selected Childhood Tumour Entities

Brachytherapy is applied similarly in children and adult patients [64]. However, in children, brachytherapy has been predominantly used for STS and adenocarcinomas in the gynaecological area [66]. Results of brachytherapy for children with sarcomas of different sites (e.g. pelvis) treated with high-dose intraoperative brachytherapy showed LC, EFS and OS after 5 years of 63, 33 and 43%, respectively. Acute and late higher-grade toxicities occurred in 2.5% of treatments in the acute and 5.3% of patients in the late follow-up [72]. A recent prospective series reported on the outcome of children treated with brachytherapy alone, brachytherapy plus external conventional radiotherapy or conventional radiotherapy alone for high-grade non-RMS STS of the extremity/trunk and at other sites. After 5 years, the incidence of local failure, EFS and OS was 14.8, 49.3 and 67.9%, respectively. The technique of radiotherapy was not significantly associated with an increased local failure [73]. Similar results were reported for children with progressive pilocytic astrocytoma [74]. When comparing results of brachytherapy and external beam radiotherapy for head and neck RMS for a selected cohort of patients surviving 2 or more years, OS after 5 years was 76.9 and 75%, respectively. However, survivors treated with brachytherapy showed a lower risk of developing high-grade adverse events than survivors treated with external beam radiotherapy [75].

Also, outcomes are promising for retinoblastoma treated with brachytherapy. In a cohort with 134 retinoblastoma patients treated with brachytherapy, tumour control rate was 94.4% at 5 years and the estimated rate of eye retention was 86.5%. At 5 years after irradiation, brachytherapy-associated complications were retinopathy (21.6%), optic neuropathy (21.1%) and cataract (17.4%). These complications were reported to be significantly more frequent when brachytherapy was carried out as second radiotherapy after previous irradiation [76].

Future Directions

The use of risk-adapted therapy concepts and technical advances in radiation therapy techniques will continue to contribute to achieve optimal tumour control and to increase the chance of reducing therapy-related side-effects. However, deep understanding of individual risk factors, normal tissues, functional body regions and dose tolerances has to be gained in order to take maximal benefit from technical solutions. It can be assumed that proton beam therapy will be increasingly used for childhood cancer in the future. Today, comparative clinical data on any modern

technique over another is sparse. As childhood cancer is rare and ethical aspects have to be considered, conducting prospective and randomised trials on technologies is unlikely. However, the collection of large data in multi-institutional registries will further improve evidence of dose effects and can help in patient triaging. International collaborations (e.g. International Society of Paediatric Oncology [SIOP] and Paediatric Radiation Oncology Society [PROS]) offer expanding collaborations and generate guidelines. In addition to classic clinical end points such as OS and LC, in future the focus will also be on end points such as quality of life [58], neurocognitive outcome, bone growth and muscle development [14].

Summary and Conclusion

The significant developments in radiation therapy techniques together with risk-adapted treatment strategies have proven to offer advantages for the treatment of children in order to limit dose exposure. Particularly proton therapy as a modern and highly conformal irradiation technique may be able to improve survival and tumour control and reduce adverse effects when compared with other external beam therapy techniques. Nevertheless, it should be noted that for any modern radiation technique, the clinical evidence is still limited and some questions remain open. So far, studies on irradiation of children often report on small cohorts, have a retrospective design and limited follow-up. Still, within international co-operation more data will emerge to improve the understanding of dose effects and the advantages or disadvantages of modern radiation techniques for the individual patient.

Conflict of interest

The authors declare no conflict of interest.

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