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REVIEW

Clinical Insight on Proton Therapy for Paediatric Rhabdomyosarcoma

Sabina Vennarini[1], Francesca Colombo[1,2], Alfredo Mirandola[3], Stefano Chiaravalli[4], Ester Orlandi[5], Maura Massimino[4], Michela Casanova[4], Andrea Ferrari [iD][4]

[1]Pediatric Radiotherapy Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [2]Department of Oncology and Hemato-Oncology (DIPO), University of Milan, Milan, Italy; [3]Medical Physics Unit, Clinical Department, National Center for Oncological Hadrontherapy (CNAO), Pavia, Italy; [4]Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy; [5]Radiation Oncology Unit, Clinical Department, National Center for Oncological Hadrontherapy (CNAO), Pavia, Italy

Correspondence: Andrea Ferrari, Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Via G. Venezian, Milano, MI, 1 20133, Italy, Tel +39 02 23902588, Fax +39 02 23902648, Email andrea.ferrari@istitutotumori.mi.it

Abstract: This paper offers an insight into the use of Proton Beam Therapy (PBT) in paediatric patients with rhabdomyosarcoma (RMS). This paper provides a comprehensive analysis of the literature, investigating comparative photon-proton dosimetry, outcome, and toxicity. In the complex and multimodal scenario of the treatment of RMS, clear evidence of the therapeutic superiority of PBT compared to other modern photon techniques has not yet been demonstrated; however, PBT can be considered an excellent treatment option, in particular for young children and patients with specific primary sites, such as the head and neck area (and especially the parameningeal regions), genito-urinary, pelvic, and paravertebral regions. The unique depth-dose characteristics of protons can be exploited to achieve significant reductions in normal tissue doses and may allow an escalation of tumour doses and greater sparing of normal tissues, thus potentially improving local control while at the same time reducing toxicity and improving quality of life. However, access of children with RMS (and more in general with solid tumors) to PBT remains a challenge, due to the limited number of available proton therapy installations.

Keywords: rhabdomyosarcoma, pediatric, proton beam therapy, local treatment, radiotherapy

Introduction

Rhabdomyosarcoma (RMS) is the most frequent soft tissue sarcoma in children and adolescents, with around 400 new cases in the 0–19-year-old population each year in Europe,[1] and 50–60 in Italy.[2,3] RMS is a highly malignant tumour characterised by local invasiveness and a high propensity to metastasize.[4] It can occur in any part of the body, with a higher frequency in the head and neck (around 35% of the cases) and genito-urinary (25%) regions, with a high variability of clinical presentation. With current international cooperative protocols and more modern multimodal therapies, overall survival (OS) is reportedly over 70% for patients with localised RMS.[5–8] However, patient outcome is influenced by many clinical variables, including tumour size and local invasiveness, regional lymph node involvement, distant metastases, tumour site, extent of residual tumour after initial surgery, and patient's age. These prognostic factors have been considered in the risk-adapted stratification systems adopted by the international rhabdomyosarcoma community over the years in order to determine how intensively to treat patients.[9] In patients whose clinical variables predict a worse prognosis, multimodal treatment is generally intensified to improve the cure rate, while in patients with more favourable features, reduction of treatment intensity is considered to limit possible side effects, without jeopardising outcomes.[10] With a better understanding of genomic features and tumorigenesis, risk stratification is becoming more refined. The identification of molecular variables capable of accurately describing intrinsic biological aggressiveness is gradually leading to a more personalised approach to treatment. FOXO1 fusion status is included in all the current RMS stratification.[11] Other molecular features will probably be considered in the near future, including MYOD1 mutation and TP53 and MYCN amplification.[12] In other words, the use of more intensive chemotherapy or the indication to prescribe

1125

radiotherapy (and its dose) will soon be related to genomic and molecular findings rather than to the site of the tumour or the degree of initial surgery.

The treatment of RMS is complex and necessarily multimodal, requiring the involvement of multiple health-care professionals. In principle, all patients with RMS should be considered as having micro-disseminated disease at the time of diagnosis, and should always receive systemic treatment. Complementary local treatment modalities – surgery and radiotherapy – are key parts of multimodal treatment. As a matter of fact, local progressions or relapses represent around 60% of treatment failures:[13] local control often represents a challenge in the therapeutic approach to RMS patients, due to the local invasiveness of the tumour but also due to the extreme heterogeneity of clinical presentations, according to the different age of the patients, for example, or the specific site of tumour origin.

Surgery is often considered to be the preferred local treatment option, but feasibility can be challenging due to many variables such as tumour size and local extent.[14,15] The clinical approach is particularly complex in specific tumour sites. A good example is RMS arising in a parameningeal site. Parameningeal tumours are often deemed inoperable due to their location, and even in the limited cases where surgery is attempted, achieving negative margins becomes challenging. Resection in these areas may cause important functional damage to vital surrounding organs and can severely compromise cosmesis.[16,17] In such cases, radiotherapy is necessarily integrated, supporting an incomplete surgical resection, or mostly having an exclusive role in controlling the disease locally.[18] Noteworthy is the historically innovative local treatment approach "AMORE" (Ablative surgery, MOuld technique after loading brachytherapy, and surgical REconstruction), which has shown a lower incidence and severity of adverse events than external beam radiotherapy while maintaining adequate overall survival.[19] Moreover, this approach has proved to be feasible and effective in salvage treatment after local recurrence.[20] Another specific example is RMS of the bladder/prostate, for which the combination of local treatments for functional organ preservation is currently the gold standard (ie conservative surgery and interstitial brachytherapy).[21,22]

The combination of conservative surgery and radiotherapy, together with timing and sequence, or radiotherapy techniques and doses aims to optimise disease control and minimise loss of organ function and other late sequelae.[23] In this scenario, the continuous technological advancements in radiotherapy techniques have contributed to an increasingly therapeutic landscape for Proton Beam Therapy (PBT).

Proton Beam Therapy: General Aspects

The ongoing pursuit of improved efficacy and reduced toxicity in paediatric oncological treatments has led to significant technological advancements, including PBT, which is a crucial development in this direction. PBT is a sophisticated technology and currently one of the most extensively utilised forms of hadron therapy, which involves the application of external ion beams for treating solid tumours.

Proton beams were first proposed more than 70 years ago by the physicist Robert R. Wilson.[24] In the early 1990s, PBT was used in a clinical environment for the first time in Loma Linda (CA, USA). Since then, many facilities have been built or are under construction,[25] and PBT can now be considered a solid therapeutic option offered to patients in many places around the world.

The intrinsic physical and biological characteristics make protons (and other ion species like helium, carbon, and oxygen) particularly effective in external radiotherapy.[26] In particular, the protons' inverse depth-dose profile compared to photons and the sharp distal fall-off after the maximum deposition of energy, known as Bragg peak, guarantee that the organs at risks traversed by the beams can be better spared compared to photons.[27] This proton characteristic also allows a smaller number of beam ports to be used, thus largely reducing the low doses given to patients. Moreover, the biological characteristic of protons makes the "cell-killing" effect more effective than photons. The Relative Biological Effectiveness (RBE) is 1.1, which means 10% higher than photons. This value, however, is not to be considered fixed, being even higher in the distal part of the dose distribution.[28] Most of the facilities in operation adopt the active pencil beam scanning (PBS) technique, in which a pencil beam is scanned in transversal directions (up to 40*40 cm field size) by scanning magnets, while the depth along the beam direction is changed, increasing the beam energy. Cyclotrons or synchrotrons are the main accelerators used in proton therapy, typically spanning the proton energy range in water from 30 to 300 mm, thus consenting to treatments of many tumour sites.

PBT is widely indicated for paediatric neoplasms.[29] The growing precision in defining irradiation volumes, aided by dedicated imaging techniques, along with the distinct physical and radiobiological characteristics of proton beams, offer potential

advantages that translate into clinical benefits. These benefits include reduced dosimetric exposure of organs at risk near the tumour site and preservation of healthy tissue by delivering the full dose to the target area.[30] This latter aspect is strongly associated with the development of late multi-organ toxicity and, more importantly, with the reduction in the occurrence of secondary radiation-induced malignancies resulting from radio-chemotherapy treatments. These concepts hold vital significance in paediatric oncology for the long-term well-being of surviving patients. The importance of Quality of Life (QoL) for long-term survivors has gained increasing recognition, now holding weight comparable to the curative aspect.[31–33]

The unique physical characteristics of protons enable significant dose escalation, leading to improved cure rates and overall survival in specific paediatric radio-resistant malignancies. This is especially beneficial for localised sarcomas situated in anatomically challenging regions that are difficult to access through surgery, while also minimising radiation exposure to nearby radiosensitive organs.[34]

Finally, the reduction of acute toxicity during treatment, along with improved therapeutic compliance (which has an impact on the psychological well-being of the patient) and increased tolerance to treatments, enables the implementation of concurrent treatment regimens, combining PBT with surgery and concomitant systemic treatment. This approach shows promising advancements in disease control and overall survival for these neoplasms, which typically require multimodal regimens.[35]

PBT centres around the world have witnessed significant growth in the past decade.

In the United States, in particular, over 50% of paediatric patients undergo proton therapy for tumours of the central nervous system, bone sarcomas, soft tissue sarcomas (with RMS being the most representative), chordoma and chondrosarcoma, retinoblastoma, neuroblastoma, Hodgkin's lymphoma, radiation-induced neoplasms, malignancies associated with genetic syndromes, and others.[36]

The absence of clinical trials comparing photons and protons (which are not feasible for various reasons, including an ethical standpoint), the limited number of patients with sufficient follow-up time, the high costs (resulting in limited treatment access), and the relatively small number of PBT centres worldwide (compared to photons) have been major criticisms voiced by the scientific community regarding the use of PBT. These concerns have called for caution, careful interpretation of results, and the need for comprehensive clinical and radiological follow-up of the provided data.[37]

The radiotherapy community has made tremendous efforts to date, with the establishment of various consortia and registries that enable the global collection of data. One such example is the Pediatric Proton/Photon Consortium Registry (PPCR),[38] where data sheets for photonic and proton treatments of major paediatric neoplasms are shared and collected.

Nonetheless, there has been a notable decrease in costs and a rapid increase in the number of proton therapy centres worldwide. Currently, there are over 60 operational systems globally (25 located in North America and Asia, 16 in Europe, and one in South Africa). As a result, there has been a rise in the number of children receiving proton treatment for elective indications.[39]

Furthermore, technological advancements in proton therapy facilities, including the introduction of gantry systems and the transition from passive scattering to active scanning techniques, such as PBS and intensity-modulated proton beam therapy (IMPT), have greatly improved the precision and dose conformity for complex targets like RMS.[40]

Nevertheless, as pointed out in the discussion session, PBT should be managed with extreme care due to the physical, dosimetric, and delivery issues inherent to the technique itself. Only after a solid learning curve should a dedicated and well-trained clinical personnel (in particular physicians and physicists) approach pediatric treatments with particle beams.

Proton Beam Therapy in Rhabdomyosarcoma

PBT has garnered significant attention in the treatment of paediatric RMS in recent years. Current protocols in both the United States and Europe now include provisions for PBT, outlining specific planning methods tailored to the use of protons.[41–43]

In this review, we have conducted a comprehensive analysis of the literature, starting with a meticulous assessment of comparative photon-proton dosimetric studies. Subsequently, we have thoroughly examined the outcome and toxicity studies involving children treated with protons for RMS across various anatomical sites. The bibliographic study was conducted in the month of August 2023, using the NCBI PubMed, Embase, and Cochrane Library databases. The search terms used were as follows: proton therapy, rhabdomyosarcoma, pediatric, and paediatric. Only manuscripts in English were consulted. Twenty-one studies were identified. Tables 1-3 report the main findings, with a specific focus on comparative dosimetric findings (for 7 studies), outcome (for 13 studies), and toxicity (for 14 studies), respectively.

Table 1 Comparative Dosimetric Studies

Authors (Publication Year)	No. of Patients	Tumor Site	Radiation Therapy Technique	Coverage of Target Volumes	Mean Maximum Dose (DMax)	Sparing OAR
Ladra et al (2014)[44]	54	Orbit, H-N, Perineal, Biliary, PM, B-P, Extremity, Chest/abdomen, Perianal	IMRT - PBT (passive scattered proton RT)	Mean CTV V95 = 100% for both modalities (range PBT 97–100%; IMRT 98–100%) Mean CTV V100 = 98% PBT (95–100%); 99% IMRT (97–100%)	PBT 107% (101–112%) IMRT 106% (103–110%)	Significant OAR sparing by PBT in 26/30 structures, for both central and lateral primaries. Parallel OAR and OAR sensitive to low doses of RT showed more benefit with PBT.
Heinzelmann et al (2011)[45]	1 (21 months)	B-P	HDR-BT - IMRT - IMPT	Similar coverage of PTV.	-	Dmean rectum and testis lower with IMPT than BT and IMRT. Growth plates: IMPT achieved the most favorable solution.
Cotter et al (2011)[46]	7	B-P	IMRT - PBT	Mean CTV V95 ≥ 99% for both modalities	PBT 103% IMRT 108%	PBT led to a significant decrease in Dmean of bladder, testis, femoral heads, growth plates and pelvic bones compared to IMRT.
Kozak et al (2009)[47]	10	PM	IMRT - PBT	Mean CTV V95 ≥ 99% for both modalities	PBT 113% IMRT 112%	PBT provided superior dose sparing for all OAR. For all organs evaluated except the lenses, PBT provided greater dose asymmetry.
Fogliata et al (2009)[48]	5	1 mediastinum, 1 anus, 3 other tumors	HT- RA- IMPT	PTV V95 HT 98.2% (± 1.2%) IMPT 93.6% (± 6.5%) RA 98.2% (± 2%)	D1% HT 113.1 ± 9.9% IMPT 114.1 ± 5.7% RA 113%± 12%	IMPT resulted significantly better than either RA or HT as expected reducing of the dose integral, the mean dose, and V10 Gy.
Yock et al (2005)[43]	7	Orbital	3D CRT - PBT	-	-	PBT shows an advantage in limiting the dose to the brain, pituitary, hypothalamus, temporal lobes, and orbital structures.
Miralbell et al (2000)[49]	4	Orbital and Paraorbital tumors (1 PM RMS)	IMRT - IMPT	Similar coverage of PTV.	-	DMean inferior for all OAR

Notes: V95 (%) = volume receiving 95% of the prescription dose; V100 (%) = volume receiving 100% of the prescription dose; Dmax (%) = dose maximum (expressed as percent of prescribed dose); Dmean = mean dose received by the organ; D1% = dose received by 1% of the volume (target volume).
Abbreviations: IMRT, intensity modulated radiation therapy; PBT, proton bean therapy; HDR-BT, high dose rate brachytherapy; IMPT, intensity modulated proton therapy; HT, helical tomotherapy; RA, rapidArc; 3D CRT, 3D conformal radiotherapy; CTV, clinical target volume; PTV, planning target volume; H-N, head-neck; PM, parameningeal; B-P, Bladder-Prostate; OAR, organ at risk.

Table 2 Survival Outcomes and Local Control

Authors (Publication Year)	N. of Patients	Median Age, Years (Range)	Histology	Tumor Site (Favorable/ Unfavorable)	Local Control (LC)	Overall Survival (OS)	Progression-Free Survival (PFS) or Event-Free Survival (EFS)
Childs et al (2012)[50]	17	3.4 (0.4–17.7)	Alveolar = 4 Embryonal = 11 Undifferentiated = 2	Fav = 0 Sfav (PM) = 17	NA	5-yr (64%)	FFS 5-yr (59%)
Ladra et al (2014)[51]	57	3.5 (0.6–19.5)	Alveolar = 16 Embryonal = 41	Fav = 19 (orbit 19, H-N 13, perineal 1, biliary 1) Sfav = 38 (PM 27, B-P 5, extremity 3, chest/ abdomen 2,) perianal 1	3-yr (81%) 5-yr (81%)	3-yr (81%) 5-yr (78%)	EFS 3-yr (73%) EFS 5-yr (69%)
Leiser et al (2016)[52]	82	4.5 (0.8–15.5)	Alveolar = 9 Embryonal = 74	Fav = 24 (orbit 17, H-N 3, GU 4) Sfav = 59 (PM 46, B-P 6, others 7)	5-yr (78.5%)	5-yr (80.6%)	NA
Weber et al (2016)[53]	39	5.8 (1.2–16.1)	Alveolar = 0 Embryonal = 38 Undifferentiated = 1	Fav = 0 Sfav (PM) = 39	NA	5-yr (73%)	PFS 5-yr (72%)
Mizumoto et al (2018)[54]	55	5.0 (0–19)	Alveolar = 18 Embryonal = 31 Others = 6	Fav (H-N) = 37 Sfav = 18 (PM 3, B-P 8, others 7)	1-yr (95.6%) 2-yr (93%)	1-yr (91.9%) 2-yr (84.8%)	PFS 1-yr (81.6%) PFS 2-yr (72.4%)
Indelicato et al (2019)[55]	30	4.8 (1–11.4)	Alveolar = 0 Embryonal = 30	Fav (Orbit) = 30 Sfav = 0	5-yr (97%)	5-yr (100%)	DFS 5-yr (97%)
Ludmir et al (2019)[56]	46	5.2 (0.1–15.6)	Alveolar = 14 Embryonal = 32	Fav = 21 (orbit 13, H-N 8) Sfav (PM) = 25	5-yr (84%)	5-yr (76%)	PFS 5-yr (57%)
Doyen et al (2019)[57]	46	5.1 (1.3–17.5)	Alveolar = 18 Embryonal = 28	Fav = 0 Sfav (PM) = 46	2-yr (83.8%)	2-yr (88.9%)	EFS 2-yr (76.9%)
Bradley et al (2020)[58]	24	3.5 (1–20.3)	Alveolar = 24 Embryonal = 0	Fav = 0 Sfav (PM) = 24	3-yr (66%)	3-yr (58%)	DFS 3-yr (40%)
Indelicato et al (2020)[59]	31	2.6 (1–20)	Alveolar = 7 Embryonal = 24	Fav = 0 Sfav (Pelvic) = 31	5-yr (83%)	5-yr (84%)	PFS 5-yr (80%)
Buszek et al (2021)[60]	62	3.3 (0.1–15.6)	Alveolar = 22 Embryonal = 71 Not specified= 1	Fav = 33 (orbit 13, H-N 8, GU 9, biliary 3) Sfav = 61 (PM 25, B-P 19, extremity 4, trunk/thorax 11, others 2)	4-yr (85%)	4-yr (71%)	4-yr (63%)
Parekh et al (2021)[61]	37	1.3 (0.1–1.9)	Alveolar = 12 Embryonal = 25	Fav = 9 (orbit 2, H-N 6, GU 1) Sfav = 28 (PM 8, B-P 12, extremity 3, trunk 3, pelvis 2)	5-yr (83%)	5-yr (83%)	PFS 5-yr (78%)
Suzuki et al (2021)[59]	48	3.8 (0.2–15.1)	Alveolar = 22 Embryonal = 26	Fav (N-N) = 24 Sfav = 24 (GU 13, extremity 2, trunk 3, others 6)	3-yr (79.3%)	3-yr (94.2%)	PFS 3-yr (68.8%)

Notes: Tumor Site Favorable (Fav): Orbit, Head and Neck not parameningeal (H-N), Perineal, Biliary, Genitourinary not bladder/prostate (GU). Tumor Site Unfavorable (Sfav): Parameningeal (PM), Bladder/Prostate (B-P), Extremity, Chest/Abdomen, Perianal, Trunk/Thorax.
Abbreviations: NA, Not Available; LC, Local control; OS, Overall Survival; PFS, Progression Free Survival; EFS, Event Free Survival; DFS, Disease Free Survival.

Table 3 Acute and Late Toxicities and Incidence of Radiation Induced Neoplasms (Only Toxicities of Grade Greater Than or Equal to 3 Were Reported)

Authors (Publication Year)	Median Follow-Up (Months)	Acute Toxicity	Late Toxicity	Radiation Induced Cancer (Yes/No)
Childs et al (2012)[50]	60 (24–129.6)	NA	Failure to maintain height velocity, endocrine deficits, mild facial hypoplasia, failure of permanent tooth eruption, dental caries, chronic nasal/sinus congestion.	No
Ladra et al (2014)*[51]	47 (14–102)	G3: odynophagia, dermatitis, mucositis Non-toxicity ≥ G4	G3: unilateral cataract, chronic otitis, retinopathy with decreased visual acuity Non-toxicity ≥ G4	No
Leiser et al (2016)*[52]	55.5 (0.9–126.3)	G3: mucositis, dermatitis Non-toxicity ≥ G4	G3: cataract, hypoacusis Non-toxicity ≥ G4	Yes
Weber et al (2016)*[53]	41 (9–106)	NA	G3: unilateral cataract, hypoacusis Non-toxicity ≥ G4	No
Mizumoto et al (2018)[62]	24.5 (1.5–320.3)	G3: hematologic toxicities, mucositis, dermatitis G4: hematologic toxicities	Non-toxicity ≥ G3	NA
Indelicato et al (2019)[54]	48 (6–114)	Mild periorbital edema, erythema, epiphora, photosensitivity, and conjunctival erythema	Cataracts, keratoconjunctivitis, severe dry eye, chronic sinusitis, recurrent epistaxis, shortened tooth roots, facial asymmetry, eyelid ptosis and entropion. Growth hormone and gonadotropin deficiency.	NA
Ludmir et al (2019)*[55]	46.8 (6–106.8)	G3: mucositis, keratopathy and conjunctivitis Non-toxicity ≥ G4	G3: cataracts, bone hypoplasia and facial asymmetries, unilateral hearing loss, unilateral epiphora and punctal stenosis, dental caries Non-toxicity ≥ G4	NA
Doyen et al (2019)*[57]	34 (6.4–56.8)	Toxicity G3: mucositis, dermatitis, dry eye, hematologic toxicities Non-toxicity ≥ G4	G3: dry eye syndrome, hyperpigmentation, loss of hair and sinusitis, cataracts Non-toxicity ≥ G4	NA
Bradley et al (2020)[56]	28.8 (3.6–67.2)	Non-toxicity ≥ G4	Non-toxicity ≥ G4	NA
Indelicato et al (2020)[58]	50.4 (12–116.4)	NA	Toxicity ≥ G3 leg length discrepancy, fracture of S1, gonadal failure	NA
Buszek et al (2021)[60]	48 (4.4–135.6)	NA	NA	NA
Parekh et al (2021)*[61]	61.2 (8.4–146.4)	Non-toxicity ≥ G3	G3: entropion, cataracts, scoliosis > 45°, anatomic hypoplasia Non-toxicity ≥ G4	NA
Suzuki et al (2021)*[59]	39.6 (4.8–141.6)	G3: mucositis, cystitis, dermatitis, hematological toxicities G4: hematological toxicities	Tooth growth disorder, facial asymmetry, trismus, cataracts, recurrent caries, hypothyroidism, growth hormone deficiency, recurrent otitis media, pollakiuria, ovarian dysfunction, myelodysplastic syndrome.	NA
Hol et al (2023)[63]	93.6 (24–274.8)	NA	Reduction in facial growth, facial asymmetry, facial deformation	NA

Note: *Toxicity was graded according to Common Terminology Criteria for Adverse Events (CTCAE).
Abbreviations: NA, Not Available: G3/4:Grade ¾.

Advancements in radiotherapy techniques over the past decade have enabled the reduction of irradiation volumes and improved dose conformity to the target area. This has contributed to a reduction in acute toxicities and long-term sequelae associated with the treatment itself. These advancements are particularly significant in the paediatric field and have a profound impact on RMS cases that necessitate high doses of radiotherapy.[42]

Comparative Dosimetric Studies

Initial comparative studies between photon therapy and PBT for orbital and/or parameningeal RMS were conducted by Ladra et al in the early 2000s.[43,49] Although these studies involved a limited number of patients, they quickly demonstrated comparable outcomes in terms of dose coverage and homogeneity within the target volume for both techniques. Moreover, PBT exhibited a clear advantage by significantly reducing the radiation dose to organs at risk.

Of particular interest are the findings from a series reported by Kozak KR et al, focusing on 10 patients with parameningeal RMS. These locations are particularly critical due to their proximity to structures involved in cognitive functions, growth, vision, and hearing. The study compared the treatment plans using intensity-modulated radiotherapy (IMRT) and proton beam therapy (PBT). Both techniques demonstrated optimal coverage of the target volume, with a Mean Clinical Target Volume (CTV) V95 ≥99% for both IMRT and PBT. However, in two cases treated with protons, a Dmax (dose maximum, expressed as percent of prescribed dose) >120% was observed. PBT exhibited dosimetric advantages in all organs evaluated, although statistical significance was not reached for the ipsilateral cochlea and mastoid and was borderline for the ipsilateral parotid gland. It is important to note that the greater dose asymmetry observed in all organs except the crystalline lens warrants further evaluation, as it may potentially lead to an increased risk of late facial asymmetry.[47]

Cotter et al, on the other hand, presents data from a comparative dosimetric study involving seven male patients with bladder/prostate RMS. The study consistently demonstrates the equivalence between IMRT and PBT in terms of dosimetry on the treatment volume (Mean CTV V95 ≥99% for both techniques). Additionally, PBT offers an advantage by reducing the average radiation dose to critical organs such as the bladder, testicles, femoral heads, growth plates, and pelvic bones.[46] These findings hold great significance due to the substantial occurrence of late sequelae reported in literature for these disease sites. In fact, only 40% of patients retain normal bladder function, and there is a risk of long-term sexual and reproductive dysfunctions.[64,65]

More recently, Ladra et al conducted the first comparative dosimetric study on patients enrolled in a prospective clinical study, which included a substantial series of patients with various disease sites affected by RMS. The extracted data confirmed the similarity in irradiated volume coverage, with Mean CTV V95 = 100% for both techniques and Mean CTV V100 = 98% for PBT and 99% for IMRT. The study also demonstrated a higher sparing rate of surrounding healthy tissues with the use of PBT. Specifically, PBT plans exhibited reduced doses to organs at risk in all tumour sites and in 26 out of 30 examined structures, with a notable advantage observed in both central and lateralised lesions, particularly in the latter. Moreover, a more pronounced benefit was observed for parallel organs (such as temporal lobes, mandibles, and pelvic bones) and organs sensitive to low doses (such as hypothalamus and gonads), compared to organs arranged in series (such as chiasma, brainstem, and spinal cord).[44]

Outcome and Toxicity

Considering the undeniable superiority of protons in sparing homo- and contralateral critical structures, as evidenced by comparative studies, Ladra et al initiated the first prospective Phase II study in 2004. The study aimed to collect outcome and toxicity data from a large series of patients with RMS treated with PBT.[51] The cohort consisted of 57 enrolled patients with diverse disease sites, including 27 with parameningeal RMS and 19 with orbital RMS. In this heterogeneous population, local disease control was comparable to the historical series of patients treated with photons. With a median follow-up of 47 months, the 3-year and 5-year overall survival (OS) rates were 81% and 78%, respectively. The 3-year and 5-year event-free survival (EFS) rates were 73% and 69%, respectively. The local control (LC) rate was 81% at both 3 and 5 years. Orbital neoplasms showed excellent outcomes, with a 5-year EFS of 92% and LC, like those reported in the IRSG-IV (Intergroup Rhabdomyosarcoma Study Group protocol IV) and COG-D9602 (Children Oncology Group) trials.[66,67] Among parameningeal RMS patients, the local recurrence rate was 23%, consistent with previously published data from the IRSG-IV and COG-D9803 trials.[68] The 5-year EFS was 60%, comparable to the findings reported by Yang et al and Eaton et al.[69,70] Regarding treatment tolerance, only 17% of patients experienced grade 3 acute toxicities, including dermatitis, odynophagia, and mucositis, which was significantly lower than the rates reported in the IRSG-IV

trial. Additionally, only three patients developed grade 3 late sequelae, including cataract, retinopathy with diffuse acuity reduction, and chronic otitis.

The initial report by the Paul Scherrer Institute,[52] which focused on patients treated with PBS-PBT, is of particular significance. The study revealed a 5-year LC and OS rate of 78.5% and 80.6%, respectively, which is comparable to the previously mentioned study by Ladra et al. However, it is important to note that this report also indicated a higher incidence of grade 3 acute and late toxicities. This outcome was likely attributed to the inclusion of patients with advanced disease and larger irradiation volumes, which could have contributed to the increased toxicities observed. Leiser et al also reported the occurrence of second malignant neoplasms (SMN) in two patients, without any established oncological predisposition or genetic syndromes.[52] It is worth noting that according to the analysis of the Surveillance, Epidemiology, and End Results (SEER) registries, the risk of SMN was found to be independent of previous radiotherapy treatments.[71]

A large series reported by Leiser et al (83 RMS cases, 59 arising in unfavourable sites) reported 5-year OS and LC rate of 80.6% and 78.5%, respectively, with no cases of grade 4 acute toxicity and 12/83 grade 3 acute toxicity (mainly mucositis and dermatitis). Regarding late toxicity, no grade 4 and 3 grade 3 toxicity (cataract and hearing loss) were reported.[52]

Doyen et al retrospectively described a cohort of 46 parameningeal RMS patients, reporting a 2-year OS, EFS, and LC of 88.9%, 76.9%, and 83.8%, respectively.[57] The study also highlighted good tolerance to radiotherapy, with only 4.4% of patients experiencing late grade 3 sequelae, including cataracts, dry eye syndrome, sinusitis, and hyperpigmentation. These percentages are comparable to those reported by Weber et al and Child et al.[53] Given the high local recurrence rate observed in parameningeal RMS, the authors conducted further evaluation on the location of recurrences in relation to the dosimetry of the initial radiotherapy treatment.[50,53] The analysis revealed that the recurrence site received an average D95 (dose to 95% of the target volume) of 52.8 Gy and an average dose of 54.5 Gy. These findings might indicate the potential benefit of dose escalation in overcoming the radio-resistance of these tumours. However, the effectiveness and safety of this therapeutic approach still require further evaluation.

A recent multicenter transatlantic study assessed four distinct local treatments (EBRT, PBT, AMORE, and Paris method) for patients with RMS exhibiting orbital, H-N, and PM localization with a focus on facial dysmorphisms. Patients deemed ineligible for surgical treatment, mainly due to intracranial disease extension, carotid artery encasement, and perineural spread, were not included in the analysis. The entire group of patients displayed a statistically significant decrease in facial growth and an increase in facial asymmetries and deformities when compared with healthy subjects. Patients with orbital RMS exhibited a more favorable profile compared to the other two localizations. The sub-analysis conducted on the RMS PM group indicated a significantly superior toxicity profile for PBT in comparison to EBRT and Paris method. However, it is important to note that the results may have been influenced by the shorter follow-up period and younger age of these patients compared to those treated with other techniques. This is because facial dysmorphisms are age-dependent processes.[63]

The largest prospective series of RMS patients treated with PBT as part of a multimodal therapeutic approach was recently published by Buszek.[60] This series includes a diverse range of sites, with a majority of patients having an unfavourable prognosis (61 out of 94 patients). Survival data, including OS, progression-free survival (PFS), and LC at 4 years (71%, 63%, and 85% respectively), appear to be comparable to modern series using IMRT or PBT. Notably, the absence of marginal relapses in patients treated with PBT provides additional reassurance regarding its effectiveness.[60,63,72,73]

Discussion

The primary objective of the treatment strategy in RMS protocols has always been to enhance survival rates, despite being aware of the significant toll it takes on young patients in terms of toxicity and the long-term impact of treatment-related toxicities on survivors. In historical European trials, the use of radiotherapy has been approached with caution, with attempts to avoid its use whenever possible in low-risk treatment categories and in children aged 3 years and younger.

In the International Society of Pediatric Oncology – Malignant Mesenchymal Tumour (SIOP-MMT) studies, the extremely conservative approach to radiotherapy aiming to cure a significant proportion of patients without irradiation

led to controversial results.[74] For patients with orbital RMS, for example, strategies for avoiding radiotherapy showed that children that did not receive radiotherapy had an increased risk of relapse, but they could be salvaged with second-line therapy. On the other hand, a large proportion of cases were treated successfully without the use of radiotherapy, with no radiation-related dysfunction and cosmetic problems.[75] However, these favourable results were not achieved in other tumour sites: a study on young children with parameningeal RMS demonstrated how the cure of patients with disease arising in this site remained unlikely without systematic use of radiotherapy.[76] More in general, effort to omit irradiation generally produced higher rates of local relapse than in patient populations treated more consistently with radiotherapy, but in many cases also lower overall survival rates.[74,77] In general agreement, radiotherapy is considered to be safely withheld in limited subsets of RMS patients, such as those with embryonal RMS completely resected (with micro-scopically free margins) at diagnosis.

Results from historical European trials led paediatric oncologists and radiotherapists to re-evaluate the role of radio-therapy in the European paediatric Soft Tissue Sarcoma Study Group (EpSSG) RMS 2005 study. The EpSSG RMS 2005 trial (conducted from 2005 to 2016) supported a more systematic use of radiotherapy: as a result, 86% of patients with high- and very high-risk localised RMS received radiotherapy for local disease control, resulting in an increase in 3-year EFS from 55% to 67%[6] for high-risk and from 39% to 56% for very high-risk (node-positive alveolar) patients.[78]

While it is important to recognise the role of systematic use of radiotherapy in achieving these outcomes, it is imperative, on the other hand, to consider the need to reduce medium-to-long-term sequelae and therefore to introduce the concept of advancing radiotherapy techniques.

As an alternative to conventional radiotherapy, PBT has gained prominence due to its radiobiological characteristics in the treatment of various paediatric tumours, including RMS. Published studies, as shown in our review, teach us that comparative photon-proton dosimetric studies have clearly demonstrated a significant advantage in reducing irradiation to organs at risk and a notable decrease in integral dose, while maintaining adequate coverage of the disease target. Outcome analyses have demonstrated comparable disease control when compared to well-established photon series, with lower rates of acute and late toxicities in specific RMS sites.

Despite the limits of published studies (ie limited number of reported series, mostly single-centre experiences, relatively small sample sizes, only one randomised study), available data suggest that PBT has demonstrated effective-ness and safety in the comprehensive local treatment of patients with RMS.

Since it is clear that a formal evidence of superiority of PBT over other radiotherapy modalities is still needed, the indication for protons in RMS and the development of dedicated clinical trials should always be discussed in a multidisciplinary setting and evaluated within the pediatric oncology community.

Despite the increase in the number of proton therapy centres worldwide, access to PBT remains a challenge. A North American study involving 12,101 children with solid malignancies included in the National Cancer Data Base (period 2004–2013) reported that 8% of patients received PBT, with the proportion increasing between 2004 (1.7%) and 2013 (17.5%). The use of PBT was more frequent in younger patients and was affected by socioeconomic factors, ie patients with private/managed care and those with higher median household income and educational attainment were more likely to receive PBT.[79]

It is therefore extremely important to define shared indications for patients with RMS.

There is a general agreement to consider PBT especially recommended for young children (ie under the age of 3) in order to minimise exposure to medium-to-low radiation doses, which can significantly affect long-term side effects and the overall quality of life for survivors. The devastating side effects of radiotherapy on growing tissues and immature organs of infants and very young children (that often have tumours disproportionate to their body mass) make local control particularly challenging in these patients.[80] In the EpSSG RMS 2005 study, 33.6% of infants (less than 12 months of age) received radiotherapy.[81] Very young patients should be considered the first candidates for PBT to have the best sparing of organs at risk[61] (Figure 1).

Other specific recommendations concern the disease site. In particular, PBT should be indicated, in principle, in unfavourable sites, such as the head and neck area (and especially the parameningeal regions), genito-urinary, pelvic, and paravertebral regions. In these locations, complete surgery may not be feasible in most cases, and surrounding organs at risk may be particularly sensitive to radiation. In these cases, the use of PBT allows for dose escalation. This approach
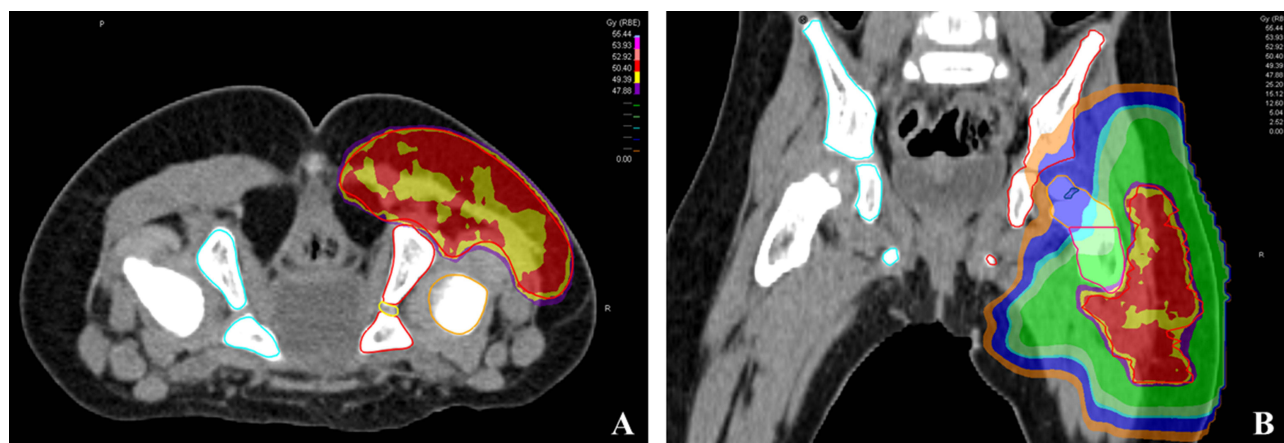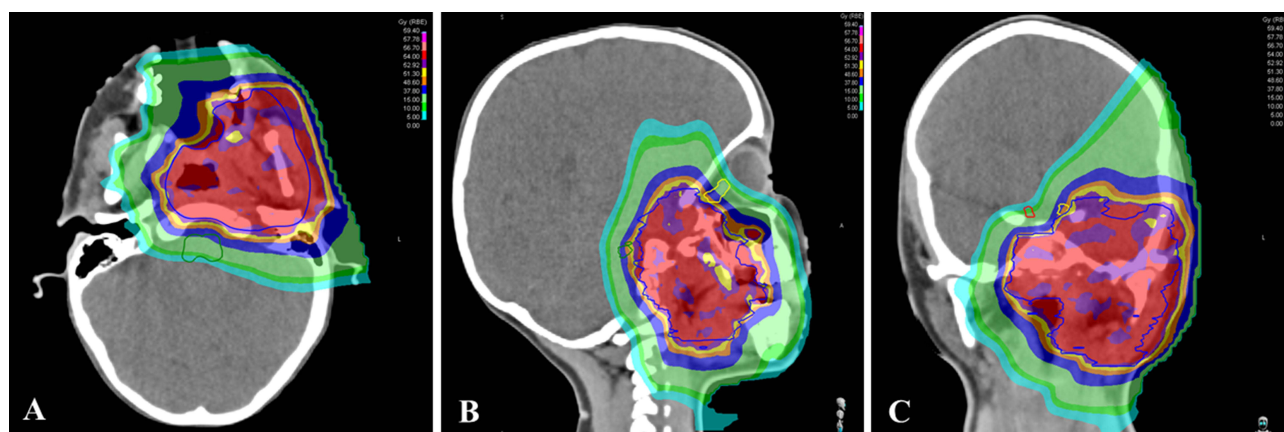
Figure 1 2-year-old girl with alveolar rhabdomyosarcoma of the right gluteus.
Notes: (**A**) Robust pencil beam scanning intensity-modulated proton beam therapy (PBS-IMPT) dose plan in axial view (prone position). Red contour: clinical target volume (CTV). Color wash represents 100% prescription dose (red); 98% (yellow); 95% (purple). (**B**) Robust PBS-IMPT dose plan in coronal view. Red contour: CTV. Color wash represents 100% prescription dose (red); 98% (yellow); 95% (purple); 50% (green); 25% (light green); 10% (blue); 5% (orange).

can improve local control while minimising radiation exposure to nearby organs. In addition, the reduced irradiation of surrounding tissues (ie mucosae), especially at medium-low doses, is particularly beneficial in improving compliance with concomitant chemotherapy treatments and reducing the occurrence of acute toxicity (Figure 2).

Unequal and unilateral locations with a favourable prognosis, such as the orbit, were among the first to be investigated in terms of dosimetry.[49] Miralbell described four cases with orbital and paraorbital location, showing that – with equal coverage and homogeneity of the target volume – there was a greater sparing of OARs with PBT, particularly in the low- and medium-dose regions. Indeed, the significant advantage of PBT over photons was immediately evident, with the preservation of contralateral organs near the target and a reduction in the integral dose.

The female genital tract and bladder/prostate represent specific and challenging tumour sites. In such cases, brachytherapy should be considered as the primary treatment mode for dose distribution.[82] However, given the age of these children, external radiotherapy with protons may play a role and is often utilised. A comprehensive comparison of brachytherapy and PBT is not available.

Figure 2 3-year-old child with parameningeal rhabdomyosarcoma.
Notes: Robust pencil beam scanning intensity-modulated proton beam therapy (PBS-IMPT) dose plan in axial (**A**), sagittal (**B**) and coronal (**C**) view. Red contour: CTV. Color wash represents 100% prescription dose (red); 98% (purple); 95% (yellow); 90% (orange); 70% (blue); green, light green and light blue represent the low doses (15, 10, and 5 GyE, respectively).

1134

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Cancer Management and Research 2023:15

Further investigations and discussions are needed on the indication of PBT in certain regions, such as the abdomen, retroperitoneum, and specific muscle areas of the trunk adjacent to the chest. In these cases, a specialised team of knowledgeable physicians and physicists plays a crucial role in determining the appropriate use of PBT.

Particular care should be addressed in managing range uncertainties in PBT that could possibly cause suboptimal dose distributions and treatment plans. Unlike photons, two severe consequences can occur due to the potential shift of the proton sharp distal dose fall-off: underestimation of dose to the target or an overdosage to the organs at risk distal to beam direction.[83] Range uncertainties arise from organ motion, setup and anatomical variations, dose calculation approximations, and biological considerations. In order to account for both setup errors and range uncertainties, robust plan optimisation[84] is highly recommended when using protons. Moreover, in particular for moving targets and when beams are passing through moving regions, an evaluation of the organs motion is needed. For these cases, mitigation strategies should be applied, both in CT simulation and treatment phases, such as breath holding and respiratory gating.

Timing of radiotherapy, and in particular its combination with surgery, represents an important aspect that needs to be investigated. There are very few data comparing pre-operative and post-operative radiotherapy in children with RMS. In adult patients with soft tissue sarcomas, pre-operative radiotherapy can limit the target volume, allowing the surrounding tissue to be spared, and therefore potentially minimising long-term side effects, although more serious wound complications have been reported.[85] This aspect is currently being studied in a randomised fashion within the ongoing EpSSG overarching study for children and adults with Frontline and Relapsed RhabdoMyoSarcoma (FaR-RMS) (NCT04625907). Concerning PBT, the role of pre-operative radiotherapy with protons, particularly in certain potentially operable areas, warrants further investigation, as the limitation of irradiation to healthy tissues could potentially reduce acute post-surgical sequelae.

The Far-RMS includes two other randomised questions on radiotherapy, ie to determine whether dose escalation of radiotherapy improves the outcome in patients with a higher local failure risk (ie age ≥ 18 years and tumour arising in unfavourable sites) and to determine whether radiotherapy treatment of all sites of metastases may improve the outcome in metastatic patients.[23] In the Far-RMS, there are no specific recommendations on the use of PBT. The protocol states that patients can receive radiotherapy treatment for the primary tumour (and for metastatic sites) using photon-based techniques (including IMRT), or proton therapy/particle therapy. A quality assurance programme is provided to give a real-time review of each case for compliance with protocol target definitions and radiation delivery requirements, ie Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials (QUARTET).[86]

Conclusions

The current paper offers an insight on the use of PBT in RMS patients. With this review, we aim to emphasise that PBT can be an excellent treatment option for patients with RMS, in particular young children and patients with various primary sites. The unique depth-dose characteristics of protons can be exploited to achieve significant reductions in normal tissue doses and may allow the escalation of tumour doses and a greater sparing of normal tissues, thus potentially improving local control while at the same time reducing toxicity and improving quality of life.[45,48,54–56,58,59,62] Nevertheless, PBT techniques should always be proposed by well-trained clinical staff with experience in managing particle beams. We also believe that any consideration of dose escalation should be limited to the context of a clinical trial.

In current years, the availability of advanced radiotherapy techniques, on one hand, and the more sophisticated understanding of RMS biology with the possible future identification of novel biomarkers, on the other, are leading to a more targeted and individualised approach to young patients with RMS. The optimal treatment approach for an individual patient may depend on various factors, which include clinical extension and patient's age, for example, but also the potential risk of late sequelae. The impact of radiotherapy on the quality of life for survivors of RMS can be profound, and the use of PBT may be critical for sparing adjacent organs at risk.

While clear evidence of therapeutic superiority of PBT to other modern photon techniques has not yet been demonstrated, it is evident that an increasing number of children (with RMS and other solid tumours) are being treated with protons in North America and in Europe. However, the number of available proton therapy installations remains

unfortunately limited. In Italy, for example, only two proton therapy centres are currently operational (with three estimated installations coming in next years). In a rough estimate, of the 50–60 RMS cases occurring each year in Italy in the 0–19-year population, approximately 10 patients received PBT (that can be seen as about one-third of the cases for which PBT may be indicated according to age, stage, and tumour sites). Access of children with RMS (and more in general with solid tumors) to PBT remains a challenge. This situation restricts the number of patients that can be treated; in addition, it makes it difficult to gather a substantial amount of follow-up clinical data, especially when compared to photon treatments.

Further progress can be achieved, in this research field, by broader collaboration, such as the recently established International Soft Tissue SaRcoma ConsorTium (INSTRuCT) that aims to pool expertise and resources on a broader international level, developing consensus standards to guide diagnosis and treatment and comparing clinical data across different groups and studies.[87]

Centralisation of care in high-level and high-volume referral hospitals/centres is a recommended strategy for modern and high-quality paediatric radiotherapy. By bringing together various specialists and equipping a select number of treatment centres with state-of-the-art technology, it becomes possible to consolidate efforts and optimise the use of limited national resources. This approach ensures equitable access to treatment for children affected by RMS and promotes optimal outcomes.

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Disclosure

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