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Original article

Tumour control and Quality of Life in children with rhabdomyosarcoma treated with pencil beam scanning proton therapy

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ABSTRACT

Purpose: To assess clinical outcomes in children with rhabdomyosarcoma (RMS) treated with pencil beam scanning (PBS) proton therapy (PT).

Methods and materials: Eighty-three RMS (embryonal, $n = 74$; 89%) patients treated between January 2000 and December 2014 were included. The median age was 4.5 years (range, 0.8–15.5). All patients received systemic chemotherapy according to prospective protocols. Patients had low-, intermediate-, and high-risk disease in 24%, 63%, and 13% of cases, respectively. The median total dose delivered was 54 Gy(RBE) (range, 41.4–64.8).

Results: After a median follow-up time of 55.5 months (range, 0.9–126.3), local failure occurred in 16 patients. The 5-year local-control survival rate was 78.5% [95% confidence interval (CI), 69.5–88.5%]. Significant predictors for local failure were group/stage, tumour location, and size. Fourteen patients (16%) died, all from tumour progression. The 5-year overall survival was 80.6% (95%CI, 71.8–90.0%). The 5-year incidence of grade 3 non-ocular late toxicity was 3.6% (95%CI, 1–12%). No grade 4–5 late toxicities were observed. One radiation-induced malignancy was observed (1.2%). The Quality of Life (QoL) scores increased significantly after PT compared to baseline values.

Conclusions: PBS PT led to excellent outcome in children with RMS. Late non-ocular toxicity was minimal and QoL good.

Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma [1] in children and accounts for approximately 4.5% of all paediatric cancers [2]. Children with RMS are treated with a combination of surgery, chemotherapy, and radiation therapy [3,4], the latter of which can be delivered with stereotactic techniques, intensity modulation, brachytherapy, or using proton therapy (PT). Unlike photon techniques, PT does not involve an exit dose, and thus decreases the integral dose delivered to the child [5,6], which in turn potentially decreases long-term radiation-induced adverse events. PT is usually delivered with passive scattering techniques, but protons can also be magnetically deflected and scanned across the tumour volume. This pencil beam scanning (PBS) technique [7] was pioneered by the Paul Scherrer Institute (PSI) since 1996 and has been used by PSI to safely treat over 1,100 patients with this delivery paradigm until now.

The purpose of this study was to evaluate clinical outcomes in children with RMS treated with PBS only PT at PSI, and to assess the Quality of Life (QoL) and prognostic factors for tumour control in this patient cohort.

Materials and methods

Patients

Between January 2000 and December 2014, 91 children (age < 18 years) with a diagnosis of RMS and treated with PBS PT at PSI were identified in our institutional database. One patient was excluded because consent to use the data for a scientific purpose was not provided and another patient was excluded because of combined photon-proton treatment. Six patients were excluded because they received PBS PT later than one year after diagnosis (median time to PT, 23.3 months; range, 13.9–34.5). A total of 83

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patients were eligible and included in the analysis, the characteristics of which are detailed in Table 1. Of the 46 PM-RMS patients 33 (71%) presented with intracranial extension (ICE) at the time point of treatment planning. All patients received chemotherapy per contemporary protocols (Supplementary Table 1). The median time from diagnosis to PT was 3.8 months (range, 1.3–9.8). Institutional Review Board (IRB) approval was obtained for this study (EKNZ 2014-358).

PT treatment

Patients were treated using PBS at the scanning gantry with energy-degraded beams from the 590-MeV cyclotron until 2005 and with the dedicated 250-MeV cyclotron after 2005. The proton dose was computed using a three-dimensional dose calculation algorithm developed at PSI [8]. All patients were immobilised using a body cast, and head and neck immobilisation was accomplished as previously published [9,10]. The tumour bed and residual tumour were identified as gross tumour volume (GTV). The clinical target volume (CTV) was defined as 1-cm extension of the GTV, taking into account the initial presentation and restricted for anatomical boundaries. Depending on tumour location and fixation method the PTV margin was according our institutional standard 4–15 mm. Specific constraints were applied as previously published [10]. Treatment plans were optimised to maximise the coverage of the gross tumour volume coverage (GTV) while observing organs at risk (OAR) dose constraints. Dose was prescribed to the mean in proton doses and expressed in terms of Gy(RBE) [Gy(RBE) = proton Gy × 1.1] [11,12]. The median delivered dose was 54 Gy(RBE) (range 41.4–64.8; Table 1). Only one patient received more than 60 Gy(RBE) and only one patient received less than 45 Gy(RBE). The median number of fractions was 30 (range, 23–36). The dose per fraction was 1.8 Gy(RBE) for 74 patients (89%) and 2 Gy(RBE) per fraction for 9 (11%) other patients.

Table 1
Patient characteristics ($n = 83$).

Characteristic		No. of Patients	%
Median age, years (range)		4.5 (0.8–15.5)	
Gender	Male	46	55
	Female	37	45
IRS group	I	2	2
	II	5	6
	III	65	78
	IV	11	13
TNM stage	1	22	27
	2	16	19
	3	34	41
	4	11	13
COG risk group	Low	20	24
	Intermediate	52	63
	High	11	13
Histology	Embryonal	74	89
	Alveolar	9	11
Favourable site	Orbital	17	20
	HN non-PM	3	4
	UG non-BP	4	5
Unfavourable site	PM	46	55
	UG-BP	6	7
	Others	7	8
Size (cm)	⩽5	42	51
	>5	41	49
Nodal disease	N0	71	86
	N1	12	14
Patents treated with: Anaesthesia		55	66
Concomitant chemotherapy		74	89
Radiation dose Gy(RBE)	Median	54	
	Range	41.4–64.8	

Abbreviations: COG: Children's Oncology Group; RMS: rhabdomyosarcoma; PM: parameningial RMS; UG: urogenital; HN: head and neck; BP: bladder/prostate

Single-field uniform dose (SFUD) plans ($n = 29$) and intensity modulated proton therapy (IMPT) plans ($n = 28$) and the combination of both ($n = 26$) were used at PSI. PT was delivered in 30–59 (median 41) days in 1–6 series (75% of the patients received 2 or 3 series).

Quality of Life

Health-related QoL was investigated in a collaborative project that started in 2005 with the University of Münster. The PedQoL questionnaire, an established, multidimensional instrument, was used to assess QoL [13]. The questionnaire covered eight domains (self-esteem, emotional functioning, body image, cognition, physical functioning, peers and family social functioning, subjective well-being) and was available in a proxy-rating version for the parents (PedQoL proxy) and in a self-rating version for children older than 4 years (PedQoL self). After obtaining informed consent, the questionnaire was distributed at the start of PT (E1), 2 months after the end of PT (E2), and one (E3), two (E4), three (E5), four (E6), and five (E7) years after PT. Higher QoL scores suggested better patient QoL.

Of the 83 patients included, five patients were treated before the initiation of the QoL study. Thirty-nine patients were excluded due to age less than 5 years. The parents of one patient did not consent to participation in the QoL study and four patients missed the baseline E1 QoL evaluation. Therefore, 34 patients completed the baseline proxy assessments. The number of answers per domain is shown in Fig. 3 and Supplemental Fig 2. Due to a markedly lower number of completed self-rating questionnaires, the analysis focused on proxy assessments by the parents. For comparison purposes, an independent norm group with proxy assessments of healthy children between 5 and 16 years of age was included in the analyses.

Follow-up

Follow-up was organised by the referring physicians per the protocol and collected as previously described [10]. Acute toxicities were defined as those adverse events that occurred from the first day of treatment through day 90 after treatment and were classified according RTOG toxicity scale. For Table 3 patients were censored at the time point of recurrence. All side effects observed 90 days after the end of PT were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 grading system (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf) and were considered late adverse events.

Statistical analysis

Local control (LC), overall survival (OS) and cumulative incidence survival times were determined from the PT start date. Death was the event for OS, whereas loco-regional tumour relapse was the event for LC survival, and the aforementioned including failure at metastatic sites or toxicity were the events for cumulative incidence. Survival rates were calculated using the Kaplan–Meier actuarial method. Cumulative incidences were calculated as described by Gooley [14]. The log–rank test and Cox regression were used to compare different survival functions

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