Parameningeal rhabdomyosarcoma- clinical profile, outcomes and prognostic factors in children treated at a single center over a decade

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Abstract

1 Background Parameningeal Rhabdomyosarcomas (PM-RMS) in children are challenging to treat. While ten-year Event Free Survival (EFS) of 62% have been reported from High-Middle Income Countries (HMICs) for localized disease, data is limited from Low-Middle Income Countries (LMICs). We studied the clinical profile, outcomes, and prognostic factors in PM-RMS.

2 Materials and Methods Children 15 years with PM-RMS treated on a uniform chemotherapy protocol from January 2013-December 2021 were retrospectively analysed. Local therapy at 10-12weeks of induction was radiotherapy (RT)+/-surgery where possible with early RT for intracranial extension (ICE).

3 Results Seventy-six patients with a median age of 6.7 years (range,3.2-15years), male to female ratio of 1.8:1 formed the study cohort. Eleven patients (14.5%) had metastasis (lungs-8, bone-2, bone marrow-1) and ICE seen in 46.1%(n=35). Twenty-five patients (49.0%) had alveolar histology with PAX3/7 positive in 17/59 (28.8%). Median tumor size(t size) at baseline was 5.2cm(range,1.2-12.8cm). Seventy-one patients received RT, 5 also underwent surgery. At a median follow-up of 6months (range,53-76months) 4year EFS, OS of the whole cohort were 47.3%(95%CI:34.8%-58.8%), 51.7%(95%CI:38.0%-64.0%) respectively. Four-year EFS, OS of localized and metastatic cohort were 47.3%(95%CI:34.8%-58.8%), 51.7%(95%CI:38.0%-64.0%) respectively. Four-year EFS, OS of localized and metastatic cohort were 54.7%(95%CI:41.3%-68.1%), 56.0%(95%CI:42.0%-70.0%) and 9.1%(95%CI:0%-26.5%), 18.2%(95%CI:0%-47.8%) respectively. Metastases (HR-3.38,95%CI:1.57-7.26,p=0.002), t size (HR-1.17,95%CI:1.02-1.34,p=0.026) were prognostic for survival on multivariate analysis. 4 Conclusions Survival of children with localized PM-RMS in our study is relatively fair compared to the reported literature probably due to application of RT in all despite higher proportion of larger tumors, unfavorable sites of primary and intracranial extension. Identification of high-risk subsets and optimizing current treatment strategies, both systemic and local therapy may partly improve outcomes.
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Outcomes and prognostic factors in parameningeal pediatric rhabdomyosarcoma
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ABBREVIATIONS:
FDG-PET Fluorodeoxyglucose-Positron Emission Tomography
PM-RMS Parameningeal Rhabdomyosarcoma
ICE Intra Cranial Extension
CBBE Cranial Base Bone Erosion
CNP Cranial Nerve Palsy
EFS Event-Free Survival
OS Overall Survival
RT Radiotherapy
IMRT Intensity modulated radiotherapy

DATA AVAILABILITY STATEMENT:
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Parameningeal rhabdomyosarcoma- clinical profile, outcomes and prognostic factors in children treated at a single center over a decade
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ABSTRACT

1 Background
Parameningeal Rhabdomyosarcomas (PM-RMS) in children are challenging to treat. While ten-year Event Free Survival (EFS) of 62% have been reported from High-Middle Income Countries (HMICs) for localized disease, data is limited from Low-Middle Income Countries (LMICs). We studied the clinical profile, outcomes, and prognostic factors in PM-RMS.

2 Materials and Methods
Children[?]15 years with PM-RMS treated on a uniform chemotherapy protocol from January 2013-December 2021 were retrospectively analysed. Local therapy at 10-12 weeks of induction was radiotherapy (RT)+/-surgery where possible with early RT for intracranial extension (ICE).

3 Results

Seventy-six patients with a median age of 6.7 years (range, 3.2-15 years), male to female ratio of 1.8:1 formed the study cohort. Eleven patients (14.5%) had metastasis (lungs-8, bone-2, bone marrow-1) and ICE seen in 46.1% (n=35). Twenty-five patients (49.0%) had alveolar histology with PAX3/7 positive in 17/59 (28.8%). Median tumor size ($t_{size}$) at baseline was 5.2 cm (range, 1.2-12.8 cm). Seventy-one patients received RT, 5 also underwent surgery. At a median follow-up of 65 months (range, 53-76 months) 4-year EFS, OS of the whole cohort were 47.3% (95% CI: 34.8%-58.8%), 51.7% (95% CI: 38.0%-64.0%) respectively. Four-year EFS, OS of localized and metastatic cohort were 54.7% (95% CI: 41.3%-68.1%), 56.0% (95% CI: 42.0%-70.0%) and 9.1% (95% CI: 0%-26.5%), 18.2% (95% CI: 0%-47.8%) respectively. Metastases (HR-3.38, 95% CI: 1.57-7.26, p=0.002), $t_{size}$ (HR-1.17, 95% CI: 1.02-1.34, p=0.026) were prognostic for survival on multivariate analysis.

4 Conclusions

Survival of children with localized PM-RMS in our study is relatively fair compared to the reported literature probably due to application of RT in all despite higher proportion of larger tumors, unfavorable sites of primary and intracranial extension. Identification of high-risk subsets and optimizing current treatment strategies, both systemic and local therapy may partly improve outcomes.

1 INTRODUCTION

Rhabdomyosarcoma (RMS), the most common soft tissue sarcoma in children and adolescents accounts for 4-5% of childhood malignancies.1,2 Parameningeal (PM) RMS is defined as tumor arising from middle ear/mastoid, nasal cavity/nasopharynx, parapharyngeal space, paranasal sinuses, infratemporal/pterygoid palatine fossa, orbital primary with bony erosion (of the orbital cavity) or parameningeal/intracranial extension. Twenty percent of RMS occurs in the parameningeal area which has a relatively unfavourable prognosis compared to other sites of origin.3 This site is challenging due to vicinity to critical anatomic structures which can affect the mode of local control precluding surgery in majority of cases and avoidance or delay of radiotherapy (RT) in young children, delayed advanced presentations due to misdiagnosis or delayed diagnosis from absence of distinctive symptoms thereby mimicking common pediatric conditions like upper respiratory tract infection, otitis media, increased local recurrences and tendency for intracranial spread especially in those cases with Intracranial Extension (ICE), Cranial Base Bone Erosion (CBBE), or Cranial Nerve Palsy (CNP). Ten-year Event Free Survival (EFS) of 62% have been reported from High-Middle Income Countries (HMICS) for localized disease and data is limited from Low-Middle Income Countries (LMICs).3 This study details the clinical profile and analyze the survival and prognostic factors of PM-RMS in children treated at a single tertiary cancer care center.

2 AIMS AND OBJECTIVES

Children with PM-RMS treated by a uniform protocol were analyzed retrospectively. The primary objectives were to assess event free survival (EFS) and overall survival (OS). Secondary objectives were to study the clinical profile of the cohort and the prognostic factors associated with survival.

3 MATERIALS AND METHODS

3.1 Methods

Children ([?]15 years) with biopsy proven, treatment naïve PM-RMS registered from January 2013 to December 2021 were retrospectively analyzed. Staging was done by $^{18}$F-FDG-PET CT and bilateral bone marrow aspiration and biopsies in all, with lymph node sampling by Fine needle aspiration cytology (FNAC) or tru-cut biopsy wherever suspicious for metastasis. MRI was used for better delineation of primary tumor when necessary. CBBE was taken as erosion of bones of skull base, even if it involved only the outer table. Any
extension beyond the inner table of skull bones which may include dural involvement or extension through foramen was taken as ICE. All patients were treated on a uniform chemotherapy protocol consisting of 12 cycles of chemotherapy (either VIE-vincristine, ifosfamide, etoposide+VCD-vincristine, cyclophosphamide, dactinomycin or VCD only). Local therapy was planned at 10-12 weeks of induction chemotherapy by a multi-disciplinary team as radiotherapy (RT) +/- surgery wherever R0 resection was feasible. Early RT by 4 weeks of induction was contemplated in those with ICE. RT to the primary was delivered at a dose of 50.4Gy/28# using Intensity Modulated RT technique (IMRT). Metastatic sites including bone and lymph nodes were also addressed with same dose of RT. Lung metastases were reassessed after 4 cycles of induction therapy. If lung lesions were in remission, only follow-up was advised; if they had significantly reduced in size, but were limited in number, metastatectomy was advised if feasible. If lung lesions were too small for surgery or multiple in number with significant response, a repeat non-contrast CT scan of chest was performed at the end of chemotherapy. Patients who received definitive radiotherapy had 18F-FDG-PET CT done 3 months after completion of definitive RT to assess the disease status and were classified as having no residual or morphological residual (presence of soft tissue lesion with no FDG avidity) or FDG-avid residual (defined as any grade of FDG activity in a residual lesion).

3.2 Statistical methods
Baseline variables were analyzed by descriptive statistics. For survival analysis, an event was defined as relapse, progression, abandonment, or death due to any cause. Event-free survival (EFS) was calculated as time from the date of diagnosis to event, or last follow-up. Overall survival (OS) was calculated as time from date of diagnosis to death due to any cause, or last follow-up. All patients without an event were censored at last follow up. Estimates of survival were computed using the Kaplan-Meier method. The Hazard Ratios (HR) and significance associated with patient characteristics were assessed in a Cox proportional hazards regression model. Variables with a p value<0.1 on univariate analysis were included in multivariate analysis, on which a p value[?]0.05 was considered significant. Statistical analysis was performed using STATA software, version 15.1. An optimal cutoff for Tumor Size (tsize) with respect to EFS and OS was chosen in this study for outcome analysis. We optimized the cutoff by maximizing the significance assessed by the log-rank test for the whole cohort. Kaplan-Meier method which was used for the above optimization analysis was executed using the function ”survfit” from the R package ”survival”.

4 RESULTS
4.1 Epidemiological and clinical profile
During the study period, 76 patients were diagnosed with PM-RMS. The median age was 6.7years (range, 0.7-15years) and male to female ratio was 1.8:1. Eleven patients (14.5%) had metastatic disease at presentation. The median tsize at baseline was 5.2cm (range, 1.2-12.8cm), and median size of regional lymph-node in involved cases was 1.6cm (range, 0.7-2.3cm). None of the patients had CSF involvement at baseline. Details in TABLE 1. Consort diagram in Figure 1.

4.2 Treatment
Five patients had events before local control (progression-3, abandoned-1, sepsis-1). For the remaining 71 patients, local treatment was definitive radiotherapy in 66 (93.0%), surgery and radiotherapy in 5 (7.0%, upfront surgery-1, delayed primary excision-4). The site of primary was maxillary sinus in 4 and infratemporal fossa in 1 patient who underwent surgical excision. Median time to RT was 9.4weeks (range, 0.9-29weeks) for the whole cohort, with a median time of 8weeks (range, 0.9-20weeks) for those with ICE.

In the metastatic cohort, 1 patient had progression before local control. Four of 7 patients with lung metastases had complete remission (CR) post induction, rest three had complete metabolic response with significant morphological response of lung nodules. (Of the above 3, 1 each had CR on end of therapy chest CT scan, progression of disease at local site, and death due to sepsis prior to follow-up imaging). None received whole lung irradiation or underwent surgery for lung metastases. Both patients with single bone metastasis had CR on interim assessment and received RT to the site. The patient with bone marrow lesion
was in complete metabolic remission at the end of induction and received no local therapy to this site.

### 4.3 Outcomes

At the time of analysis, 43 patients are alive. There were 33 deaths in the cohort. Disease related mortality was 36.8% (n=28). Non-relapse mortality was 6.6% (n=5, sepsis-3, viral encephalitis-1, cause not known-1). There were 39 events in the cohort (relapse-20, progression-11, abandonment-3, death-5). Two patients abandoned treatment post local treatment with RT while on maintenance chemotherapy and the remaining patient abandoned post induction chemotherapy just before local therapy was delivered.

At a median follow-up of 65 months (range, months) 4-year EFS and OS of the whole cohort were 47.3% (95%CI: 34.8%-58.8%) and 51.7% (95%CI: 38.0%-64.0%) respectively. Four-year EFS and OS of localized cohort were 54.7% (95%CI: 41.3%-68.1%), 56.0% (95%CI: 42.0%-70.0%) and the corresponding values for metastatic cohort were 9.1% (95%CI: 0%-26.5%), 18.2% (95%CI: 0%-47.8%) respectively. There were 31 progression/relapses in this study cohort. The site of relapse was isolated local in 45% (n=14), regional lymph-node only in 6.5% (n=2), locoregional in 6.5% (n=2), metastatic in 32.3% (n=10, leptomeningeal-5, dural based mass-1, bone marrow-1, bone and bone marrow-1, lung-1, soft tissue deposits-1) and combined in 9.7% (n=3). Survival curves are in Figure 2.

A tumor size cut-off of 7.1 cm was found to be prognostic for outcomes in our cohort in contrast to 5 cm cut-off in co-operative group studies. For the whole cohort, 4-year EFS when tsize was <7.1 cm and >7.1 cm were 56.5% (95%CI: 44.5%-71.6%) and 15.5% (95%CI: 4.3%-55.3%) respectively. The corresponding values for localized cohort were 63.8% (95%CI: 51.6%-78.7%) and 22.2% (95%CI: 6.6%-75.4%) respectively. Four-year OS when tsize was <7.1 cm and >7.1 cm for the whole cohort was 59.9% (95%CI: 47.7%-75.4%) and 29.0% (95%CI: 11.9%-70.6%). For the localized cohort, the corresponding 4-year OS were 65.0% (95%CI: 52.1%-81.0%) and 33.3% (95%CI: 13.2%-84.0%) respectively.

In the 66 children who had received definitive RT as local therapy, 18F-FDG-PET CT scan post 3 months of RT was available in 49 patients (rest had either not reached the time point for PET scan due to progression or were from earlier years where PET scan was not followed as a routine protocol). This showed no residual in 17 patients (34.7%), anatomic only residual in 25 (51.0%), FDG-avid residual in 7 (14.3%). Of these 7 patients with FDG-avid residual, 5 had progression/relapse and died (local relapse-4, dural based mass-1). Median time to relapse was 21 weeks from end of treatment (range, 12 weeks-64 weeks). Four-year EFS of the whole cohort based on this PET response was 28.6% (95%CI: 8.9%-92.2%) for FDG-avid residual and 57.7% (95%CI: 43.2%-76.9%), (p=0.026) for no residual/anatomical residual combined respectively. The corresponding OS for the above groups were 28.6% (95%CI: 8.8%-92.2%) and 66.9% (95%CI: 52.2%-85.9%), (p=0.014) respectively. The localized cohort had a 4-year EFS of 33.3% (95%CI: 10.8%-100%) for those with FDG-avid residual and 66.2% (95%CI: 51.2%-85.6%), (p=0.0094) for those with no residual/anatomical residual combined. Four-year OS for the above groups were 33.3% (95%CI: 10.8%-100%) and 71.6% (95%CI: 56.1%-91.2%), (p=0.024) respectively.

### 4.4 Prognostic factors

For whole cohort, univariate analysis showed metastases (p=0.001), tsize (p=0.008) and post RT PET FDG-avid residual (p=0.034) to be prognostic for EFS. Metastases (p=0.023) retained significance on multivariate, while tsize showed a trend towards better survival in smaller tumors (p=0.059). For OS, gender (p=0.038), metastases (p=0.005), tsize (p=0.007) and post RT PET FDG-avid residual (p=0.021) were prognostic on univariate, with multivariate showing both metastases (p=0.012) and tsize (p=0.019) to be significant. Details in TABLE 2. The analysis showed similar prognostic significance for the rest of the variables when post RT PET FDG-avid residual was dropped from the analysis as it was not available in all. In the subset of patients with ICE, time to RT in weeks as a continuous variable and at a cut-off of 4 weeks and 12 weeks was not prognostic for EFS (HR-1.01, 95% CI: 0.97-1.04, p=0.719) or OS (HR-1.00, 95% CI: 0.96-1.05, p=0.856). Similar results were noted for EFS (HR-1.01, 95% CI: 0.97-1.04, P=0.643) and OS (HR-1.00, 95% CI: 0.96-1.05, P=0.998) for patients with CBBE.
5 DISCUSSION

One of the challenges encountered in PM-RMS compared to other locations due to its anatomic complexity and proximity to vital cranial structures is delivery of optimal local therapy. This site precludes surgery in majority as attainment of disease-free surgical margins and suitable surgical access is difficult which is supplemented by attendant morbidities, both functional and cosmetic post extensive surgeries. In our cohort, radiotherapy was a part of local control in all those who received local treatment of the primary, with RT being the only modality in 93% and surgery as an additional therapy in only 7%. Taking into consideration that most of the relapses were local, optimizing local control with increased doses, appropriate timing of application of RT (especially in young children) in the present context of availability of proton therapy needs further prospective exploration. Likewise, advanced surgical techniques with reconstructive options warrants further investigation.

PM-RMS has the least favorable prognosis when compared to other locations of primary due mainly to reasons mentioned previously. Four-year EFS of 47.7% of the whole cohort and 54.7% of localized cohort though inferior to the cohorts reported in the pooled North American and European cooperative groups analysis of PM-RMS (5year EFS of whole cohort and localized disease being 64.9% and 69% respectively), is relatively good. These outcomes are despite the higher proportion of larger tumors (tsize > 5cm - 58% in our cohort vs 48% in pooled analysis), unfavorable sites of primary (42% vs 34%), lymph-nodal involvement (36% vs 14%), intracranial extension (51% vs 37%), alveolar histology (33% vs 24%) in our cohort. The pooled analysis of patients treated by the cooperative groups also reiterated the superior outcomes with delivery of RT to primary keeping in line with SIOP studies. All children in our study received chemotherapy with VCD at cyclophosphamide doses of 2.2g/m² per cycle or a combination of VIE and VCD with equivalent cyclophosphamide doses. This together with universal application of RT may be the reason for relatively good outcomes despite unfavorable characteristics, though far from optimal. The role of both dose-intensity and cumulative dose of cyclophosphamide affecting outcomes in PM-RMS was studied in a cohort from Memorial Sloan Kettering Cancer Center, which showed significantly better local control rates with a trend towards better EFS when a cumulative dose of cyclophosphamide of >20g/m² was used. PM-RMS may define a high-risk subset where 2.2g/m² per cycle of cyclophosphamide should be delivered without an attempt for dose reduction to optimize outcomes. As relapse in RMS portends poor outcomes in general and more so in these high-risk sites, where options of re-irradiation and surgery especially in local relapses are limited and difficult, treatment at initial presentation with optimal chemotherapy and local therapy seems prudent. This is more so relevant in LMICs where treatment of relapses may not be feasible many a times.

Baseline tumor size was not prognostic of outcomes in our study when a cut-off of 5cm, which is included in IRSG staging was used. But tsize was prognostic of outcomes in our cohort when used as a continuous variable and at a higher cut-off of 7.1cm. This higher tsize cut-off of 7.1cm requires prospective multi-center validation and can be used for refining risk stratification in PM-RMS for LMICs. Treatment of this subset with advanced disease may warrant exploring newer strategies with either chemotherapy intensification, identifying molecular targets for targeted therapy or dose intensification of radiotherapy in the current context of wider availability and applicability of proton therapy to improve survival. Metastatic patients in this study cohort had extremely poor outcomes and these subsets would require enrollment on clinical trials for improvement in survival. In LMICs with very limited resources, the feasibility of treating this subset of patients should be discussed with the family prior to initiating treatment.

FDG-PET 3month post RT in those who received definitive RT affected outcomes as was previously shown in our study where FDG-avid residual portended worse outcomes in this group. Prognostic significance of this variable on EFS and OS was shown on univariate analysis, though multivariate failed to demonstrate this significance, most probably due to small number of patients (n=49). Nevertheless, 5 of 7 patients with FDG-avid residual had progression/relapse and died. This reiterates the need for a differential treatment approach to this rare group of patients. As proposed in previous studies, surgical resection alone of this residual did not improve outcomes, and alternative treatment strategies like administration of metronomic maintenance therapy after treatment completion needs to be studied in the setting of a clinical trial.
The site of primary had no prognostic significance probably due to small sample size. Presence of ICE or CBBE did not affect survival, though small sample size precludes any robust conclusions. Several studies have debated the impact of early (day 0) versus late (9-12 weeks) timing of application of RT in PM-RMS with high-risk features of meningeal impingement with conflicting results. There was no effect of timing of delivery of RT administered based on the institutional protocol for this subset in our study. But the sample size was small, and the timing of RT was heterogeneous even though the protocol mandated early RT within 4 weeks.

The limitations of the study are the retrospective design and relatively small sample size which precludes evaluation of a few prognostic factors, especially the molecular status which was unavailable in some patients. Nevertheless, it’s a sizeable cohort of a rare subset of RMS treated at a single center which could be the basis for further prospective studies on a larger multicenter cohort from the country.

6 CONCLUSIONS
Survival of children with localized PM-RMS in our study is comparable to the reported literature probably due to application of RT and higher cumulative cyclophosphamide dose in all despite higher proportion of larger tumors, unfavorable sites of primary and intracranial extension. Identification of high-risk subsets and optimizing current treatment strategies, both systemic and local therapy may partly improve outcomes.

7 CONFLICT OF INTERESTS
The authors declare that there is no conflict of interest.

8 REFERENCES


9 LEGENDS

TABLE 1. Demographic and clinical characteristics of patients in this cohort

TABLE 2. Prognostic factors A) Univariate analysis- EFS B) Univariate analysis- OS C) Multivariate analysis- EFS and OS of whole cohort

Figure 1. Consort diagram of this retrospective study

Figure 2. A) EFS of whole cohort B) OS of whole cohort C) EFS of localized and metastatic cohorts D) OS of localized and metastatic cohorts E) EFS based on tumor size (tsize) at baseline F) OS based on tumor size (tsize) at baseline G) EFS based on PET response 3 months after definitive radiotherapy H) OS based on PET response 3 months after definitive radiotherapy
Figure 1. Consort diagram of this retrospective study

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D) 

E)
Residual vs Morphed
No residual Morph
Metabolic residual

Survival probability

Time in months

Survival probability

Time in months

p = 0.026

Number at risk

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H)
Survival probability

Time in months

Number at risk

Residual vs Morphed

No residual Morph  Metabolic residual

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