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Rhabdomyosarcoma of the head and neck in children: Review and update

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ABSTRACT

Objective: To review the clinical presentation, histology, staging, treatment modalities, and survival for pediatric head and neck rhabdomyosarcoma (non-orbital).
Study design: Retrospective chart review at a tertiary pediatric hospital of children treated over 18 years (1996–2014) for primary head and neck non-orbital rhabdomyosarcoma.
Methods: Medical charts were examined for clinical presentation, staging, histology, genetic abnormalities, treatment modalities, recurrence and complications from treatment.
Results: Our cohort was 17 children (7 male, 10 female) with rhabdomyosarcoma with a median age of 6.3 years (range <1–19). The majority of tumors were of parameningeal location (13/17) with embryonal histology (11/17). Twenty-nine percent (5/17) demonstrated advanced metastatic disease at initial referral. Fifty-three percent (9/17) had skull base erosion and/or cranial nerve deficits. PET CT scan was performed in 4 patients. The overall survival was 75% for the duration of the study. Primary surgical excision was performed in all 4 patients with nonparameningeal tumors as compared to only 1 patient with a parameningeal tumor. All received chemotherapy and radiotherapy, as none had completely resectable disease.
Conclusion: Pediatric non-orbital primary rhabdomyosarcoma of the head and neck usually has a rapid onset and presents with advanced disease. Our analysis found that the majority of patients in our series had a cranial neuropathy at presentation, which highlights how advanced the disease is in these patients at presentation. The first mode of surgical intervention should be directed toward biopsy in junction with a metastatic work-up. Primary excision with negative microscopic margins for nonparameningeal rhabdomyosarcoma is ideal to spare radiotherapy but was not achievable in our cohort. The benefits of second-look biopsy after chemotherapy and radiation are still unproven; however, we believe that it was beneficial in two patients in our review for further resection thus decreasing subsequent radiation. Fluorodeoxy-D-glucose positron emission tomography (PET) to evaluate disease post treatment may further define the role for second look surgery.

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Table 1A
Current risk stratification for rhabdomyosarcoma[a].

Risk	5 year FFS (%)	Stage	Group	Histology
Low, subset 1	90	1 or 2	I or II	EMB
Low, subset 2	87	1	III nonorbit	EMB
		3	I or II	EMB
Intermediate	65–73	2 or 3	III	EMB
		1, 2 or 3	I, II or III	ALV
High	<30	4	4	EMB or ALV

1. Introduction

Rhabdomyosarcoma (RMS) remains one of the most common pediatric soft tissue sarcomas accounting for 4.5% of pediatric cancers and also the most common sarcoma of the head and neck region [1]. Approximately 35% of pediatric sarcomas will manifest in the head and neck region, but the paucity of cases (only about 115/year in the pediatric population) in the United States makes this a difficult disease to study at a single institution [2]. The Intergroup Rhabdomyosarcoma Study Group (IRSG) created a clinically useful grouping and staging system three decades ago to classify the severity of tumors. Current Children's Oncology Group (COG) protocols utilize these stagings and groupings to risk stratify patients for protocol treatment (Tables 1A and 1B) [3,4]. The ideal management of RMS remains a multimodal approach involving a combination of chemotherapy and local control with surgery and/or radiotherapy [5].

The IRSG surgical and pathological groupings including margin status aid in predicting patient overall survival. Risk assessment of RMS includes histology and grouping with embryonal and group I having a better prognosis than that of alveolar and group IV tumors [5]. The alveolar subtype can be further classified by those with the PAX3–FOXO1 fusion gene and those without. Alveolar tumors with this fusion gene have a more aggressive clinical course [6]. Despite intensification of therapy, children with high-risk RMS continue to have a relatively poor prognosis [7].

The prognosis and course of treatment for head and neck sarcoma also depends largely on its anatomical location as either parameningeal or nonparameningeal, which is a determinant of staging. Parameningeal tumor sites include the nasopharynx and nasal cavities, paranasal sinuses, infratemporal and pterygopalatine fossae, as well as the middle ear. Nonparameningeal sites include all other sites within the head and neck and represent more favorable prognostic sites. Tumor involvement of the soft tissue of the face, nose, orbit, sinonasal tract, skull base, and cervical neck each requires a tailored approach. Nonparameningeal tumors theoretically should be able to undergo a more complete surgical resection compared to resections of parameningeal tumors.

We reviewed the medical and surgical treatment of patients with non-orbital head and neck RMS in children at the Children's National Medical Center over a 18-year period to better understand how the management of pediatric head and neck RMS has evolved based on location and imaging, histological subtype, tumor location, nodal involvement, and extent of distant metastases. In particular, we focused on the current role of surgery in therapy and analyzed new trends in the evaluation and treatment of RMS.

Table 1B
TNM pretreatment staging classification.

Stage	Site	T	Size	Node	Metastases
1	Non-parameningeal	T1 or T2	*a* or *b*	N0 or N1 or Nx	M0
2	Parameningeal	T1 or T2	*a*	N0 or Nx	M0
3	Parameningeal	T1 or T2	*a*	N1	M0
			b	N0 or N1 or Nx	M0
4	Any	T1 or T2	*a* or *b*	N0 or N1 or Nx	M1

a—Data adapted from rhabdomyosarcoma: review of Children's Oncology Group (COG) Soft-Tissue Committee Experience and Rationale for Current COG Studies. ALV, alveolar; EMB, embryonal. FFS = failure free survival. T: T1 confined to anatomic site of origin, T2 extension and/or fixative to surrounding tissue. Size: $a \leq 5$ cm in diameter; $b > 5$ cm in diameter. Nodes: N0, regional nodes not involved; N1, regional nodes involved; Nx, regional status unknown. Metastases: M0, no distant metastases; M1, metastases present (includes positive cytology in CSF).

2. Material and methods

We performed a retrospective chart review of children treated from 1996 to 2014 for non-orbital RMS of the head and neck at a pediatric tertiary care medical center. All patients in the oncology database maintained over an 18-year period were analyzed for primary RMS of parameningeal and nonparameningeal tumors. We cross-referenced these children with the hospital registry for ICD 9 codes for sarcoma (239.89 and 238.8) to confirm accuracy of diagnosis. The study had approval by the Children's National Medical Center Institutional Review Board.

For each patient, we examined the following baseline characteristics: age, sex, tumor location, group, stage, and histology. We reviewed treatment modalities, recurrence, and overall survival rates. We also examined complications from surgical resection, radiotherapy, and chemotherapy treatment protocols. Baseline characteristics were analyzed as descriptive variables and summary statistics were generated. The risk categories were based on standards from COG. Using Prism 6 to generate Kaplan–Meier survival analyses, overall survival was calculated from time of diagnosis to death. In total, three Kaplan–Meier graphs were generated: one overall survival curve, a second based on site, and a third based on the PAX3–FOXO1 genotype. Follow-up time was measured from the date of diagnosis to the last contact or death. Remission was defined as the disappearance of the tumor on imaging and exam.

3. Results

Baseline characteristics are described in Table 2. There were 17 children (7 male, 10 female) diagnosed with primary non-orbital head and neck RMS with a median age of 6.3 years (range 8 months to 19 years). Twenty-nine percent (5/17) were metastatic at presentation. The median age at diagnosis was 6.2 years for embryonal ($n = 11$) and 10.9 years for alveolar ($n = 6$). None of our patients had any associated genetic syndromes (Li–Fraumeni) or history of previous radiation exposure. Fifty-three percent (9/17) of patients had skull base erosion and/or cranial nerve deficits including optic neuropathy (6), facial palsy (1), trigeminal involvement (1), and hearing loss (1).

The majority of tumors were parameningeal (13/17), with specific subsites including the nasal cavity (1), nasopharynx (6), paranasal cavity (1), infratemporal fossa (2), maxillary (2) and middle ear (1) (Table 3). Nonparameningeal locations included the nasal/cheek area (3) and submandibular region (1).

Ninety-four percent (16/17) of patients underwent both CT and MRI to evaluate the extent of disease. Twenty-four percent (4/17) patients also underwent PET or PET/CT imaging, either at initial presentation or in post-treatment follow-up. Primary resection was feasible in only 5 patients (4 of which were nonparameningeal), but all had positive margins. There were no major surgical complications in these patients who underwent gross excision. None of the patients underwent a microvascular free tissue transfer. All patients received chemotherapy combined with