

Staging and survival for sinus cancer in the pediatric population

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ABSTRACT

Objective: To determine histology, staging, and survival for pediatric sinus cancer.

Methods: Cases of pediatric sinus cancer (maxillary, ethmoid, and frontal/sphenoid) were extracted from the Surveillance, Epidemiology, and End Results database (1988–2005). Demographic data were tabulated and non-lymphoid malignancies were staged according to the TNM system. Kaplan–Meier survival analyses were conducted for the cohort and individual histologies.

Results: 63 pediatric sinus cancers were identified (38 maxillary sinus, 19 ethmoid sinus, and 6 frontal/sphenoid sinus) with a mean age at diagnosis of 10.5 years and a 1:1 male to female ratio. After exclusion of 11 lymphomas (17.5%), rhabdomyosarcoma was the most commonly encountered malignancy (52.0%) followed by sarcoma (17.3%) and olfactory neuroblastoma (13.5%). 41.4% and 42.1% of maxillary sinus and ethmoid sinus tumors presented as T4 tumors, respectively. At 47 months of follow-up, cumulative survival was 54.1% with a maximum follow-up of 196 months. Median survival for pediatric sinus rhabdomyosarcoma cases was estimated at 33.0 months.

Conclusions: Pediatric sinus malignancy commonly presents with advanced stage, and rhabdomyosarcoma is the most commonly encountered histology. Due to the rarity of pediatric sinus cancer, survival estimates are difficult to obtain. The SEER database provides large population-based data, although limitations of such a data set impact the analysis.

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1. Introduction

Paranasal sinus malignancies are exceedingly rare in children. Chronic upper respiratory tract infections, nasal congestive symptoms, epistaxis, and rhinosinusitis are much more prevalent in the pediatric population, and manifest many symptoms that overlap with those of sinus malignancy. Symptoms may be non-specific and indolent for months or even years, leading to delay in diagnosis and consequent advanced diseased stage at presentation. Descriptive reviews, single-case reports, and single-institutional series have been published suggesting that rhabdomyosarcoma is the most common paranasal sinus malignancy in children, followed by lymphoma, sarcoma, and olfactory neuroblastoma [1,2]. The majority of these tumors in the literature have presented with advanced stage, resulting in generally poor survival outcomes. Given the rarity of the paranasal sinus malignancies, data on type of tumors, staging, and survival statistics have been difficult to obtain in the pediatric population.

The Surveillance, Epidemiology, and End Results (SEER) database is a large, government-funded and maintained database that has been useful in examining clinical outcomes of other adult and pediatric head and neck tumors [3–6]. This data source circumvents many of the limitations of sample size, institutional bias, and individual patient loss to follow-up. This study evaluates the survival outcomes of pediatric sinus malignancies using the SEER database over a 17-year period to better understand the staging and clinical outcomes of these rare, yet aggressive, malignancies.

2. Patients and methods

From the SEER database (calendar years: 1988–2005) all cases of pediatric sinus cancer were extracted for the following subsites: maxillary sinus (C31.0), ethmoid sinus (C31.1), frontal (C31.2) and sphenoid sinuses (C31.3). For each case, data extracted included: (1) sinus involved, (2) tumor histology, (3) extent of disease and (4) survival data. From the SEER database, extent of disease variables corresponding TNM stage for each primary site was determined according to the AJCC Cancer Stage 6th Edition.

Data were tabulated and imported into SPSS 17.0 (Chicago, IL). For the purposes of staging and survival analysis, cases of primary

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Table 1
Solid tumor histologies encountered among pediatric paranasal sinus malignancies (lymphomas excluded).

Rhabdomyosarcoma	27
Sarcoma	9
Olfactory neuroblastoma	7
Yolk sac tumor	2
Peripheral neuroectodermal tumor	2
Malignant peripheral nerve sheath tumor	1
Adenoid Cystic Ca	1
Mucoepidermoid carcinoma	1
Spindle cell tumor	1
Neuroendocrine carcinoma	1
Grand Total	52

sinonasal lymphoma were excluded from further analysis. Standard descriptive statistics for the demographic and clinical variables were computed and staging according to primary site was determined. Kaplan–Meier survival analysis was conducted for the entire non-lymphoma cohort and for individual histologies with $n \geq 10$. Similarly, Kaplan–Meier analysis was conducted for the overall cohort according to T-stage and N-stage. Statistical significance was set at $p = 0.05$.

3. Results

A total of 63 pediatric sinus malignancies were identified during the time period 1988–2005. The mean age at presentation was 10.5 years, with a 1:1 male:female ratio. The most common location was maxillary sinus (38 patients; 60%), followed by ethmoid sinus (19 patients; 30%) and frontal/sphenoid sinus (6 patients; 10%). Eleven primary sinonasal lymphomas (17.5%) were identified and excluded from subsequent analysis. Table 1 lists the distribution of tumor histologies encountered. A large proportion of both maxillary and ethmoid sinus malignancies (12/21 and 8/12, respectively) presented as T4 tumors. Tables 2 and 3 present the TNM staging distribution for the tumors involving the maxillary and ethmoid sinuses. The majority of patients (67%) presented without nodal disease.

The 3-year and 5-year actuarial survivals for the entire cohort were 60.9% and 54.1%, respectively (Fig. 1). For the subset of patients with rhabdomyosarcoma, the 3-year and 5-year actuarial

Table 2
T-stage.

T-stage	Primary site	
	Maxillary sinus	Ethmoid sinus
1	3	1
2	1	
3	5	3
4	12	8
Not stated	8	7
Grand total	29	19

Table 3
N-stage.

N-stage	Primary site	
	Maxillary sinus	Ethmoid sinus
0	10	2
1		1
2	3	
3		1
Not stated	16	15
Grand total	29	19

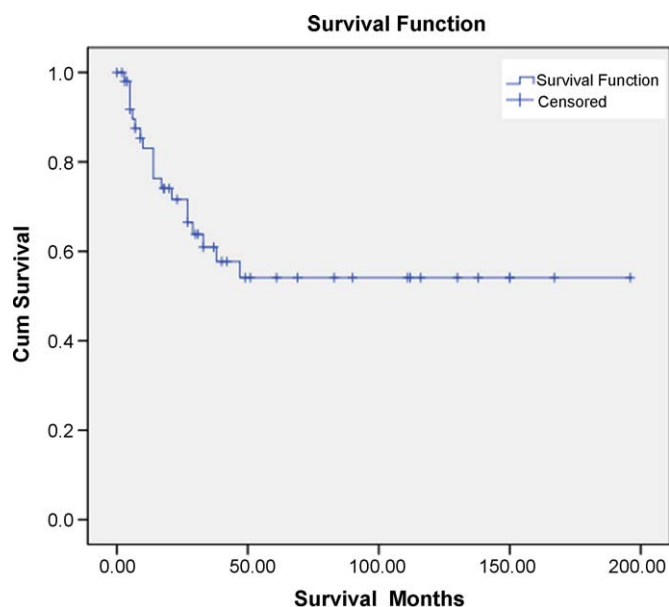


Fig. 1. Kaplan–Meier survival curve for entire cohort.

survivals were 49.1% and 43.0%, respectively (Fig. 2). The variations in histopathology and small cell counts for T-stage and N-stage precluded statistical analysis according to staging variables.

4. Discussion

Analysis of such a rare disease entity as pediatric sinus carcinoma requires review of a large population over a substantial time period. While the paranasal sinuses are not typical locations for pediatric malignancies, the tumor types seen in pediatric sinus cancer are similar to those seen in other locations in the head and neck [1].

The Surveillance, Epidemiology, and End Results (SEER) database program of the National Cancer Institute (NCI) collects and publishes cancer incidence and survival data from fifteen population-based cancer registries covering 26% of the United States population. The population in this database is comparable to

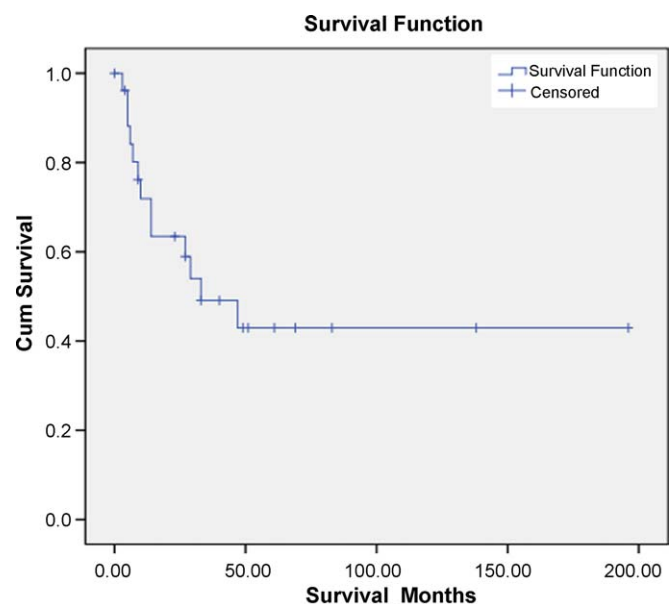


Fig. 2. Kaplan–Meier survival curve for rhabdomyosarcoma.

the general US population with regard to race, ethnicity, poverty level, foreign-born status, and urban dwelling. Besides patient demographics, the SEER program tabulates primary tumor site, tumor morphology and stage at diagnosis, first course of treatment, and follow-up for vital status. Approximately 350,000 cases are added to the database each year, with over six million cancer cases included since its inception in 1973 (www.seer.cancer.gov) [7]. It is particularly useful for the study of uncommon tumors in select populations. In our small patient cohort, treatment course was not uniformly available, particularly for lymphoma and rhabdomyosarcoma.

While the SEER database is an excellent source of population-based cancer survival information, it has several limitations, especially when the cohort is relatively small. In this study, tumor type was not stratified by age, and survival for T, N, and M stages was not able to be differentiated. Also, because the information provided by SEER is solely based on survival, differing treatment modalities and recurrence patterns were not able to be assessed.

In agreement with other single-institutional case series, rhabdomyosarcoma was the most commonly found malignancy in the pediatric paranasal sinus. Rhabdomyosarcoma is the third most commonly seen extracranial solid tumor seen in children [1] and over one-third of rhabdomyosarcomas in children occur in the head and neck [8,9]. It is a highly aggressive neoplasm originating from embryonal mesenchyma with potential to differentiate to striated muscle. Incidence of this tumor is most commonly seen in the first decade, with a second peak in adolescence. Histologic subtypes include embryonal (seen more commonly in younger children), alveolar (seen more commonly in adolescence), pleomorphic, and mixed-type [1,8]. Embryonal subtype is associated with the highest 5-year survival compared with other subtypes. Pre-treatment staging for rhabdomyosarcoma is based on the TNM-UICC system [8]. T1 indicates tumor limited to the anatomic site of origin, T2 includes tumor extension beyond this site, with suffixes 'a' and 'b' representing tumor size (≤ 5 cm diameter and > 5 cm diameter, respectively.). The 'N' and 'M' indicated regional nodal involvement and distant metastases, as is standard staging nomenclature for most head and neck malignancies. The Intergroup Rhabdomyosarcoma Study (IRS) system is a post-operative staging system, based on achievement of complete resection, resection with retained tumor tissue left behind, or only biopsy for tissue diagnosis performed. Therapy for rhabdomyosarcoma is guided by extent of disease [8].

While rhabdomyosarcoma is a common extracranial tumor of childhood [1], primary involvement of the nose and paranasal sinuses is quite rare. If tumor is confined to the nose and paranasal sinuses, surgical resection in efforts for complete or near-complete tumor margins is recommended. If tumor is left behind, post-operative radiochemotherapy is advised. For those with skull base involvement, primary radiochemotherapy is given. In one study (Wurm et al.), if tumor involved the skull base, the tumor-specific survival rate was 28%, as opposed to 62% if confined to the nose and paranasal sinuses. As in our study, the overall 5-year survival and tumor-specific 5-year survival in Wurm's study were 40% and 46%, respectively [8].

Olfactory neuroblastoma, also termed esthesioneuroblastoma, is very rare in children, with an estimated incidence of < 0.1 per 100,000 children aged less than 15 years. There have been fewer than 100 pediatric patients with this tumor in the literature [10]. It is a malignant neoplasm that arises from olfactory epithelium, most frequently located at the cribriform plate, the upper surface of the superior turbinates, and the upper third of the nasal septum. It is a locally aggressive malignant tumor that can often spread outside the nasal cavity into the paranasal sinuses, skull base, and brain [11]. Patients present primarily with unilateral nasal obstruction, epistaxis, anosmia, and later with proptosis, diplopia

and headaches. In 1976, Kadish and colleagues developed a staging system. Group A included tumor confined to the nasal cavity, group B had extension to the paranasal sinuses, and group C had tumor extending beyond the paranasal sinuses [12]. More recently, TNM staging for this disease has been utilized based on radiologic criteria [13]. Primary presenting signs are often difficult to assess in children, due to the similar presentation of chronic respiratory illnesses and difficulty in obtaining specific symptoms. Because it is so rare and indolent in children, it has been difficult to develop standard treatment protocols. However, multimodal therapy including surgery, chemotherapy, and radiation therapy have been indicated, especially in patients with advanced disease [2]. In patients with stage A disease, surgery alone is standard treatment. In patients with stage B disease, surgery followed by adjuvant radiation therapy provides the most favorable outcome. In patients with stage C disease, combined therapy including craniofacial resection, chemotherapy, and radiation therapy had better outcomes than patients without multimodal therapy [10].

Eich et al. evaluated 19 pediatric patients with olfactory neuroblastoma. Mean age at diagnosis was 14 years, with all patients presenting with Kadish stage B (4/19) or stage C (15/19) disease. Overall 5-year survival was 73%, and 5-year disease-free survival was 55%. This is in keeping with our overall 5-year survival of 54% [10].

Other histologic tumor types seen in pediatric sinonasal carcinoma include sarcomas, primitive neuroectodermal tumor (PNET), neuroendocrine carcinoma, yolk sac tumors, spindle cell tumors, adenoid cystic carcinoma, and mucoepidermoid carcinoma.

Chondrosarcomas are malignant mesenchymal tumors of unclear etiology, and are usually low-grade and slow-growing. Less than 10% are seen in the head and neck, and the majority of patients are in the 4–6th decades. Symptoms of chondrosarcoma of the sinus include nasal obstruction and epistaxis, and treatment includes surgical removal with post-operative radiation therapy. For high-grade tumors, radiochemotherapy may be indicated [14].

Primitive neuroectodermal tumors (PNETs) of the sinuses are rare in children, but must be considered in the differential diagnosis of a paranasal sinus mass. Histologic features of undifferentiated small round cells elicit a differential diagnosis including Ewing sarcoma, olfactory neuroblastoma, and rhabdomyosarcoma. Treatment may include surgery and chemoradiation. Prognosis for PNET is extremely poor, with a high incidence of both local recurrences and distant metastases [15].

Pediatric sinonasal neuroendocrine carcinoma may be seen as a secondary sinonasal malignancy years after radiation therapy for retinoblastoma. Several case series have presented patients who develop this poorly differentiated malignancy an average of 26.2 years following radiation therapy for retinoblastoma. It is an aggressive neoplasm with frequent local recurrences and distant metastases despite multimodal therapies [16].

Pediatric sinonasal tumors are exceedingly rare, and the available literature provides either case reports or small case series. Expanding upon data obtained from other prior studies, our patient cohort presented with advanced disease, and related survival outcomes were poor. Despite access to the large database from the SEER program, the relatively small patient cohort for this disease did not allow for ability to establish survival data based on T-stage or N-stage. Future work should be directed at obtaining multi-institutional registries for these rare tumors in the pediatric population.

5. Conclusions

Due to the rarity of pediatric sinus malignancies, survival outcomes are difficult to ascertain. The SEER database provides a

thorough population-based assessment of histology, tumor stage, and survival outcomes for these exceedingly rare tumors. Based on this analysis, rhabdomyosarcoma and sarcomas accounted for the largest fraction of pediatric sinus malignancies, although lymphoma may not infrequently present in the pediatric paranasal sinuses. Unfortunately, these lesions present typically with advanced stage resulting in poor prognostic outcomes.

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