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Delayed radiotherapy following dose intensive chemotherapy for parameningeal rhabdomyosarcoma (PM-RMS) of childhood

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ABSTRACT

Purpose: To evaluate the local control rates and survival rates of patients with Group III parameningeal rhabdomyosarcoma (PM-RMS) treated with a dose intensive chemotherapy regimen followed by irradiation.

Materials and methods: Twenty-six patients with group III, PM-RMS were enrolled in a prospective pilot trial at the Mayo Clinic, Rochester, MN and Children's Hospital and Regional Medical Center Seattle, WA. The median age at diagnosis was 8.5 years (range 1.5–19 years). The male to female patient ratio was 1.6:1. Twenty-three patients had embryonal histology with the remaining three alveolar. Risk factors indicating high risk disease included intracranial extension (10 patients), base of skull erosion (12 patients), and cranial nerve palsy (10 patients). The median follow-up period for all patients was 82 months (range 17–148 months). Patients were treated with an intensified chemotherapy regimen followed by definitive local irradiation at week 12 following further chemotherapy. The median time from initiation of chemotherapy to irradiation was 16 weeks (range 6–23). The median dose delivered was 50.4 Gy (50.4–66.6 Gy).

Results: Response was assessed after the fourth course of chemotherapy. Three patients exhibited a complete response, 22 a partial response, and 1 patient had no response after two cycles of chemotherapy and proceeded to irradiation at week 6. The 5-year estimated event free survival was 81% (±15%, 95% CI). Two patients died from progressive metastatic disease; 1 patient died from secondary malignancy; and 2 patients died from locally progressive disease. The 5-year local control rate was 92% (±10.6%, 95% CI).

Conclusions: Treatment of group III PM-RMS patients with neo-adjuvant, intensive chemotherapy with a delay in irradiation resulted in excellent local-regional control rates and survival rates and may allow for a response-based radiotherapy approach.

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1. Introduction

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma of childhood and adolescence, accounting for 350 new cases of cancer each year in the United States.[1] The prognosis for paediatric RMS has improved significantly over the past 30 years[2–11] Parameningeal sites (PM-RMS) constitute half of all head and neck RMS cases and 17% of RMS overall. PM-RMS sites were identified in IRS-I as unfavourable sites because the invasion of critical anatomic structures usually precludes complete resection and the tendency to develop early leptomeningeal progression.[4] PM-RMS is responsive to multi-modal therapy; 84% of 424 patients with PM-RMS enrolled on IRSG protocols from 1984 to 1995 achieved either a complete or partial response to chemotherapy.[10] The most common site of initial failure for unresected, non-metastatic RMS (Clinical Group III) enrolled in IRS-III and IV was local (local-failure rate of 15–17%).[5,7]

Radiotherapy guidelines for clinical Group III PM-RMS patients have also evolved over the successive IRSG studies.[8,12,13] Recently reported results from IRS-IV for patients with non-metastatic PM-RMS showed an estimated 5-year EFS of 74%.[7] Under the current IRSG legacy study (Children's Oncology Group (COG) study D9803) guidelines, patients with PM-RMS start irradiation at week 12, except for patients with intra-cranial extension (ICE), for whom radiotherapy begins during the first 1–2 weeks of treatment. Based upon previous IRSG studies, 35% of PM-RMS patients have ICE and are expected to receive early radiotherapy on the current D9803 study.

Toxicity from combined chemotherapy and irradiation has been well described in the literature. With intensive chemotherapy regimens, the potential for combined chemotherapy and radiation toxicity increases, and refinement of radiation therapy including timing, dose and volume has been explored. Delayed radiotherapy may permit the delivery of intensive chemotherapy by avoiding the additive mucosal toxicity of radiation and chemotherapy. An additional benefit to delaying radiotherapy is that the dose and/or field of treatment could be modified based upon the response of the primary tumour to chemotherapy, potentially reducing the short- and long-term morbidity of irradiation, such as has been found in other childhood tumour types. We have previously shown, in a single institution study, the efficacy of intensified induction chemotherapy followed by delayed irradiation.[14] In this report, we expand upon our previous series to include an additional institution's experience treating Group III patients with an identical chemotherapy regimen.

2. Materials and methods

Twenty-six patients with group III PM-RMS were enrolled in an IRB approved prospective pilot protocol at the Mayo Clinic, Rochester, MN, or Children's Hospital and Regional Medical Center, Seattle, WA, from 12/1/1991 to 12/9/1999.

2.1. Patient characteristics (Table 1)

The median age at diagnosis was 8.5 years (range 1.5–19 years). The male to female patient ratio was 1.6:1. Twenty-three patients had embryonal histology with the remaining three alveolar. Risk factors indicating high risk disease included intracranial extension (10 patients), base of skull erosion (12 patients) and cranial nerve palsy (10 patients). The median follow-up period for all patients was 82 months (range 17–148 months). Patients were treated with an intensified chemotherapy regimen followed by definitive local irradiation at week 12 following further chemotherapy. The median time from initiation of chemotherapy to irradiation was 16 weeks (range 6–23). The median dose delivered was 50.4 Gy (50.4–66.6 Gy).

2.2. Treatment schema (Fig. 1)

The details of the chemotherapy regimen have been reported previously.[15] Briefly, patients were treated with an intensified chemotherapy regimen consisting of vincristine (1.5 mg/m^2), doxorubicin (37.5 mg/m^2/day × 2 days) and cyclophosphamide (600 mg/m^2/day × 2 days) alternating every 3 weeks with ifosfamide (1800 mg/m^2/day × 5 days) and etoposide (100 mg/m^2/day × 5 days) (Fig. 1). MESNA was given for bladder protection with each dose of cyclophosphamide and ifosfamide. Granulocyte colony stimulating factor (GCSF) was given after each course of chemotherapy. Vincristine was also given at weeks 1, 2, 7 and 8. By protocol design, radiotherapy was delayed until after week 12 chemotherapy regardless of risk factors.

2.3. Response to chemotherapy

All patients were assessed for response by CT or MR after completion of the 4th chemotherapy course. Responses were defined in the following manner: complete response (CR), no radiographic evidence of residual disease; partial response (PR), more than 50% reduction in the sum of the products of the maximum perpendicular diameters of all measurable lesions; and no response (NR), no change in the size of the lesion by the criteria above.

2.4. Statistical analysis

Local-regional control rates, cause-specific survival rates and disease free survival rates were calculated using Kaplan–Meier,[16] product-limit method using the Statview 4.5 statistical package (Abacus Concepts, Inc., Berkeley, CA, 1996). Patients were censored at the date of last contact if no measured event had occurred. Depending on the analysis, events were defined as local recurrence, distant recurrence, death from recurrent RMS, or death from any cause.

2.5. Toxicity coding

The Radiation Therapy Oncology Group (RTOG)–European Organisation for Research and Treatment of Cancer (EORTC) scoring system was used to grade mucosal toxicity and haematological toxicities.

3. Results

Three patients did not complete all 39 weeks of planned chemotherapy due to complications or patient refusal. Two pa-

Table 1 – Patient characteristics and radiotherapy parameters

Clinical characteristics	Percent (%)	Response at week 12	Percent (%)	Radiation parameters	
Age				*Timing*	
<5 years	48	NR	4	None	4%
5–9	15	PR	74	⩽Week 12	11%
>9	38	CR	22	Weeks 12–20	63%
				Week ⩾21	22%
Sex					
Male	63				
Female	27				
Histology				*Dose*	
Embryonal	74			Median	5040 cGy
Alveolar	26			Range	5040–6300 cGy
Parameningeal extension					
None	11				
ICE	33				
CNP	41				
BSE	59				
Three risk factors	12				
ICE + BSE	19				
CNP + ICE	4				
Primary site (n)					
NP (6)	23				
PPh (6)	23				
MS (6)	23				
Ptg (2)	23				
ITF (2)	8				
Orb (1)	4				
NC (1)	4				
PN (1)	4				
ME (1)	4				

ICE, intracranial extension; BSE, base of skull erosion; CNP, cranial nerve palsy; NR, no response; PR, partial response; CR, complete response; NP, nasopharynx; PPh, parapharyngeal; MS, maxillary sinus; Ptg, pterygoid space; ITF, ifratemporal fossa; Orb, orbit; NC, nasal cavity; PN, paranasal sinus; ME, middle ear.

week	0	1	2	3	4	5	6	7	8	9	12	15	18	21	24	27	30	33	36	39	42
	V	V	V				V	V	V		V		V		V		V		V		
	C						C				C		C		C		C		C		E
	D						D				D				D		D		D		N
				E						E		E		E		E		E		E	D
				I						I		I		I		I		I		I	
											Radiotherapy										

Vincristine 1.5 mg/m^2(2 mg maximum dose) IVP, day 0
Doxorubicin 37.5 mg/m^2 IV over 18 hours, days 0-1
Cyclophosphamide 600 mg/m^2 IV over 30 minutes, days 0-1
Alternating with
Ifosfamide 1800 mg/m^2 IV over 1 hour, days 0-4
Etoposide 100mg/m^2 IV over 1 hour, days 0-4

*For BSA < 0.6m^2, chemotherapy doses calculated as mg/kg.

Fig. 1 – Chemotherapy treatment schedule.

tients did not receive the final course of therapy, and one patient did not receive the final three courses of chemotherapy. Fourteen patients who completed all 39 weeks of planned therapy had delays in the initiation of one or more courses. The median cumulative days of delay in this group was 27 days (range 5–84 days). Twelve patients required a reduction of doxorubicin during at least one course due to severe mucositis or prolonged haematological toxicity.

Ninety-four percent of patients achieved a radiographic response to neo-adjuvant chemotherapy, including 3 patients with CR (22%) 22 and patients with PR (74%) (Table 1). One patient who did not have a radiographic response to neo-adju-

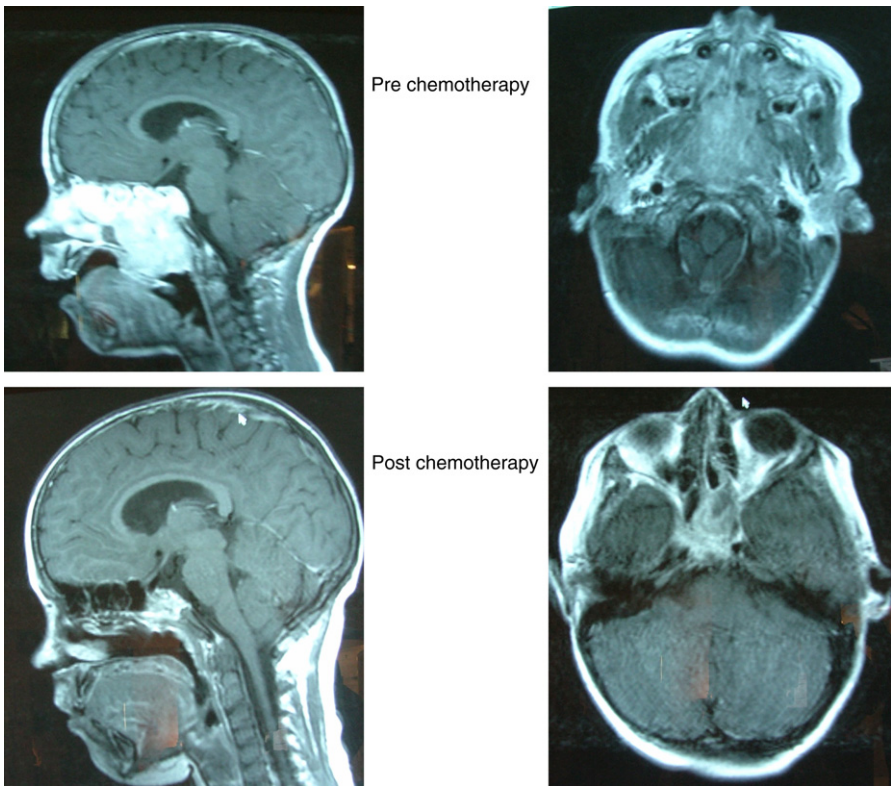

Fig. 2 – Pre and post chemotherapy MRIs of a patient having a partial response (PR).

vant chemotherapy received radiotherapy earlier (at 6 weeks) than intended by protocol. Fig. 2 shows an example of a PR.

4. Radiotherapy parameters

4.1. *Timing*

Patients were scheduled to begin irradiation as soon as their counts had recovered after completing their 5th course of chemotherapy (week 12). The median time from on study to initiation of radiotherapy was 14.5 weeks (range 6–23 weeks). In all cases, the delay between planned and actual initiation of radiotherapy was due to prolonged neutropenia after chemotherapy despite the use of G-CSF support.

4.2. *Treated volume, dose and fractionation*

The treated volume consisted of the pre-chemotherapy volume as determined by CT or MR with a 2–3-cm margin from the defined tumour border to block edge, unless otherwise indicated by anatomic constraints. The treatment dose was not mandated in the protocol but was at the discretion of the treating radiotherapist. All but one patient was treated with a fractionation scheme of 1.8 Gy per fraction 5 days a week to a median total dose of 50.4 Gy (range 50.4–66.6 Gy; 10 patients 50.4 Gy, 3 patients 54 Gy, 3 patients 55.8 Gy, 1 patient 66.6 Gy). One patient was treated with a hyperfractionated regime using 1.10 Gy per fraction bid to a total dose of 50.6 Gy. The median duration of treatment was 42 days (range 33–58). Three patients had $\geqslant$5 days consecutive break in radiotherapy because of mucositis. Two of these patients required total parenteral alimentation during treatment. The dose was not purposefully increased for intracranial tumour extension. Eight of the 10 patients with ICE received a dose of 50.4 Gy.

4.3. *Disease free survival/cause specific survival*

The 5-year estimated event free survival rate (EFS) was 81% (66–96%, 95% CI) (Fig. 3). Four failures were observed, two local and two distant. The 5-year estimated cause specific survival rate (CSS) was 84% (68.8–99.2%, 95% CI). Two patients died from relapsed local disease (19 and 20 months); two patients died from distant metastatic disease (at 17 and 18 months

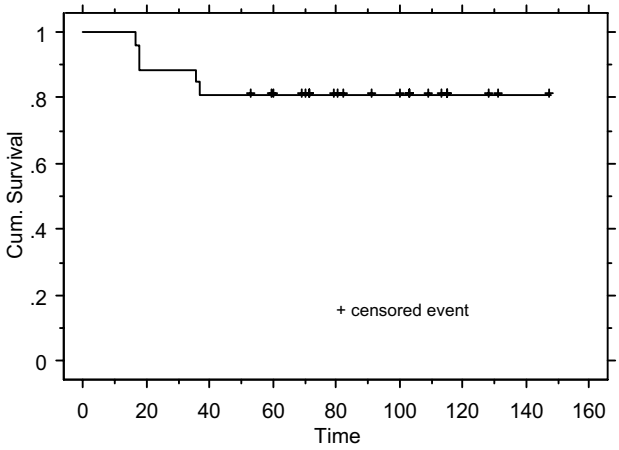

Fig. 3 – Kaplan–Meier curve for event free survival.

from the time of diagnosis) and one patient died from acute myelogenous leukaemia (18 months), a treatment induced second malignancy.

4.4. *Local-failure free survival control*

The 5-year estimated local-failure free survival rate was 92% (81.4–102.6%, 95% CI) (Fig. 4). The two local failures occurred at 19 and 20 months from diagnosis and were in-field failures as determined by comparison of the relapsed scan with the ports treated. Because of the rarity of events and small sample size, no prognostic factors associated with outcome could be determined.

4.5. *Toxicities related to radiotherapy*

All patients developed grades 3–4 haematological toxicity during induction chemotherapy and delayed the initiation of radiotherapy in 17 patients to a median of 16 weeks (range 13–23). RTOG/EORTC grades 3–4 mucosal toxicity was documented in 7 patients during radiotherapy and required a break in radiotherapy in 3 patients. The days of delay in radiotherapy were 3, 5, and 5 for these patients. One patient had a 4 day delay in treatment because of severe neutropenia.

5. Discussion

The treatment of PM-RMS has markedly changed since the initiation of the IRSG studies in the 1970s.[3–7,10,12,13,17–20] Radiotherapy parameters have also significantly changed from earlier studies, when craniospinal axis and whole brain irradiation were used. The survival and local control for this disease has also remarkably improved over the past 2–3 decades, with an overall survival rate of 70% in the most recently reported study.[13] This improvement in survival is largely attributable to the intensification of chemotherapy regimens and improvements in the delivery of radiotherapy. The toxicity of treatment, however, is not trivial. Raney et al.[21] reported that 77% of patients with PM RMS enrolled on IRSG II and III had at least one long-term sequela of the disease or treatment. The most frequent complications included poor statural growth (48%), facial/nuchal asymmetry (35%), dental abnormalities (29%), impaired vision (17%), hearing decrease (17%) and neurocognitive dysfunction (16%).[21]

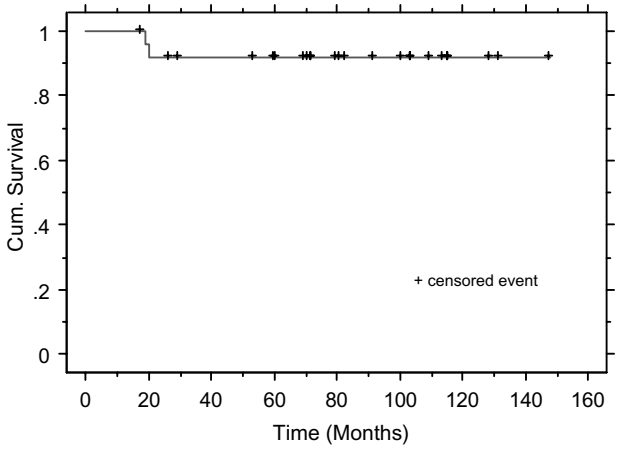

Fig. 4 – Kaplan–Meier curve for local-failure free survival.

The current recommendation for patients with PM-RMS, who have ICE according to COG D9803, is to begin irradiation as early as possible, typically during weeks 1 or 2. This strategy is based on the results of previous IRSG studies, which have suggested an increased local-failure rate if irradiation was delayed. Recently, Donaldson et al. have reported a decrease in local control for patients with PM-RMS and ICE on IRSG studies II–IV who had a delay of greater than 2 weeks in initiation of radiotherapy.[22] Although this difference was not statistically significant ($p = 0.07$), an expanded analysis of these data[23] showed an inferior 5-year local control by univariate analysis for patients with any high risk feature (ICE, BSE, or CNP) when radiotherapy was delayed >2 weeks ($p = 0.028$). Delayed radiotherapy did not influence failure free survival or overall survival. Upon multivariate analysis, delayed radiotherapy was no longer statistically significant; showing that delay in irradiation was not an independent factor predicting local control. Factors significant by multivariate analysis for decreased local control included age greater than 10 years; radiotherapy dose <47.5 Gy; and the presence of ICE, BSE, or CNP.

One limitation of the analyses of IRSG studies is that delay of radiotherapy was a violation of protocol mandated radiotherapy timing. It is possible that other clinical (such as poor clinical status) or treatment factors (such as poor compliance with other protocol mandated therapies) were associated with delayed radiotherapy and accounted for the apparent worse outcome seen with delayed radiotherapy. In addition, the IRSG studies were not prospectively designed to assess the role of radiotherapy timing in local control. Therefore, one must be cautious in the interpretation of such subset analysis.

Our results, on the other hand, suggest that intensification of neo-adjuvant chemotherapy prior to radiotherapy for patients with PM-RMS results in excellent local control and survival. Initial chemotherapy intensification may reduce distant failure. Delaying local therapy to allow treatment of systemic disease is a reasonable approach and might improve survival without compromising local control. While our sample size is small, our results suggest that this approach is feasible and results in at least comparable if not improved local control and survival rates compared to IRSG studies.

A second theoretical advantage of a delay in the initiation of irradiation after intensified induction chemotherapy is to allow for response-adapted radiotherapy. Response-adapted radiotherapy is used for other non-ICE positive, PM-RMS sites in COG protocol 9803. Such an approach has been used in the treatment of Ewing's sarcoma with studies demonstrating that not only are margin status and histological response prognostic factors, but they may also be used for guiding radiotherapy parameters.[24–26] Our data show that there is a favourable response to neo-adjuvant chemotherapy with all but 1 of the 18 patients showing at least a partial response (15 PR, 2 CR) with fairly substantial reductions in tumour volume. One could propose using the initial pre-chemotherapy volume with margin and treating to 36–41.4 Gy with a volume reduction using the post chemotherapy volume assuming only microscopic disease in the non-enhancing MR post Gad-

olinium volume. For patients with a CR the total dose could be diminished to 41.4–45 Gy, while a dose of 50.4 Gy would be delivered to the remaining enhancing MR post Gadolinium volume in those patients exhibiting a PR. Similarly, one could consider a volume reduction based upon response to irradiation if radiotherapy was initiated during weeks 1–2 in lieu of intensive chemotherapy. Either approach could substantially reduce the volume of normal tissue (particularly the brain) treated and the associated long-term complications of irradiation.

6. Conclusions

Treatment of Group III PM-RMS patients with neo-adjuvant, intensified chemotherapy with a delay in irradiation resulted in excellent local-regional control rates and survival rates and may allow for a response-based therapy approach.

Conflict of interest statement

None declared.

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