Radiotherapy and Oncology 134 (2019) 143–150

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

# Patterns of failure following proton beam therapy for head and neck rhabdomyosarcoma

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ARTICLE INFO

*Article history:*
Received 2 January 2019
Received in revised form 30 January 2019
Accepted 3 February 2019
Available online 14 February 2019

*Keywords:*
Rhabdomyosarcoma
Radiotherapy
Proton beam therapy
Intracranial extension
Parameningeal
Cyclophosphamide

ABSTRACT

*Purpose:* Pediatric patients with rhabdomyosarcoma (RMS) of the head and neck (H&N) are treated with multimodal therapy, often with radiotherapy (RT) as definitive local therapy. We report on the patterns of failure following proton beam therapy (PBT) for H&N RMS.

*Methods:* Forty-six H&N RMS patients were enrolled on a prospective registry protocol between 2006 and 2015. All were treated with a combination of chemotherapy (ChT) and PBT. Most patients (25 patients, 54%) had parameningeal tumors, of which 11 (24%) had intracranial extension (ICE). Thirteen patients (28%) had primary tumors greater than 5 cm. Median total cyclophosphamide (CPM) equivalent dose was 13.2 g/m$^2$ (range 0–16.8 g/m$^2$). Median RT dose was 50.4 Gy(RBE) (range 36 Gy[RBE]–50.8 Gy[RBE]).

*Results:* With median follow-up of 3.9 years, five-year overall survival was 76%, and five-year progression-free survival was 57%. Seventeen patients (37%) experienced relapse, including 7 with local failure (LF). Five-year local control (LC) was 84%. Tumor size greater than 5 cm predicted increased risk of LF (hazard ratio [HR] 6.49, $p = 0.03$), as did the presence of ICE at diagnosis (HR 5.21, $p = 0.03$). Six relapses occurred in patients with ICE; all included a component of central nervous system relapse, with leptomeningeal disease and/or LF with an intracranial component. Delayed RT delivery after week 4 of ChT predicted increased risk of relapse for ICE patients (HR 10.49, $p = 0.006$).

*Conclusions:* PBT confers excellent LC, and a favorable late toxicity profile as compared with prior photon RT data. Our observations support ongoing trial efforts to dose-escalate RT for patients with larger tumors. However, these data raise concerns regarding excess failures among patients with ICE.

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Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma of childhood and adolescence, accounting for approximately 5% of all pediatric malignancies [1,2]. RMS is treated with multimodal therapy, incorporating a combination of systemic chemotherapy (ChT) as well as local therapy. Approximately 40% of RMS cases are primary head and neck (H&N) tumors [3]. To achieve local control of H&N RMS lesions, radiotherapy (RT) is often utilized as the definitive local therapy modality, given the morbidity associated with extensive surgical resections in this region [3,4]. Increasingly, proton beam therapy (PBT) has been used in place of photon-based RT in the treatment of RMS [5–7]. The primary benefit of PBT over photon-based techniques centers on the absence of exit dose from a proton beam, in turn sparing nearby critical structures from unnecessary radiation exposure. These considerations are particularly important for pediatric patients with H&N lesions where late toxicity can be severe. To that end, dosimetric data have supported the use of PBT in the treatment of RMS, particularly for H&N primary tumors [6,8,9].

With data emerging regarding clinical outcomes for RMS patients treated with PBT, here we report patterns of failure for pediatric H&N RMS patients treated with PBT [5]. Particular attention is placed on the rates of local control (LC), as well as risk factors for local failure (LF). Outcomes for high-risk subgroups of H&N RMS patients, such as those with tumors with intracranial extension (ICE), are analyzed as well. The implications of these findings to ongoing cooperative group trials are discussed.

## Methods

Between January 2006 and January 2015, 46 patients with newly diagnosed H&N RMS were enrolled on an institutional prospective IRB-approved registry protocol for all pediatric patients undergoing PBT; this registry tracked disease-related outcomes as well as treatment-related toxicities. Informed consent

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https://doi.org/10.1016/j.radonc.2019.02.002
0167-8140/

from patients' parents/legal guardians was obtained for this protocol at the time of enrollment prior to treatment initiation; all patients were less than 18 years old at time of PBT.

Staging evaluation of patients included magnetic resonance imaging (MRI) of the primary site, as well as bilateral bone marrow (BM) aspiration and biopsies in all patients. Further staging was performed with a combination of computed tomography (CT) imaging of the chest, CT imaging of the head and neck, fluorodeoxyglucose positron emission tomography (PET) imaging, and technetium-99 bone scan. Patients were considered to have ICE at time of diagnosis if ICE was identified on initial staging MRI. Patients with cranial nerve palsy and/or bone erosion without radiographic evidence of ICE were not considered to have ICE in this cohort. All patients with ICE were further staged with cerebrospinal fluid (CSF) cytology from a lumbar puncture. Histologic specimens of the tumor were assessed for *FOXO1* fusion transcript status based on reverse transcription polymerase chain reaction assay [10]. Patients were risk-stratified into low-, intermediate-, and high-risk subgroups as per the Children's Oncology Group (COG) risk classification system [11].

Patients were treated with multimodal therapy, including PBT and ChT for all patients, as well as surgical resection for some patients (Table 1). Treatment planning for PBT was based on CT simulation and custom immobilization for all patients. Anesthesia was utilized for patients too young or unable to tolerate simulation/daily PBT treatments while awake; anesthesia was utilized for 24 patients (52%) in this series. For the treatment planning process, all patients had diagnostic MRI scans fused to the treatment planning CT to facilitate target volume and critical structure delineation. No patient in this series underwent MRI in the treatment position with immobilization devices (that is, MRI simulation) as our institutional MRI simulator was not yet available for use during the study period. Patients were treated with either passive-scattered PBT (PSPT) or pencil-beam scanning PBT (PBS-PT); 9 patients (20%) were treated with PBS-PT, while 37 (80%) were treated with PSPT. PBT treatment planning aimed to target gross disease; institutional practice during this study period did not include any elective nodal irradiation for H&N RMS patients. Target volumes were defined by clinical exam as well as radiographic data. A clinical margin of 5–20 mm (median 10 mm, variable by anatomic site) was added to the contoured gross disease to generate the clinical tumor volume (CTV). For patients treated with PSPT, beam-specific uncertainty margins were used, including a range uncertainty of 3 mm [12]. For patients treated with PBS-PT, patients were treated with intensity-modulated proton therapy (IMPT), with CTV-based robust optimization as previously described [13]. PBT was delivered in daily fractional doses of 1.8–2 Gy(RBE) (Gray [Radiobiological Effectiveness]). Resimulation and replanning were performed in 6 cases (13%); 2 cases of replanning were due to improper fitting of patients' thermoplastic masks. The remaining 4 cases of adaptive replanning were to adapt and shrink treatment fields in response to decreased tumor size with ongoing RT.

ChT was delivered as per cooperative group protocols (Table 1). Most patients were treated per North American COG protocols, and therefore received cyclophosphamide (CPM) as part of their ChT regimen; several patients, however, were treated per European protocols (European Pediatric Soft Tissue Sarcoma Study Group [EpSSG]), and received ifosfamide rather than CPM as part of their ChT. To standardize, we converted ifosfamide dosing into CPM equivalent dosing as previously described, and provided a CPM equivalent dose for all patients, representing the total equivalent dosing of CPM/ifosfamide delivered to patients in this cohort [14].

Disease-related outcomes including overall survival (OS), progression-free survival (PFS), LC, regional nodal control (RNC), and CNS-C (central nervous system [CNS] control) were calculated using the Kaplan–Meier method. Disease-related outcomes were calculated from the date of PBT completion. PFS events were defined by death, disease relapse or progression. LC and RNC events were defined by local and regional nodal failure, respectively. CNS-C events were defined by failure with a CNS component, including LMD as well as a LF with the relapse volume having ICE. To characterize sites of failure relative to the initial PBT treatment plans, in-field relapse was defined as >80% of the relapse volume within the 95% isodose line [IDL] of the initial

**Table 1**
Patient, tumor, and treatment characteristics. Abbreviations: N, number; RT, radiotherapy; H&N, head and neck; IRS, Intergroup Rhabdomyosarcoma Study Group; COG, Children's Oncology Group; EpSSG, European Pediatric Soft Tissue Sarcoma Study Group; CPM, cyclophosphamide; Gy(RBE), Gray (Radiobiological Effectiveness); ChT, chemotherapy.

| | | | |
|---|---|---|---|
| *N* = 46 patients | | | |
| Age at diagnosis: | Median | 5.2 | years |
| | Range | 0.1–15.6 | years |
| Age at RT: | Median | 5.4 | years |
| | Range | 0.7–15.7 | years |
| | | N | % |
| Gender | Male | 20 | 43% |
| | Female | 26 | 57% |
| Site: | Favorable – Orbit | 13 | 28% |
| | Favorable – Other H&N | 8 | 17% |
| | Unfavorable – Parameningeal | 25 | 54% |
| Intracranial extension: | Yes | 11 | 24% |
| | No | 35 | 76% |
| Histology: | Embryonal | 32 | 70% |
| | Alveolar | 14 | 30% |
| Cytogenetics | *PAX3-FOXO1* fusion transcript [t(2;13)] | 13 | 28% |
| | No fusion transcript detected | 33 | 72% |
| Primary tumor size (cm) | ≤5cm | 33 | 72% |
| | >5cm | 13 | 28% |
| T stage: | T1a | 21 | 46% |
| | T1b | 1 | 2% |
| | T2a | 12 | 26% |
| | T2b | 12 | 26% |
| N stage: | N0 | 35 | 76% |
| | N1 | 11 | 24% |
| M stage: | M0 | 41 | 89% |
| | M1 | 5 | 11% |
| IRS stage (IRS-IV; pre-surgical) | 1 | 20 | 43% |
| | 2 | 7 | 15% |
| | 3 | 14 | 30% |
| | 4 | 5 | 11% |
| IRS group (post-surgical) | I | 1 | 2% |
| | II | 5 | 11% |
| | III | 35 | 76% |
| | IV | 5 | 11% |
| COG risk stratification | Low | 13 | 28% |
| | Intermediate | 28 | 61% |
| | High | 5 | 11% |
| Study enrollment: | COG ARST 0331 | 10 | 22% |
| | COG ARST 0431 | 3 | 7% |
| | COG ARST 0531 | 21 | 46% |
| | EpSSG 2005 | 5 | 11% |
| | Other | 7 | 15% |
| CPM equivalent dose | Median | 13.2 | g/m2 |
| | Range | 0–16.8 | g/m2 |
| RT dose to primary tumor | Median | 50.4 | Gy (RBE) |
| | Range | 36–50.8 | Gy (RBE) |
| Timing of RT (following ChT initiation) | Median | 13 | weeks |
| | Range | 1–56 | weeks |

treatment plan; marginal relapse was defined as >20% and ≤80% of the relapse volume within the 95% IDL of the initial plan; out-of-field relapse was defined as ≤20% of the relapse volume within the 95% IDL of the initial plan [15]. Treatment-related toxicities were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 definitions [16].

Statistical analyses included log-rank testing using the Cox proportional-hazard model to compare differences in disease-related outcomes between groups. Comparisons of ratios across groups were performed using *chi*-squared testing. All tests performed were two-sided with an *a priori* $\alpha = 0.05$ as a threshold for statistical significance. Analyses were performed using the SPSS statistical package (Version 22.0, Armonk, NY) [17].

## Results

### *Cohort and treatment characteristics*

Patient, disease, and treatment characteristics of the full cohort of 46 patients with H&N RMS treated with PBT are summarized in Table 1. Median age at diagnosis was 5.2 years (range 0.1–15.6 years). In addition to staging evaluation with primary-site MRI and bilateral BM aspiration and biopsies, patients were staged with a combination of chest CT (46/46 patients, 100%), contrast enhanced CT of the H&N (40/46, 87%), PET (15/46, 33%), and technetium-99 bone scan (21/46, 46%). No patient had evidence of LMD at time of diagnosis, including the 11 patients with ICE who were further evaluated with CSF cytology.

All patients were treated with a combination of PBT and ChT. ChT was delivered per COG or EpSSG protocols as highlighted in Table 1. While most patients were treated on COG protocols, 5 patients (11%) were treated on EpSSG protocols utilizing ifosfamide rather than cyclophosphamide. Median CPM equivalent dose for the cohort was 13.2 g/m$^2$ (range 0–16.8 g/m$^2$) (Table 1) [14]. PBT was delivered at a median time of 13 weeks following initiation of ChT (range 1–56 weeks).

### *Patterns of failure*

Median follow-up for all patients in the cohort following completion of PBT was 3.9 years (range 0.5–8.9 years). Five-year OS and PFS rates for the cohort were 76% (95% confidence interval [CI] 57%–87%) and 57% (95% CI 38%–73%), respectively (Fig. 1). By risk-stratification, 5-year OS rates for low-, intermediate-, and high-risk patients were 100%, 65%, and 80%, respectively. Seventeen patients (37%) experienced disease relapse. These relapses included 4 patients with isolated LF, 2 with LMD relapse, 2 with concurrent LF and LMD relapse, 8 with isolated regional nodal failure (RNF), and 1 with concurrent LF and RNF. No extra-CNS distant metastatic relapses were observed in this series. Median time to relapse was 12.5 months (range 3.0–59.9 months) following completion of PBT. Only one patient experienced disease relapse beyond 24 months following PBT completion; this patient presented with an orbital embryonal tumor, with gross nodal disease at diagnosis. The patient was treated to 45 Gy[RBE] to the primary and 41.4 Gy[RBE] to the gross node, with subsequent in-field nodal relapse of the initially involved node 59.9 months following PBT. All other patients with relapse (16/17, 94%) recurred within 24 months following PBT completion.

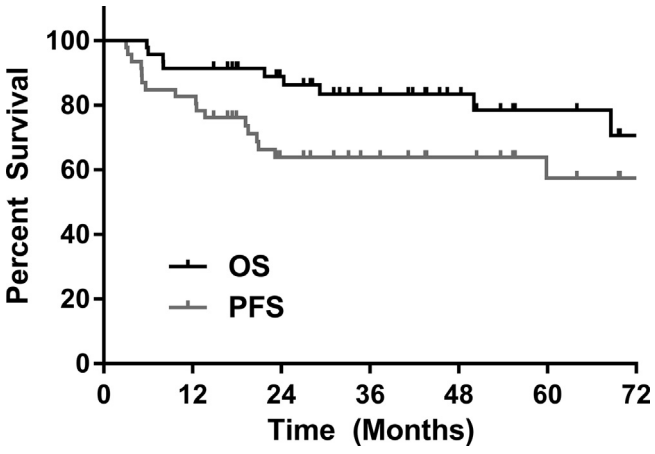


**Fig. 1.** Disease-related outcomes. Disease-related outcomes for the full cohort ($N = 46$) with the Kaplan–Meier survival curves for overall survival (OS, black) and progression-free survival (PFS, gray).

### *Local control*

A total of 7 patients (15%) experienced LF (isolated or concurrent with other sites of relapse) (Table 2). Five-year LC rate was 84% (95% CI 69–92%). For all 7 cases of LF, the local recurrence volume was in-field relative to the initial PBT treatment plan, as defined in Methods above. Four of 7 patients with LF presented with ICE at diagnosis; all 4 of these patients had an intracranial component of their LF at time of relapse (Patients 3 through 6, Table 2). Two of these 4 patients further presented with concurrent disseminated LMD at time of LF (Table 2). Examining risk factors for LF, univariate analyses demonstrated a significant effect of primary tumor size on LF (tumor >5 cm, HR 6.49, 95% CI 1.26–33.46, $p = 0.03$). Five of 13 patients (38%) with tumors >5 cm experienced LF, compared with 2 of 31 patients (6%) with tumors ≤5 cm. The presence of ICE at diagnosis also conferred a higher risk of LF (HR 5.21, 95% CI 1.16–23.54, $p = 0.03$). No effect of primary tumor site ($p = 0.38$), age ($p = 0.61$), histology ($p = 0.36$), study protocol ($p = 0.33$), post-surgical risk group (Intergroup Rhabdomyosarcoma Study [IRS] group; $p = 0.35$), CPM equivalent dose ($p = 0.22$), use of PBS-PT versus PSPT ($p = 0.50$), RT dose ($p = 0.97$), or RT timing ($p = 0.56$) on LF incidence was identified. By COG risk stratification, five-year LC rates were 100%, 82%, and 60% for low-, intermediate-, and high-risk patients, respectively ($p = 0.10$).

### *ICE and CNS control*

Of 11 patients presenting with ICE at diagnosis, 6 (55%) experienced disease relapse (Table 2). This includes the 4 patients above with LF with intracranial component, 2 of whom concurrently presented with disseminated LMD at time of relapse. The remaining 2 ICE patients with relapse presented with LMD at relapse, without a component of local recurrence (Table 2). All patients with a component of CNS involvement at relapse (either locally recurrent disease with intracranial involvement or LMD) initially presented at diagnosis with ICE. For the full cohort, 5-year CNS-C rate was 86% (95% CI 72–94%); among patients presenting with ICE ($N = 11$), 5-year CNS-C was 42% (95% CI 14–69%). CNS-C for ICE patients was identical to PFS, as no ICE patients experienced non-CNS relapse; 5-year OS for ICE patients was 61% (95% CI 25–83%). Among patients with ICE, the additional intracranial margin to generate the CTV based on the extent of gross disease varied between 5 and 20 mm (median 10 mm). On univariate analyses, the sole variable predicting disease relapse among patients with ICE was the timing of RT relative to the initiation of ChT. Four of 11 ICE patients (36%) started RT within the first 4 weeks of ChT, of whom none experienced disease relapse (Table 3). In contrast, 6 of the remaining 7 ICE patients who initiated RT at or after week 5 of ChT experienced disease relapse (Table 3). Patients who received RT beyond week 4 had a significantly higher rate of

**Table 2**
Local and CNS relapse characteristics. Patients with local and/or CNS relapses are listed with associated treatment characteristics. Abbreviations: CNS, central nervous system; Dx, diagnosis; N/A, not applicable; ICE, intracranial extension; CPM, cyclophosphamide; RT, radiotherapy; Gy(RBE), Gray (Radiobiological Effectiveness); ChT, chemotherapy; PBT, proton beam therapy; LF, local failure; LMD, leptomeningeal disease; DOD, expired due to disease; NED, alive without evidence of disease; AWD, alive with evidence of disease.

| Patient number | Age at Dx (years) | Site | Subsite | ICE | Histology | Primary tumor size (cm) | CPM equivalent dose ($g/m^2$) | RT dose (Gy [RBE]) | RT timing relative to ChT (weeks) | Time of relapse following PBT (months) | Local relapse? | Intracranial component of LF? | LMD relapse? | Last known status | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 5.2 | Favorable Non-Orbital | Mandibular ramus | N | Embryonal | 6.3 | 16.8 | 50.4 | 13 | 5.1 | Y | N | N | DOD | |
| 2 | 4.8 | Parameningeal | Parapharyngeal space | N | Embryonal | 5.5 | 8.4 | 50.4 | 4 | 23.2 | Y | N | N | NED | |
| 3 | 4.3 | Parameningeal | Infratemporal fossa | Y | Embryonal | 6.0 | 16.8 | 50.4 | 8 | 20.7 | Y | Y | N | NED | |
| 4 | 6.8 | Parameningeal | Pterygopalatine fossa | Y | Embryonal | 5.2 | 16.8 | 48.6 | 13 | 12.5 | Y | Y | N | AWD | |
| 5 | 15.5 | Parameningeal | Nasal cavity | Y | Embryonal | 6.0 | 8.4 | 50.4 | 10 | 5.7 | Y | Y | Y | DOD | Concurrent in-field LF and LMD relapse |
| 6 | 0.7 | Parameningeal | Paranasal sinus | Y | Embryonal | 4.1 | 16.8 | 50.4 | 22 | 3.8 | Y | Y | Y | DOD | Concurrent in-field LF and LMD relapse |
| 7 | 10.2 | Parameningeal | Paranasal sinus | Y | Alveolar | 4.3 | 16.8 | 50.4 | 13 | 5.2 | N | N | Y | DOD | |
| 8 | 15.4 | Parameningeal | Paranasal sinus | Y | Alveolar | 7.0 | 7.2 | 50.4 | 13 | 20.9 | N | N | Y | DOD | |
| 9 | 0.1 | Orbital | (N/A) | N | Alveolar | 3.0 | 12.0 | 45 | 56 | 3.0 | Y | N | N | DOD | Concurrent out-of-field regional nodal relapse |

relapse (HR 10.49, 95% CI 1.94–56.67, $p = 0.006$; Fig. 2). Other disease- and treatment-related factors did not predict for recurrence among patients with ICE, including CPM equivalent dose ($p = 0.95$), tumor size ($p = 0.64$), RT dose ($p = 0.37$), or intracranial margin utilized for CTV generation ($p = 0.45$). In addition to RT timing as a predictor for PFS, patients with ICE initiating RT beyond week 4 trended toward worse OS (HR 7.34, 95% CI 0.97–55.38, $p = 0.05$; Fig. 2).

Among the 7 patients with RT initiation beyond week 4 of ChT, only one patient had RT delayed past week 4 due to clinical considerations. This patient (Patient 6; Table 2, Table 3) was diagnosed at 8 months of age, and RT was delayed until 22 weeks of chemotherapy had been delivered to forestall the delivery of RT until after the patient had turned 1 year old in an effort to minimize long-term toxicity [18]. All other patients had RT delivered beyond week 4 due to the timing of patient referral for RT ($N = 6$). No tumor-related or chemotherapy-related toxicities led to a clinical decision to delay RT initiation.

### *Regional nodal control*

Nine patients with a component of RNF were identified in this cohort. Of these, 8 patients presented with alveolar histology tumors, and the relationship between alveolar histology with risk of regional nodal relapse (particularly in first-echelon draining lymph node basins) was recently characterized by our group [19]. Among the full cohort, five-year RNC rate was 73% (95% CI 49–87%); among patients with alveolar histology lesions, five-year RNC was 37% (95% CI 12–62%), with 8 of 14 alveolar-histology patients (57%) experiencing RNF. In contrast, only one patient of 32 with embryonal histology tumors (3%) developed RNF, resulting in a 5-year RNC of 88% among embryonal histology patients (95% CI 39–98%). As discussed above, the sole patient with embryonal histology RMS with subsequent RNF presented with an orbital tumor with involved regional nodes; this patient experienced late relapse, at 59.9 months following PBT, with an in-field relapse at the initially involved node.

### *Salvage therapy*

Of 17 patients with disease relapse, at last follow-up 10 (59%) had expired due to disease progression (DOD), 3 (18%) were alive with disease (AWD), and 4 (24%) were alive without evidence of disease (NED). Salvage chemotherapy was utilized for 16 patients (94%), and salvage RT for 8 (47%). Median follow-up time after disease relapse was 3.0 years. All patients who received salvage RT also received salvage ChT. The sole patient who did not receive salvage ChT (or RT) expired within 3 months of disease relapse; this patient (Patient 6; Tables 2, 3) presented at relapse with disseminated LMD as well as concurrent LF, and deteriorating performance status precluded salvage ChT. Among patients who received salvage ChT, median survival after relapse was 24.7 months. No difference was detected in post-relapse survival among patients who received salvage ChT alone compared with those who received salvage ChT as well as salvage RT (median post-relapse survival 18.7 months versus 24.7 months, respectively; HR 1.31, 95% CI 0.33–5.30, $p = 0.70$). Among patients with local failure, one patient (Patient 2; Table 2) was treated with reirradiation; the disease recurred in the parapharyngeal space (in-field), and was treated with salvage ChT, resection (with positive margins, the sole patient in this series who underwent salvage surgery), and adjuvant re-irradiation with a second course of PBT to 36 Gy (RBE). This patient is alive and without evidence of disease 44.4 months following relapse.

**Table 3**
Outcomes for ICE patients. Individual patient outcomes for patients presenting at diagnosis with ICE. Abbreviations: ICE, intracranial extension; Dx, diagnosis, CPM, cyclophosphamide; RT, radiotherapy; Gy(RBE), Gray (Radiobiological Effectiveness); ChT, chemotherapy; NED, alive without evidence of disease; AWD, alive with evidence of disease; DOD, expired due to disease; LF, local failure; CNS, central nervous system; LMD, leptomeningeal disease.

| Patient number | Age at Dx (years) | Subsite | Histology | Primary tumor size (cm) | CPM equivalent dose (g/m$^2$) | RT dose (Gy [RBE]) | RT timing relative to ChT (weeks) | Disease relapse? | Last known status | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| 3 | 4.3 | Infratemporal fossa | Embryonal | 6.0 | 16.8 | 50.4 | 8 | Y | NED | LF with CNS component |
| 4 | 6.8 | Pterygopalatine fossa | Embryonal | 5.2 | 16.8 | 48.6 | 13 | Y | AWD | LF with CNS component |
| 5 | 15.5 | Nasal cavity | Embryonal | 6.0 | 8.4 | 50.4 | 10 | Y | DOD | Concurrent LF (with CNS component) and LMD relapse |
| 6 | 0.7 | Paranasal sinus | Embryonal | 4.1 | 16.8 | 50.4 | 22 | Y | DOD | Concurrent LF (with CNS component) and LMD relapse |
| 7 | 10.2 | Paranasal sinus | Alveolar | 4.3 | 16.8 | 50.4 | 13 | Y | DOD | LMD relapse |
| 8 | 15.4 | Paranasal sinus | Alveolar | 7.0 | 7.2 | 50.4 | 13 | Y | DOD | LMD relapse |
| 10 | 5.9 | Middle ear | Embryonal | 3.2 | 16.8 | 50.4 | 1 | N | NED | |
| 11 | 3.3 | Masticator space | Embryonal | 7.0 | 12.0 | 50.4 | 4 | N | NED | |
| 12 | 5.5 | Nasopharynx | Embryonal | 6.3 | 16.8 | 50.4 | 4 | N | NED | |
| 13 | 1.8 | Infratemporal fossa | Embryonal | 5.6 | 16.8 | 50.4 | 4 | N | NED | |
| 14 | 3.3 | Mastoid region | Embryonal | 4.5 | 16.8 | 50.4 | 14 | N | NED | |

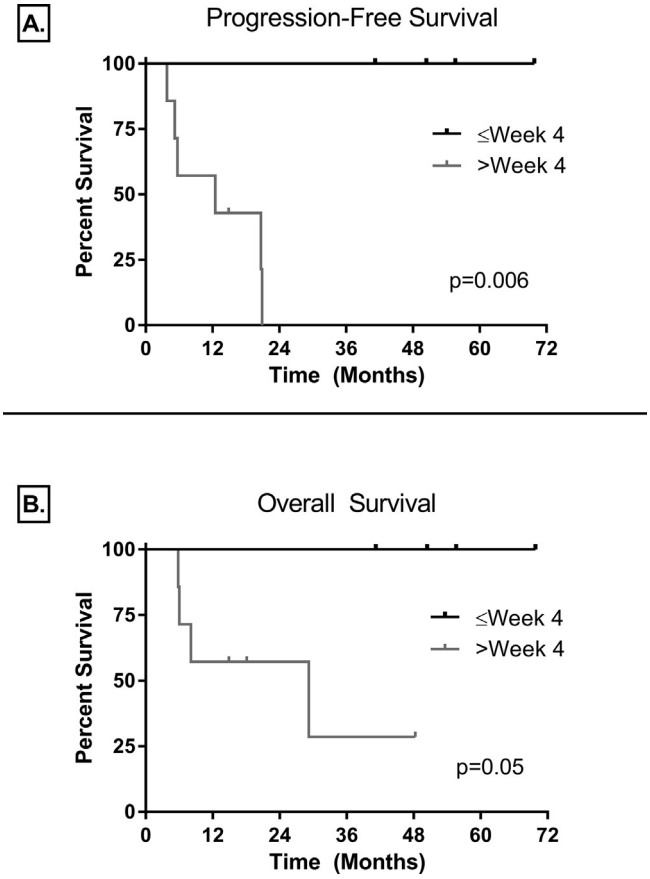


**Fig. 2.** Role of RT timing for patients with ICE. (A) Progression-free survival and (B) overall survival as a function of RT timing relative to ChT initiation for patients with ICE at presentation ($N = 11$). Analysis performed based on whether patients received RT by week 4 of chemotherapy (black curve, "≤Week 4", $N = 4$) or after week 4 (gray curve, ">Week 4", $N = 7$). Log-rank test p-values shown for PFS ($p = 0.006$) and OS ($p = 0.05$).

### *Toxicity*

Acute toxicities of PBT included 4 patients (9%) with grade 3 toxicity, and 31 patients (67%) with grade 2–3 toxicity. Grade 3 acute toxicities observed included 3 patients (7%) with mucositis, and 1 patient (2%) with keratopathy and conjunctivitis. Grade 2 acute toxicities included dermatitis (16 patients, 35%), mucositis (11 patients, 24%), conjunctivitis (6 patients, 13%), xerostomia (3 patients, 7%).

Late toxicities related to PBT were observed in 12 patients (26%) with grade 3 toxicity, and 19 patients (41%) with grade 2–3 toxicity. Long-term grade 3 toxicities included cataract development (7 patients, 15%), bone hypoplasia and facial asymmetry (2 patients, 4%), unilateral hearing loss (1 patient, 2%), unilateral epiphora and punctal stenosis (1 patient, 2%), and dental caries (1 patient, 2%). Six of 7 patients who developed cataracts had orbital primary tumors, with ipsilateral-only (unilateral) cataract development; one patient treated for a nasopharyngeal primary tumor developed a unilateral ipsilateral cataract as well. No patients with bilateral (synchronous or metachronous) cataract development were observed in this series. Non-cataract grade 3 toxicity was observed in 5 patients (11%). Late grade 2 toxicities included thyroid endocrinopathy (secondary hypothyroidism; 5 patients, 11%), decreased growth velocity (5 patients, 11%), chronic sinusitis (3 patients, 7%), xerostomia (2 patients, 4%), and xerophthalmia (2 patients, 4%). Use of PBS-PT (compared with PSPT) did not confer lower rates of acute grade 2–3 ($p = 0.96$) or grade 3 ($p = 0.77$) toxicity; similarly, PBS-PBT did not confer lower rates of late grade 2–3 ($p = 0.59$) or grade 3 ($p = 0.77$) toxicity. No acute or late grade 4–5 toxicities were observed in this cohort.

## Discussion

Here we report a large series of patients with H&N RMS treated with PBT as part of multimodal therapy. Disease-related outcomes, including LC (85% at 5 years), compare favorably to other modern series utilizing either photon-based intensity-modulated RT (IMRT) or PBT. Prior reports with either RT modality (photon-based RT or PBT) have generally described LF rates between 12% and 38%, with most describing LF rates in the range of 19–22% [4,5,7,20–26]. This includes the recent publication of overall outcomes for COG ARST0531, where the LF rate for intermediate-risk RMS patients was 22.4% [23]. Moreover, concerns have been raised previously regarding the possibility of increased marginal recurrences with highly conformal techniques such as PBT, which has

limited low-dose radiation "bath" in the peritumoral region compared with photon-based approaches such as IMRT [27,28]. No marginal failures were found in the present series, with all local relapses in-field from the delivered RT treatment plan. This observation is consistent with the existing literature reporting comparable local control between PBT and IMRT among H&N RMS patients [5,7,20,21].

Given that the primary therapeutic benefit to the use of PBT over photon RT is to spare unnecessary dose to critical structures, the toxicity profile observed in this series is notable as well. In the present study, toxicity rates are consistent with existing reports [5,7]. We report an acute grade 3 toxicity rate of 9%, as compared with prior PBT reports of 13–15% of patients with acute grade 3 toxicity [5,7]. With regard to late toxicity, our observed rate of non-cataract late grade 3 toxicity (11%) similarly mirrors the existing PBT literature, with non-cataract/non-ocular late grade 3 toxicity rates reported in the 4–5% range [5,7]. This is in contrast to IMRT H&N RMS series, which have reported non-cataract late grade 3 toxicity rates of 47% [16,29]. It is also noted that the present series, as well as prior PBT RMS studies, have not reported any late grade 4 toxicities, in contrast to published photon RT data [5,7,29]. While further long-term follow-up is needed for a more complete landscape of the late toxicities of PBT, these clinical observations support dosimetric data that PBT may confer an improved toxicity profile as compared with IMRT [6,8,9]. Collectively, data in this series support the efficacy and safety of PBT in the treatment of H&N RMS.

With regard to LC, the role of tumor size highlighted in the present series is of particular significance looking toward future cooperative group trials for RMS. Our data demonstrate higher rates of LF for patients with tumors >5 cm (38%) compared with those $\leq$5 cm (6%). The latest COG protocol for intermediate-risk RMS, ARST1431, includes an RT-dose-escalation component whereby RT for patients with tumors >5 cm is dose-escalated from 50.4 Gy to 59.4 Gy [30]. This is based on the results of the COG D9803 trial; subgroup analysis from this trial showed a difference in LF rates based on tumor size (LF 25% for >5 cm, versus 10% for $\leq$5 cm) [4,30,31]. The present series supports this observation of LC as a function of tumor size, and the prevalence of isolated LF in this series further suggests that strategies such as RT dose escalation may be efficacious given the pattern of spread.

Notably, no other treatment-related factors predicted LC in this series, including CPM dose. With successive cooperative group trials, CPM (equivalent) doses have been steadily decreased with the hopes of mitigating toxicity (including acute hematologic and infectious complications as well as long-term risk of infertility) [4,23,30,32]. As the trend to decrease CPM dosing has progressed, cooperative-group-level evidence from other risk stratifications of RMS have pointed to higher rates of disease relapse [33]. The D9803 protocol, which demonstrated the effect of tumor size on LC as above, included treatment with CPM doses between 25.1 g/m$^2$ and 30.8 g/m$^2$ [4,32]. By contrast, patients on more recent protocols, including ARST0531 and EpSSG 2005, were treated with substantially lower total CPM doses (or CPM equivalent doses), from 8.4 g/m$^2$ to 16.8 g/m$^2$ [23,34]. Reports regarding patterns of failure and risk factors for LC are still pending from these more recent trials (ARST0531 and EpSSG 2005), and therefore the effect of lower CPM dosing on LC risk factors is unclear; this is especially important given that currently the ARST1431 protocol is using lower-dose CPM (total dose 8.4 g/m$^2$). The present series provides the first evidence of patterns of failure and LC risk factors at these lower dose ranges of CPM. Our data demonstrate the continued role of tumor size (at a threshold of 5 cm) on LF incidence. Furthermore, we observed low rates of LF (6%) among patients with tumors $\leq$5 cm, suggesting that lower CPM dose ranges did not result in increased LF compared with the historical cohort from D9803. This remained the case even if intermediate-risk patients only were examined in our series (LF 43% for tumor size >5 cm, versus 13% for $\leq$5 cm). Therefore, lower CPM dose ranges, including those utilized for ARST0531, EpSSG 2005, and ARST1431, may not result in higher LF incidence among patients with smaller tumors. Collectively, these data provide evidence that tumor size, but potentially not CPM dosing (including modern-era lower CPM doses), affects LC. This supports the investigation into RT dose-escalation for patients with larger tumors on ARST1431.

Turning to RNC, we observed high rates of RNF among patients with alveolar histology tumors. As previously reported by our group, there may be a role for more extensive nodal evaluation during staging of patients with alveolar lesions [19]. Similarly, there may be a role for elective nodal irradiation of at-risk draining nodal basins, as well as complete coverage of any nodal basin initially involved at diagnosis [19]. The sole patient with RNF who had an embryonal histology tumor, it should be noted, was treated to 41.4 Gy(RBE) to a grossly involved node; this may represent undertreatment of gross disease in a lymph node, and consequently account for subsequent disease relapse. This was the sole relapse that occurred after 2 years following PBT completion, with RNF presenting 5 years after PBT.

Among patients with ICE, we observed high rates of disease recurrence (6/11 patients, 55%). All relapses for patients with ICE included LMD and/or LF with an intracranial component, highlighting the CNS-centric pattern of failure for this particularly high-risk subgroup. The strongest risk factor observed for relapse for ICE patients was the timing of RT. No patient initiating RT by week 4 of chemotherapy experienced relapse, whereas nearly all patients (6/7 patients, 86%) initiating RT after week 4 developed subsequent disease failure. No other clinical or treatment characteristics were identified to account for the observed rates and patterns of failure among this subgroup. These results were confirmed in an exploratory analysis in which patients treated with *either* PBT or IMRT were included, adding a further 4 ICE patients treated with IMRT to this group of 11 PBT-treated ICE patients [35]; the role of RT timing was confirmed in this analysis, in which all 5 patients treated by week 4 remained disease-free, while 9 of 10 patients treated after week 4 experienced relapse [35]. The importance of RT timing for patients with ICE has been explored in earlier cooperative-group trials. One analysis of the IRS II-IV trials demonstrated a two-fold increase in LF rate among ICE patients if RT was initiated after week 2 of ChT [36]. The recommendations for patients with ICE, therefore, had been to initiate RT as early as possible, ideally within the first week of ChT initiation. While this paradigm of treating patients with ICE at week 0 was included in the IRS-IV and D9803 trials, subsequent protocols have delayed RT for ICE patients with the goal of reducing the size of RT fields after allowing for disease response following induction ChT [4,23,30]. The ARST0531 protocol included RT initiation at week 4 for all enrolled patients, including those with ICE at presentation; the current ARST1431 trial is further delaying RT to week 13 for all patients. The patterns of failure data from ARST0531, including outcomes for ICE patients in particular, is still pending [23]. Our data, while limited by being retrospective in nature and having less statistical power than larger cooperative-group studies, provide evidence that early initiation of RT for patients with ICE may still be an important factor to decrease risk of relapse.

Expanding on this, the role of CPM must be evaluated as well for patients with ICE. Of standard RMS chemotherapeutics, CPM has the most significant CNS penetration and bioavailability [37]. As noted previously, successive trials have decreased the CPM dosing, from D9803 (total CPM dose 25.1–30.8 g/m$^2$) to ARST0531 (8.4–16.8 g/m$^2$) and now to ARST1431 (8.4 g/m$^2$ per current protocol). While outcomes and patterns of failure for ICE patients from ARST0531 have not yet been reported, it is possible that reduced

CPM dosing may be affecting disease control rates as well. With lower overall CPM dose ranges in our series (among ICE patients, ranging from 7.2 g/m$^2$ to 16.8 g/m$^2$), we hypothesize that the combination of lower CPM doses and delayed RT initiation beyond week 4 collectively may account for the observed high rates of relapse among ICE patients treated after week 4. Our data suggest that excess treatment failures may be observed among patients with parameningeal tumors, similar to the results of another recent institutional series [38]. We further support an analysis of ARST0531 in which outcomes for patients with ICE are compared based on treatment arm, given the two-fold difference in CPM dosing between these arms (8.4 g/m$^2$ versus 16.8 g/m$^2$) with RT timing set at week 4 across all arms. Such an analysis could provide insight into the optimal treatment approach for these high-risk patients.

Together, our data highlight successes as well as areas for improvement in the treatment of H&N RMS. Use of PBT yields comparable LC rates as with photon RT, without evidence of increased marginal failures. While long-term toxicity data with further follow-up are pending, this series demonstrates a toxicity profile similar to that of other PBT reports, and a seemingly improved late toxicity profile as compared with prior IMRT series. This cohort, treated with lower doses of CPM, provides the first modern experience to support the role of tumor size in the risk of LF, and bolsters the incorporation of RT dose-escalation into ARST1431 for patients with larger tumors. Finally, the high rates of relapse among patients with ICE, and the role of RT timing for these patients, provides cautionary data as successive trials further delay RT while reducing CPM dose. We speculate that treatment de-escalation combination of RT delay and CPM dose reduction contributes to increased risk of relapse among ICE patients, and continued monitoring of ongoing clinical trials will be critical.

## Conflict of interest/disclosures

All authors report no conflicts of interest or relevant financial disclosures related to this work.

## Funding

None.

## Presentations

Presented in part in oral presentation form at the 2017 International Congress of the Pediatric Radiation Oncology Society (PROS, June 21–24, 2017).

## References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7–30.
[2] Huh WW, Skapek SX. Childhood rhabdomyosarcoma: new insight on biology and treatment. Curr Oncol Rep 2010;12:402–10.
[3] Crist WM, Anderson JR, Meza JL, et al. Intergroup rhabdomyosarcoma study-IV: results for patients with nonmetastatic disease. J Clin Oncol 2001;19:3091–102.
[4] Arndt CA, Stoner JA, Hawkins DS, et al. Vincristine, actinomycin, and cyclophosphamide compared with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan, and cyclophosphamide for intermediate-risk rhabdomyosarcoma: children's oncology group study D9803. J Clin Oncol 2009;27:5182–8.
[5] Ladra MM, Szymonifka JD, Mahajan A, et al. Preliminary results of a phase II trial of proton radiotherapy for pediatric rhabdomyosarcoma. J Clin Oncol 2014;32:3762–70.
[6] Ladra MM, Edgington SK, Mahajan A, et al. A dosimetric comparison of proton and intensity modulated radiation therapy in pediatric rhabdomyosarcoma patients enrolled on a prospective phase II proton study. Radiother Oncol 2014;113:77–83.
[7] Leiser D, Calaminus G, Malyapa R, et al. Tumour control and Quality of Life in children with rhabdomyosarcoma treated with pencil beam scanning proton therapy. Radiother Oncol 2016;120:163–8.
[8] Yock T, Schneider R, Friedmann A, Adams J, Fullerton B, Tarbell N. Proton radiotherapy for orbital rhabdomyosarcoma: clinical outcome and a dosimetric comparison with photons. Int J Radiat Oncol Biol Phys 2005;63:1161–8.
[9] Kozak KR, Adams J, Krejcarek SJ, Tarbell NJ, Yock TI. A dosimetric comparison of proton and intensity-modulated photon radiotherapy for pediatric parameningeal rhabdomyosarcomas. Int J Radiat Oncol Biol Phys 2009;74:179–86.
[10] Sorensen PH, Lynch JC, Qualman SJ, et al. PAX3-FKHR and PAX7-FKHR gene fusions are prognostic indicators in alveolar rhabdomyosarcoma: a report from the children's oncology group. J Clin Oncol 2002;20:2672–9.
[11] Meza JL, Anderson J, Pappo AS, et al. Analysis of prognostic factors in patients with nonmetastatic rhabdomyosarcoma treated on intergroup rhabdomyosarcoma studies III and IV: the Children's Oncology Group. J Clin Oncol 2006;24:3844–51.
[12] McGovern SL, Okcu MF, Munsell MF, et al. Outcomes and acute toxicities of proton therapy for pediatric atypical teratoid/rhabdoid tumor of the central nervous system. Int J Radiat Oncol Biol Phys 2014;90:1143–52.
[13] Liu W, Frank SJ, Li X, et al. Effectiveness of robust optimization in intensity-modulated proton therapy planning for head and neck cancers. Med Phys 2013;40:051711.
[14] Green DM, Nolan VG, Goodman PJ, et al. The cyclophosphamide equivalent dose as an approach for quantifying alkylating agent exposure: a report from the Childhood Cancer Survivor Study. Pediatr Blood Cancer 2014;61:53–67.
[15] Children's Oncology Group. ACNS0831: Phase III randomized trial of post-radiation chemotherapy in patients with newly diagnosed ependymoma ages 1 to 21 years. URL: https://childrensoncologygroup.org/index.php/acns0831. [Accessed: 10/23/18].
[16] National Cancer Institute. Common Terminology Criteria for Adverse Events v4.0. May 29, 2009. NIH publication #09-7473.
[17] IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.
[18] Paulino AC, Simon JH, Zhen W, Wen BC. Long-term effects in children treated with radiotherapy for head and neck rhabdomyosarcoma. Int J Radiat Oncol Biol Phys 2000;48:1489–95.
[19] Ludmir EB, Paulino AC, Grosshans DR, et al. Regional nodal control for head and neck alveolar rhabdomyosarcoma. Int J Radiat Oncol Biol Phys 2018;101:169–76.
[20] Yang JC, Wexler LH, Meyers PA, Wolden SL. Parameningeal rhabdomyosarcoma: outcomes and opportunities. Int J Radiat Oncol Biol Phys 2013;85:61–6.
[21] Vern-Gross TZ, Indelicato DJ, Bradley JA, Rotondo RL. Patterns of failure in pediatric rhabdomyosarcoma after proton therapy. Int J Radiat Oncol Biol Phys 2016;96:1070–7.
[22] Childs SK, Kozak KR, Friedmann AM, et al. Proton radiotherapy for parameningeal rhabdomyosarcoma: clinical outcomes and late effects. Int J Radiat Oncol Biol Phys 2012;82:635–42.
[23] Hawkins DS, Chi Y-Y, Anderson JR, et al. Addition of vincristine and irinotecan to vincristine, dactinomycin, and cyclophosphamide does not improve outcome for intermediate-risk rhabdomyosarcoma: a report from the Children's Oncology Group. J Clin Oncol 2018;36:2770–7.
[24] Ladra MM, Mandeville HC, Niemierko A, et al. Local failure in parameningeal rhabdomyosarcoma correlates with poor response to induction chemotherapy. Int J Radiat Oncol Biol Phys 2015;92:358–67.
[25] Curtis AE, Okcu MF, Chintagumpala M, Teh BS, Paulino AC. Local control after intensity-modulated radiotherapy for head-and-neck rhabdomyosarcoma. Int J Radiat Oncol Biol Phys 2009;73:173–7.
[26] Weber DC, Ares C, Albertini F, et al. Pencil beam scanning proton therapy for pediatric parameningeal rhabdomyosarcomas: clinical outcome of patients treated at the Paul Scherrer Institute. Pediatr Blood Cancer 2016;63:1731–6.
[27] Lin C, Donaldson SS, Meza JL, et al. Effect of radiotherapy techniques (IMRT vs. 3D-CRT) on outcome in patients with intermediate-risk rhabdomyosarcoma enrolled in COG D9803–a report from the Children's Oncology Group. Int J Radiat Oncol Biol Phys 2012;82:1764–70.
[28] Schulz-Ertner D, Tsujii H. Particle radiation therapy using proton and heavier ion beams. J Clin Oncol 2007;25:953–64.
[29] Lockney NA, Friedman DN, Wexler LH, Sklar CA, Casey DL, Wolden SL. Late Toxicities of intensity-modulated radiation therapy for head and neck rhabdomyosarcoma. Pediatr Blood Cancer 2016;63:1608–14.
[30] Children's Oncology Group ARST1431: A Randomized Phase 3 Study of Vincristine, Dactinomycin, Cyclophosphamide (VAC) Alternating with Vincristine and Irinotecan (VI) Versus VAC/VI Plus Temsirolimus (TORI, Torisel, NSC#683864, IND# 122782) in Patients with Intermediate Risk (IR) Rhabdomyosarcoma (RMS). Online protocol, version 03/22/16. URL: http://rpc.mdanderson.org/RPC/credentialing/files/ARST1431_ProtocolDoc_032216.pdf. [Accessed 10/23/2018].
[31] Wolden SL, Lyden E, Arndt C, et al. Local Control for intermediate-risk rhabdomyosarcoma: results from D9803 according to histology, group, site, and size: a report from the Children's Oncology Group. Int J Radiat Oncol Biol Phys 2015;93:1071–6.
[32] Gupta AA, Anderson JR, Pappo AS, et al. Patterns of chemotherapy-induced toxicities in younger children and adolescents with rhabdomyosarcoma: a report from the Children's Oncology Group Soft Tissue Sarcoma Committee. Cancer 2012;118:1130–7.

[33] Walterhouse DO, Pappo AS, Meza JL, et al. Reduction of cyclophosphamide dose for patients with subset 2 low-risk rhabdomyosarcoma is associated with an increased risk of recurrence: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. Cancer 2017;123:2368–75.
[34] Bisogno G, Jenney M, Bergeron C, et al. Addition of dose-intensified doxorubicin to standard chemotherapy for rhabdomyosarcoma (EpSSG RMS 2005): a multicentre, open-label, randomised controlled, phase 3 trial. Lancet Oncol 2018;19:1061–71.
[35] Ludmir EB, Paulino AC, Grosshans DR, et al. Timing of radiation therapy for parameningeal rhabdomyosarcoma with intracranial extension. Int J Radiat Oncol Biol Phys 2018;101:1008.
[36] Michalski JM, Meza J, Breneman JC, et al. Influence of radiation therapy parameters on outcome in children treated with radiation therapy for localized parameningeal rhabdomyosarcoma in Intergroup Rhabdomyosarcoma Study Group trials II through IV. Int J Radiat Oncol Biol Phys 2004;59:1027–38.
[37] Arndt CA, Balis FM, McCully CL, Colvin OM, Poplack DG. Cerebrospinal fluid penetration of active metabolites of cyclophosphamide and ifosfamide in rhesus monkeys. Cancer Res 1988;48:2113–5.
[38] Lucas Jr JT, Pappo AS, Wu J, Indelicato DJ, Krasin MJ. Excessive treatment failures in patients with parameningeal rhabdomyosarcoma with reduced-dose cyclophosphamide and delayed radiotherapy. J Pediatr Hematol Oncol 2018;40:387–90.