Rare Head and Neck Cancers

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Key Points

- Rare head and neck cancers can be divided into those arising from epithelial (e.g., esthesioneuroblastoma, mucosal melanoma), nervous (e.g., malignant nerve sheath tumors), and soft and connective tissue (e.g., sarcomas) origin.
- Most of these rare cancers affect older adults, although rhabdomyosarcoma and Ewing's sarcoma are typically pediatric malignancies, and esthesioneuroblastoma can present across age groups.
- These pathologies have varying natural histories: while mucosal melanoma, neuroendocrine carcinomas, and certain sarcomas are aggressive and have poor survival rates, others like chondrosarcoma and Ewing's sarcomas have excellent prognosis.
- Many of these tumors are optimally treated with surgical resection with negative margins with or without adjuvant therapy; however, patients with extensive tumors involving critical structures and patients with metastatic spread are often treated non-operatively.
- The lack of large scale data detailing these rare pathologies poses a challenge in terms of standardized staging systems and treatment algorithms, especially as less invasive and potentially more efficacious treatment options like immunotherapy, targeted therapy, and stereotactic radiosurgery are increasingly introduced into practice.

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Exemplar Case

A 19-year-old man with 1.5 pack-year smoking history presented with progressive discomfort of the right jaw. Over a period of about 6 months he noticed the development of a 5 cm subcutaneous, fixed, mildly tender right-sided facial mass. A biopsy was consistent with synovial cell sarcoma. He had full facial nerve function bilaterally at the time of presentation. Imaging with CT, MRI, and a full-body PET scan at the time of diagnosis showed a large, destructive lesion of his right face extending over the mandible and invading the masticator space, parapharyngeal space, right maxilla, infratemporal fossa, and pterygoid space.

Medical Oncology and Radiation Oncology recommended neoadjuvant chemoradiation before surgical resection. He tolerated his neoadjuvant therapy well and then underwent segmental mandibulectomy, resection of right masseteric space, parapharyngeal space, infratemporal fossa, and skull base with parotidectomy and right facial nerve dissection, and limited right neck dissection as well as reconstruction of the mandible with a free fibular flap. Significant manipulation of the facial nerve branches were required to free the tumor, although at the end of the case all branches were structurally intact. His pathology did show positive margins.

He then tolerated adjuvant chemoradiation well and had partial return of facial movement on the right side of his face postoperatively although he had expected numbness in the V3 distribution.

Approximately 3.5 years after initial diagnosis he was found to have a new pulmonary nodule on surveillance chest imaging. This nodule was resected and found to be metastatic synovial cell carcinoma. He has not had any further evidence of metastasis since and continues to undergo serial surveillance imaging.

Introduction

The specialized tissues in the head and neck allow for an array of mechanical and sensory functions; however, this cellular diversity also provides a wide spectrum of potential malignancies. While the majority of head and neck cancers arise from epithelial cells, specifically the squamous cell mucosa of the aerodigestive tract [1], less common malignancies arise from specialized epithelia, as well as connective, muscle, nervous, and endocrine tissue.

In this chapter, we cover these rare head and neck malignancies, organized by the cell type of origin. We combine malignancies arising from muscle and connective tissue given the nonspecific derivation of sarcomas arising broadly from soft tissue origin, and include malignancies which affect pediatric populations given head and neck surgeons may be involved in care for these patients in addition to pediatric otolaryngologists. We focus specifically on natural history, diagnosis, and management for these pathologies and include pertinent elements of epidemiology; management strategies are summarized in Table 13.1. As precision medicine is increasingly integrated into head and neck cancer treatment along with less invasive radiation-based treatment options, we give special attention to emerging literature in these areas, allowing potentially both for greater treatment efficacy and less morbidity. Given the extensive breadth of rare head and neck malignancies, this chapter is not meant to be all-inclusive and covers those pathologies more frequently encountered within this group.

Table 13.1 Management modalities by pathology: Given the rarity of these pathologies and the lack of standardized treatment regimens, treatment modality supported by highest level of evidence and most commonly described in the available literature is included in the table. "+/−" is meant to reflect both the variability in whether adjuvant therapy may be warranted in patients (e.g., only in patients with positive surgical margins) and the overall uncertainty of benefit of adjuvant therapies in these pathologies

Pathology	Treatment
Esthesioneuroblastoma	Early stage: Radiation alone
	Late stage: Surgical resection +/− adjuvant radiation
Mucosal melanoma	Surgical resection + adjuvant radiation
Neuroendocrine carcinoma	Surgical resection +/− adjuvant chemotherapy and/or radiation versus chemoradiation alone
Chondrosarcoma	Surgical resection or debulking
Osteogenic sarcoma	Surgical resection +/− adjuvant radiation with or without chemotherapy
Synovial cell sarcoma	Surgical resection + adjuvant chemotherapy and/or radiation
Ewing's sarcoma	Surgical resection +/− adjuvant radiation
Rhabdomyosarcoma	Chemotherapy + surgical resection or chemoradiation alone if unresectable
Leiomyosarcoma	Surgical resection +/− adjuvant radiation
Angiosarcoma	Surgical resection + chemoradiation or chemoradiation alone if unresectable
Liposarcoma	Surgical resection +/− adjuvant radiation and/or chemotherapy
Kaposi sarcoma	Antiretroviral therapy + chemotherapy; surgical resection reserved for symptomatic localized or minimally aggressive cases
Teratocarcinosarcoma	Surgical resection +/− adjuvant radiation and/or chemotherapy
Malignant nerve sheath tumors	Surgical resection +/− adjuvant radiation or chemotherapy
Malignant paraganglioma	Surgical resection +/− adjuvant radiation

Epithelial Tissue

Head and neck cancers arising from epithelial cell lines are by far the most common malignancies in this region, dominated by squamous cell carcinoma [1]. The epithelium in the head and neck not only is exposed to the potential toxins both from the environment (e.g., inhaled irritants, human papilloma virus) and the body itself (e.g., refluxed gastric acid, trauma from teeth), but is forced to regenerate upon injury or chronic inflammation, providing an opportunity for uncontrolled growth if cellular mechanisms to prevent this process are disrupted. Integration of sensory organs and neurons as well as endocrine glands increases the complexity of the epithelial layers in this region.

Esthesioneuroblastoma

Arising from the olfactory neuroepithelium, esthesioneuroblastoma occurs in 1 per 2.5 per million people and generally presents in a bimodal fashion in either the second or sixth decade of life, although rare pediatric presentations have been reported as well [2]. These tumors can fill the nasal cavity and extend into nearby structures, such as the orbits and intracranially ([3], [Fig. 13.1]), and most commonly present as an obstructing nasal mass causing headaches, congestion, and epistaxis although metastatic neck masses are possible at the time of presentation. Histological examination of this tumor is notable for neurosecretory granules with neurofilaments and microtubules along with clas-

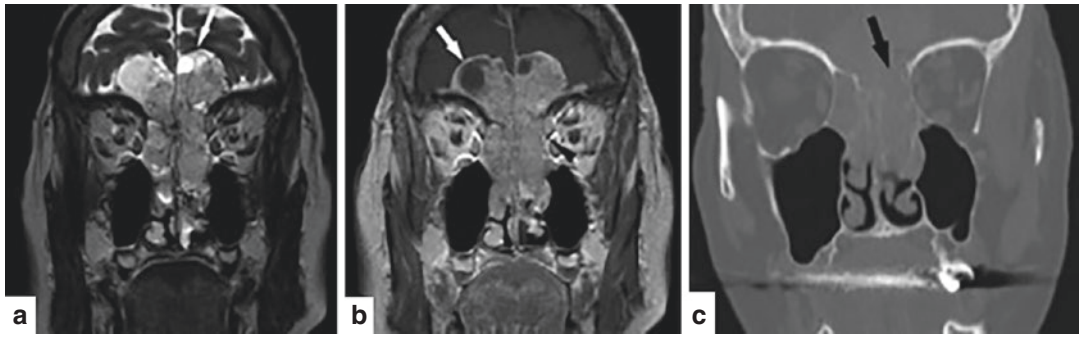

Fig. 13.1 Esthesioneuroblastoma. A 70-year-old female who presented with nasal congestion. (**a**) Coronal T2-weighted MR image shows a bulky lobulated mass of intermediate T2 signal in bilateral nasal cavities with intracranial extension. Note the cysts at the leading edge of the intracranial component (arrow), a characteristic feature of esthesioneuroblastoma when extending intracranially. (**b**) Coronal contrast-enhanced T1-weighted MR image shows homogeneous avid enhancement of the mass except in the cysts at the leading edge (white arrow). Note extension of the mass to the left orbit abutting the left superior oblique muscle (black arrowhead), suggesting invasion of the periorbita. (**c**) Coronal CT image in bone algorithm shows bony erosion of the ethmoid septations and ethmoid roof (arrow)

sic pathological features of high nucleus to cytoplasm ratio and scant, poorly defined cytoplasm [4]. Esthesioneuroblastomas are assessed based on their histological grade with the Hyams grading system which correlates with prognosis and disease-free survival [5].

Multiple meta-analyses and systemic reviews focus on treatment options given these tumors are chemo- and radio-sensitive as well as potentially amenable to surgical resection [6–8]. Current data suggests that early stage tumors can be treated with radiotherapy alone, while more extensive tumors require surgery. In terms of surgical management, subtotal endoscopic resection followed by adjuvant radiation is in many treatment centers replacing attempted total resection; for example, endoscopic endonasal surgery is recommended for low grade tumors due to its lower morbidity. Other more invasive approaches can also be used for resection, including a transcranial approach with lumbar drain placement and bifrontal craniotomy, or for more extensive tumors crossing midline, a Draf III frontal sinus approach. And while both pre- and post-operative radiation have been shown to improve surgical outcomes, there is again no standard management algorithm to clarify optimal timing of different treatment modalities. In patients who present with cervical disease, upfront neck dissection and adjuvant radiation treatment seem to be beneficial, although adjuvant chemotherapy may also play a role in preventing nodal recurrence after surgery. Newer treatment modalities like stereotactic radiosurgery as well as proton-beam therapy appear promising. Given the recent finding of frequent expression of somatostatin receptor 2a in these tumors, there is also potential for diagnosis with radioreceptor techniques as well as treatment with somatostatin analogues [4].

Recurrence rates vary widely (from 0% to 86%) across studies, and also vary based on initial tumor stage as well as treatment modality [4]. Post-treatment, these tumors have an average time of recurrence of 2–6 years, although tumors can recur up to 19 years after treatment [9]. Given these late recurrences, serial MRIs [3] as well as yearly chest radiographs [10] should be done to monitor metastases. Survival is similarly dependent both on tumor grade and extent as well as treatment modality. Five-year overall survival for patients undergoing combined chemoradiation alone and surgical resection alone may be similar—51% [6] versus 48–78% [4]. Survival in this time interval may be improved with the addition of adjuvant treatment to surgery, as surgical resection with adjuvant radiation has a reported 5-year survival rate of 65–75% [4].

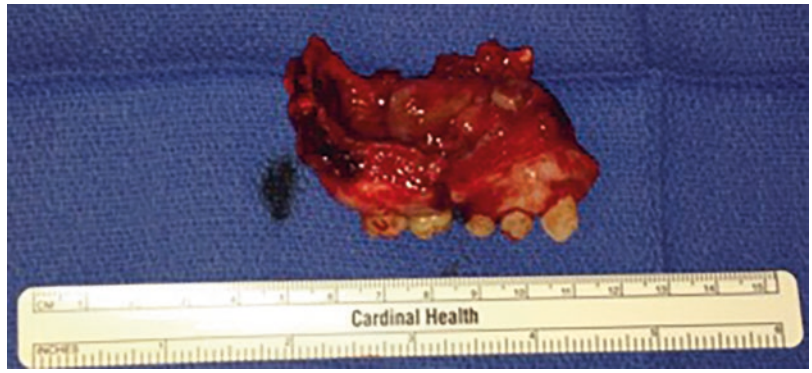

Fig. 13.2 Sinonasal mucosal melanoma: Specimen from a partial maxillectomy with mucosal melanoma arising from the floor of the right maxillary sinus

Mucosal Melanomas

Arising from melanocytes and most commonly in the nasal cavity, paranasal sinus, and oral cavity [11], mucosal melanoma (MM) is an exceedingly rare and aggressive tumor, with a reported incidence in Europe of 1 per 660,000 [12]. Smoking and exposure to formaldehyde may be risk factors [13, 14], as well as advanced age and male gender [12]. Presentation varies with the primary tumor site, as patients may present with signs and symptoms of nasal obstruction, epistaxis, facial pain and may have a polypoid, fleshy and pigmented lesion (Fig. 13.2) with possible surrounding satellite lesions up to centimeters away from the main tumor. Similar to other pathologies described in this chapter, no specific staging system exists for mucosal melanoma [15].

Multiple meta-analyses note that surgery with adjuvant radiation is optimal treatment for locoregional control, as the addition of radiation to surgery decreases local recurrence rates and has moderate survival benefit [16–18]. Radiation is recommended for patients with unresectable tumors, and immunotherapy may be a potential option for control of distant metastases [17]. While the use of targeted therapies is widespread in cutaneous melanoma, the pathophysiology of mucosal melanoma is, in contrast, poorly understood. MM has been excluded from many clinical trials in cutaneous melanoma, and thus data is limited for the use of molecular targeted therapies in MM. Additionally, response of MM to immunotherapy agents like ipilimumab is largely unknown [15]. Unfortunately, prognosis for mucosal melanoma is poor: 1-year, 3-year, and 5-year survival rates are 63%, 30%, and 20%, respectively [12].

Neuroendocrine Carcinomas

Because neuroendocrine tumors have dual tissue origin, they have historically been divided between those of epithelial versus neuronal origin (e.g. paragangliomas or olfactory neuroblastomas) [19]. We cover the former in this section. Per a proposal from the International Agency for Research on Cancer (IARC) and World Health Organization (WHO), these epithelial-derived tumors are classified as well-differentiated (typical carcinoids), moderately differentiated (atypical carcinoids), or poorly differentiated tumors. These latter tumors are referred to collectively as neuroendocrine carcinomas (NECs), and can be further divided into small or large cell tumors histologically [20]. Analysis with immunohistochemical markers is the hallmark for diagnosis [21]. Given the rarity of NECs in the head and neck, the available data to describe their presentation and outcomes is generally from small case series which either differentiate between small and large cell tumors or collectively group all NECs together.

Small cell NECs have an array of presentations, as they have been documented arising in an array of head and neck sites, including the oral cavity, nasopharynx, oropharynx, hypopharynx, and paranasal sinuses [22, 23]. Large cell

NECs again present broadly and have been reported in the oropharynx, sinonasal tract, and larynx [24].

Because there is not a standardized treatment algorithm for NECs as a whole, and because NEC presents in multiple sites with varying ability to completely resect, patients in these studies have undergone an array of treatment regimens, from surgical resection with and without adjuvant treatment to radiation and chemotherapy alone. Even within patients with identical tumor sites, treatment modalities vary across and within studies. However, there is growing evidence that treatment of NECs must be more aggressive and involve chemoradiotherapy as opposed to their lower grade counterparts, typical and atypical carcinoids, which may be addressed with surgery alone [25]. One recent meta-analysis, in fact, suggested that combined chemoradiotherapy yielded the best disease-specific survival for patients with laryngeal small cell NEC instead of surgery, radiation, or chemotherapy alone [26]. In contrast, another meta-analysis recommended sinonasal NECs be treated with surgery alone and with supplemental radiotherapy only in poorly differentiated tumors, as chemotherapy did not appear to influence survival [27].

Both small and large cell carcinomas of the head and neck are aggressive cancers and characterized by widespread metastases [22, 24]; in fact, one meta-analysis found almost 70% of patients with small and large cell carcinomas of the larynx had metastases at the time of presentation [26]. Survival rates for small cell NEC have been reported as 56% and 36% at 1 year and 3 years, respectively [22]. Five-year survival has been reported as low as 10% [23]. Large cell carcinoma similarly has a reported 5-year disease-free survival of 15% [28].

While current survival rates are poor, the understanding of the pathophysiology and treatment for these tumors is evolving—interestingly, tumors which show evidence of human papilloma virus (HPV) infection have been shown in a small study to be associated with better prognosis amongst a group of patients with poorly differently head and neck NEC [29]; additionally, there is increasing interest in the expression of PD-1 in these pathologies and potential use of immunotherapies as treatment [30].

Connective and Muscle Tissue

Malignant tumors arising from connective tissue and muscle (sarcomas) are both rare and aggressive tumors with poor survival and warrant evaluation by medical oncologists who specialize in sarcoma treatment.

Chondrosarcoma

Chondrosarcoma, which arises from chondroid matrix in cartilage, soft tissue, or bone, represents only 0.1% of head and neck neoplasms [31]. The most common primary sites include mandible, larynx, nasal cavity, sinus, and maxilla [31, 32]. Chondrosarcoma arising from cartilaginous or soft tissue origin is more common in males over 50 years of age and in women less than 50. Patients may present with an array of symptoms related to their primary site: for example, patients with paranasal sinus primaries presenting with ocular symptoms, or patients with jugular foramen primary tumors presenting with facial swelling. Invasion into surrounding neurological structures may be seen at the time of presentation—for example, tumors arising from the mastoid may present with ipsilateral facial paralysis. Patients with laryngeal involvement may present solely with a neck mass [33] or with voice changes (Fig. 13.3). On histological assessment, chondrosarcomas can be difficult to diagnose given they have varying histological appearance from benign chondroid tumor to undifferentiated neoplasm [34]. A histological grading system developed by Evans et al. can be used which may correlate with recurrence rates [33].

While there is not high-level evidence comparing treatment regimens for chondrosarcoma of the head and neck as a whole, a review of the American College of Surgeons' National Cancer Database in 2000 described surgery as the mainstay of treatment for this malignancy, with some patients additionally undergoing adjuvant radia-

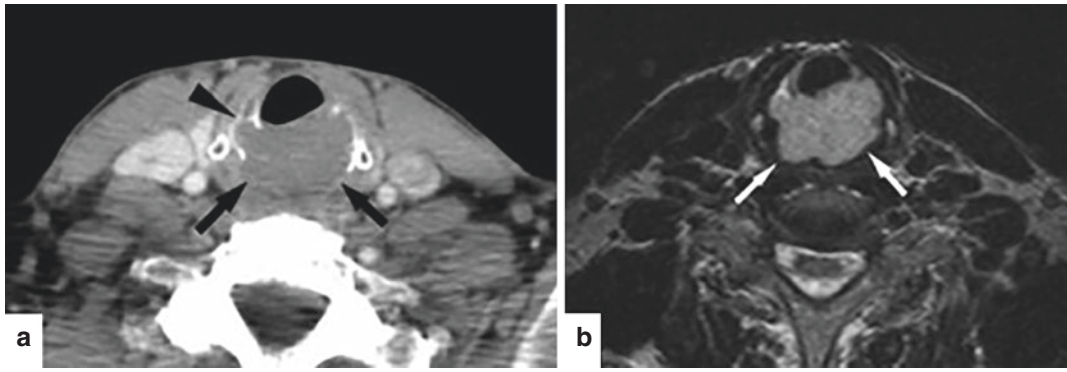

Fig. 13.3 Cricoid chondrosarcoma. A 64-year-old male with hoarseness. (**a**) Axial contrast-enhanced CT image in soft tissue algorithm shows an expansile relatively hypodense lesion involving and destroying the posterior cricoid ring (arrows). Note the sharp, well-defined, scalloped margin (arrowhead) and normal cricoid cartilage anteriorly (**b**) Axial T2-weighted MR image shows high T2 signal of the mass, characteristic of a chondroid lesion. Surgical pathology revealed a grade 1 chondrosarcoma

tion [31]. Technique of surgical resection is dependent on primary tumor site and size—for example, laser and robotic resections may be appropriate in patients with epiglottic lesions. Because chondrosarcoma is slower growing and less likely to metastasize than most cancers, subtotal debulking may be utilized, especially in areas with high morbidity like the larynx. In fact, a more recent systematic review of laryngeal chondrosarcoma reflected the important role of surgical treatment, with less than 1% of patients studied undergoing either radiation or chemotherapy [35]. Survival rates for head and neck chondrosarcoma are generally favorable, with literature quoting survival rates of 70–87.5% (with variable follow-up durations) [32, 33].

Osteogenic Sarcoma

Sarcomas arising from bone origin include both osteosarcoma, arising from mesenchymal cells producing osteoid and immature bone, and fibrosarcoma, arising from fibroblasts [36]. These tumors can occur both spontaneously and after prior head and neck radiation—this radiation-induced sarcoma of the head and neck reportedly occurs in 0.15% of patients with a mean interval between radiation and occurrence of 11 years. The most common radiation-induced sarcomas are osteosarcomas in the nasopharynx [37]. Osteosarcomas a whole account for approximately 1% of all head and neck cancers, and generally arise in the maxilla or mandible in patients in their fourth decade.

Optimal treatment for osteo- and fibrosarcomas is complete resection with consideration for adjuvant radiotherapy in patients with close or positive margins. While in a prior meta-analysis the role of adjuvant chemotherapy appeared unclear in osteosarcomas of the head and neck [38], a recent study suggested there may be a benefit for patients with maxillary tumors, positive surgical margins, or high-grade tumors [39]. The 5-year disease-specific and overall survival rates are approximately 60–70%, and if patients do have a recurrence, most are within 5 years [40]. Although data is limited, fibrosarcoma appears to have similar recurrence and survival rates as osteosarcoma [36].

Synovial Cell Sarcoma

Also arising from mesenchymal cells, and named after their histologic resemblance to the synovium, synovial sarcomas (SS) usually arise in the extremities, although they can be found in head and neck and compose about 3% of head and neck sarcomas [41]. These head and neck SS arise most commonly in men during middle age, and have been reported in a variety of loca-

tions, including face, oral cavity, pharynx, larynx, oral cavity, and other soft tissues of the neck, and can present with hoarseness, dysphagia, odynophagia, and bleeding [42]. Rarely orbital involvement has been reported [43]. These tumors are divided into monophasic and biphasic tumors depending on the presence of an epithelial component in addition to a spindle cell component (versus a spindle cell component alone), and almost all (90%) tumors exhibit chromosomal translocation t(X; 18), resulting in a fusion gene product between the two genes, synaptotagmin1 gene, *SYT1* and either SSX family member 1 or 2 genes, *SSX1* and *SSX2*, respectively [41].

These tumors are treated with surgical excision with adjuvant treatment with radiation or chemotherapy [42, 44]. More studies and higher level evidence is needed to clarify which patients may benefit from adjuvant therapy. One study suggests chemotherapy as a treatment option in high-risk surgical candidates given the chemosensitivity of these tumors [41]. Synovial cell sarcomas have high rates of metastasis to the lungs and have survival rates at 10 years of less than 50% [45], although head and neck synovial cell sarcomas may have better survival rates up to 82% [46].

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children and is derived from mesenchymal cells not yet differentiated into skeletal muscle; about 40% of RMS present in the head and neck [47]. These tumors are generally divided into those in parameningeal (nasopharynx, nasal cavity, paranasal sinus, infratemporal and pterygopalatine fossa, middle ear) and nonparameningeal locations (all other sites) and present with a variety of symptoms. Given that parameningeal tumors can spread along the dura and encase vessels, many patients have cranial nerve deficits and skull base erosion and orbital involvement at the time of presentation (Fig. 13.4). MRI is an essential in characterizing dural involvement, involvement of orbital structures, and perineural spread in these tumors, and FDG PET can elucidate the extent of metastatic disease [48].

Treatment includes a combination of chemotherapy as well as local control with surgery or radiation [49]. Nonparameningeal tumors may be entirely resectable, but because of the extent of disease at presentation, many patients with parameningeal tumors may not have resectable disease [48]. While there are no meta-analyses

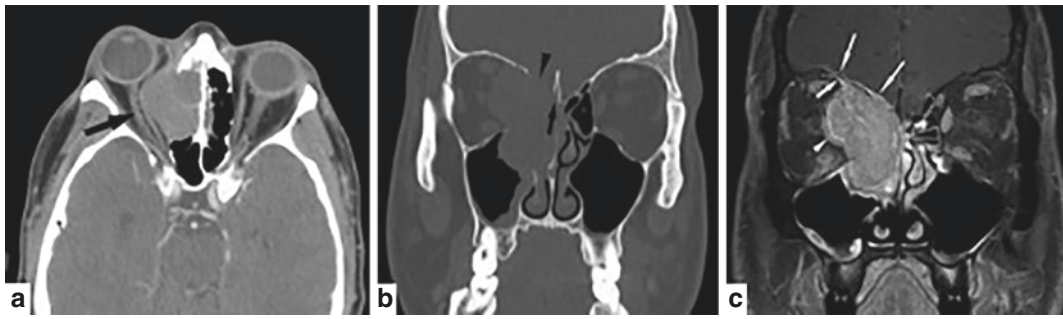

Fig. 13.4 Sinonasal rhabdomyosarcoma. A 34-year-old male who presented to the emergency department with right proptosis and nasal congestion. (**a**) Axial contrast-enhanced CT image in soft tissue algorithm shows a bulky lobulated mass in the right ethmoid region bulging laterally through eroded bone into the right orbit, displacing the medial rectus and optic nerve (arrow) laterally and causing right proptosis. (**b**) Coronal CT image in bone algorithm demonstrates bony destruction around the margins of the mass, including the right lamina papyracea, right orbital floor, floor of the right anterior cranial fossa (arrowhead), and the right aspect of the crista galli (arrow). (**c**) Coronal contrast-enhanced T1-weighted MR image shows avid homogeneous enhancement of the mass. There is right orbital invasion, with tumor extending along the orbital roof (small arrow) and displacing the medial rectus muscle laterally (small white arrowhead). It crosses midline to the left (black arrowhead), and there is intracranial involvement as evidenced by thickened dural enhancement (long arrows)

defining optimal treatment regimens for head and neck RMS, a recent pooled analysis in parameningeal RMS noted patients who received radiation as part of their initial treatment regimen exhibited better survival at 5 and 10 years than patients without radiation early in their treatment course [50]. Prognosis varies broadly with histologic, genetic, as well as anatomical factors of tumors along with extent of disease at presentation. For example, patients with nonparameningeal disease without metastases have reported survival rates up to 100% at 3 years [48] while the overall survival for patients with metastatic disease is 39% [51].

Ewing Sarcoma

In contrast to osteosarcoma, Ewing's sarcoma, a tumor of small round cells arising from soft tissue, most frequently affects children and adolescents and can present in the skull, mandible, and maxilla. Although it is the second most common primary bone malignancy in these age groups [52], only 1–15% of Ewing's sarcomas are found in the head and neck [53]. Treatment generally consists of adjuvant chemotherapy followed by local treatment with surgical resection or radiation combined with consolidation or maintenance chemotherapy. While data for head and neck Ewing's tumor is limited, a recent meta-analysis of patients with Ewing's sarcoma across all sites (all of whom underwent neoadjuvant chemotherapy) showed improved outcomes in terms of local recurrence and survival rates in patients who underwent surgery alone and surgery with adjuvant radiation than in patients who underwent radiation alone [54]. Risk factors for recurrence include metastases at the time of diagnosis, poor histological response to therapy, and large tumor size. In contrast to osteosarcoma, the survival rates of Ewing's sarcoma in the head and neck are favorable—up to 90% at 5 years. However, long-term sequelae from treatment is common (occurring in up to 88% of patients) including functional deficits, growth abnormalities with facial asymmetry, aesthetic defects, psychosocial impairments, and endocrine and neurological disorders [55].

Leiomyosarcoma

In contrast to the prior two pediatric pathologies, leiomyosarcoma is a smooth-muscle derived malignancy that typically presents in the sixth or seventh decade of life. These tumors present generally as solitary nodules and can be divided based on their site of presentation into cutaneous (arising from erector pili muscles of hair follicles) and noncutaneous (arising from article tunica media) [56]. Noncutaneous tumors have been reported in a variety of head and neck sites, including oral cavity, nasopharynx, nasal cavity and sinuses, larynx and hypopharynx, as well as parotid and thyroid in rare cases. A review of the National Cancer Database in 2018 noted surgical therapy with tumor excision is the most common treatment modality used in the majority of patients, although radiation has been used both in the adjuvant and neoadjuvant setting for patients with positive surgical margins [57]. Chemotherapy may play a role in treatment, as improved local and distal recurrence has been reported in patients who underwent adjuvant chemotherapy prior to other treatment modalities [58]. Although neck metastasis is rare with this disease, prognosis overall is again poor—about half of patients survive 5 years after their diagnosis [56].

Angiosarcoma

Arising from endothelial cells lining vasculature, angiosarcoma is a rare tumor generally affecting older patients over 60 years of age [59, 60]. In the head and neck region, these tumors are found in the scalp or face although they have been reported in the larynx, hypopharynx, and sinuses as well [61]. These tumors appear as bruise-like macules with possible ulceration and palpable nodules [60]. While there is not high-level evidence specifically comparing different treatment modalities for head and neck angiosarcoma, patients with these tumors generally undergo wide surgical resection with negative margins, although this may not be possible given the microscopic subcutaneous spread of these tumors. Adjuvant therapy with chemotherapy, radiation, or combined chemoradiation treatments have all been reported

[62], with data clearly supporting the use of adjuvant radiation to improve survival [63]. Patients with unresectable tumors generally undergo chemoradiation [62]. Local recurrence rates after surgery have been reported as high as 90–94% [60, 64] and occur usually within a year of treatment, although patients with negative margins may present later with recurrences [61]. Survival rates are poor with studies reporting both 2- and 5-year overall survival rates of 20–30% [61, 64].

Liposarcoma

Liposarcomas arising from adipose tissue are malignant tumors including well-differentiated liposarcomas, as well as de-differentiated, myxoid, and pleomorphic liposarcomas [65]. Like the prior pathologies already discussed, surgery with negative margins is the ideal treatment, although adjuvant radiation as well as systemic chemotherapy have been shown to improve overall survival in high-risk patients with positive margins, high-grade, deep, and larger tumors and are recommended for these subsets of patients by the European Society for Medical Oncology (ESMO) and European Rare Cancer (EURACAN) practice guidelines from 2018 [66]. Liposarcomas of the head and neck, in comparison to lipomas in the rest of their body, are more likely present early stage, and low grade, as well as to be treated with surgery alone, and had better overall survival (approximately 80% vs. 70% overall survival at 5 years [67]).

Kaposi Sarcoma

Kaposi sarcoma is another malignancy arising in adults from mesenchymal cells lining lymphatic channels or vessels and is associated with human herpes virus 8 (HHV8) infection. While the majority of reported cases have been in patient with human immunodeficiency virus (HIV), there are also reported cases in HIV-negative patients [68]. Tumors arise in a variety of locations including the skin, oral and oropharyngeal mucosa, nasal cavity and paranasal sinuses, cervical lymph nodes, and ear (pinna and external auditory canal). While patients with tumors in the nasal cavity may present with symptoms secondary to blockage, patients with disease in the neck may present with painless neck masses with skin color changes. Mucosal and skin lesions appear as slightly raised colored spots or small purple, brown, or red lumps [69]. Although data is limited to case reports and series, HIV status may be related to tumor location, as HIV-negative patients may be more likely to have tonsillar or ear tumors, while HIV-positive may have tumors presenting more often in the oral cavity, sinuses, or neck [70]. Many patients may have multifocal disease with tumors in non-head and neck locations as well [68]. This diagnosis should be distinguished from bacillary angiomatosis which also presents as a similar vasoproliferative lesion in HIV positive patients with *Bartonella henselae* infection; immunohistochemistry, Warthin–Starry stain, and/or molecular testing can distinguish these diagnoses. Kaposiform hemangioendothelioma may also present similarly, although it presents in patients without evidence of immunodeficiency or HHV8 infection.

As described in two Cochrane reviews, the standard of treatment for adults and children is systemic therapy with chemotherapy in combination with antiretrovirals in patients with HIV. Local treatments such as surgical excision, freezing, or radiation are reserved only for symptomatic localized or minimally aggressive cases [71, 72]. Although immune-modulating agents like interferon (IFN) have been used in the past with variable tolerance [73], data is now growing regarding the use of immune checkpoint inhibitors like nivolumab and pembrolizumab, which may have efficacy in achieving partial response in patients [74]. Prognosis of this tumor is difficult to discern from existing data as many patients in these studies have a concurrent AIDS diagnosis and thus poor survival prior to tumor diagnosis [69].

Teratocarcinosarcoma

Teratocarincosarcoma is a rare and aggressive tumor found primarily in the sinonasal region.

These tumors are morphologically heterogeneous and have multiple components on histological examination including benign respiratory-type epithelium, malignant glands resembling adenocarcinoma, squamous differentiation including fetal-type, primitive neuroepithelium, and mesenchymal components [75]. They present most commonly in middle aged men in the sinonasal region with nasal obstruction and epistaxis [75, 76], although they have also been reported as a congenital tumor presenting in the nasopharynx of an infant with the congenital absence of the ipsilateral Eustachian tube [77].

Much of the data on this malignancy is from small case series and reports, describing treatment most commonly with a combination of surgery and radiation although with limited success [75, 76, 78]. A recent meta-analysis in fact found up to 67% of patients treated with surgery and 80% of patients treated initially with radiation had recurrence, metastasis, or were unresponsive to treatment [79]; this study noted, however, that of the patients who did survive to 1 year post-diagnosis, the majority (70%) had undergone combined surgery and adjuvant therapies, supporting the use of aggressive treatment regimens. A recent small study explored the use of neoadjuvant chemotherapy in patients with large and unresectable tumors at presentation [80]; although both patients described in this study were noted to be asymptomatic post-treatment, follow-up ranged only 2–3 months, so more studies with longer-term follow-up are needed to confirm its efficacy. Given the ability of these tumors to spread rapidly intracranially and have high rates of recurrence, less than half of patients survive to 3 years post diagnosis even with aggressive treatment [81].

Nervous Tissue

Nervous tissue in the head and neck consists of autonomic nerve fibers as well as sensory and motor nerves and their surrounding supportive cells. We cover malignancies derived from these tissues below, as we include neuroendocrine and neuroepithelial malignancies in the first section.

Malignant Nerve Sheath Tumors

Malignant nerve sheath tumors arise in the peripheral nervous system although they are considered a type of soft tissue sarcoma. They are most commonly associated with neurofibromatosis type 1 (in 50–60% of patients) and less commonly occur after prior radiation exposure or sporadically [82] Patients are diagnosed generally between the third and seventh decade of life. Traditionally these tumors have been treated with surgical excision, as the role of adjuvant radiation and chemotherapy is unclear [83, 84]. A recent meta-analysis investigating prognostic factors for malignant peripheral nerve sheath tumors found that chemotherapy and radiation therapy individually were associated with patients with better survival [85]; however, more studies are needed to define this benefit and clarify which subsets of patients with these tumors may benefit from adjuvant treatment. Survival overall for these tumors is poor, with 5-year rates between 35% and 65%. Current staging system is likely inadequate for prognostication. Interestingly, patients of extremes of age (patients younger than 40 or older than 60) and patients with larger tumor size are at higher risk of worse outcomes [86].

Paraganglioma

Paragangliomas are tumors arising from the ganglia of the paraganglion system throughout the body, and most are benign and occur in the adrenal paraganglia. However, 3% of these tumors occur in the head and neck [87], arising most commonly in the carotid body, jugular foramen (Fig. 13.5) and along the vagus nerve, although they can occur in the larynx, nasal cavity, orbit, trachea, aortic body, and mediastinum [88]. About 9–19% of head and neck paragangliomas are malignant [89, 90], as certain mutations in the gene encoding the enzyme succinate dehydrogenase (SDH) may deem these tumors higher risk for malignant transformation [91]. We focus on this important distinction between benign and malignant paragangliomas later in this section.

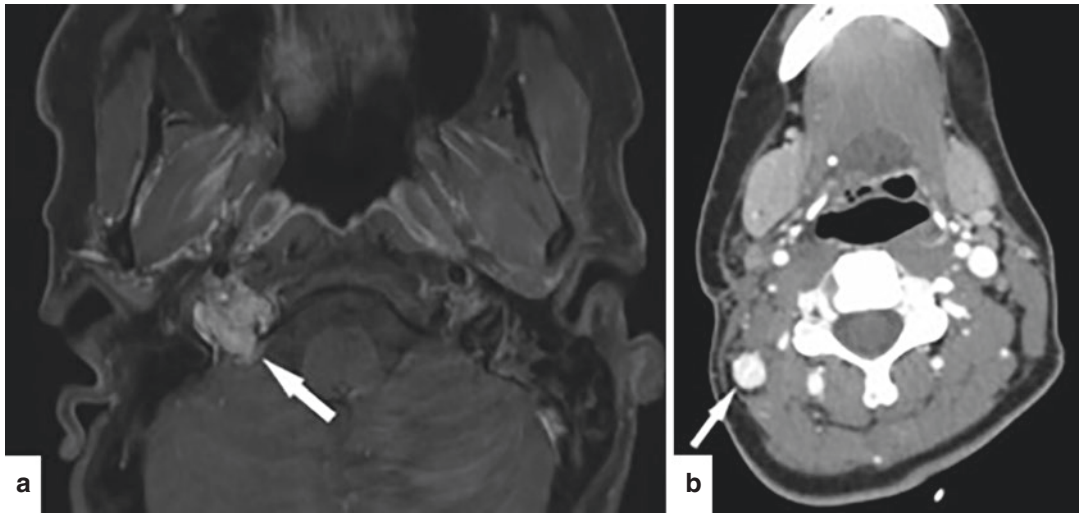

Fig. 13.5 Metastatic paraganglioma. A 33-year-old female with a right jugular foramen paraganglioma (glomus jugulare). (**a**) Axial contrast-enhanced T1-weighted MR image shows an avidly enhancing mass in the right jugular foramen (arrow) representing a paraganglioma. (**b**) Axial contrast-enhanced CT image in soft tissue algorithm shows an avidly enhancing soft tissue nodule (arrow). Surgical resection of this nodule was performed, with pathology revealing paraganglioma involving a lymph node and considered highly indicative of metastatic disease

Patients with paragangliomas, both benign and malignant, may present with neck masses or cranial neuropathies depending on the location of the tumor—vagal tumors may present with difficulty speaking or swallowing, while jugular foramen tumors may present with hearing loss, shoulder weakness and pain, or facial paralysis. Workup of these tumors includes a detailed history and physical exam including laryngoscopy to assess vocal fold motion, as well as imaging with a CT, MRI, or MRA to assess tumor relationship to surrounding vasculature. Patients may additionally undergo testing with plasma or urine catecholamines, metanephrines, chromogranin A, and vanillylmandelic acid (VMA) to assess functional status of these tumors, as up to a third of both benign and malignant paragangliomas can secrete catecholamines [89, 92]. Chromogranin A, often secreted with catecholamines, can be monitored throughout a patient's course as a marker of secretory function [93]. Patients with malignant paragangliomas may also present with evidence of regional or distant metastases.

Treatment for both malignant and secretory paragangliomas is surgical excision [89]. However, given the extensive vascularity of these tumors and their proximity to cranial nerves, these surgeries often have significant associated morbidity both intraoperatively in terms of blood loss and postoperatively in terms of patient quality of life. Thus special preoperative considerations may be taken into account: for example, if carotid artery resection or reconstruction is considered, preoperative carotid artery balloon occlusive testing with single-photo emission CT may be used to evaluate cerebral perfusion [91]. Prior to resection of jugular foramen and high vagal tumors preoperative embolization is recommended—while this has been shown to reduce blood loss intraoperatively, strokes and cranial neuropathies have also been reported with its use [94].

Importantly, benign and malignant paragangliomas cannot be differentiated preoperatively based on cytological, histological, immunohistochemical, or molecular criteria given they are indistinguishable in these assays; however, lymph node tissue obtained intraoperatively can provide this diagnosis [89]. Thus traditionally selective neck dissection has been recommended for patients with evidence of metastasis noted [95].

However, a recent review suggests selective neck dissection in all patients in order to avoid delay in treatment for patients who do have a malignant tumor [89, 96]. There may be additional benefit to adjuvant radiation in these patients with malignant paragangliomas [97, 98], as well as a potential role for chemotherapy in patients with metastatic or unresectable disease [99].

For patients with malignant paraganglioma, survival at 5 years has been reported to be 88.1% for patients who underwent surgical excision alone and 66.5% in patients undergoing adjuvant radiation (a nonsignificant difference in this study). Patients with carotid body tumors and younger patients (less than 50 years of age) have a survival advantage when compared to patients with other primary sites and advanced age, respectively [90].

Conclusions

The rare cancers discussed above arise from several unique and specialized tissue types in the head and neck and show significant variation in their epidemiology. Given their rarity, randomized clinical trials identifying the optimal treatment for each entity are unlikely. Best level evidence tends to be retrospective cohort studies with all of the inherent limitations thereof. Multidisciplinary treatment approaches are of paramount importance to successfully managing these rare cancers, especially given rapid innovations in targeted therapeutics and immunotherapies. Inter-institutional collaboration as well as nationwide and international databases may allow for better delineation of optimal treatment modalities, natural history, and long-term prognosis.

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