Chapter

Pediatric Head and Neck Malignancies

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Abstract

Head and neck malignancies are a part of the differential diagnosis of head and neck masses seen in the pediatric age group. It is critical to make prompt diagnosis and employ proper treatment. We will review the most common malignant pathologies as well as their specific clinical presentations and management. Centers that are able to provide multidisciplinary care for pediatric patients with head and neck pathology can help achieve the best outcomes.

Keywords: pediatric tumor, malignancy, neck mass, pediatric cancer, head and neck cancer

1. Introduction

Head and neck malignancies are rare within the pediatric population and represent 12% of all pediatric cancers according to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database [1]. While epithelial tumors are more common in adults, childhood tumors are more frequently derived from mesenchymal and endothelial cells. Genetic conditions, previous chemotherapy, or exposure to ionizing radiation predispose this population to both primary and secondary malignancies, but the cumulative environmental carcinogen exposures (e.g. cigarette smoke inhalation, ultraviolet radiation) are much less common given the patients' younger ages [2].

The most common pediatric head and neck cancers include lymphoma (Hodgkin and non-Hodgkin), rhabdomyosarcoma, thyroid carcinoma, nasopharyngeal carcinoma, and salivary gland malignancies (**Figure 1**). While other malignancies such as neuroblastoma, neuroendocrine tumors, various soft-tissue sarcomas, cutaneous tumors, and metastases infrequently manifest within the head and neck region, a complete and thorough discussion of these cancers is outside the scope of this review and are covered elsewhere throughout literature. The primary aim of this review is to highlight the more common head and neck childhood malignancies and present a focused examination of the etiology, presentation, workup, and treatment of these conditions.

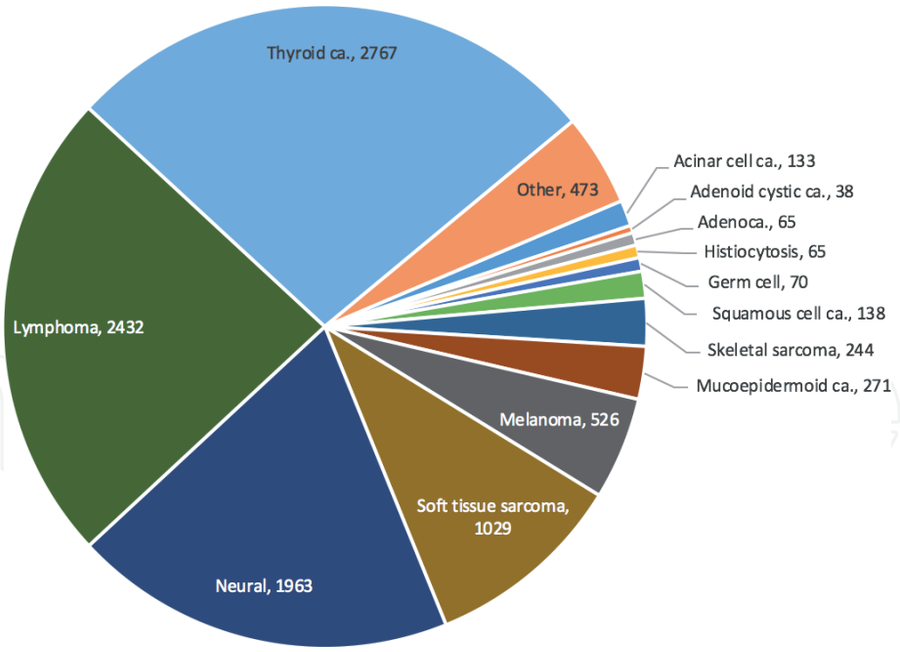

Figure 1.
Childhood head and neck malignancies by incidence 1973–2010.

2. Lymphomas

Lymphoma is the third most common pediatric malignancy - following leukemia and brain tumors - and the most common head and neck cancer in children and adolescents [3]. The broad differential diagnosis for small round blue cell tumors, like lymphoma is shown in **Table 1**. The treatment of childhood lymphoma has experienced significant improvements in recent decades and is now associated with cure rates approaching 80 to 90% [4, 5]. Lymphoma is divided into two groups: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). HL is further subdivided into two clinical subtypes by the World Health Organization (WHO) classification which includes classic Hodgkin lymphoma (CHL), which accounts for approximately 95% of HL cases within the United States, and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). Overall, HL is less common

Melanoma
Lymphoma
Burkitt lymphoma
Anaplastic large cell lymphoma
Rhabdomyosarcoma
Alveolar
Embryonal
Undifferentiated sarcoma
Ewing Sarcoma
Primitive neuroectodermal tumors (PNET)
Clear cell sarcoma (“melanoma of soft parts”)
Neuroendocrine carcinoma
Mesenchymal chondrosarcoma
Sinonasal undifferentiated carcinoma (SNUC)
Nephroblastoma (Wilms tumor)
Retinoblastoma
Neuroblastoma
Hepatoblastoma

Table 1.
Differential diagnosis of small round blue cell tumors.

in developed countries with distribution patterns that vary widely according to geography and ethnicity. HL is characterized by a bimodal distribution with a peak in adolescence between 15 and 40 years of age and another in adulthood beyond 60 years of age. Recently, HL has been shown to cluster within certain families with associations to specific HLA loci, thus suggesting vertical transmission of susceptible genotypes [6]. Pediatric HL exhibits a 2:1 male predominance with as many as 40 to 50% of cases linked to the Epstein Barr virus (EBV) infection as well as the pathognomonic Reed-Sternberg cell morphology [7–9]. Four subtypes of HL have been characterized: nodular sclerosis, mixed cellularity, lymphocyte predominant, and lymphocyte depleted, which account for roughly 50%, 30%, 15%, and less than 10% of the cases, respectively [10]. The Ann Arbor staging system is used to stratify these tumors based on the extent of disease and whether organs on one or both sides of the diaphragm are involved (**Table 2**).

In contrast to HL, the incidence of pediatric NHL is lower in younger children and increases with age. Pediatric NHL is more frequently associated with higher grades and extranodal involvement when compared to cases of adult NHL. Average survival rates are greater than 80%, regardless of histologic subtype, of which there are several [4]. The most common pediatric NHL subtype is Burkitt lymphoma (BL) which accounts for 50 to 60% of childhood cases, followed by T-cell lymphoblastic lymphoma (1520%), anaplastic large cell lymphoma (1015%), diffuse large B-cell lymphoma (510%), followed by other rare subtypes [11]. BL, a highly aggressive tumor, is derived from the classic t(8;14) cytogenetic translocation of the *MYC* oncogene resulting in a constitutive overexpression of c-*myc* leading to rapid cell division [12, 13]. EBV is a well-known endemic oncogenic driver and is most prevalent in regions such as Africa where malaria continues to thrive. Young patients often present with the characteristic mandibular tumor with extranodal and multifocal involvement (in gastrointestinal, hematologic, breast, and ovarian tissues) [14]. Compared to endemic BL, its sporadic form is more common in non-endemic regions such as the United States and Europe [15]. Sporadic form patients are more likely to be male and older (median age 30 years old) with localized lymphadenopathy, large abdominal masses, extranodal disease (2385%), central nervous system involvement (10%), and bone marrow manifestations (13–40%) [16, 17]. Moreover, children with

Stage	Description
I	Involvement of a single lymph node region (cervical, axillary, inguinal, mediastinal) or lymphoid structure (spleen, thymus, or Waldeyer's ring) (I); or extralymphatic site in the absence of involved nodes (I-E)
II	Two or more sites on the same side of the diaphragm (II) including: • Two or more lymph node regions • Regional lymph nodes with associated local lymphoid structure involvement • Extralymphatic site with regional node involvement (II-E)
III	Involvement of regional lymph nodes or lymphoid structures on both sides of the diaphragm (III): • With or without extension to extralymphatic tissue (III-E), the spleen (III-S), or both (III-E,S)
IV	Diffuse or disseminated involvement (IV) of: • One or more extralymphatic organs with or without associated lymph node involvement • Non-contiguous extralymphatic involvement in conjunction with stage II nodal disease • Involvement of the liver, bone marrow, lungs, or cerebrospinal fluid

Table 2.
Ann Arbor staging for Hodgkin lymphoma.

immunodeficiency syndromes or medical treatment for primary malignancies carry an increased risk for developing NHL. Predisposing conditions such as ataxia telangiectasia, Nijmegen syndrome, and various mismatch repair diseases incur not only increased risk of developing NHL but also increase mortality rates from anti-tumor interventions [18]. Immunodeficiency-associated BL is diagnosed in patients with Human Immunodeficiency virus (HIV), though the risk of tumor development declines with the use of antiretroviral therapy [19–21].

Lymphomas of the head and neck can present insidiously, but are typically discovered as a "rubbery," enlarged cervical or supraclavicular lymph node on physical examination. The majority of HL patients present with asymptomatic cervical adenopathy with or without the constitutional "B" symptoms including fever, night sweats, chills and weight loss which are also incorporated into the HL Ann Arbor staging system. While adult NHL is characterized by nodal disease, pediatric NHL has a predisposition for extranodal involvement with the most common head and neck extranodal localizations involving the larynx, sinonasal cavities, salivary glands and orbit. Lymphoma is present within Waldeyer's ring in approximately 44% of cases especially in NHL patients [7, 22]. Oguz et al. conducted a retrospective study of 457 pediatric patients with lymphadenopathy and demonstrated that chronic lymphadenopathy (greater than 4 weeks in duration), generalized and supraclavicular involvement, and lymph nodes measuring greater than 3 cm were findings most commonly associated with malignancy among 111 patients with confirmed disease [23]. Other causes for concern include persistent lymphadenopathy despite antibiosis, nodal firmness, immobility, fixation to underlying tissues, and progressive nodal enlargement [7].

Otolaryngologists and other surgeons primarily serve diagnostic roles via lymph node biopsy As the initial differential diagnosis for pediatric cervical adenopathy is broad and widely varied, a detailed history and physical examination is critical to stratify the likelihood of malignancy against other processes such as infection, hypersensitivity reactions, granulomatous diseases, and rheumatic or lymphoproliferative disorders as these patients may present prior to evaluation by other clinicians. Prior to surgery, management and workup should include an array of laboratory testing which includes complete blood count (CBC) with differential and peripheral blood smear, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, lactate dehydrogenase (LDH), as well as a serum ferritin, copper and alkaline phosphatase levels. Bone marrow biopsy and lumbar puncture (LP) are also routinely performed. Imaging should include chest radiograph and ultrasound (US) with computed tomography and magnetic resonance imaging (MRI) reserved for more suspicious or concerning presentations. Ultrasound is often the imaging mainstay given its accessibility without the need for sedation or radiation exposure (**Table 3**); however, CT continues to play an integral role in surveillance because of simplicity and rapidity. F-fluorodeoxyglucose positron emission tomography (FDG-PET) has demonstrated improved sensitivity and specificity in accurately diagnosing lymphoma compared to conventional imaging modalities [24, 25] (**Figure 2**).

Following imaging, biopsy is needed to obtain a sufficient amount of tissue for frozen and permanent histopathologic analysis along with flow cytometry and immunohistochemistry as indicated. These specimens should be sent fresh rather than in formalin to provide a viable sample responsive to flow cytometry. Following diagnosis, staging of disease typically requires bone marrow biopsy and lumbar puncture to assess extent of bone marrow involvement and to determine whether malignant cells are present in the CSF, respectively. Diagnosis based on fine needle aspiration biopsy (FNAB) has remained controversial and challenging as it results in a dearth of cellularity from sclerosis, decreased detection of clonal populations, and a lack of diagnostic Reed-Sternberg cells [26]. As such, excisional biopsy remains the gold standard in the primary diagnosis of pediatric lymphoma.

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	Size	Shape	Borders	Hilar fat, Cortex	Vascular flow[a]	Chronicity	Additional Characteristics
Benign	Typically <2 cm	Long axis to short axis ratio ≥ 2:1; Oval or reniform	Typically blurred, regular	Echogenic, hypoechoic	Hilar (radiating from center), avascular Low vascular resistance	N/A	Calcifications possible
Reactive	Variable	Long axis to short axis ratio ≥ 1:1	Blurred, regular	Echogenic, hypoechoic	Hilar flow, avascular Low vascular resistance	Typically acute (0–2 weeks) or subacute (2–6 weeks)	Calcifications possible
Malignant	Typically >2 cm	Long axis to short axis ratio < 2:1 Round	Typically sharp, irregular. Matting indicates malignancy[b]	Hypoechogenic, hypoechoic	Peripheral flow (cortical), mixed flow Elevated vascular resistance	Chronic, >6 weeks suggests malignancy	Necrosis (cystic or coagulation), calcifications, reticular internal pattern

[a]*Hilar (radiating from hilum to cortex), peripheral (flow around cortex); Vascular resistance <0.7 associated with benign process.*
[b]*Matting: Blending capsules of adjacent lymph nodes.*

Table 3.
Ultrasound findings of benign versus malignant head and neck lymph nodes.

Treatment of pediatric lymphoma is non-surgical and includes multi-agent chemotherapy with or without radiotherapy (RT) as the first line. With respect to the treatment of HL, various combinations of chemotherapeutic agents have been utilized with 3- and 8-year event-free survival (EFS) approximating 90% and greater than 80%, respectively, while overall survival (OS) has been demonstrated to range from 80 to 90% [27, 28]. Some regimens include MOPP (mechlorethamine, vincristine, procarbazine, prednisone), COPP (cyclophosphamide, vincristine, procarbazine, prednisone), and ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) [7], each uniquely selected based upon the subtype of HL and the side-effect profiles. RT is also commonly added in combination with

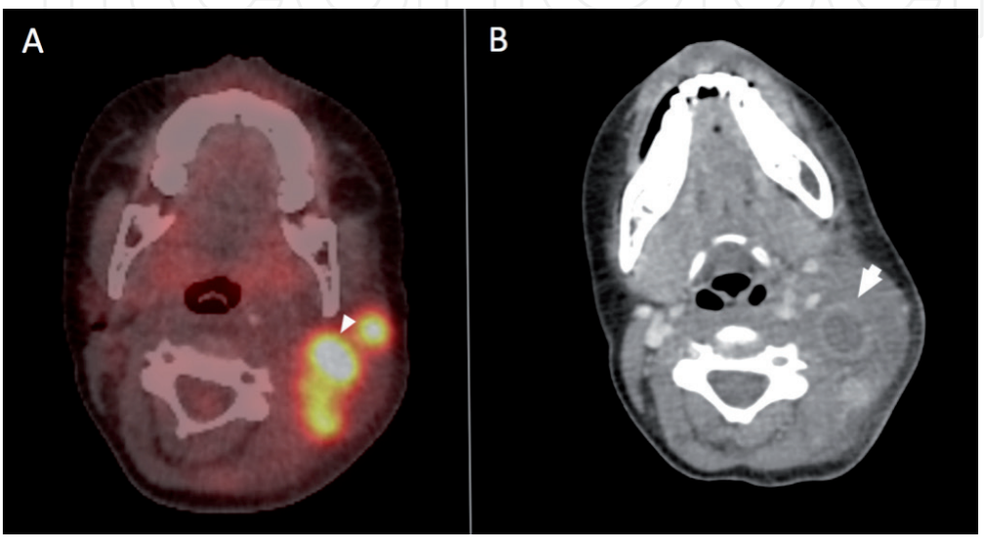

Figure 2.
Axial CT/PET (A) and axial CT neck with contrast (B) of 10-year-old patient with lymphoblastic lymphoma most notable in the left cervical chain. The left jugulodigastric nodes are hypermetabolic (arrowhead) on CT/PET and enlarged with a hypodense central core with rim-enhancement (arrow) on contrasted CT.

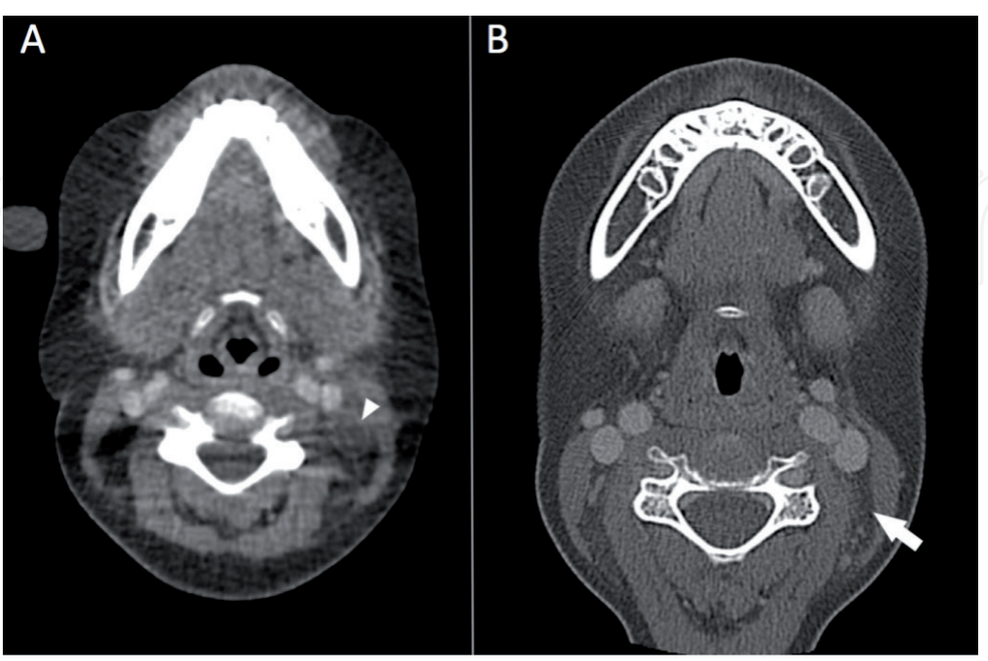

Figure 3.
(A) Axial CT 1 month status post induction chemotherapy for the same patient noted in **Figure 2** *with lymphoblastic lymphoma. Note residual 1.5 cm node (arrowhead). (B) Axial CT scan of the same patient 8 months following diagnosis, following completion of chemotherapy. The previously noted adenopathy has resolved (arrow) and there is no evidence of recurrence.*

chemotherapy. With NHL, a large number of chemotherapeutic combinations are possible, as outlined by Kahn et al.: ABV (doxorubicin, bleomycin, and vinblastine), CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) COPDAC (cyclophosphamide, vincristine, prednisone, and dacarbazine), and COPP [29]. In contrast to HL, RT is infrequently used to treat NHL. Additionally, if high-grade NHL is present, intrathecal chemotherapy may be indicated. Postoperative surveillance examinations and imaging are obtained at regular intervals to monitor for evidence of disease recurrence (**Figure 3**).

3. Rhabdomyosarcoma

Rhabdomyosarcoma (RMS), a malignant tumor of mesenchymal origin, is the most common pediatric soft tissue sarcoma affecting approximately 250 children per year within the United States [30]. It accounts for 4.5% of all childhood malignancies and is the third most common extracranial pediatric solid tumor following Wilms' tumor (nephroblastoma) and neuroblastoma. RMS of childhood is characterized by a bimodal distribution and presents between the ages of 2 and 6 and again between 10 and 18 years of age [31]. Although this tumor may arise throughout the body given its mesenchymal nature, the head and neck is the most commonly involved, comprising 35% of all cases [32–34]. Of the cases involving the head and neck, nearly 75% arise within the orbit or parameningeal regions (e.g. nasopharynx, nasal cavity, paranasal sinuses, infratemporal fossa, pterygopalatine fossae, and middle ear) (**Figure 4**). The remainder originates primarily in the oral cavity, cheek, parotid region and soft tissues of the neck, which are commonly referred to as non-orbital or non-parameningeal lesions [35, 36]. Although most tumors occur sporadically, some RMS cases are associated with familial syndromes such as Li Fraumeni and neurofibromatosis type I [31, 37, 38]. The tumor typically presents as a painless, asymptomatic mass in the majority of cases but may cause compressive symptoms and cranial neuropathies secondary to mass effect in more advanced disease.

RMS histology classically appears as a small round blue cell tumor of childhood and is classified alongside similar appearing neoplasms including lymphoma,

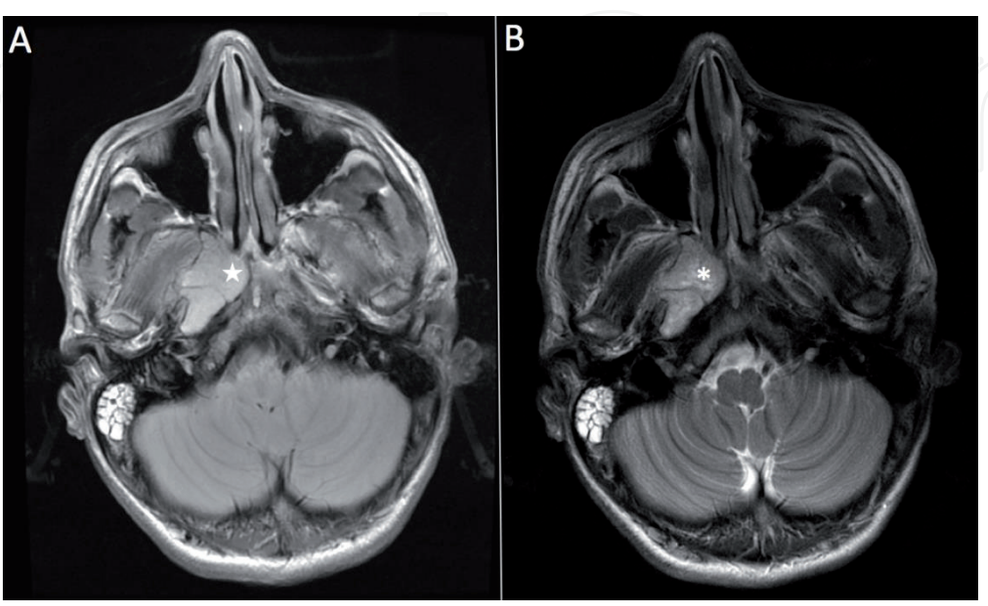

Figure 4.
Embryonal rhabdomyosarcoma. Axial T1 fat-saturated MRI (A) reveals slightly hyper-intense lobular mass of the sphenoid wing (star). Axial T2 MRI (B) reveals the same lesion with similar signal intensity (asterisk).

neuroblastoma, Wilms' tumor, Ewing's sarcoma and peripheral neuroectodermal tumors. There are two main histologic subtypes of RMS: embryonal (ERMS) and alveolar (ARMS). ERMS is the more common subtype and comprises approximately 75% of cases with a preponderance for younger patients. In contrast, the ARMS subtype—appearing histologically similar to pulmonary parenchyma—represents approximately 25% of cases and is more prevalent among older children and adolescents with the majority occurring in children greater than 10 years of age. Compared to ERMS, the ARMS subtype is associated with an unfavorable prognosis. A review of the SEER database performed by Ognjanovic et al. analyzed the incidence and survival rates for pediatric and adolescent RMS between 1975 and 2005 with five-year overall survival rates ranging from 40.1–47.8% and 60.9–73.4% for the ARMS and ERMS types, respectively [39]. Similar findings were reported by Pappo et al. with five-year survival rates of 97% for non-orbital, non-parameningeal embryonal cases versus 67% for ARMS subtypes [35]. With respect to head and neck tumors, the ERMS subtype occurs more frequently and may be further classified into the botryoid and spindle-cell variants with botryoid histology demonstrating a more favorable prognosis [34].

Patients with suspected RMS should undergo a thorough workup including a complete head and neck physical exam along with laboratory testing, imaging and pathologic confirmation prior to treatment. Evaluation for metastatic disease often includes a lumbar puncture for cerebrospinal fluid analysis. Imaging studies of the primary tumor site often involve CT - which is useful for the evaluation of osseous erosion - and MRI for further characterization of the primary tumor and the surrounding anatomy. This is especially beneficial in determining whether the tumor may be safely resected with primary surgery or if neoadjuvant treatment is required to decrease the morbidity. FDG-PET imaging has so far seen limited use in the pediatric population. However, several studies have suggested an increased utility in evaluating the presence of lymphadenopathy, occult disease, response to treatment, and detection of recurrence compared to standard imaging alone [40–43]. Biopsy is required for definitive diagnosis and may often be achieved via fine needle aspiration or open biopsy while taking care to obtain an adequate amount of tissue for accurate histopathologic analysis. Although lymph node involvement in pediatric head and neck RMS is uncommon, determining the presence of locoregional and metastatic lymph node involvement is critical in establishing pre-treatment staging and, in cases of suspected disease, pathologic evaluation should be undertaken which will further influence radiotherapy fields. In an analysis of regional lymph node disease in 898 patients within the pivotal Intergroup Rhabdomyosarcoma Study IV, Rodeberg and colleagues demonstrated that the presence of nodal disease is an independently poor prognostic indicator for both failure-free and overall survival, further underlining the need to establish the extent of disease prior to treatment [44].

In an effort to design effective and tailored treatment regimens for these patients, the Intergroup Rhabdomyosarcoma Study and its subsequent iterations (IRS I-IV) established a staging and grouping system to aid in directing treatment strategy based upon tumor location, disease extent, and completeness of surgical resection [45–48]. Within this classification scheme, the pre-operative "stage" is based upon pre-operative standard TNM staging guidelines whereas the post-operative clinical "group" refers to the extent of disease and completeness of surgical resection prior to adjuvant therapy. Group I reflects complete resection with negative pathologic margins. Group II consists of patients with complete gross resection but microscopically positive residual disease (close or positive margins, presence of regional nodal disease, or both). Group III includes patients with gross residual disease following incomplete resection or unresectable disease. Group IV reflects those with distant metastatic disease other than first echelon nodal metastases.

An overview of the IRS pre-treatment staging (**Tables 4** and **5**) and post-treatment grouping classification (**Table 6**) is provided.

Chemotherapy and radiation have remained the mainstay of multimodal treatment for childhood RMS. Recently, there has been an increasing trend towards

Stage	Sites	T	Tumor size	N	M
I	Orbit	T1 or T2	a or b	N0, N1, or Nx	M0
	Head and neck (excluding parameningeal)		a or b	N0, N1, or Nx	
	Genitourinary (non-bladder/non-prostate)		a or b	N0, N1, or Nx	
II	Bladder/prostate	T1 or T2	a	N0 or Nx	M0
	Extremity		a	N0 or Nx	
	Head and neck (parameningeal)		a	N0 or Nx	
	Other (includes trunk, retroperitoneum, etc.)		a	N0 or Nx	
III	Bladder/Prostate	T1 or T2	a	N1	M0
	Extremity		b	N0, N1, or Nx	
	Head and neck (parameningeal)		b	N0, N1, or Nx	
	Other (includes trunk, retroperitoneum, etc.)		b	N0, N1, or Nx	
IV	All	T1 or T2	a or b	N0 or Nx	M1

Table 4.
TNM pre-treatment staging system for rhabdomyosarcoma.

Classification	Description
Tumor	
T1	Confined to anatomic site of origin
a	<5 cm in diameter
b	≥5 cm in diameter
T2	Extension and/or fixation to surrounding tissue
a	<5 cm in diameter
b	≥5 cm in diameter
Regional lymph nodes	
N0	Not clinically involved
N1	Clinically involved
Nx	Clinical status unknown
Metastases	
M0	No distant metastases
M1	Distant metastases present

Table 5.
Pre-treatment rhabdomyosarcoma TNM classifications.

Clinical Group	Criteria
Group 1	Localized disease, complete resection, no microscopic residual disease
A	Confined to site of origin, complete resection
B	Infiltrating beyond site of origin, complete resection
Group 2	Gross total resection
A	Gross resection with microscopic residual disease
B	Regional disease with spread to regional lymph nodes, complete resection without residual microscopic disease
C	Regional disease with spread to regional lymph nodes, gross total resection, but evidence of microscopic residual disease
Group 3	Incomplete resection or biopsy with gross residual disease remaining
Group 4	Distant metastases present irrespective of surgical approach to tumor

Table 6.
Post-surgical clinical group staging system for rhabdomyosarcoma.

primary surgical resection in localized tumors involving the head and neck [49]. The success of surgical treatment is often dependent on the specific location of tumor [35, 36, 50, 51]. Orbital RMS, associated with a favorable prognosis, is rarely associated with meningeal extension and is treated with primary chemotherapy and radiation with surgery reserved for salvage cases [52]. On the other hand, parameningeal lesions are more challenging to remove and are often categorized as IRS Group III tumors because they are not typically amenable to complete surgical resection. Given its anatomic location in close proximity to vital neurovascular structures, parameningeal RMS is associated with an increased likelihood of cranial neuropathies, cranial base erosion, and intracranial extension [53]. As primary surgical resection with wide margins is often infeasible for these tumors, chemotherapy with or without radiation is the preferred treatment modalities. (**Figures 4** and **5**). Reilly et al. conducted a retrospective chart review of 17 children diagnosed with head and neck RMS over an 18-year period and found that the majority presented with cranial neuropathies, thus reflecting the aggressive nature of this disease upon symptom

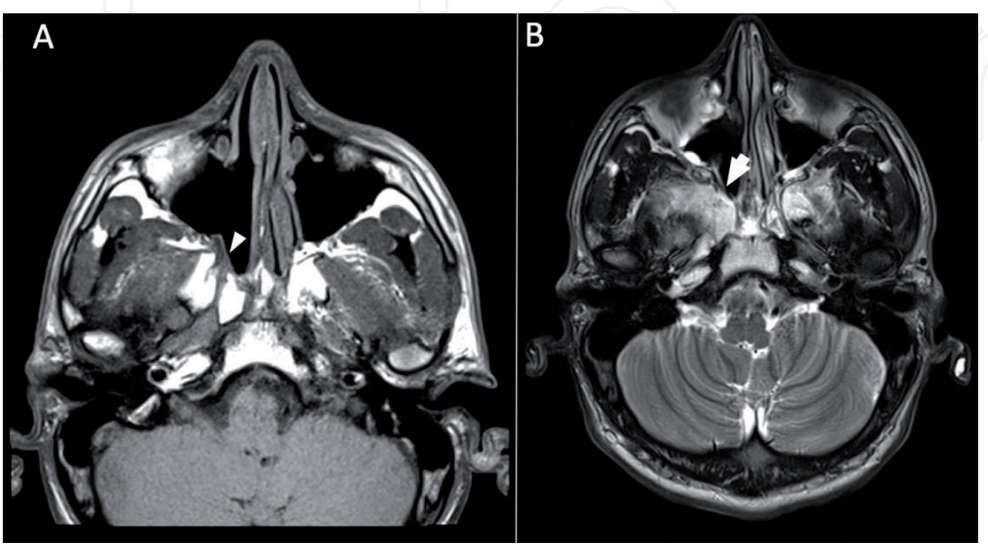

Figure 5.
Axial T1 MRI (A) performed 18 months after biopsy, chemotherapy, and proton therapy to treat embryonal rhabdomyosarcoma noted in **Figure 4** *with no evidence of recurrence at the primary site (arrowhead). Axial T2 MRI (B) of the same patient at 39 months post-treatment, still with no evidence of recurrence (arrow).*

onset with 5 of 17 (29.4%) patients demonstrating advanced metastatic disease at first referral. Within their series, 4 of 4 patients with non-parameningeal disease underwent primary surgical resection but tumor-free margins were unobtainable and adjuvant chemotherapy with radiation was ultimately required. All patients with parameningeal disease underwent multimodal treatment [54]. However, Daya et al. also demonstrated that many children may avoid radiation therapy without compromising survival in cases of completely resected RMS [49].

In general, pediatric RMS necessitates systemic treatment in the form of chemotherapy with local control achieved with surgery and/or radiation. The treatment approach must nonetheless be carefully tailored for each individual patient according to tumor location and the potential morbidities associated with each modality. Although primary surgical resection may be possible in select non-parameningeal tumors, the decision for adjuvant therapy is ultimately determined by margin status.

4. Thyroid carcinoma

Thyroid carcinoma represents approximately 21% of all pediatric head and neck malignancies with an annual reported incidence of 0.54 per 100,000 persons within the United States [55, 56]. In contrast to adults, thyroid nodules are less likely to be palpable in children (2% vs. 35%) and carry a much higher likelihood of malignancy with a risk of 1 in 4 in pediatric patients compared to less than 1 in 10 for adults [57]. The majority of thyroid cancers are differentiated with papillary thyroid cancer (PTC) accounting for greater than 90% of cases [56]. Less common variants include follicular thyroid cancer (FTC) and medullary thyroid cancer (MTC) while anaplastic and poorly differentiated subtypes are even rarer [58]. MTC is more common among younger children (ages 0–4) and declines with increasing age while the incidence of PTC increases as one approaches adolescence and adulthood [55]. A significant number of patients present with regional lymph node involvement (60–80%) and distant metastatic disease may occur in up to 20% of children with the lungs most commonly involved [59]. Despite the frequency of advanced disease at initial presentation, several case series have demonstrated an excellent prognosis with greater than 95% long-term survival for papillary and follicular variants [58, 60–62]. Notably, previous radiation exposure and treatment of other childhood malignancies increases the risk for developing pediatric thyroid cancer with an 18-fold greater risk of thyroid cancer compared to the general population, thus highlighting the importance of close follow up and frequent surveillance among this cohort [63–65].

The diagnosis of suspected pediatric thyroid cancer involves a focused history and physical examination with particular attention to previous radiation exposure and treatment of prior childhood malignancies, such as lymphoma. Patients typically present with an asymptomatic thyroid nodule or mass following incidental discovery on surveillance imaging studies. US and FNAB of the most suspicious thyroid nodules should be completed along with histocytologic analysis. A review of 89 pediatric patients by Buryk et al. examined patients with thyroid nodules $\geq$0.8 cm and demonstrated that larger-sized nodules, palpable nodules, and palpable lymphadenopathy were significant predictors of malignancy [66]. Sonographic characteristics associated with malignant nodules include larger size, solid parenchyma, taller-than-wide shape, microcalcifications, irregular margins, and abnormal-appearing lymph nodes [67–69]. Richman et al. also found significantly increased rates of cancer in patients with solitary nodules compared to those with multiple nodules (29.4% vs. 14.2%, $p = 0.003$) [69]. Although US is essential characterizing thyroid lesions, results may vary according to sonographer skill. Neck and chest CT may be useful in evaluating for metastatic disease, cervical

lymphadenopathy, and in surgical planning, especially in cases with large-volume or bulky disease. Laboratory testing is particularly important and should include thyroid-stimulating hormone (TSH), T3, and T4 levels. Serum calcitonin level should also be obtained in any patient with known or suspected multiple endocrine neoplasia (MEN) syndrome, although routine use remains controversial in patients with seemingly isolated MTC [70]. Genetic testing and referral should be considered in familial cases and in patients with confirmed MTC or MEN syndrome.

Surgical resection is the primary treatment modality for childhood thyroid cancer with options including total thyroidectomy and lobectomy with isthmusectomy. The American Thyroid Association (ATA) guidelines utilize the American Joint Committee on Cancer (AJCC) pTMN staging system to stratify patients into low, intermediate, and high-risk groups. Total thyroidectomy is the preferred surgical method for PTC given an increased likelihood of bilateral and multifocal disease in these tumors [71] (**Table 7**). The extent of resection nonetheless remains a source of controversy. Nice et al. performed a retrospective review of 3861 patients less than 21 years old with primary PTC nodule greater than 1 cm in diameter and found no significant difference between total thyroidectomy compared to partial thyroidectomy (e.g. sublobar resection, lobectomy, or lobectomy with isthmusectomy) on both univariate and multivariate analyses, with both groups demonstrating

ATA risk level	Definition[a]	Initial post-operative staging[b]	Surveillance for pediatric patients with no evidence of disease
Low	Disease grossly confined to the thyroid with N0/Nx disease or Disease grossly confined to the thyroid with N0/Nx disease (microscopic metastases to a small number of central neck lymph nodes)	Tg[c]	US at 6 months postoperatively, then annually x 5 years Tg[c] on LT_4 every 3–6 months x 2 years, then annually
Intermediate	Extensive N1a or minimal N1b disease	TSH-stimulated Tg[c] and diagnostic ^{123}I scan	US at 6 months postoperatively, every 6–12 months x 5 years, then less frequently Tg[c] on LT_4 every 3–6 months x 3 years, then annually Consider TSH-stimulated Tg[c] ± diagnostic ^{123}I scan in 1–2 years in patients previously treated with ^{131}I
High	Regionally extensive disease (extensive N1b) or Locally invasive disease (T4 tumors), with or without distant metastasis	TSH-stimulated Tg[c] and diagnostic ^{123}I scan	US at 6 months postoperatively, every 6–12 months x 5 years, then less frequently Tg[c] on LT_4 every 3–6 months x 3 years, then annually Consider TSH-stimulated Tg[c] ± diagnostic ^{123}I scan in 1–2 years in patients previously treated with ^{131}I

[a] *TNM staging from the AJCC Cancer Staging Manual, 7th edition.*
[b] *Completed within 12 weeks following surgery.*
[c] *Assumes the absence of thyroglobulin autoantibodies.*
LT_4, levothyroxine.

Table 7.
American Thyroid Association (ATA) pediatric thyroid cancer risk classification and post-operative management for papillary thyroid carcinoma in children.

96% 15-year overall survival (OS) [72]. In contrast, Bargen et al. found that, while there were no significant increase in surgical complications, patients receiving less than total thyroidectomy were at an increased risk for requiring revision surgery ($p = 0.03$) [73]. Despite these differences, outcomes for PTC are excellent with long-term survival rates greater than 95% [56, 58, 60–62]. Unlike PTC, FTC is more likely to be unifocal and metastasize via hematogenous spread. FTC is commonly managed with thyroid lobectomy, but total thyroidectomy with radioactive iodine ablation (RAI) is indicated in cases of metastasis, advanced disease, vascular invasion, or extracapsular extension. Selective neck dissection, particularly central node dissection, is recommended for clinically involved or radiographically abnormal lymph nodes, extrathyroidal tumor extension, and evidence of locoregional disease [71]. The utility of neck dissection in the absence of clear clinical indications remains poorly defined, but prophylactic neck dissection may be performed in patients with advanced disease [74].

MTC is a unique variant of thyroid carcinoma. Most pediatric cases are inherited in an autosomal-dominant fashion although sporadic cases are possible. Pediatric MTC patients commonly present with bilateral and multifocal thyroid nodules, with metastatic disease common at the time of diagnosis. Parafollicular C-cell hyperplasia results in an excess production of calcitonin and carcinoembryonic antigen (CEA). Mutations in the *RET* proto-oncogene are responsible for the development of the multiple endocrine neoplasia 2 (MEN 2) syndrome which is divided into three distinct entities based on the endocrine tissues involved: MEN-2A, MEN-2B, and familial MTC [75]. MEN-2A (exons 10 and 11 mutations) is characterized by MTC, pheochromocytoma, and primary hyperparathyroidism from the presence of parathyroid adenomas. MEN-2B (exon 16 mutations) involves MTC, pheochromocytoma, mucosal neuromas (with predisposition for the lips and tongue), ganglioneuromas, and marfanoid body habitus. Familial MTC, a variant of MEN-2A which accounts for 15% of hereditary MTCs, is characterized by a strong familial predisposition to MTC without pheochromocytoma and parathyroid adenomas [76, 77]. In suspected cases, thyroid US and FNAB should be performed. In addition to thyroid function studies, serum calcitonin and CEA levels should be obtained. If concern exists for pheochromocytoma, metanephrine and catecholamine testing should be included along with the imaging studies. Genetic testing is indicated for children with a familial history of *RET* mutations and allows for close surveillance in these patients prior to the development of disease. Prophylactic total thyroidectomy with or without central lymph node dissection is the surgical treatment of choice and may be performed safely in children as early as 5 years of age with a family history of germline RET mutations or MEN-2A syndrome [78–80]. For those with the MEN-2B syndrome, prophylactic thyroidectomy before age 1 may be appropriate, especially if patients are carriers of aggressive codon mutations [81]. There is no clear consensus regarding central neck dissection, although this is often performed at the time of prophylactic total thyroidectomy [71, 74, 82, 83]. The five-year OS for MTC is similarly high at approximately 96%, but, the 15- and 30-year survival rates are lower at 86% [55].

Following total thyroidectomy, hormone replacement is necessary. Together with RAI therapy, it may reduce the risk of tumor recurrence. Long-term surveillance includes serum thyroglobulin levels, thyroid US, and radioiodine-123 (^{123}I) diagnostic whole-body scans. Radioiodine-131 (^{131}I) may be used for ablation of residual thyroid tissue and is indicated in select pediatric patients with distant metastases or residual disease not amenable to surgical resection [71, 84, 85]. Complications of RAI are dose-dependent and include pulmonary fibrosis, infertility, and the development of secondary cancers, thus highlighting the importance of careful patient selection as well as follow-up [86].

5. Nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC) is a rare pediatric malignancy. Overall, NPC accounts for less than 1% of all childhood cancers and represents approximately 20–50% of nasopharyngeal tumors [87, 88]. Globally, the incidence of pediatric NPC is highest throughout southeast Asia, southern China, and the Mediterranean. In the United States, childhood NPC is more commonly diagnosed in the southern states. The age distribution is bimodal with the first peak in adolescence followed by mid-adulthood (ages 40–60) while the distribution in endemic regions (e.g. Southeastern Asia and China) is unimodal without a pediatric peak [89]. In all regions, the etiology and pathogenesis of NPC is closely related to Epstein–Barr virus (EBV) infection with children sharing a closer association with EBV than adults [88, 90].

The WHO separates three distinct histopathologic subtypes of NPC: Type I (keratinizing squamous cell carcinoma), Type II (non-keratinizing epidermoid carcinoma), and Type III (undifferentiated carcinoma) (**Table 8**) [88, 91]. Type I is characterized by the production of keratin, is commonly associated with alcohol and tobacco exposure and, as such, is less common in the pediatric population. Type I NPC may be found in those with EBV infections in endemic areas. Type II and III commonly demonstrate lymphoid, plasmoid, and eosinophilic cell infiltration. Type III, also referred to as lymphoepithelioma or Schminke tumor, is the most common histopathologic subtype in pediatric patients and may be found in as many as 90% of patients with a high rate of distant metastases [88].

Childhood NPC most commonly presents a painless neck mass, which may be appreciated in 70–90% of patients at the time of first diagnosis. Nasal obstruction, epistaxis, and Eustachian tube dysfunction with resultant conductive hearing loss and serous otitis media may occur from tumor mass effect [92]. In more advanced disease, trismus, headache, facial pain, diplopia with vision changes, and other cranial nerve palsies may be present secondary to skull base involvement [88, 93, 94]. Patients with systemic disease may present with paraneoplastic syndromes such as syndrome of inappropriate antidiuretic hormone (SIADH) or dermatomyositis [95]. Evaluation involves a thorough clinical examination with contrast-enhanced CT and MRI with particular attention to skull base structures. Recommended laboratory testing includes a CBC, serum chemistry, lactic acid dehydrogenase (LDH) level, and liver function panel. More specifically, elevated LDH levels carry prognostic significance with higher values shown to correlate with decreased OS, disease-free survival (DFS), and distant metastasis-free survival (DMFS) [96, 97]. Bone marrow biopsy and CSF cytologic analysis is indicated in cases of distant metastases or when skull base extension is suspected while biopsy of the primary tumor is required for accurate tissue diagnosis.

Given the rarity of pediatric NPCs, treatment strategies have been tailored from established adult guidelines. As these tumors are rarely amenable to surgical resection, the standard of care for locoregional NPC involves a combination of high-dose

Type	Description
I	Keratinizing squamous cell carcinoma
II	Non-keratinizing carcinoma
III	Undifferentiated carcinoma (Lymphoepithelioma or Schminke tumor)

Table 8.
World Health Organization (WHO) classification of nasopharyngeal carcinoma.

radiotherapy (RT) to the primary nasopharyngeal tumor bed and the surrounding nodal basin with lower doses targeted at surrounding tissues and uninvolved lymph nodes. Due to high rates of locoregional and distant failure in patients presenting with advanced disease, chemotherapeutic regimens have recently been incorporated into treatment schemas. With combined RT and chemotherapy, survival rates ranging from 60 to 70% have been reported with some studies documenting as high as 90% [89, 90, 94, 98, 99]. In patients with early-stage T1 or T2 disease, single modality RT may be utilized. In locally advanced cases, dual modality treatment has been shown to result in improved OS compared to RT alone. A meta-analysis by Langendijk et al. demonstrated that concurrent chemotherapy was associated with a pooled hazard ratio (HR) of 0.48 (95% CI, 0.32–0.72) which corresponded to a 20% improvement in five-year OS compared to RT alone while neoadjuvant chemotherapy was associated with improved locoregional control with a decreased rate of distant metastases [100]. Similar results have been documented throughout the literature [101–105]. Despite these advances, many patients continue to present with locoregional or systemic recurrence with most relapses occurring within the first two years (median 8 months) following treatment [98, 106, 107]. The short interval between therapy completion and distant metastases may be a result of occult disease at the time of presentation. Notably, T and N classification, total irradiation dose, presence of metastatic disease at diagnosis, and delay in time to RT have all been demonstrated as prognostic factors in locoregional control of NPC [93, 105–110].

6. Salivary gland malignancy

Pediatric salivary gland malignancies are rare and comprise approximately 3% of head and neck cancers in the pediatric population and 5% of salivary gland malignancies overall [111]. In contrast to adults, the majority of salivary gland neoplasms in children are malignant in nature (40–60%) and most are epithelial in origin. The parotid gland is the most common site and mucoepidermoid carcinoma (MEC) represents the vast majority of salivary gland malignancies. Less common histologic subtypes include acinic cell carcinoma (24–40%) and adenoid cystic carcinoma (15–26%) [112]. Several series have evaluated treatment outcomes associated with these tumors and demonstrate surgical resection as the mainstay of treatment followed by adjuvant RT in select instances [112–119]. A retrospective study by Ribeiro and colleagues reviewed outcomes associated with the treatment of 38 pediatric patients with salivary gland neoplasms, 27 (71.1%) of whom presented with malignant tumors [116]. MEC was the most frequent pathology occurring in 17 of 27 (69.3%) cases followed by 3 patients with adenoid cystic carcinoma; the remaining seven patients had a diverse range of rare malignancies. The parotid gland was the most common primary site followed by minor salivary glands and submandibular gland with 74.1%, 22.2%, and 7.4% of the cases, respectively. All were treated with surgical resection while 10 patients underwent concurrent neck dissection; however, only 6 were found to have pathologically positive lymph node disease. RT was administered to a total of 10 patients (neoadjuvant in 2 patients, adjuvant in 8 patients) and chemotherapy in 3 individuals. Overall, five and ten-year survival rates were both 81.6% with tumor differentiation found to be a significant prognostic factor in those with MEC with a five-year OS of 100% in low-grade histology compared to 50% for intermediate and high-grade histology ($p = 0.01$). Similar findings have been reported throughout the literature [118–121]. Despite the limited sample size in these series, the results highlight the central role of surgery in these patients with favorable long-term outcomes and facial nerve preservation. Moreover, while adjuvant therapy

is utilized in select cases, no standard criteria has been agreed upon likely owing to the relative rarity of these tumors. The decision to pursue RT and chemotherapy varies between institutions with some centers advocating its use in high-grade histology and in the presence of aggressive histological features such as perineural or intravascular invasion; however, soft-tissue extension and multi-level lymph node involvement are findings which more commonly result in its use [118, 119].

While MEC is the most common adult and childhood malignant salivary gland tumor, it has also been reported to occur more frequently in patients previously treated with RT and/or chemotherapy regimens for both cancerous and benign pathology [122–124]. A literature review by Verma et al. assessed the characteristics and treatment outcomes of 58 patients selected from 23 studies with treatment-related MEC and showed a significantly shorter latent time to the development of MEC from initial treatment in those treated with chemotherapy with or without RT compared to RT alone (7.9 years vs. 27.2 years) [120]. The primary MEC treatment modality was surgery alone in the majority of patients (64.9%) or in combination with radiation (29.8%) while the remaining patients received surgery plus chemotherapy, or underwent RT alone. Survival was similar to those documented in previous studies with two and five-year OS rates of 98.0% and 93.4%, respectively. Despite favorable survival, the potential for the development of secondary malignancy underscores the importance of continued surveillance in these patients for not only salivary gland cancers but other solid tumor malignancies (**Table 1**).

Clinically, most salivary gland neoplasms present as asymptomatic masses and are rarely associated with cranial neuropathies; the presence of facial nerve weakness or other cranial nerve deficits should heighten the suspicion for malignant potential [111, 112, 125, 126]. US remains the first-line imaging modality and has been shown to be useful in combination with FNAB in establishing a timely diagnosis, specifically in parotid tumors [127]. While CT is useful for further imaging characterization, MRI is superior in demonstrating soft-tissue enhancement which is particularly beneficial in evaluating the status of the facial nerve, lingual nerve, and other surrounding neurovascular structures [128]. Open biopsy should be avoided given the potential for injury to the facial nerve, especially in children with parotid tumors, and possibility for tumor seeding [129, 130]. Treatment consists of local excision with tumor-free margins of the affected salivary gland. In the case of partial or total parotidectomy, careful attention to preserving facial nerve function is recommended as the critical neurovascular structures are smaller in pediatric patients. The same principles hold true in cases of submandibular gland malignancy where the marginal mandibular and lingual nerve should be preserved [112, 131]. A review of the SEER database from 1973 to 2006 by Sultan et al. identified a total of 263 children and adolescents with salivary gland carcinoma and, in comparison to adults, found that disease is more often localized (50%) with regional lymph node metastases being less common (11% vs. 31%) [117]. The need for neck dissection in children is poorly understood as the majority of tumors are low-grade without occult nodal disease. As a result, several authors have suggested that neck dissection be performed in cases of clinically evident nodal involvement and high-grade histology which may altogether avoid the need for adjuvant therapy in the absence of positive margins or pathologically positive nodal disease [116, 125, 132, 133].

7. Osteosarcoma

Sarcomas account for 14% of primary head and neck malignancies in children and adolescents. Osteosarcoma remains the most common subtype consisting of

approximately 0.5% of the cases and Ewing sarcoma is the second most common cancer of bone [1]. Osteosarcoma most frequently involves the long bones of the extremities (e.g. distal femur, proximal tibia, proximal humerus) but may occur in the mandible or maxilla which are the most commonly involved head and neck subsites [134–139]. In general, childhood mandibular and maxillary tumors are benign and are discovered incidentally during routine dental examinations or non-related imaging studies [140, 141]. Head and neck osteosarcoma is also associated with a better prognosis when compared to their long bone counterparts with three and five-year survival rate at approximately 65% [142–144]. Patients tend to present during adolescence with a painless mandibular mass, but pain, edema, loose dentition, paresthesias, diplopia, or cranial nerve palsies are especially suspicious for malignancy [134, 135, 144].

Management and treatment protocols are primarily based upon large trials or meta-analyses focused on osteosarcoma of the limbs and trunk [145]. In addition to laboratory studies, imaging commonly involves a combination of plain radiographs, CT, MRI, and 99 m technetium methylene disphosphonate bone scans [146–148]. The classic "sunburst" finding in addition to a "fluffy" or spiculated osseous appearance suggests the presence of an aggressive periosteal reaction along with osteolytic or osteoblastic bony destruction associated with malignancy. Lesions are sampled for histologic determination of subtype which includes the osteoblastic, chondroblastic, and fibroblastic high-grade forms with tumor grade carrying prognostic significance [137, 149–152]. Estimating survival rates for pediatric head and neck osteosarcoma is difficult as studies tend to group adult and pediatric patients together. Despite this, surgical resection appears to play an important role with negative surgical margins being the most important prognostic factor [142, 143, 153–157]. Similar to other surgically resected tumors, adjuvant RT and chemotherapy are reserved for use in cases with incompletely resected disease or in the setting of positive surgical margins. In the case of unresectable disease, RT and chemotherapy either as single or multi-modal therapy may be indicated,

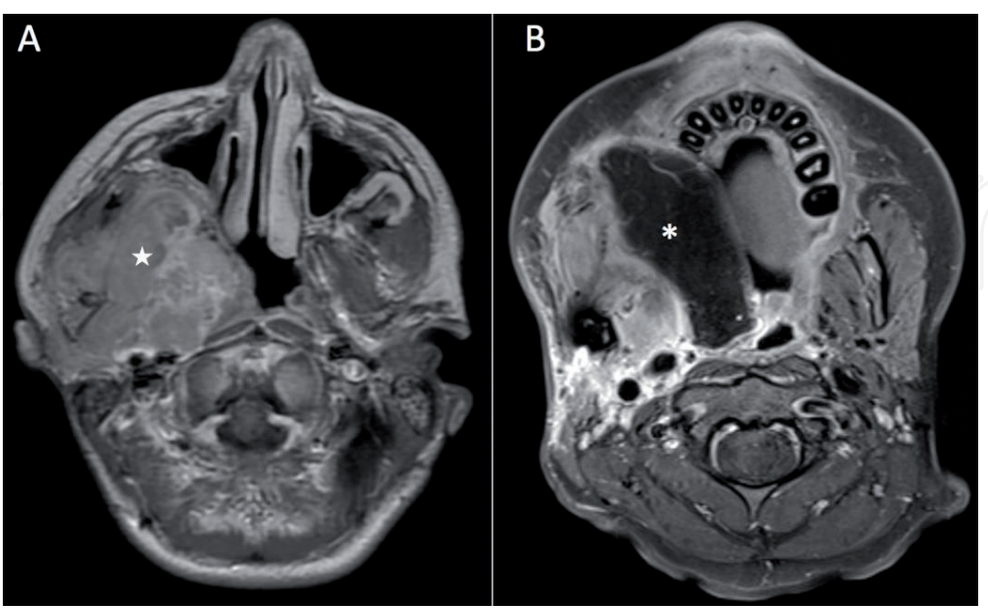

Figure 6.
Monophasic synovial sarcoma. (A) Post-contrast axial T1 MRI demonstrating a T4aN0M0 monophasic synovial cell sarcoma of the right infratemporal fossa and parapharyngeal space in a 15-year-old male (star). Post-contrast axial T1 fat suppressed MRI (B) status-post composite resection demonstrating a right segmental mandibulectomy and resection of tumor involving the infratemporal fossa, parapharyngeal space, and pterygoid base. A total parotidectomy with facial nerve preservation and right selective neck dissection (levels I-IV) was also performed. The 1-month postoperative fibula free flap is visualized (asterisk).

though RT should be approached with particular care as some studies attribute RT as a causative intervention for OS. Other less common sarcomas exist (e.g., fibrosarcoma, synovial cell sarcoma, chondrosarcoma, liposarcoma), although a complete discussion of the management of these entities is outside the scope of this review. Nonetheless, surgical resection remains the mainstay of treatment in many of these diagnoses and leads to a successful outcome when complete resection with tumor-free margins is obtained (**Figure 6**).

8. Conclusion

Pediatric head and neck malignancies represent a minority of childhood tumors. Although the relative rarity of these tumors largely prevents initiation of high-volume trials, experiences from adult cases and in pediatric case reports stipulate that multimodal therapy is often indicated based upon the specific histopathology, stage, and anatomic sites involved. In select instances, primary surgical management with or without free tissue transfer and microvascular reconstruction may also be indicated. While adjuvant therapy including post-operative radiation may improve long-term survival rates, careful consideration must be given to the potential for the development of deleterious side effects in young children including secondary malignancies later in life.

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Conflict of interest

The authors declare no relevant conflicts of interest.

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References

[1] Albright JT, Topham AK, Reilly JS. Pediatric head and neck malignancies: US incidence and trends over 2 decades. Archives of otolaryngology--head & neck surgery. 2002;128:655-9.

[2] Choi DK, Helenowski I, Hijiya N. Secondary malignancies in pediatric cancer survivors: perspectives and review of the literature. International journal of cancer. 2014;135:1764-73.

[3] Linabery AM, Ross JA. Trends in childhood cancer incidence in the U.S. (1992-2004). Cancer. 2008;112:416-32.

[4] Minard-Colin V, Brugieres L, Reiter A, Cairo MS, Gross TG, Woessmann W, et al. Non-Hodgkin Lymphoma in Children and Adolescents: Progress Through Effective Collaboration, Current Knowledge, and Challenges Ahead. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33:2963-74.

[5] Gross TG, Termuhlen AM. Pediatric non-Hodgkin's lymphoma. Current oncology reports. 2007;9:459-65.

[6] Kharazmi E, Fallah M, Pukkala E, Olsen JH, Tryggvadottir L, Sundquist K, et al. Risk of familial classical Hodgkin lymphoma by relationship, histology, age, and sex: a joint study from five Nordic countries. Blood. 2015;126:1990-5.

[7] Gaini RM, Romagnoli M, Sala A, Garavello W. Lymphomas of head and neck in pediatric patients. International journal of pediatric otorhinolaryngology. 2009;73 Suppl 1:S65-70.

[8] Weiner MA, Leventhal BG, Marcus R, Brecher M, Ternberg J, Behm FG, et al. Intensive chemotherapy and low-dose radiotherapy for the treatment of advanced-stage Hodgkin's disease in pediatric patients: a Pediatric Oncology Group study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1991;9:1591-8.

[9] Linabery AM, Erhardt EB, Fonstad RK, Ambinder RF, Bunin GR, Ross JA, et al. Infectious, autoimmune and allergic diseases and risk of Hodgkin lymphoma in children and adolescents: a Children's Oncology Group study. International journal of cancer. 2014;135:1454-69.

[10] Donaldson SS. Pediatric Hodgkin's disease--up, up, and beyond. Int J Radiat Oncol Biol Phys. 2002;54:1-8.

[11] Burkhardt B, Zimmermann M, Oschlies I, Niggli F, Mann G, Parwaresch R, et al. The impact of age and gender on biology, clinical features and treatment outcome of non-Hodgkin lymphoma in childhood and adolescence. Br J Haematol. 2005;131:39-49.

[12] Casulo C, Friedberg JW. Burkitt lymphoma- a rare but challenging lymphoma. Best practice & research Clinical haematology. 2018;31:279-84.

[13] Dave SS, Fu K, Wright GW, Lam LT, Kluin P, Boerma EJ, et al. Molecular diagnosis of Burkitt's lymphoma. The New England journal of medicine. 2006;354:2431-42.

[14] Blum KA, Lozanski G, Byrd JC. Adult Burkitt leukemia and lymphoma. Blood. 2004;104:3009-20.

[15] Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood. 2006;107:265-76.

[16] Hoelzer D, Walewski J, Dohner H, Viardot A, Hiddemann W,

Spiekermann K, et al. Improved outcome of adult Burkitt lymphoma/leukemia with rituximab and chemotherapy: report of a large prospective multicenter trial. Blood. 2014;124:3870-9.

[17] Mead GM, Sydes MR, Walewski J, Grigg A, Hatton CS, Pescosta N, et al. An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study. Annals of oncology : official journal of the European Society for Medical Oncology. 2002;13:1264-74.

[18] Attarbaschi A, Carraro E, Abla O, Barzilai-Birenboim S, Bomken S, Brugieres L, et al. Non-Hodgkin lymphoma and pre-existing conditions: spectrum, clinical characteristics and outcome in 213 children and adolescents. Haematologica. 2016;101:1581-91.

[19] Barta SK, Samuel MS, Xue X, Wang D, Lee JY, Mounier N, et al. Changes in the influence of lymphoma- and HIV-specific factors on outcomes in AIDS-related non-Hodgkin lymphoma. Annals of oncology : official journal of the European Society for Medical Oncology. 2015;26:958-66.

[20] Simcock M, Blasko M, Karrer U, Bertisch B, Pless M, Blumer L, et al. Treatment and prognosis of AIDS-related lymphoma in the era of highly active antiretroviral therapy: findings from the Swiss HIV Cohort Study. Antiviral therapy. 2007;12:931-9.

[21] Gabarre J, Raphael M, Lepage E, Martin A, Oksenhendler E, Xerri L, et al. Human immunodeficiency virus-related lymphoma: relation between clinical features and histologic subtypes. The American journal of medicine. 2001;111:704-11.

[22] Shen Y. [Clinical analysis of non-Hodgkin lymphoma of the head and neck (report of 25 cases)]. Lin chuang er bi yan hou ke za zhi = Journal of clinical otorhinolaryngology. 2005;19:311-2.

[23] Oguz A, Karadeniz C, Temel EA, Citak EC, Okur FV. Evaluation of peripheral lymphadenopathy in children. Pediatric hematology and oncology. 2006;23:549-61.

[24] Kluge R, Kurch L, Georgi T, Metzger M. Current Role of FDG-PET in Pediatric Hodgkin's Lymphoma. Seminars in nuclear medicine. 2017;47:242-57.

[25] Elstrom R, Guan L, Baker G, Nakhoda K, Vergilio JA, Zhuang H, et al. Utility of FDG-PET scanning in lymphoma by WHO classification. Blood. 2003;101:3875-6.

[26] Caraway NP. Evolving role of FNA biopsy in diagnosing lymphoma: past, present, and future. Cancer cytopathology. 2015;123:389-93.

[27] Kung FH, Schwartz CL, Ferree CR, London WB, Ternberg JL, Behm FG, et al. POG 8625: a randomized trial comparing chemotherapy with chemoradiotherapy for children and adolescents with Stages I, IIA, IIIA1 Hodgkin Disease: a report from the Children's Oncology Group. Journal of pediatric hematology/oncology. 2006;28:362-8.

[28] Mauz-Korholz C, Metzger ML, Kelly KM, Schwartz CL, Castellanos ME, Dieckmann K, et al. Pediatric Hodgkin Lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33:2975-85.

[29] Kahn JM, Ozuah NW, Dunleavy K, Henderson TO, Kelly K, LaCasce A. Adolescent and young adult lymphoma: collaborative efforts toward optimizing care and improving outcomes. Blood advances. 2017;1:1945-58.

[30] Simon JH, Paulino AC, Smith RB, Buatti JM. Prognostic factors in head and neck rhabdomyosarcoma. Head & neck. 2002;24:468-73.

[31] Miller RW, Young JL, Jr., Novakovic B. Childhood cancer. Cancer. 1995;75:395-405.

[32] Dasgupta R, Fuchs J, Rodeberg D. Rhabdomyosarcoma. Seminars in pediatric surgery. 2016;25:276-83.

[33] Dasgupta R, Rodeberg DA. Update on rhabdomyosarcoma. Seminars in pediatric surgery. 2012;21:68-78.

[34] Leaphart C, Rodeberg D. Pediatric surgical oncology: management of rhabdomyosarcoma. Surgical oncology. 2007;16:173-85.

[35] Pappo AS, Meza JL, Donaldson SS, Wharam MD, Wiener ES, Qualman SJ, et al. Treatment of localized nonorbital, nonparameningeal head and neck rhabdomyosarcoma: lessons learned from intergroup rhabdomyosarcoma studies III and IV. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2003;21:638-45.

[36] Pappo AS, Shapiro DN, Crist WM, Maurer HM. Biology and therapy of pediatric rhabdomyosarcoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1995;13:2123-39.

[37] Coffin CM, Davis JL, Borinstein SC. Syndrome-associated soft tissue tumours. Histopathology. 2014;64:68-87.

[38] Huh WW, Skapek SX. Childhood rhabdomyosarcoma: new insight on biology and treatment. Current oncology reports. 2010;12:402-10.

[39] Ognjanovic S, Linabery AM, Charbonneau B, Ross JA. Trends in childhood rhabdomyosarcoma incidence and survival in the United States, 1975-2005. Cancer. 2009;115:4218-26.

[40] Katal S, Gholamrezanezhad A, Kessler M, Olyaei M, Jadvar H. PET in the Diagnostic Management of Soft Tissue Sarcomas of Musculoskeletal Origin. PET clinics. 2018;13:609-21.

[41] Kumar R, Shandal V, Shamim SA, Halanaik D, Malhotra A. Clinical applications of PET and PET/CT in pediatric malignancies. Expert review of anticancer therapy. 2010;10:755-68.

[42] Mody RJ, Bui C, Hutchinson RJ, Yanik GA, Castle VP, Frey KA, et al. FDG PET imaging of childhood sarcomas. Pediatric blood & cancer. 2010;54:222-7.

[43] Tateishi U, Hosono A, Makimoto A, Nakamoto Y, Kaneta T, Fukuda H, et al. Comparative study of FDG PET/CT and conventional imaging in the staging of rhabdomyosarcoma. Annals of nuclear medicine. 2009;23:155-61.

[44] Rodeberg DA, Garcia-Henriquez N, Lyden ER, Davicioni E, Parham DM, Skapek SX, et al. Prognostic significance and tumor biology of regional lymph node disease in patients with rhabdomyosarcoma: a report from the Children's Oncology Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29:1304-11.

[45] Crist W, Gehan EA, Ragab AH, Dickman PS, Donaldson SS, Fryer C, et al. The Third Intergroup Rhabdomyosarcoma Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1995;13:610-30.

[46] Crist WM, Anderson JR, Meza JL, Fryer C, Raney RB, Ruymann FB, et al. Intergroup rhabdomyosarcoma study-IV: results for patients with nonmetastatic disease. Journal of clinical oncology : official journal of the

American Society of Clinical Oncology. 2001;19:3091-102.

[47] Maurer HM, Beltangady M, Gehan EA, Crist W, Hammond D, Hays DM, et al. The Intergroup Rhabdomyosarcoma Study-I. A final report. Cancer. 1988;61:209-20.

[48] Maurer HM, Gehan EA, Beltangady M, Crist W, Dickman PS, Donaldson SS, et al. The Intergroup Rhabdomyosarcoma Study-II. Cancer. 1993;71:1904-22.

[49] Daya H, Chan HS, Sirkin W, Forte V. Pediatric rhabdomyosarcoma of the head and neck: is there a place for surgical management? Archives of otolaryngology--head & neck surgery. 2000;126:468-72.

[50] Walterhouse DO, Pappo AS, Baker KS, Parham DM, Anderson JR, Donaldson SS, et al. Rhabdomyosarcoma of the parotid region occurring in childhood and adolescence. A report from the Intergroup Rhabdomyosarcoma Study Group. Cancer. 2001;92:3135-46.

[51] Wiener ES. Head and neck rhabdomyosarcoma. Seminars in pediatric surgery. 1994;3:203-6.

[52] Raney B, Huh W, Hawkins D, Hayes-Jordan A, Million L, Rodeberg D, et al. Outcome of patients with localized orbital sarcoma who relapsed following treatment on Intergroup Rhabdomyosarcoma Study Group (IRSG) Protocols-III and -IV, 1984-1997: a report from the Children's Oncology Group. Pediatric blood & cancer. 2013;60:371-6.

[53] Hawkins DS, Anderson JR, Paidas CN, Wharam MD, Qualman SJ, Pappo AS, et al. Improved outcome for patients with middle ear rhabdomyosarcoma: a children's oncology group study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2001;19:3073-9.

[54] Reilly BK, Kim A, Pena MT, Dong TA, Rossi C, Murnick JG, et al. Rhabdomyosarcoma of the head and neck in children: review and update. International journal of pediatric otorhinolaryngology. 2015;79:1477-83.

[55] Hogan AR, Zhuge Y, Perez EA, Koniaris LG, Lew JI, Sola JE. Pediatric thyroid carcinoma: incidence and outcomes in 1753 patients. The Journal of surgical research. 2009;156:167-72.

[56] Shapiro NL, Bhattacharyya N. Population-based outcomes for pediatric thyroid carcinoma. The Laryngoscope. 2005;115:337-40.

[57] Niedziela M. Pathogenesis, diagnosis and management of thyroid nodules in children. Endocrine-related cancer. 2006;13:427-53.

[58] Dermody S, Walls A, Harley EH, Jr. Pediatric thyroid cancer: An update from the SEER database 2007-2012. International journal of pediatric otorhinolaryngology. 2016;89:121-6.

[59] La Quaglia MP, Black T, Holcomb GW, 3rd, Sklar C, Azizkhan RG, Haase GM, et al. Differentiated thyroid cancer: clinical characteristics, treatment, and outcome in patients under 21 years of age who present with distant metastases. A report from the Surgical Discipline Committee of the Children's Cancer Group. Journal of pediatric surgery. 2000;35:955-9; discussion 60.

[60] Astl J, Chovanec M, Lukes P, Katra R, Dvorakova M, Vlcek P, et al. Thyroid carcinoma surgery in children and adolescents - 15 years experience surgery of pediatric thyroid carcinoma. International journal of pediatric otorhinolaryngology. 2014;78:990-4.

[61] Diesen DL, Skinner MA. Pediatric thyroid cancer. Seminars in pediatric surgery. 2012;21:44-50.

[62] Spinelli C, Strambi S, Rossi L, Bakkar S, Massimino M, Ferrari A, et al. Surgical management of papillary thyroid carcinoma in childhood and adolescence: an Italian multicenter study on 250 patients. Journal of endocrinological investigation. 2016;39:1055-9.

[63] Acharya S, Sarafoglou K, LaQuaglia M, Lindsley S, Gerald W, Wollner N, et al. Thyroid neoplasms after therapeutic radiation for malignancies during childhood or adolescence. Cancer. 2003;97:2397-403.

[64] Constine LS, Tarbell N, Hudson MM, Schwartz C, Fisher SG, Muhs AG, et al. Subsequent malignancies in children treated for Hodgkin's disease: associations with gender and radiation dose. Int J Radiat Oncol Biol Phys. 2008;72:24-33.

[65] von der Weid NX. Adult life after surviving lymphoma in childhood. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2008;16:339-45.

[66] Buryk MA, Simons JP, Picarsic J, Monaco SE, Ozolek JA, Joyce J, et al. Can malignant thyroid nodules be distinguished from benign thyroid nodules in children and adolescents by clinical characteristics? A review of 89 pediatric patients with thyroid nodules. Thyroid : official journal of the American Thyroid Association. 2015;25:392-400.

[67] Koltin D, O'Gorman CS, Murphy A, Ngan B, Daneman A, Navarro OM, et al. Pediatric thyroid nodules: ultrasonographic characteristics and inter-observer variability in prediction of malignancy. Journal of pediatric endocrinology & metabolism : JPEM. 2016;29:789-94.

[68] Mussa A, De Andrea M, Motta M, Mormile A, Palestini N, Corrias A. Predictors of Malignancy in Children with Thyroid Nodules. The Journal of pediatrics. 2015;167:886-92.e1.

[69] Richman DM, Benson CB, Doubilet PM, Peters HE, Huang SA, Asch E, et al. Thyroid Nodules in Pediatric Patients: Sonographic Characteristics and Likelihood of Cancer. Radiology. 2018;288:591-9.

[70] Costante G, Meringolo D, Durante C, Bianchi D, Nocera M, Tumino S, et al. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. The Journal of clinical endocrinology and metabolism. 2007;92:450-5.

[71] Francis GL, Waguespack SG, Bauer AJ, Angelos P, Benvenga S, Cerutti JM, et al. Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid : official journal of the American Thyroid Association. 2015;25:716-59.

[72] Nice T, Pasara S, Goldfarb M, Doski J, Goldin A, Gow KW, et al. Pediatric papillary thyroid cancer >1 cm: is total thyroidectomy necessary? Journal of pediatric surgery. 2015;50:1009-13.

[73] Bargren AE, Meyer-Rochow GY, Delbridge LW, Sidhu SB, Chen H. Outcomes of surgically managed pediatric thyroid cancer. The Journal of surgical research. 2009;156:70-3.

[74] Moley JF. Medullary thyroid carcinoma: management of lymph node metastases. Journal of the National Comprehensive Cancer Network : JNCCN. 2010;8:549-56.

[75] Wells SA, Jr., Pacini F, Robinson BG, Santoro M. Multiple endocrine

neoplasia type 2 and familial medullary thyroid carcinoma: an update. The Journal of clinical endocrinology and metabolism. 2013;98:3149-64.

[76] Mulligan LM, Marsh DJ, Robinson BG, Schuffenecker I, Zedenius J, Lips CJ, et al. Genotype-phenotype correlation in multiple endocrine neoplasia type 2: report of the International RET Mutation Consortium. Journal of internal medicine. 1995;238:343-6.

[77] Farndon JR, Leight GS, Dilley WG, Baylin SB, Smallridge RC, Harrison TS, et al. Familial medullary thyroid carcinoma without associated endocrinopathies: a distinct clinical entity. The British journal of surgery. 1986;73:278-81.

[78] Lallier M, St-Vil D, Giroux M, Huot C, Gaboury L, Oligny L, et al. Prophylactic thyroidectomy for medullary thyroid carcinoma in gene carriers of MEN2 syndrome. Journal of pediatric surgery. 1998;33:846-8.

[79] Moore SW, Appfelstaedt J, Zaahl MG. Familial medullary carcinoma prevention, risk evaluation, and RET in children of families with MEN2. Journal of pediatric surgery. 2007;42:326-32.

[80] Machens A, Niccoli-Sire P, Hoegel J, Frank-Raue K, van Vroonhoven TJ, Roeher HD, et al. Early malignant progression of hereditary medullary thyroid cancer. The New England journal of medicine. 2003;349:1517-25.

[81] Gomez IGC, Ponce Marco JL, Belda Ibanez T, Bosca Robledo A, Sebastian Pastor C, Navarro Milla R, et al. The optimal age for performing surgery on patients with MEN 2B syndrome. Oncology letters. 2011;2:929-30.

[82] Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. The Journal of clinical endocrinology and metabolism. 2001;86:5658-71.

[83] Spinelli C, Strambi S, Rossi L, Elisei R, Massimino M. Surgical Management of Medullary Thyroid Carcinoma in Pediatric Age. Current pediatric reviews. 2016;12:280-5.

[84] Albano D, Bertagna F, Panarotto MB, Giubbini R. Early and late adverse effects of radioiodine for pediatric differentiated thyroid cancer. Pediatric blood & cancer. 2017;64.

[85] Chow SM, Yau S, Lee SH, Leung WM, Law SC. Pregnancy outcome after diagnosis of differentiated thyroid carcinoma: no deleterious effect after radioactive iodine treatment. Int J Radiat Oncol Biol Phys. 2004;59:992-1000.

[86] Pawelczak M, David R, Franklin B, Kessler M, Lam L, Shah B. Outcomes of children and adolescents with well-differentiated thyroid carcinoma and pulmonary metastases following (1)(3)(1)I treatment: a systematic review. Thyroid : official journal of the American Thyroid Association. 2010;20:1095-101.

[87] Pao WJ, Hustu HO, Douglass EC, Beckford NS, Kun LE. Pediatric nasopharyngeal carcinoma: long term follow-up of 29 patients. Int J Radiat Oncol Biol Phys. 1989;17:299-305.

[88] Ayan I, Altun M. Nasopharyngeal carcinoma in children: retrospective review of 50 patients. Int J Radiat Oncol Biol Phys. 1996;35:485-92.

[89] Ozyar E, Selek U, Laskar S, Uzel O, Anacak Y, Ben-Arush M, et al. Treatment results of 165 pediatric patients with non-metastatic nasopharyngeal carcinoma: a Rare Cancer Network study. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2006;81:39-46.

[90] Mertens R, Granzen B, Lassay L, Bucsky P, Hundgen M, Stetter G, et al. Treatment of nasopharyngeal carcinoma in children and adolescents: definitive results of a multicenter study (NPC-91-GPOH). Cancer. 2005;104:1083-9.

[91] Ayan I, Kaytan E, Ayan N. Childhood nasopharyngeal carcinoma: from biology to treatment. The Lancet Oncology. 2003;4:13-21.

[92] Noorizan Y, Chew YK, Khir A, Brito-Mutunayagam S. Nasopharyngeal carcinoma: recognizing it early in children with otitis media with effusion. The Medical journal of Malaysia. 2008;63:261-2.

[93] Cvitkovic E, Bachouchi M, Armand JP. Nasopharyngeal carcinoma. Biology, natural history, and therapeutic implications. Hematology/oncology clinics of North America. 1991;5:821-38.

[94] Zubizarreta PA, D'Antonio G, Raslawski E, Gallo G, Preciado MV, Casak SJ, et al. Nasopharyngeal carcinoma in childhood and adolescence: a single-institution experience with combined therapy. Cancer. 2000;89:690-5.

[95] Toro C, Rinaldo A, Silver CE, Politi M, Ferlito A. Paraneoplastic syndromes in patients with nasopharyngeal cancer. Auris, nasus, larynx. 2009;36:513-20.

[96] Zhou GQ, Ren XY, Mao YP, Chen L, Sun Y, Liu LZ, et al. Prognostic implications of dynamic serum lactate dehydrogenase assessments in nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy. Scientific reports. 2016;6:22326.

[97] Zhang M, Wei S, Su L, Lv W, Hong J. Prognostic significance of pretreated serum lactate dehydrogenase level in nasopharyngeal carcinoma among Chinese population: A meta-analysis. Medicine. 2016;95:e4494.

[98] Mertens R, Granzen B, Lassay L, Gademann G, Hess CF, Heimann G. Nasopharyngeal carcinoma in childhood and adolescence: concept and preliminary results of the cooperative GPOH study NPC-91. Gesellschaft fur Padiatrische Onkologie und Hamatologie. Cancer. 1997;80:951-9.

[99] Ingersoll L, Woo SY, Donaldson S, Giesler J, Maor MH, Goffinet D, et al. Nasopharyngeal carcinoma in the young: a combined M.D. Anderson and Stanford experience. Int J Radiat Oncol Biol Phys. 1990;19:881-7.

[100] Langendijk JA, Leemans CR, Buter J, Berkhof J, Slotman BJ. The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: a meta-analysis of the published literature. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2004;22:4604-12.

[101] Nikitovic M, Popovic-Vukovic M, Stanic D, Bokun J, Paripovic L, Ilic V, et al. Treatment outcome of childhood nasopharyngeal carcinoma: A single institution experience. International journal of pediatric otorhinolaryngology. 2018;113:168-72.

[102] Cooper JS, Lee H, Torrey M, Hochster H. Improved outcome secondary to concurrent chemoradiotherapy for advanced carcinoma of the nasopharynx: preliminary corroboration of the intergroup experience. Int J Radiat Oncol Biol Phys. 2000;47:861-6.

[103] Chua MLK, Wee JTS, Hui EP, Chan ATC. Nasopharyngeal carcinoma. Lancet (London, England). 2016;387:1012-24.

[104] Casanova M, Bisogno G, Gandola L, Cecchetto G, Di Cataldo A,

Basso E, et al. A prospective protocol for nasopharyngeal carcinoma in children and adolescents: the Italian Rare Tumors in Pediatric Age (TREP) project. Cancer. 2012;118:2718-25.

[105] Wolden SL, Steinherz PG, Kraus DH, Zelefsky MJ, Pfister DG, Wollner N. Improved long-term survival with combined modality therapy for pediatric nasopharynx cancer. Int J Radiat Oncol Biol Phys. 2000;46:859-64.

[106] Jenkin RD, Anderson JR, Jereb B, Thompson JC, Pyesmany A, Wara WM, et al. Nasopharyngeal carcinoma--a retrospective review of patients less than thirty years of age: a report of Children's Cancer Study Group. Cancer. 1981;47:360-6.

[107] Serin M, Erkal HS, Elhan AH, Cakmak A. Nasopharyngeal carcinoma in childhood and adolescence. Medical and pediatric oncology. 1998;31:498-505.

[108] Cheuk DK, Billups CA, Martin MG, Roland CR, Ribeiro RC, Krasin MJ, et al. Prognostic factors and long-term outcomes of childhood nasopharyngeal carcinoma. Cancer. 2011;117:197-206.

[109] Vokes EE, Liebowitz DN, Weichselbaum RR. Nasopharyngeal carcinoma. Lancet (London, England). 1997;350:1087-91.

[110] Uzel O, Yoruk SO, Sahinler I, Turkan S, Okkan S. Nasopharyngeal carcinoma in childhood: long-term results of 32 patients. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2001;58:137-41.

[111] Yoshida EJ, Garcia J, Eisele DW, Chen AM. Salivary gland malignancies in children. International journal of pediatric otorhinolaryngology. 2014;78:174-8.

[112] Aro K, Leivo I, Makitie A. Management of salivary gland malignancies in the pediatric population. Current opinion in otolaryngology & head and neck surgery. 2014;22:116-20.

[113] Krolls SO, Trodahl JN, Boyers RC. Salivary gland lesions in children. A survey of 430 cases. Cancer. 1972;30:459-69.

[114] Fang QG, Shi S, Li ZN, Zhang X, Liu FY, Sun CF. Epithelial salivary gland tumors in children: a twenty-five-year experience of 122 patients. International journal of pediatric otorhinolaryngology. 2013;77:1252-4.

[115] Cockerill CC, Gross BC, Contag S, Rein S, Moore EJ, Olsen KD, et al. Pediatric malignant salivary gland tumors: 60 year follow up. International journal of pediatric otorhinolaryngology. 2016;88:1-6.

[116] Ribeiro Kde C, Kowalski LP, Saba LM, de Camargo B. Epithelial salivary glands neoplasms in children and adolescents: a forty-four-year experience. Medical and pediatric oncology. 2002;39:594-600.

[117] Sultan I, Rodriguez-Galindo C, Al-Sharabati S, Guzzo M, Casanova M, Ferrari A. Salivary gland carcinomas in children and adolescents: a population-based study, with comparison to adult cases. Head & neck. 2011;33:1476-81.

[118] Callender DL, Frankenthaler RA, Luna MA, Lee SS, Goepfert H. Salivary gland neoplasms in children. Archives of otolaryngology--head & neck surgery. 1992;118:472-6.

[119] Kessler A, Handler SD. Salivary gland neoplasms in children: a 10-year survey at the Children's Hospital of Philadelphia. International journal of pediatric otorhinolaryngology. 1994;29:195-202.

[120] Verma J, Teh BS, Paulino AC. Characteristics and outcome of radiation and chemotherapy-related mucoepidermoid carcinoma of the salivary glands. Pediatric blood & cancer. 2011;57:1137-41.

[121] Vedrine PO, Coffinet L, Temam S, Montagne K, Lapeyre M, Oberlin O, et al. Mucoepidermoid carcinoma of salivary glands in the pediatric age group: 18 clinical cases, including 11 second malignant neoplasms. Head & neck. 2006;28:827-33.

[122] DeLaat CA, Lampkin BC. Long-term survivors of childhood cancer: evaluation and identification of sequelae of treatment. CA: a cancer journal for clinicians. 1992;42:263-82.

[123] Preston-Martin S, Thomas DC, White SC, Cohen D. Prior exposure to medical and dental x-rays related to tumors of the parotid gland. Journal of the National Cancer Institute. 1988;80:943-9.

[124] Land CE, Saku T, Hayashi Y, Takahara O, Matsuura H, Tokuoka S, et al. Incidence of salivary gland tumors among atomic bomb survivors, 1950-1987. Evaluation of radiation-related risk. Radiation research. 1996;146:28-36.

[125] Guzzo M, Locati LD, Prott FJ, Gatta G, McGurk M, Licitra *L. major* and minor salivary gland tumors. Critical reviews in oncology/ hematology. 2010;74:134-48.

[126] Orvidas LJ, Kasperbauer JL, Lewis JE, Olsen KD, Lesnick TG. Pediatric parotid masses. Archives of otolaryngology--head & neck surgery. 2000;126:177-84.

[127] Lee DH, Yoon TM, Lee JK, Lim SC. Clinical utility of fine needle aspiration cytology in pediatric parotid tumors. International journal of pediatric otorhinolaryngology. 2013;77:1272-5.

[128] Koyuncu M, Sesen T, Akan H, Ismailoglu AA, Tanyeri Y, Tekat A, et al. Comparison of computed tomography and magnetic resonance imaging in the diagnosis of parotid tumors. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2003;129:726-32.

[129] Eveson JW. Salivary tumours. Periodontology 2000. 2011;57:150-9.

[130] Shikhani AH, Johns ME. Tumors of the major salivary glands in children. Head & neck surgery. 1988;10:257-63.

[131] Andry G, Hamoir M, Locati LD, Licitra L, Langendijk JA. Management of salivary gland tumors. Expert review of anticancer therapy. 2012;12:1161-8.

[132] Rahbar R, Grimmer JF, Vargas SO, Robson CD, Mack JW, Perez-Atayde AR, et al. Mucoepidermoid carcinoma of the parotid gland in children: A 10-year experience. Archives of otolaryngology--head & neck surgery. 2006;132:375-80.

[133] Thariat J, Vedrine PO, Temam S, Ali AM, Orbach D, Odin G, et al. The role of radiation therapy in pediatric mucoepidermoid carcinomas of the salivary glands. The Journal of pediatrics. 2013;162:839-43.

[134] Brady JS, Chung SY, Marchiano E, Eloy JA, Baredes S, Park RCW. Pediatric head and neck bone sarcomas: An analysis of 204 cases. International journal of pediatric otorhinolaryngology. 2017;100:71-6.

[135] Trosman SJ, Krakovitz PR. Pediatric maxillary and mandibular tumors. Otolaryngologic clinics of North America. 2015;48:101-19.

[136] Huh WW, Fitzgerald N, Mahajan A, Sturgis EM, Beverly Raney R, Anderson PM. Pediatric sarcomas and related tumors of the head

and neck. Cancer treatment reviews. 2011;37:431-9.

[137] Peng KA, Grogan T, Wang MB. Head and neck sarcomas: analysis of the SEER database. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2014;151:627-33.

[138] Daw NC, Mahmoud HH, Meyer WH, Jenkins JJ, Kaste SC, Poquette CA, et al. Bone sarcomas of the head and neck in children: the St Jude Children's Research Hospital experience. Cancer. 2000;88:2172-80.

[139] Ottaviani G, Jaffe N. The epidemiology of osteosarcoma. Cancer treatment and research. 2009;152:3-13.

[140] Alam K, Khan R, Jain A, Maheshwari V, Agrawal S, Chana RS, et al. The value of fine-needle aspiration cytology in the evaluation of pediatric head and neck tumors. International journal of pediatric otorhinolaryngology. 2009;73:923-7.

[141] Gibson SE, Prayson RA. Primary skull lesions in the pediatric population: a 25-year experience. Archives of pathology & laboratory medicine. 2007;131:761-6.

[142] Patel SG, Meyers P, Huvos AG, Wolden S, Singh B, Shaha AR, et al. Improved outcomes in patients with osteogenic sarcoma of the head and neck. Cancer. 2002;95:1495-503.

[143] Gadwal SR, Gannon FH, Fanburg-Smith JC, Becoskie EM, Thompson LD. Primary osteosarcoma of the head and neck in pediatric patients: a clinicopathologic study of 22 cases with a review of the literature. Cancer. 2001;91:598-605.

[144] Fernandes R, Nikitakis NG, Pazoki A, Ord RA. Osteogenic sarcoma of the jaw: a 10-year experience. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons. 2007;65:1286-91.

[145] Allison DC, Carney SC, Ahlmann ER, Hendifar A, Chawla S, Fedenko A, et al. A meta-analysis of osteosarcoma outcomes in the modern medical era. Sarcoma. 2012;2012:704872.

[146] Sun Y, Liu X, Pan S, Deng C, Li X, Guo Q. Analysis of imaging characteristics of primary malignant bone tumors in children. Oncology letters. 2017;14:5801-10.

[147] Costelloe CM, Madewell JE. Radiography in the initial diagnosis of primary bone tumors. AJR American journal of roentgenology. 2013;200:3-7.

[148] Kaste SC. Imaging pediatric bone sarcomas. Radiologic clinics of North America. 2011;49:749-65, vi-vii.

[149] Klein MJ, Siegal GP. Osteosarcoma: anatomic and histologic variants. American journal of clinical pathology. 2006;125:555-81.

[150] Chui MH, Kandel RA, Wong M, Griffin AM, Bell RS, Blackstein ME, et al. Histopathologic Features of Prognostic Significance in High-Grade Osteosarcoma. Archives of pathology & laboratory medicine. 2016.

[151] Nie Z, Peng H. Osteosarcoma in patients below 25 years of age: An observational study of incidence, metastasis, treatment and outcomes. Oncology letters. 2018;16:6502-14.

[152] Kaste SC, Fuller CE, Saharia A, Neel MD, Rao BN, Daw NC. Pediatric surface osteosarcoma: clinical, pathologic, and radiologic features. Pediatric blood & cancer. 2006;47:152-62.

[153] Price CH, Zhuber K, Salzer-Kuntschik M, Salzer M,

Willert HG, Immenkamp M, et al. Osteosarcoma in children. A study of 125 cases. The Journal of bone and joint surgery British volume. 1975;57:341-5.

[154] Smeele LE, van der Wal JE, van Diest PJ, van der Waal I, Snow GB. Radical surgical treatment in craniofacial osteosarcoma gives excellent survival. A retrospective cohort study of 14 patients. European journal of cancer Part B, Oral oncology. 1994;30b:374-6.

[155] Huh WW, Holsinger FC, Levy A, Palla FS, Anderson PM. Osteosarcoma of the jaw in children and young adults. Head & neck. 2012;34:981-4.

[156] Chen Y, Shen Q, Gokavarapu S, Lin C, Yahiya, Cao W, et al. Osteosarcoma of head and neck: A retrospective study on prognostic factors from a single institute database. Oral oncology. 2016;58:1-7.

[157] Guadagnolo BA, Zagars GK, Raymond AK, Benjamin RS, Sturgis EM. Osteosarcoma of the jaw/craniofacial region: outcomes after multimodality treatment. Cancer. 2009;115:3262-70.