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Update from the 5th Edition of the World Health Organization Classification of Head and Neck Tumors: Soft Tissue Tumors

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Abstract
The fifth (5th) edition of the World Health Organization (WHO) Classification of Head and Neck Tumors introduces a new chapter dedicated to soft tissue neoplasms commonly affecting the head and neck. While the diversity, rarity, and wide anatomic range of soft tissue tumors precludes a discussion of all entities that may be found in the head and neck, the addition of this new chapter to the head and neck "blue book" aims to provide a more comprehensive and uniform reference text, including updated diagnostic criteria, of mesenchymal tumor types frequently (or exclusively) arising at head and neck sites. Since publication of the previous edition in 2017, there have been numerous advances in our understanding of the pathogenesis of many soft tissue tumors which have facilitated refinements in tumor classification, identification of novel entities, development of diagnostic markers, and improved prognostication. This review will provide a focused discussion of the soft tissue tumors included in the 5th edition WHO Head and Neck classification, with an emphasis on updates.

Keywords Soft tissue · Sarcoma · Immunohistochemistry · Molecular genetics · Head and neck pathology

Introduction

Soft tissue neoplasms often pose diagnostic challenges in head and neck pathology, due to their diversity and overlapping histologic spectra. A vast number of soft tissue tumors may arise throughout the upper aerodigestive tract and salivary glands, and some entities arise preferentially or nearly exclusively in specific anatomic sites. The fourth (4th) edition World Health Organization (WHO) Classification of Head and Neck Tumors (2017) [1] included a small number of relevant soft tissue tumors within each site-specific chapter. The fifth (5th) edition of the WHO Classification of Head and Neck Tumors [2] now includes a dedicated chapter for soft tissue tumors, providing a centralized and more practical reference to aid pathologists in the diagnosis of these challenging tumors. This chapter is organized by line of differentiation, mirroring the 5th edition of WHO Classification of Soft Tissue and Bone Tumors (published in 2020) [3]: adipocytic, fibroblastic and myofibroblastic, vascular, pericytic (perivascular), smooth muscle, skeletal muscle, chondro-osseous, peripheral nerve sheath, tumors of uncertain differentiation, and undifferentiated small round cell sarcomas. A small number of anatomic site-specific mesenchymal tumors remain in their respective chapters, including biphenotypic sinonasal sarcoma in "Soft Tissue Tumors of the Nasal Cavity, Paranasal Sinuses, and Skull Base" and ectomesenchymal chondromyxoid tumor in "Oral Cavity and Mobile Tongue." This review is a focused discussion of the soft tissue tumors included in the 5th edition WHO Classification of Head and Neck Tumors, with an emphasis on recent advances in our understanding of tumor pathogenesis, diagnostic and prognostic criteria, and novel immunohistochemical markers. Table 1 summarizes the molecular genetic alterations and surrogate immunohistochemical markers of included entities.

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Table 1 Molecular alterations and available surrogate immunohistochemical (IHC) markers of soft tissue tumors included in the 5th edition WHO Classification of Head and Neck Tumors

Tumor type	Molecular alterations	IHC marker
Adipocytic tumors		
Lipoma	*HMGA* rearrangement	
Angiolipoma	*PRKD2* mutation	
Spindle cell/pleomorphic lipoma	13q14 (*RB1 locus*) deletion	RB1
Atypical spindle cell/pleomorphic lipomatous tumor	Deletions of *RB1* and flanking genes	RB1
Atypical lipomatous tumor/well-differentiated liposarcoma	12q13-15 (*MDM2*) amplification	MDM2, CDK4
Dedifferentiated liposarcoma	12q13-15 (*MDM2*) amplification	MDM2, CDK4
Myxoid liposarcoma	*FUS-DDIT3* (rarely *EWSR1-DDIT3)*	DDIT3
Myxoid pleomorphic liposarcoma	Large deletions of *RB1*	RB1
Fibroblastic and myofibroblastic tumors		
Nodular fasciitis	*MYH9-USP6*	
Desmoid fibromatosis	*CTNNB1* or *APC* mutation	β-catenin
Solitary fibrous tumor	*NAB2-STAT6*	STAT6
Inflammatory myofibroblastic tumor	*ALK* rearrangements (~60%) *ROS1* rearrangements (rare)	ALK ROS1
Vascular tumors		
Epithelioid hemangioma	*FOSB* or *FOS* fusions	FOSB
Epithelioid hemangioendothelioma	*WWTR1-CAMTA1* Rare *YAP1-TFE3*	CAMTA1 TFE3 or loss of YAP1
Angiosarcoma	Heterogeneous features, including mutations in *KDR*, *PTPRB,* and *PLCG1*	
Pericytic tumors		
Myofibroma	*PDGFRB* mutation	
Skeletal muscle tumors		
Alveolar rhabdomyosarcoma	*PAX3-FOXO1* (or *PAX7-FOXO1*)	PAX3/7-FOXO1
Spindle cell/sclerosing rhabdomyosarcoma	*VGLL2* and *NCOA2* rearrangements *MyoD1* mutation	MyoD1 (diffuse)
Rhabdomyosarcoma with *TFCP2* rearrangement	*EWSR1/FUS-TFCP2* or *MEIS-NCOA2*	
Chondro-osseous tumors		
Soft tissue chondroma	*FN1-FGFR2* or *FN1-FGFR1*	
Peripheral nerve sheath tumors		
Neurofibroma	*NF1* inactivation	
Schwannoma	*NF2* inactivation	
MPNST	*NF1* inactivation, *SUZ12* or *EED* mutations	H3K27me3 loss
Tumors of uncertain differentiation		
Phosphaturic mesenchymal tumor	*FN1-FGFR1* fusion	
Myxoma	*PRKAR1A* mutation	PRKAR1A loss
Extraskeletal myxoid chondrosarcoma	*EWSR1-NR4A3*	
Synovial sarcoma	*SS18-SSX*	SS18-SSX, SSX
GLI1-altered soft tissue tumor	*GLI1* rearrangement or *GLI1* amplification	
Undifferentiated small round cell sarcomas of bone and soft tissue		
Ewing sarcoma	*EWSR1-FLI1*	
Adamantinoma-like Ewing sarcoma	*EWSR1-FLI1*	

Adipocytic Tumors

This section includes benign ("Lipoma family") and malignant ("Liposarcoma" family) entities. Lipomas are anatomically ubiquitous tumors of mature white fat, characterized by frequent *HMGA2* rearrangement [4]. Angiolipomas are driven by *PRKD2* mutations [5]. Spindle cell/pleomorphic lipoma commonly arise in the subcutis of the posterior neck, back and shoulder of adult men, and are

characterized by frequent 13q14 deletions. This deletion includes the *RB1* locus and corresponds with immunohistochemical loss of nuclear RB1 protein expression in neoplastic cells [6].

Atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLPS) and dedifferentiated-liposarcoma (DDLPS) are the most likely liposarcoma subtypes to arise in head and neck sites, often in the upper aerodigestive tract [7]. The terms ALT and WDLPS are synonyms, with the former applied to tumors in sites where curative resection is possible (e.g. limbs). In the head and neck, such tumors are almost always classified as WDLPS given that margin-negative resection is often impossible due to anatomic constraints. ALT/WDLPS can progress to DDLPS, which most frequently appears as a non-lipogenic sarcoma and encompasses a broad range of morphologic appearances. High-grade DDLPS (based on the French Fédération Nationale des Centres de Lutte Contre le Cancer grading system) and DDLPS with myogenic differentiation (specifically rhabdomyoblastic) have been associated with worse outcomes [8–11]. ALT/WDLPS and DDLPS are associated with amplification of 12q13-15 via ring and giant marker chromosomes [12], while other amplified genes may contribute to tumor biology in ways that are not fully characterized. Immunohistochemistry for proteins encoded on this amplified locus, MDM2 and CDK4 (as well as HMGA2) has been established as diagnostic tools for ALT/WDLPS and DDLPS. Most cases show nuclear staining for MDM2 and CDK4, which is highly sensitive although not entirely specific for the diagnoses, as staining (albeit more limited) can be seen in other sarcomas, particularly those with polysomy 12 or low copy number increases in 12q, such as myxofibrosarcoma and malignant peripheral nerve sheath tumor [13]. Staining may also be seen in histiocytes, and fat necrosis may pose a pitfall for misinterpretation as ALT/WDLPS [14]. Fluorescence in situ hybridization (FISH) analysis to detect *MDM2* gene amplification is considered the gold standard for ALT/WDLPS and DDLPS, being more sensitive and specific than immunohistochemistry [15], and confirmatory FISH testing is helpful in cases with equivocal or inconsistent MDM2/CDK4 staining and for cases of ALT/WDL and DDLPS arising in unusual sites.

Presentation of myxoid liposarcoma or pleomorphic liposarcoma in this anatomic region should always elicit a strong suspicion for metastasis, as both tumor types typically arise in the extremities and only rarely present primarily in the head and neck. Myxoid liposarcoma is defined by recurrent *FUS-DDIT3* fusion (or rarely *EWSR1-DDIT3*) [16, 17]. DDIT3 immunohistochemistry is highly sensitive and specific for myxoid liposarcoma, including high-grade cases showing predominant round cell morphology [18, 19]. The term “round cell liposarcoma” is no longer endorsed by the WHO Classification of Soft Tissue and Bone Tumors, as the hypercellular areas of high-grade myxoid liposarcoma are not exclusively round cell in appearance. Pleomorphic liposarcoma has no specific immunophenotype or molecular features, and is notably indistinguishable from DDLPS showing "homologous" differentiation, both having characteristic regions of pleomorphic tumor cells resembling myxofibrosarcoma or unclassified pleomorphic sarcoma with variable foci of large atypical lipoblasts [20]; MDM2 and CDK4 are negative in pleomorphic liposarcoma.

Two new adipocytic entities are introduced in this edition: atypical spindle cell lipomatous tumor/atypical pleomorphic lipomatous tumor (ASLT/APLT) and myxoid pleomorphic liposarcoma. While ASLT/APLT is included in the "Liposarcoma family," it should be noted that these tumors have only a low risk of local recurrence (~ 12%) and virtually no risk for metastasis or dedifferentiation [21–24]. ASLT/APLT are histologically diverse tumors comprised of variable proportions of adipocytes, atypical spindle cells, lipoblasts, and floret-like giant cells, with a frequently myxoid or collagenous stroma (Fig. 1). Although showing some overlapping features with spindle cell/pleomorphic lipoma, ASLT/APLT differs by its wide anatomic distribution and infiltrative growth, and may have increased nuclear pleomorphism, with or without rare atypical mitotic figures which may prompt a misdiagnosis of pleomorphic liposarcoma. *RB1* deletions (and immunohistochemical loss of nuclear

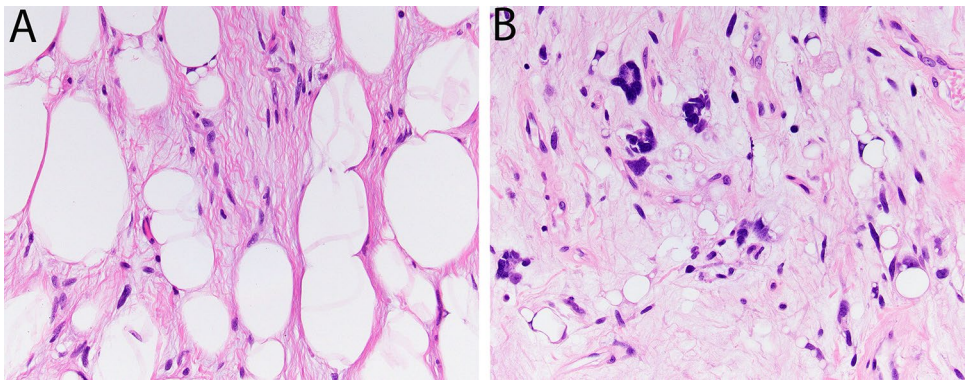

Fig. 1 Atypical spindle cell/pleomorphic lipomatous tumor. Tumors show varying proportions of admixed adipocytes, spindle cells with appreciable cytologic atypia, lipoblasts, and myxoid or collagenous stroma (**A**). Some examples show multinucleated floret-like giant cells and more abundant lipoblasts (**B**)

expression) are characteristic of ASLT/APLT, although deletions of 13q14 are larger than those seen in spindle cell/pleomorphic lipoma, and span flanking genes (including *TCBTB2, DLEU1,* and *ITM2B*) [21–23]. ASLT/APLT shows variable staining for CD34 (60%), S-100 (40%), and desmin (20%). The so-called "dysplastic lipoma" (or "anisometric cell lipoma") included in this volume is a controversial entity which likely represents a spindle cell-poor variant of ASLT/APLT, and as such was not included in the more comprehensive 5th edition Classification of Soft Tissue and Bone Tumours.

Myxoid pleomorphic liposarcoma has been reported in the head and neck, although its typical presentation is in the mediastinum of young patients [25, 26]. These tumors are aggressive and show mixed features of myxoid liposarcoma and pleomorphic liposarcoma. Diagnosis requires exclusion of characteristic molecular alterations of other liposarcoma mimics (e.g. *MDM2* amplification and *FUS-DDIT3*). Genomic studies indicate *RB1* inactivation secondary to large deletions of the 13q14 region [26, 27]. It should be noted that deletion or inactivation of the *RB1* tumor suppressor is a common event in neoplasia and its presence in multiple subsets of lipomas and liposarcomas does not necessarily indicate a pathogenic relationship or tumor evolution between benign and malignant entities.

Fibroblastic and Myofibroblastic Tumors

Tumors of fibroblastic and myofibroblastic differentiation encompass the largest group of soft tissue neoplasms, five of which are included in the 5th edition WHO Head and Neck Classification: nodular fasciitis, desmoid fibromatosis, solitary fibrous tumor, low-grade myofibroblastic sarcoma, and inflammatory myofibroblastic tumor. Among these, only low-grade myofibroblastic sarcoma has no identified recurrent molecular alterations. Approximately 30% of cases show nuclear β-catenin staining (in the absence of *CTNNB1* mutation), which may result in a misdiagnosis of desmoid fibromatosis. However, low-grade myofibroblastic sarcoma shows increased cellularity and cytologic atypia relative to desmoid fibromatosis [28]. Desmoid fibromatosis has *CTNNB1* exon 3 mutations in the majority of sporadic cases, and a smaller subset are associated with *APC* mutations in the context of familial adenomatous polyposis [29, 30]. Both mutations result in nuclear β-catenin nuclear expression, although up to 20% of cases are negative by immunohistochemistry. With more sensitive next generation sequencing techniques *CTNNB1* mutations can be detected in > 95% of non-*APC* mutated desmoids.

Nodular fasciitis has the pathognomonic presentation of rapid growth and spontaneous regression. Although once hypothesized to be a reactive process, nodular fasciitis is now understood to be a "transient" neoplasm, based on the presence of the hallmark recurrent *MYH9-USP6* fusion [31].

Major insights have been made in the pathogenesis and prognostication of solitary fibrous tumor (SFT). SFT is composed of a haphazard arrangement of spindled and ovoid cells set within a collagenous stroma, with characteristic thin-walled "staghorn" vessels (Fig. 2A). In 2013, two groups reported recurrent *NAB2-STAT6* fusion in SFT of all anatomic sites [32, 33]. Notably, the fusion results from a small paracentric inversion of chromosome 12q13 with variable breakpoints, which cannot be detected by karyotype or FISH. STAT6 immunohistochemistry is a useful surrogate marker and has proven to be highly sensitive and specific for SFT [34] (Fig. 2B). Secondary *TERT* promoter mutations and *TP53* mutations have been identified to be associated with more aggressive behavior (including increased metastases) and dedifferentiation [35, 36].

The application of rigorous statistical analysis has resulted in improved prognostic criteria for SFT, with several validated multivariate risk models applicable to SFT of all sites, including SFT of the head and neck (but not meninges) available. These models describe low, intermediate, and high-risk tumor groups and replace the historical terminology of "benign" and "malignant" SFT, the use of which is now discouraged. The most widely adopted risk stratification three-tier model has shown to be reliable for predicting metastasis based on the variables of patient age,

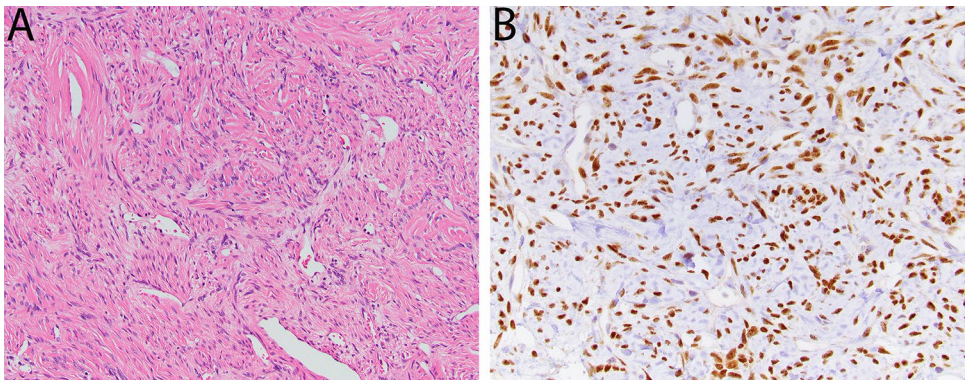

Fig. 2 Solitary fibrous tumor is comprised of spindle and ovoid cells haphazardly arranged in a collagenous stroma, with frequent "staghorn" vessels (**A**). STAT6 immunohistochemistry is a useful surrogate marker for *NAB2-STAT6* fusion (**B**)

Table 2 Risk stratification for predicting metastases in solitary fibrous tumor

Risk factor	Score
Age	
< 55 years	0
≥ 55 years	1
Tumor size	
< 5 cm	0
5 cm to < 10 cm	1
10 cm to < 15 cm	2
≥ 15 cm	3
Mitotic count (per 10 high-power fields/5 mm^2)	
0	0
1–3	1
≥ 4	2
Tumor necrosis	
< 10%	0
≥ 10%	1
Risk class	**Total score**
Low	0–3
Intermediate	4–5
High	6–7

Adapted from Demicco et al. [35]

tumor size, mitotic count, and necrosis [37] (see Table 2). Separate risk calculators have been proposed by the French Sarcoma group, which predict overall survival, local recurrence, and metastasis based on various combinations of patient age, tumor site, mitotic count, and history of radiotherapy [38]. While site-specific risk models have been proposed to take into account the smaller size of head and neck tumors, there is as yet no biologic evidence to suggest that head and neck SFT behave differently than SFT arising at other extrameningeal sites in terms of metastatic potential, and local recurrence risk remains largely a matter of the completeness of surgical excision together with use of adjuvant radiation therapy.

Inflammatory myofibroblastic tumor (IMT) may arise in the head and neck, the larynx being the most common site. It has been well established that *ALK* rearrangements occur in up to 60% in IMT, particularly in younger patients [39]. *ALK* is paired with a broad range of 5' fusion partners which all result in aberrant ALK homodimerization in the absence of ligand and constitutive activation. In the head and neck a recent series of IMTs in the head and neck, *TIMP3* was the most frequent (~ 50%) fusion partner [40]. Most *ALK*-rearranged IMTs show cytoplasmic positivity for ALK by immunohistochemistry, which can helpful in distinguishing IMT from potential mimics in the head and neck, including sarcomatoid squamous cell carcinoma, embryonal rhabdomyosarcoma, and IgG4-sclerosing disease, although demonstration of rearrangement by FISH or NGS is the gold standard for detection of *ALK* rearrangements. Among the many ALK antibody clones available, 5A4 AND D5F3 are highly sensitive, particularly in the detection of *ALK*-rearranged lung adenocarcinomas [41]. A subset of *ALK*-negative IMT are driven by *ROS1* fusions and are positive for ROS by immunohistochemistry [42]. Similarly to lung adenocarcinomas, IMT with *ALK* rearrangements respond to targeted therapy with Crizotinib [43, 44].

Vascular Tumors

Among the benign vascular tumors, one major advance is the discovery of *FOSB* or *FOS* fusions in epithelioid hemangioma [45, 46], which corresponds with nuclear expression for FOSB that is detectable by immunohistochemistry [47, 48]. Notably, epithelioid hemangioma can show morphologic features resembling the reactive process angiolymphoid hyperplasia with eosinophilia. Demonstration of *FOS/FOSB* rearrangements, when present, can aid in the diagnosis of epithelioid hemangioma in some difficult cases. Although not included in the WHO Classification for Head and Neck, it deserves mention that *FOSB* fusions (commonly *SERPINE-FOSB* or *ACTB-FOSB*) and FOSB nuclear staining are also a feature of pseudomyogenic hemangioendothelioma, a vascular neoplasm of

intermediate biologic potential that was fully characterized in 2011 [47, 49–51]. These tumors show a characteristic multifocal presentation across multiple tissue planes, histologically resembling epithelioid sarcoma and myoid differentiation, and may rarely arise in the head and neck.

There are no major updates for Kaposi sarcoma, a vascular proliferation induced by HHV8 infection. Most cases in the head and neck present in the oral cavity, frequently the AIDS-related subtype. While some cases act aggressively, with widespread visceral involvement and poor response to treatment, Kaposi sarcoma is only locally aggressive and does not metastasize, and thus does not represent a true sarcoma.

Epithelioid hemangioendothelioma (EHE) is a malignant vascular neoplasm composed of epithelioid cells arranged in cords and strands in a myxohyaline stroma (Fig. 3A). Most cases harbor recurrent *WWTR1-CAMA1* gene fusions [52], and CAMTA1 nuclear staining is a reliable marker in distinguishing EHE from other vascular tumors [53] (Fig. 3B). Vascular markers (ERG, CD31, and CD34) are positive. Up to 50% of cases may show keratin expression, which poses a diagnostic pitfall, particularly with myoepithelial neoplasms [54]. EHE harboring variant *YAP1-TFE3* account for less than 5% of all EHEs [55], and show a distinctive histological appearance of tumor cells with abundant eosinophilic cytoplasm and more vasoformative and solid architecture. EHE with *TFE3-YAP1* shows strong nuclear TFE3 staining, however the specificity of this marker is somewhat limited [55]. Since preparation of the 5th edition WHO, it has been reported that immunohistochemistry using an antibody for the C-terminus of YAP1 shows frequent (77%) nuclear loss in cases of EHE with *TFE3-YAP1* and retained expression in nearly all mimics [56], and may serve as a helpful diagnostic adjunct given the limitations of TFE3.

Angiosarcoma is an aggressive malignancy associated with poor outcomes, though histologic grade does not appear to predict prognosis. Most primary angiosarcomas in the head and neck have been reported in the sinonasal tract and oral cavity [57, 58] and show heterogeneous genetic features, including mutations in *KDR*, *PTPRB,* and *PLCG1* [59–61]. Cutaneous angiosarcoma arises in sun-exposed areas of the head and neck and shows a high tumor mutational burden and ultraviolet damage mutational signature [61].

Pericytic (Perivascular) Tumors

Myofibroma and myopericytoma form a morphologic spectrum and are now classified together. Most tumors arise in adults, but some present at birth or during infancy. It has been discovered that *PDGFRB* mutation is the key pathogenic driver for both familial and sporadic cases of myofibroma and myopericytoma [62–64], further supporting their relationship. The rare variant of cellular (atypical) myofibroma has recently been described, which shows fascicular growth and can be infiltrative; these tumors may be confused with leiomyosarcoma as desmin staining is strong and diffuse (whereas desmin is largely negative in conventional myofibroma). Cellular myofibroma harbors recurrent *SRF-RELA* fusion [65].

Smooth Muscle Tumors

This section includes soft tissue leiomyoma and leiomyosarcoma, and introduces smooth muscle tumor of uncertain malignant potential for cases that fall between the diagnostic criteria of benign and malignant; most have been reported in sinonasal sites [66]. While formal criteria have not been established for smooth muscle tumors of uncertain malignant potential in soft tissue, published examples in the head and neck show increased cellularity, mild cytologic atypia, and mitotic counts of 4 or less per 2 mm^2.

The major classification update is that EBV-associated smooth muscle tumor (EBV-SMT) is now listed separately from leiomyosarcoma, as EBV-SMT are indolent tumors that do not metastasize (although they may be multifocal), and are therefore not considered true sarcomas. EBV-SMT arises in the setting of immunosuppression, commonly HIV infection or post-organ transplantation, and prognosis is related

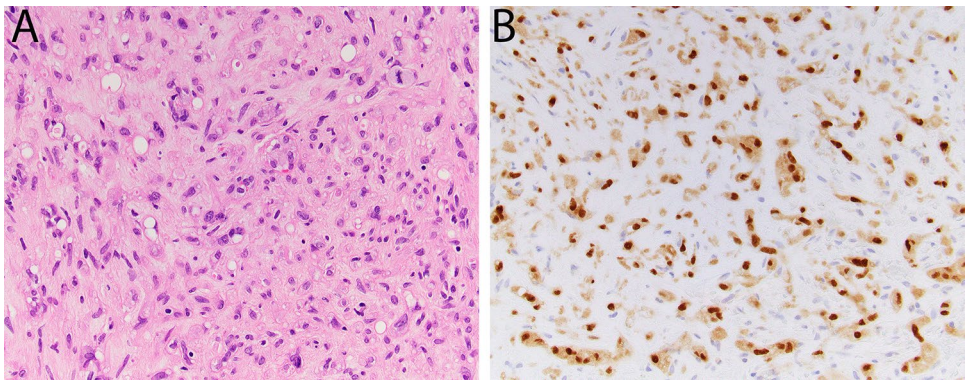

Fig. 3 Epithelioid hemangioendothelioma. Epithelioid tumor cells are arranged in cords and strands set in a myxohyaline stroma; intracytoplasmic vacuoles are common (**A**). Most harbor *WWTR1-CAMA1* fusion, corresponding with CAMTA1 nuclear staining (**B**)

to the patient's degree of immunosuppression. EBV-SMT tend to show only mild-to-moderate cytologic atypia and pleomorphism, low mitotic activity, and infrequent necrosis; some cases may show a uniform ovoid or round cell component. Intratumoral T-lymphocytic infiltrates may be present. Smooth muscle markers SMA and caldesmon are positive but desmin is more variable. Detection of EBV-encoded RNA by in situ hybridization is diagnostic and should be considered for smooth muscle tumors arising in immunocompromised patients or a well-differentiated smooth muscle neoplasm showing unusual cellular uniformity and inflammation.

Skeletal Muscle Tumors

Benign rhabdomyomas and many rhabdomyosarcoma subtypes arise frequently in the head and neck. There are no major updates for fetal-type and adult-type rhabdomyomas. The 5th edition WHO Head and Neck Classification includes all four rhabdomyosarcoma subtypes: embryonal, alveolar, spindle cell/sclerosing, and pleomorphic. While all subtypes are positive for skeletal muscle markers desmin, MYOD1, and myogenin, diffuse myogenin staining is a specific feature of alveolar rhabdomyosarcoma [67]. This pattern is especially helpful in distinguishing alveolar rhabdomyosarcoma from examples of poorly differentiated embryonal rhabdomyosarcoma with predominant round cell morphology. *PAX3-FOXO1* (and less commonly *PAX7-FOXO1*) is the genetic hallmark of alveolar rhabdomyosarcoma [68]. Recently, immunohistochemistry using an antibody for the PAX3/7-FOXO1 fusion protein has been shown to be highly sensitivity and specific for alveolar rhabdomyosarcoma, specifically for cases with *PAX3-FOXO1* (but less reliable for cases with *PAX7-FOXO1*) [69]. It is important to remember that keratin and neuroendocrine markers are positive in a subset of alveolar rhabdomyosarcoma, which can lead to a mistaken diagnosis of neuroendocrine carcinoma [70, 71].

Recent discoveries identifying different recurrent molecular alterations in spindle cell/sclerosing rhabdomyosarcoma support its division into several clinicopathologic subgroups. Three main groups have emerged thus far: (1) congenital/infantile tumors with fusions involving *VGLL2* and *NCOA2* that are associated with favorable prognosis [72, 73]; (2) tumors with *MYOD1* mutations predominantly arising in adolescent and young adults that show aggressive behavior [74–77]; and (3) tumors lacking known recurrent molecular genetic alterations. Diffuse staining for MYOD1 is a feature of *MYOD1*-mutant tumors (Fig. 4). There is also a newly recognized variant of spindle cell/sclerosing rhabdomyosarcoma associated with *EWSR1/FUS-TFCP2* or *MEIS-NCOA2* fusions [78, 79]; this variant arises preferentially in the bone and can show positivity for keratin and ALK, which may pose diagnostic pitfalls (and is listed in the "Odontogenic and maxillofacial bone tumors" chapter).

Chondro-osseous Tumors

The single included entity in this section, soft tissue chondroma, only rarely arises in head and neck sites. Recurrent *FN1-FGFR2* and *FN1-FGFR1* fusions have been identified in 50% and are associated with grungy calcifications [80]. However, such cases do not show elevated FGF23 mRNA expression and are thus unrelated to phosphaturic mesenchymal tumor, which is also characterized by grungy calcifications and *FN1-FGFR1* fusion. Although not included in this edition, synovial chondromatosis may arise in the temporomandibular joint. Tumors are comprised of multiple nodules of hyaline cartilage which may undergo endochondral ossification if longstanding. Similar to soft tissue chondroma, synovial chondromatosis frequently demonstrates *FN1* rearrangement, however *ACVR2A* is the most common 3' partner, seen in 56% [81].

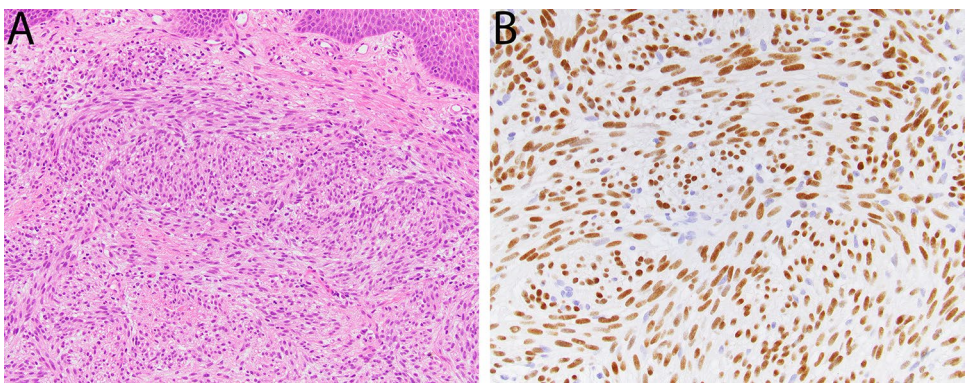

Fig. 4 Spindle cell rhabdomyosarcoma arising in the oral cavity (**A**). Tumors with *MYOD1* mutations show diffuse nuclear staining for MYOD1 (**B**)

Peripheral Nerve Sheath Tumors

This section includes the well characterized benign entities neurofibroma (characterized by *NF1* inactivation), schwannoma (associated with *NF2* inactivation), and neuroma. The neuroma section groups together traumatic neuroma and solitary circumscribed neuroma with syndrome-associated mucosal neuromas (MEN2B-mucosal neuroma, oral pseudoperineurioma, and *PIK3CA*-related overgrowth spectrum-associated neuroma (*PIK3CA*-neuroma)).

Granular cell tumor is listed separately in the "Oral Cavity and Mobile Tongue" chapter, but warrants mention as tumors can arise elsewhere such as the larynx. Granular cell tumor is now known to harbor frequent (~70%) inactivating mutations of *ATP6AP1* and *ATP6AP2* [82, 83], which encode endosomal pH regulators. Interestingly, these pathogenic events show a phenotypic association, resulting in abnormal accumulation of intracytoplasmic granules that is a characteristic feature of these tumors.

There have been important insights into the pathogenesis of malignant peripheral nerve sheath tumor (MPNST). MPNST appears as a fascicular spindle cell sarcoma and diagnosis can be challenging as neural markers (S-100, SOX10, and GFAP) are frequently negative. Association with a large nerve, the setting of neurofibromatosis type 1, or history of radiation are helpful features. The majority (80%) of cases show *SUZ12* or *EED* mutations, which encode subunits of the polycomb repressive complex 2 (PRC2) [84, 85]. Resultant dysregulation of PRC2 function leads to loss of the trimethylation mark on histone 3 lysine 27 (H3K27me3), which can be detected by immunohistochemistry (Fig. 5). Immunohistochemistry demonstrating loss of H3K27me3 is overall a useful diagnostic marker for MPNST, specifically for high grade and radiation-associated tumors, although specificity is somewhat limited, as loss of expression can be seen in small subsets of other malignancies, including synovial sarcoma, melanoma, and non-MPNST radiation-associated sarcomas [86–90], as well as some carcinomas.

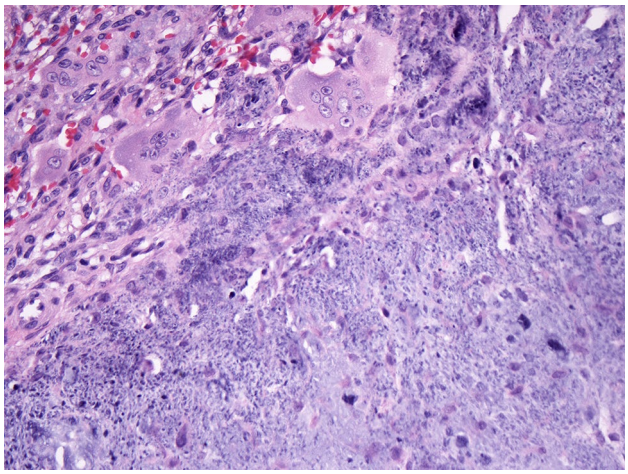

Fig. 6 Phosphaturic mesenchymal tumor. Spindle and stellate tumor cells admixed with osteoclast-like giant cells and distinctive "grungy" stromal calcifications

Tumors of Uncertain Differentiation

This category comprises a diverse group of soft tissue neoplasms for which there is no identifiable line of differentiation. There remains a section for "undifferentiated sarcoma" which is a heterogeneous group and strictly a diagnosis of exclusion, after thorough histologic evaluation, application of relevant ancillary studies, and clinical correlation. These undifferentiated sarcomas are typically reported descriptively based on predominant morphologic pattern (round cell, spindle cell, epithelioid, and pleomorphic). Many tumors in this group are high-grade pleomorphic sarcomas and associated with poor prognosis. Genetic subsets and putative novel entities are increasingly being identified among these undifferentiated tumors, particularly within the round cell group.

Phosphaturic mesenchymal tumor is included in the head and neck classification for the first time. These tumors may arise in the soft tissue or bone of adults with a wide anatomic

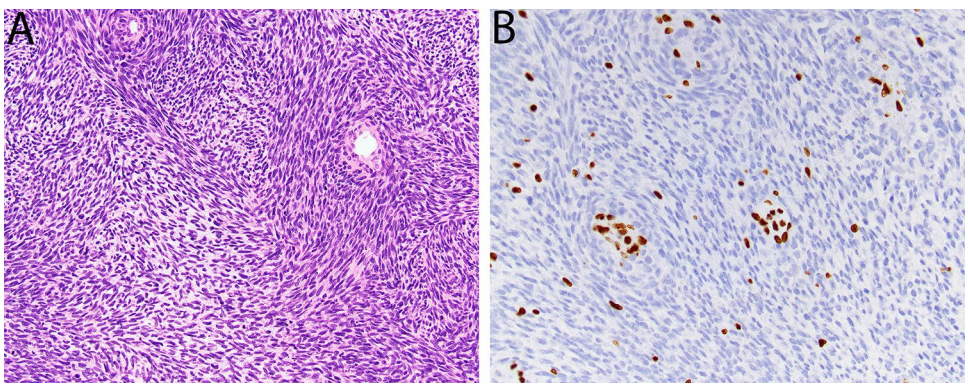

Fig. 5 Malignant peripheral nerve sheath tumor is a fascicular spindle cell sarcoma, often showing alternating hypercellular and hypocellular areas (**A**). Immunohistochemical loss of expression for H3K27me3 is common, especially in high grade tumors, and occurs secondary to PRC2 dysregulation (**B**)

distribution, including head and neck. As mentioned earlier, these tumors harbor *FN1-FGFR1* fusion, and are associated with tumor-induced osteomalacia secondary to secretion of FGF23 which leads to renal wasting of phosphate [91–93]. Tumors are comprised of sheets of bland, spindle and stellate cells associated with hemangiopericytoma-like vessels and frequently admixed with osteoclast-like giant cells. The tumor cells produce distinctive "grungy" appearing stromal calcifications (Fig. 6). Most tumors are benign and osteomalacia typically resolves after resection.

The section for myxoma refers to the benign myxoid neoplasms that can be associated with Carney complex (distinct from the entities odontogenic myxoma and intramuscular myxoma). These myxomas are histologically indistinguishable from superficial angiomyxoma. Presentation in the upper aerodigestive tract is rare, but has been reported in the sinonasal tract and larynx. Carney complex should be considered in the following settings: myxomas in the external auditory ear, multiple cutaneous myxomas, and/or presence of other clinical stigmata (such as spotty pigmentation and malignant melanotic nerve sheath tumor). Germline inactivating *PRKAR1A* mutations occur in Carney complex [94], and immunohistochemical loss of PRKAR1A is seen in Carney complex-associated tumors, including cardiac myxoma, malignant melanotic nerve sheath tumor, and superficial angiomyxoma [95, 96]. *PRKAR1A* mutation also appears to be a feature of sporadic counterparts, as sporadic superficial angiomyxoma may show immunohistochemical loss of expression of PRKAR1A [97].

Extraskeletal myxoid chondrosarcoma is only rarely encountered in the head and neck, but shows histologic overlap with soft tissue and salivary myoepithelial neoplasms. It should be noted that despite the terminology, tumors show no evidence of cartilaginous differentiation. Microscopically, tumors demonstrate lobulated growth with intervening fibrous septa, with uniform ovoid cells arranged in interconnected corded, reticular, and trabecular growth patterns embedded in an abundant chondromyxoid stroma. *EWSR1-NR4A3* fusion is the molecular hallmark [98]. Molecular testing may be necessary as tumors have a non-specific immunophenotype, with only variable staining for S-100 (20%). While INSM1 is frequently positive (80%), specificity is somewhat limited [99].

It has been well established that synovial sarcoma harbors recurrent *SS18-SSX* fusions, involving one of three highly homologous *SSX* genes (*SSX1, SSX2,* or *SS4)* [100]. Most synovial sarcomas appear as uniform spindle cell sarcomas that enter the differential diagnosis of entities such as MPNST and biphenotypic sinonasal sarcoma. While most are monophasic with purely spindled morphology, approximately one third are biphasic showing an epithelial component (often glandular) admixed with spindle cells. Poorly differentiated variants show predominant round cell morphology and are associated with more aggressive behavior. Focal-to-multifocal EMA (and infrequent keratin) staining may be seen across all subtypes. The conventional immunohistochemical marker TLE1 is frequently used, and while sensitivity for synovial sarcoma is high, specificity is only moderate [101–103]. Recently, the SS18-SSX fusion-specific antibody and an SSX C-terminus-specific antibody have both been shown to have high sensitivity and specificity for synovial sarcoma, including poorly differentiated tumors, and can serve as reliable immunohistochemical surrogates for molecular testing [104, 105] (Fig. 7).

Lastly, there is a section for the emerging group of *GLI1*-altered mesenchymal tumors, including tumors having *GLI1* rearrangement (~2/3 of cases; most commonly *ACTB-GLI1*) and *GLI1* amplification (~1/3) [106]. Among the fewer than 40 cases reported in the literature, approximately 40% arise in the head and neck, most commonly on the tongue [107]. *ACTB-GLI1* was first reported in 2004 in five tumors termed "pericytoma with t(7;12)" on the basis of SMA expression and indolent behavior [108]. Subsequent descriptions of similar tumors having *GLI1* fused to *ACTB, PTCH1,* or *MALAT1* demonstrated a significant risk of metastasis (~20%) [107, 109, 110]. The morphologic spectrum of these tumors is broad, but commonly shows nested and sheetlike growth of epithelioid, ovoid, or spindled tumor cells, with ovoid to round nuclei and eosinophilic or cleared cytoplasm. Intervening thin-walled vessels between tumor nests

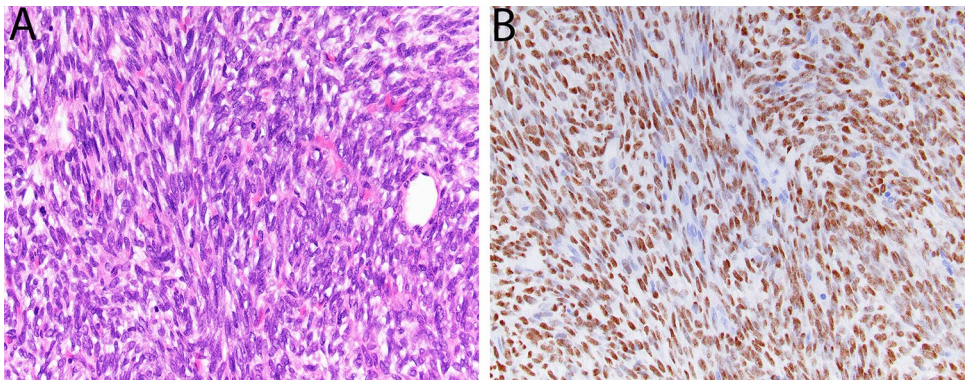

Fig. 7 Synovial sarcoma shows a uniform fascicular growth of spindle cells (**A**). Diffuse nuclear staining for the SS18-SSX fusion-specific antibody is highly sensitive and specific for the diagnosis (**B**)

is a common feature, frequently with tumor cells protruding into vascular spaces. The immunophenotype is inconsistent and non-specific; S-100 is most likely to be positive (60%) and there is variable staining for SMA, CD99, EMA, and keratin. *GLI1* amplifications often include flanking genes *CDK4, MDM2,* and *STAT6*, which corresponds with MDM2, CDK4, and STAT6 staining [106]. It remains to be determined whether this provisional group represents a uniform clinicopathologic entity.

Undifferentiated Small Round Cell Sarcomas of Bone and Soft Tissue

This section of the WHO Head and Neck classification is devoted to Ewing sarcoma, as 10% of cases (both extra- and intraosseous) may arise in this anatomic region. Ewing sarcoma, the first sarcoma type recognized to have a recurrent cytogenetic abnormality, harbors *EWSR1-FLI1* fusion [111], with rare variant fusions involving other members of the ETS (erythroblast transformation specific) family (e.g. *EWSR1-ERG)* and *FUS* in lieu or *EWSR1*. Integration of clinical, morphologic, and immunohistochemical features should guide confirmatory molecular testing. While not specific, Ewing sarcoma characteristically shows diffuse membranous CD99 staining. NKX2.2 has been shown to have high sensitivity (93%), although specificity is moderate as staining can be seen in several mimics including small cell carcinoma, olfactory neuroblastoma, and mesenchymal chondrosarcoma [112, 113]. There are now recognized genetic subsets among undifferentiated round cell sarcomas that were often classified as "atypical Ewing sarcoma", including *CIC*-rearrangement, *BCOR* alterations, and *EWSR1* fusions to non-ETS partner genes, which are detailed in the 5th edition WHO Soft Tissue and Bone Classification [3].

Adamantinoma-like Ewing sarcoma is introduced in this section. Deeper characterization over the recent years has shown that tumors frequently arise in the head and neck, particularly salivary gland [114, 115]. Adamantinoma-like Ewing sarcoma also harbors *EWSR1-FLI1* fusion, and some authors regard this as a variant of Ewing sarcoma that demonstrates epithelial differentiation. Tumors show lobules, nests, and sheets of uniform basaloid cells, often with peripheral nuclear palisading, and a frequently hyalinized or myxoid stroma (Fig. 8A). Tumors show diffuse positivity for keratin and p40 (Fig. 8B, C); rarely keratin pearl formation is seen. Basaloid carcinomas among other round cell sarcomas enter the differential diagnosis. CD99 and NKX2.2 are positive, similar to conventional Ewing sarcoma (Fig. 8D). It remains to be determined whether this distinctive entity is truly related to Ewing sarcoma or is a carcinoma that shares an identical fusion, and further investigation is needed to determine optimal management as a sarcoma or carcinoma.

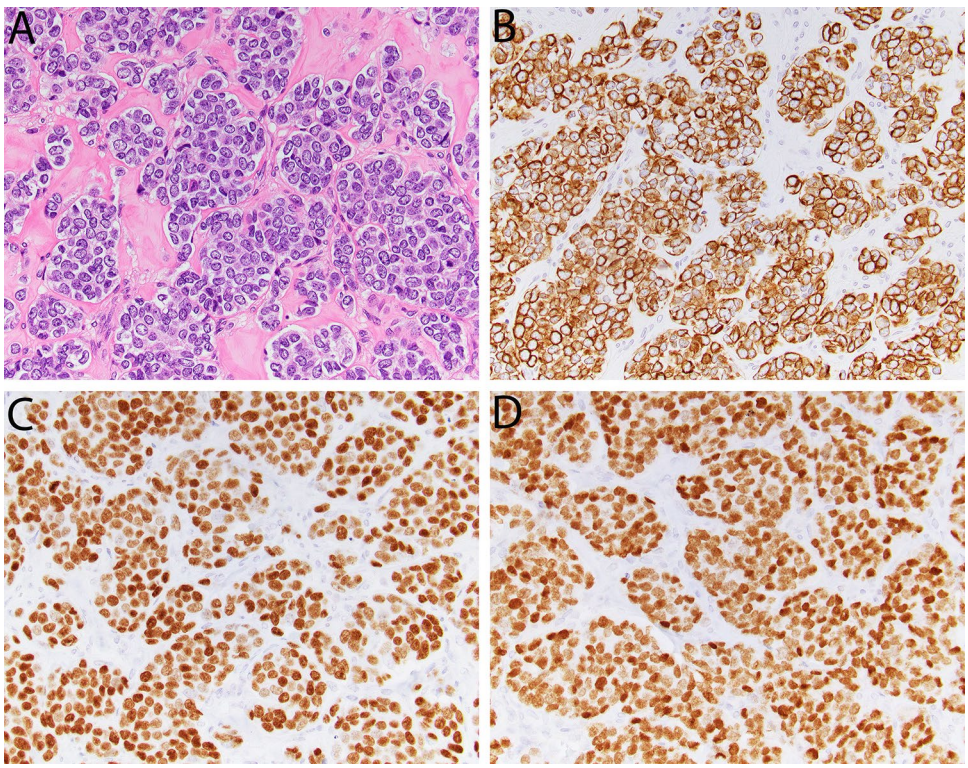

Fig. 8 Adamantinoma-like Ewing sarcoma. Lobules and nests of basaloid cells set in a hyalinized stroma (**A**). Tumors show epithelial differentiation with positivity for pan-keratin (**B**) and p40 (**C**). Nuclear NKX2.2 is characteristic (**D**)

Summary

The 5th edition WHO Classification of Head and Neck Tumors introduces a new chapter dedicated to soft tissue tumors and provides an updated text of the clinicopathologic and molecular features of both common and rare neoplasms encountered in the head and neck. This updated classification will ideally facilitate more accurate diagnosis and increased understanding of these challenging tumor types, leading to improved patient care.

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Consent for Publication Not applicable.

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