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UPDATE FROM THE 5TH EDITION OF THE WORLD HEALTH ORGANIZATION CLASSIFICATION OF HEAD AND NECK TUMORS

Update from the 5th Edition of the World Health Organization Classification of Head and Neck Tumors: Nasal Cavity, Paranasal Sinuses and Skull Base

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Abstract
The World Health Organization Classification of Head and Neck Tumours recently published the 5th edition. There are new entities, emerging entities, and significant updates to the taxonomy and characterization of tumor and tumor-like lesions, specifically in this article as it relates to nasal cavity, paranasal sinuses and skull base. Importantly, the number of diagnostic entries has been reduced by creating category-specific chapters for soft tissue, hematolymphoid, melanocytic, neuroectodermal, and metastatic tumors. Bone and salivary gland tumors are also not separately reported in the sinonasal tract, but included in the jaw and salivary gland sections, respectively. Repetition of characteristic entities in each anatomic site was also reduced, instead highlighting only the unique features in each anatomic site. Two new entities (SWI/SNF complex-deficient sinonasal carcinomas and HPV-related multiphenotypic sinonasal carcinoma) will be highlighted in this review, with a discussion of several emerging entities. There is a short description of updated information for all 24 diagnostic entities included in this edition to allow the reader a snapshot of current state of knowledge, but to encourage more investigation and further broaden understanding of these diverse and rare entities.

Keywords Nasal cavity · Paranasal sinuses · Paranasal sinus neoplasms · Skull base · Carcinoma · World Health Organization · SWI/SNF complex · Papillomavirus neoplasms · Immunohistochemistry

Introduction

The 2022 5th edition of the World Health Organization (WHO) Classification of Tumours of the Head and Neck, specifically as it relates to the nasal cavity, paranasal sinuses and skull base (Chapter 1, herein after referred to collectively as sinonasal tract [1]), has undergone a significant classification realignment, in keeping with all of the 5th series WHO classification books.

While several of these changes are stylistic, they allow for a more logical development of a hierarchical classification with successive entities in the system viewed as more significant and progressive towards malignant and then higher grades of malignancy, modified to take tumor incidence into account. As such, sinonasal tract hamartomas are followed by sinonasal papillomas, and then carcinomas and adenocarcinomas. A broad category of other tumors includes several unique sinonasal tract mesenchymal entities (sinonasal tract angiofibroma, glomangiopericytoma, biphenotypic sinonasal sarcoma, and chordoma) or tumor types that are considered within the differential diagnosis for other neoplasms (ameloblastoma, adamantinomatous craniopharyngioma, meningioma, olfactory neuroblastoma).

One of the most significant systematic changes is to aggregate tumors which affect all head and neck sites and move them into their own chapter, recognizing the tumors

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can affect specific sites, but to avoid unnecessary duplication and redundant repetition of epidemiology, pathogenesis and pathology criteria, these entities are all included in a single chapter. Thus, all head and neck soft tissue tumors are included in a soft tissue tumor chapter, with some site-specific exceptions. Similarly, hematolymphoid proliferations and neoplasms are reported in a chapter devoted to these entities, while melanocytic tumors and metastases to head and neck sites are also each included in their own separate chapters. Bone tumors may develop in the sinonasal tract but are included in the odontogenic and maxillofacial bone tumors chapter. Salivary gland-type neoplasms may arise from the minor mucoserous glands of the sinonasal tract, but again, all salivary gland tumors are classified within their own chapter rather than being repeated in each head and neck anatomic site. A new chapter was introduced for all neuroendocrine neoplasms and paraganglioma, taking into consideration the major emphasis towards nomenclature harmonization across all organ systems, using neuroendocrine tumor (grade 1, 2 and 3) and neuroendocrine carcinoma (small cell, large cell, and Merkel cell), with a separate entry for head and neck paragangliomas. Ectopic/invasive pituitary neuroendocrine tumor (PitNET; formerly pituitary adenoma) is reported in the neuroendocrine neoplasms chapter rather than in the sinonasal tract or nasopharynx chapters. Finally, given the complex interplay between head and neck tumors and various genetic tumor syndromes, a new chapter devoted specifically to genetic tumor syndromes that have head and neck manifestations as their major clinical findings was introduced and includes 15 different syndromes.

Five additional changes deserve specific mention, as they represent major improvements in access and in providing gold standards for pathology. The books are hosted as interactive on-line books. Optimized for both desktop and mobile devices, these online versions of the books allow for anytime, anywhere, on-demand access. All diagnostic entity sections contain at least one virtual whole slide image of the category, which allows the user to personally review an expert-vetted case to help reinforce diagnostic criteria. All references are linked to PubMed identification numbers (PMID), which can be clicked to open a new browser window directly to the PubMed.gov website, permitting the reader access to the source material used in classification development. To further aid in snapshot review, *essential and desirable diagnostic criteria* are included for each diagnostic entity, features considered indispensable in rendering the pathological diagnosis. Finally, this is the first time that a radiologist and a cytopathologist were included as editorial board members, facilitating the incorporation of pertinent imaging findings into the classification as a multidisciplinary approach to meaningful diagnosis and patient management, while the cytology and fine needle aspiration findings were highlighted were applicable to further aid in diagnostic evaluation and triage. These enhancements to the volume significantly contribute to ease of use and transparency of the process.

For the sinonasal tract, there is a very focused coverage of entities unique to the site (i.e., olfactory neuroblastoma) or those that develop anywhere in the head and neck but account for a significant proportion of disease in the sinonasal tract. Obviously, squamous cell carcinoma (SCC) is covered in each major anatomic site, but specific attention to given to the keratinizing and non-keratinizing types along with related tumors in the sinonasal tract (Table 1). Spindle cell (sarcomatoid) squamous cell carcinoma is now covered in the larynx chapter, where the tumor subtype is more frequent. The new entities in this chapter include SWI/SNF complex-deficient sinonasal carcinoma (provisionally included in the 4th edition) and HPV-related multiphenotypic sinonasal carcinoma (provisionally included as HPV-related carcinoma with adenoid cystic-like features in the 4th edition), and will be the focus of this discussion, along with including selected emerging entities to reflect the current state of understanding for these tumors. Further, a brief snapshot of each diagnostic entity is included to highlight updated information.

Hamartomas

Respiratory epithelial adenomatoid hamartoma (REAH) may represent a neoplasm rather than a hamartoma based on increased fractional allelic loss [2], but clonal studies have not yet documented a clonal expansion [3]. Imaging studies frequently show olfactory cleft expansion without bone erosion [4] (Fig. 1a). Lesions are polypoid benign acquired overgrowths of indigenous glands of the sinonasal tract that arise from the surface epithelium, lacking any ectodermal or mesodermal elements. A serrated hyperplastic, ciliated epithelium is surrounded by a thick, eosinophilic basement membrane which displaces normal elements (Fig. 1b). When cartilaginous or osseous trabecular are admixed, then the lesion is called a chondroosseous and respiratory epithelial (CORE) hamartoma [5]. It is not uncommon to have a combined REAH with seromucinous hamartoma (SH) [6]. However, SH is a benign proliferation of small eosinophilic glands without atypia arising within the sinonasal tract (Fig. 1c). This proliferation resembles microglandular adenosis of the breast, lacking destructive or infiltrative growth, any complex architecture, while also lacking papillae and gland fusion [3, 6]. The cuboidal cells have small nuclei, are noted lining tubules or glands while lacking any significant myoepithelial component [7, 8].

Chondromesenchymal hamartoma remains a distinct lesion, although whether the tumor is a neoplasm is still unresolved. There is a strong association with *DICER1*

Table 1 2022 5th edition of the World Health Organization (WHO) Classification of Tumours of the nasal cavity, paranasal sinuses, and skull base

Diagnostic Group	Category	Diagnostic Entity Section
Hamartomas		Respiratory epithelial adenomatoid hamartoma Seromucinous hamartoma Nasal chondromesenchymal hamartoma
Respiratory epithelial lesions		
	Sinonasal papillomas	Sinonasal papilloma, inverted type Sinonasal papilloma, oncocytic type Sinonasal papilloma, exophytic type
	Carcinomas	Keratinizing squamous cell carcinoma Non-keratinizing squamous cell carcinoma NUT carcinoma SWI/SNF complex-deficient sinonasal carcinoma Sinonasal lymphoepithelial carcinoma Sinonasal undifferentiated carcinoma Teratocarcinosarcoma HPV-related multiphenotypic sinonasal carcinoma
	Adenocarcinoma	Intestinal-type adenocarcinoma of the sinonasal tract Non-intestinal-type sinonasal adenocarcinoma
Mesenchymal tumors of sinonasal tract		Sinonasal tract angiofibroma Sinonasal glomangiopericytoma Biphenotypic sinonasal sarcoma Chordoma
Other tumors		Sinonasal ameloblastoma Adamantinomatous craniopharyngioma Meningioma of sinonasal tract Olfactory neuroblastoma

mutations, and as such is considered part of the pleuropulmonary blastoma tumor predisposition syndrome, where pediatric patients comprise the majority of affected individuals [9–11]. A spindled stroma with variably sized nodules of hyaline cartilage (primitive to mature) are often associated with bony trabeculae (Fig. 1d) and mature adipose tissue [10, 12, 13].

Respiratory Epithelial Lesions

Sinonasal Papillomas

Updated information for the inverted, oncocytic, and exophytic types of sinonasal papilloma (SNP, formerly Schneiderian papilloma family) includes imaging findings, epidemiology, etiology, and pathogenesis. An inverted SNP can be suggested when imaging shows lateral nasal cavity origin, associated osteitis, a lobulated shape, with a cerebriform (columnar) pattern on T2 weighted and post-contrast T1 weighted magnetic resonance imaging (MRI). The lack of bone erosion helps to exclude a malignant tumor [10, 14].

Updated RNA in situ hybridization (ISH) shows a consistent lack of high-risk HPV E6/E7 transcripts in inverted SNP, though low-risk HPV transcripts can be seen in a subset of cases [15, 16]. Further work on *EGFR* profiling shows consistent somatic mutations in about 90% of inverted SNP, and about 80% of carcinomas developing from these tumors [16–18], mutually exclusive from the occasional low-risk HPV infection that can be an alternative oncogenic driver [16, 19]. Malignant progression is associated with *TP53* and/or *CDKN2A* alterations [20].

Oncocytic sinonasal papilloma (OSP) frequently display a high signal on T1 weighted MR, multiple mucinous cystic foci, and generally lack focal osteitis [14]. Importantly, HPV infection is not an etiologic factor but instead hotspot mutations in *KRAS* have been consistently identified [21, 22], with malignant progression also associated with *TP53* and/or *CDKN2A* alterations [20].

Exophytic SNP frequently harbor low-risk HPV (types 6 and 11) [23, 24], without a well-developed pathogenesis identified yet. While the majority arise on the lower anterior nasal septum [25], malignant transformation is exceptionally rare, although recurrences are common due to incomplete excision [26, 27].

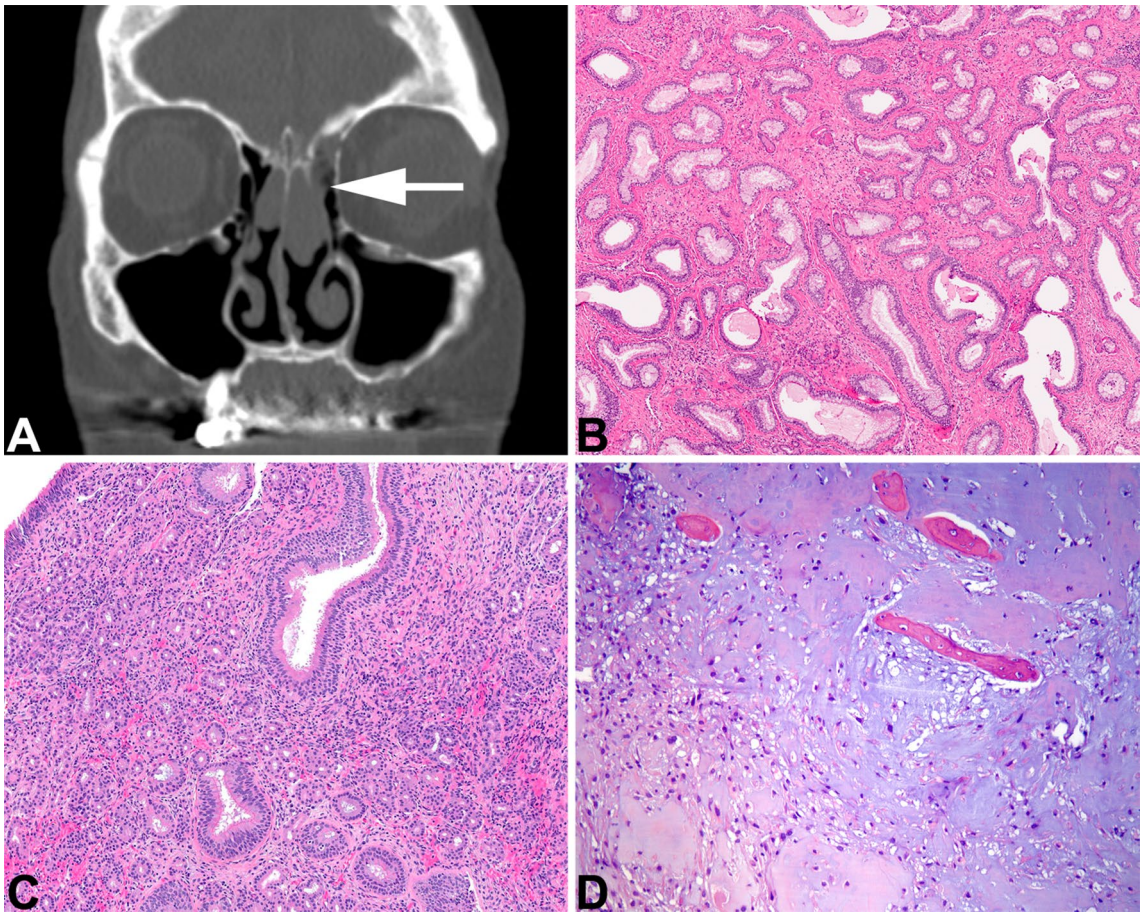

Fig. 1 Sinonasal hamartomas. **A** Respiratory epithelial adenomatoid hamartoma. An axial computed tomography shows expanded olfactory cleft (white arrow) with a soft tissue-density mass. **B** Evenly spaced glandular units have a prominent basement membrane surrounding them. **C**. Seromucinous hamartoma shows a proliferation of small eosinophilic glands in the stroma, lacking destructive growth. **D** A chondromesenchymal hamartoma shows cartilaginous nodules with a myxoid stroma and islands of bony tissue (courtesy Dr. D. Baumhoer)

Carcinomas

Keratinizing Squamous Cell Carcinoma

Keratinizing squamous cell carcinoma (KSCC) is histologically identical to any other affected site, arranged in sheets, nests, islands, and single cells, showing a variable degree of keratinization, and separated into well, moderately and poorly differentiated categories. This category is only rarely associated with transcriptionally active high-risk human papillomavirus (HR HPV) [28, 29]. In some cases, KSCC may be associated with a precursor SNP [30].

Non-keratinizing Squamous Cell Carcinoma

Non-keratinizing squamous cell carcinoma (NKSCC) is a distinctive sinonasal tumor. By imaging, the tumor is a soft tissue density that often erodes bone (Fig. 2a). It is histologically characterized by minimal to no keratinization combined with invasion in the form of expansile nests, lobules, or ribbons with a smooth stromal interface and minimal associated desmoplastic response (Fig. 2**b**). Papillary architecture, both exophytic and inverted, is also common. At the cellular level these tumors are often more monotonous than pleomorphic, with hyperchromatic round nuclei often with prominent nucleoli (Fig. 2c). NKSCC is diffusely positive for squamous markers such as p40 (Fig. 2d) and CK5/6, an important feature that separates it from morphologic mimics like sinonasal undifferentiated carcinoma (SNUC) and neuroendocrine carcinoma (NEC) which are negative or at most focal for these stains. NKSCC can also closely resemble NUT carcinoma and adamantinoma-like Ewing sarcoma; negative results for NUT, CD99, and NKX2.2 help rule out these possibilities. [31–33].

In contrast to KSCC, NKSCC commonly harbors transcriptionally active HR HPV in up to 60% of cases [29, 34–39]. In addition, up to half of NKSCC harbor

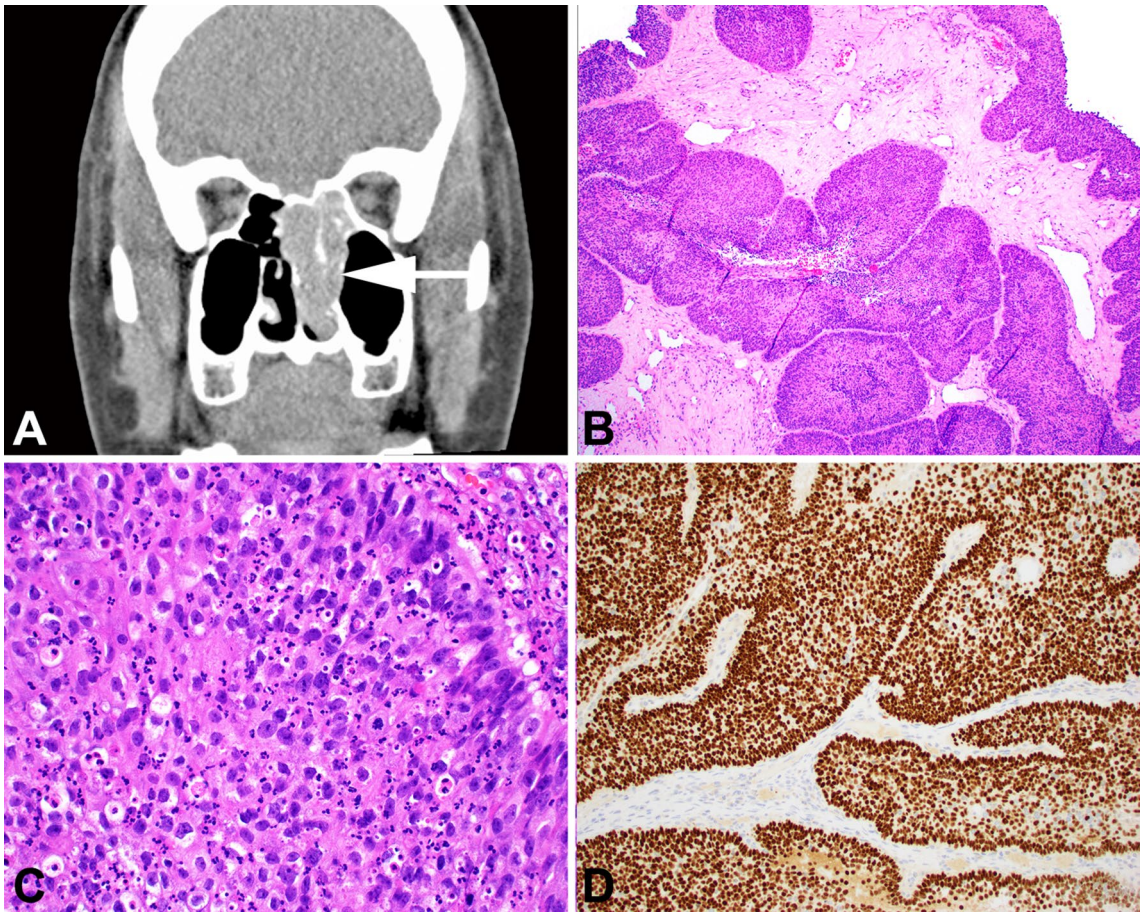

Fig. 2 Nonkeratinizing SCC. **A** A computed tomography scan demonstrates a soft tissue mass involving the nasal cavity and maxillary sinus, with bone erosion. **B** Tumor invasion is as smooth-edged lobules and ribbons, reminiscent of inverted papilloma. **C** This case harbored *DEK::AFF2*. Cases with this fusion typically have nuclear monotony and in infiltrate of neutrophils. **D** Nonkeratinizing SCC is characteristically positive for p40 in a diffuse pattern

DEK::AFF2. *DEK::AFF2* carcinomas may represent an emerging, distinctive tumor type analogous to NUT carcinoma and others. Carcinomas with this fusion tend to be rich with inflammatory cells, especially neutrophils, and are often deceptively bland; these features, when combined with similar growth patterns, often result in misdiagnoses as inverted SNP [40–42]. Despite its sometimes bland features, *DEK::AFF2* carcinoma often behaves in an aggressive manner.

NUT Carcinoma

With improved testing by increased availability of commercial antibodies, NUT carcinoma has been recognized in up to 18% of upper aerodigestive tract poorly differentiated carcinomas [43, 44]. Further case evaluation has identified that *NUTM1* gene (chromosome 15q14) is either translocated or fused to an expanded number of partner genes, although *BRD4* is identified in the majority of cases, while *BRD3*, *NSD3*, *ZNF532*, *ZNF592*, and unidentified genes make up the remainder [45–47]. These NUT-fusion oncoproteins act as the single drivers of carcinoma by blocking differentiation and maintaining proliferation [45, 48]. The neoplasm is composed of monotonous evenly spaced sheets of evenly-sized nuclei with vesicular chromatin and prominent nucleoli. Abrupt keratinization is classic, but only seen in about a third of cases [49], while a rich inflammatory infiltrate is common. The monoclonal NUT antibody yielding a nuclear speckled pattern of reactivity is highly specific [33, 50, 51], recognizing epithelial markers (CK-pan, p40, p63) are seen in the majority of cases.

SWI/SNF Complex-Deficient Sinonasal Carcinoma

This tumor group is defined by inactivation of one of the SWI/SNF complex genes. By far the most common subtype is SMARCB1-deficient sinonasal carcinoma. Most cases have a basaloid, undifferentiated appearance (Fig. 3a), but

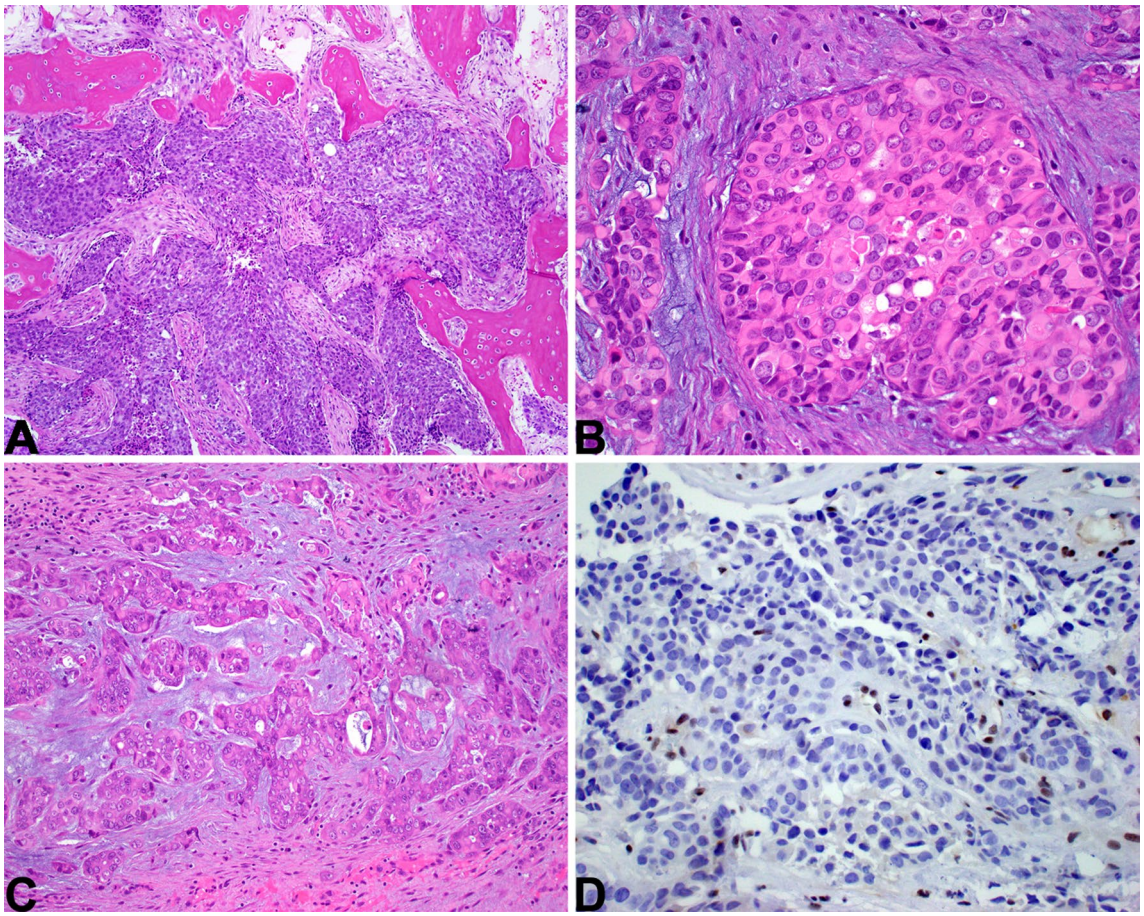

Fig. 3 SMARCB1-deficient sinonasal carcinoma. **A** Most cases have a basaloid low-power appearance. Bone invasion is common. **B** A minority of cases have a "pink" cell appearance, where the tumor cells are somewhat plasmacytoid, with hyaline-appearing cytoplasm. **C** Rare cases show glandular or even yolk sac-like differentiation. **D** A complete loss of SMARCB1 expression by immunohistochemistry defines this tumor. Note the retained staining in lymphocytes, a helpful internal control

about a third are more eosinophilic, with tumor cells showing plasmacytoid cytomorphology (Fig. 3b) [52–54]. While SMARCB1-deficient sinonasal carcinoma usually has an undifferentiated appearance, occasionally they can be overtly gland-forming (Fig. 3c) or even yolk sac-like [55]. By immunohistochemistry, SMARCB1-deficient sinonasal carcinoma is cytokeratin positive and completely SMARCB1 negative (Fig. 3d), but is otherwise quite variable. Gland-forming SMARCB1-deficient sinonasal adenocarcinomas frequently express yolk sac markers (e.g., SALL4, AFP, CDX2). [55].

SMARCA4-deficient sinonasal carcinoma is much less common. While cases have a similar appearance to SMARCB1-deficient carcinomas, most SMARCA4-deficient sinonasal carcinomas actually more closely resemble high-grade neuroendocrine carcinomas with trabecular and nested architecture and abortive rosettes. SMARCA4 expression is lost by definition, while SMARCB1 is retained. Many cases express neuroendocrine markers focally. Because teratocarcinosarcoma also exhibits neuroendocrine differentiation and may show SMARCA4 loss, some cases may be difficult to categorize into either group, especially on a small biopsy.

SWI/SNF complex-deficient sinonasal carcinomas are highly aggressive neoplasms, with more than 50% of patients dying within 2 years of diagnosis. Mortality may be higher for SMARCA4-deficient cases compared to SMARCB1-deficient carcinomas [56, 57].

Sinonasal Lymphoepithelial Carcinoma

The histologic features of sinonasal lymphoepithelial carcinoma (LEC) are identical to nasopharyngeal carcinoma (NPC), and it is only the sinonasal tract location that aids in separation. Just like NPC, sinonasal LEC are strongly associated with Epstein-Barr virus (EBV) infection, even more so when identified in endemic area patients [58, 59]. The syncytium of large neoplastic cells with vesicular chromatin, associated with a heavy lymphoplasmacytic infiltrate and reactive with EBV-encoded small RNA (EBER) by ISH

will help to confirm the diagnosis in the vast majority of cases [60, 61].

Sinonasal Undifferentiated Carcinoma

Sinonasal undifferentiated carcinoma is a diagnosis of exclusion, consisting of a high-grade carcinoma that lacks any significant squamous, glandular, or neuroendocrine differentiation by histology and/or immunohistochemistry. Tumors are typically large and locally destructive (Fig. 4a) [62, 63]. Its histologic appearance is nonspecific, consisting of lobules or sheets of basaloid tumor cells with high-grade features but no evidence of differentiation (Fig. 4b–c). SNUC is negative or, at most, focally positive with squamous markers (e.g., p40, CK5/6) (Fig. 4d) and neuroendocrine markers (e.g., synaptophysin, INSM1).

As tumor classification has been refined, this diagnosis is becoming less common, with newly defined entities (e.g., SWI/SNF complex-deficient sinonasal carcinomas) being removed from this group. Recent genetic studies have shown that a significant subset of what remains in the sinonasal undifferentiated carcinoma group harbors *IDH2* hotspot mutations, and these tumors appear to have an improved prognosis [64–67]. While these tumors are not easily distinguished from *IDH2*-wild type sinonasal undifferentiated carcinomas by routine histology or immunohistochemistry, *IDH2* mutated sinonasal carcinoma may nevertheless be regarded as a separate tumor entity in future editions.

Teratocarcinosarcoma

A high-grade mixed epithelial, mesenchymal, and primitive neuroectodermal malignancy, teratocarcinosarcoma (TCS) has recently been shown to have recurrent molecular alterations, specifically as biallelic inactivation of *SMARCA4* and activating *CTNNB1* mutations [68, 69]. The multitude of elements in this tumor result in significant difficulties rendering a diagnosis, especially in limited or crushed/electrocauterized material. It is important to recognize epithelial (squamous and/or glandular) components, whether benign or

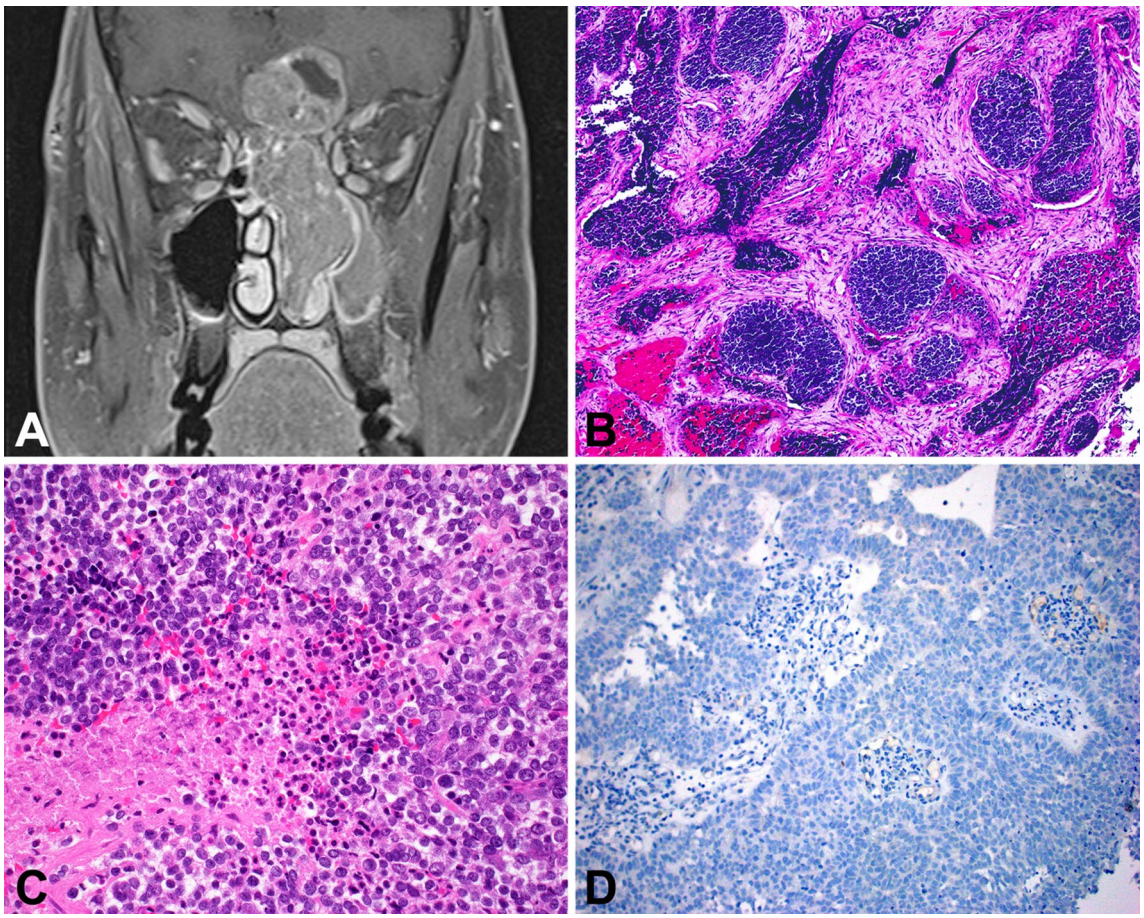

Fig. 4 Sinonasal undifferentiated carcinoma (SNUC). **A** SNUC is an aggressive tumor, commonly showing invasion of local structures like the orbit or brain. **B** A nonspecific, basaloid, nested appearance is typical. **C** The tumor cells are monotonous with necrosis and a high mitotic rate. **D** SNUC is usually completely negative for squamous markers like p40

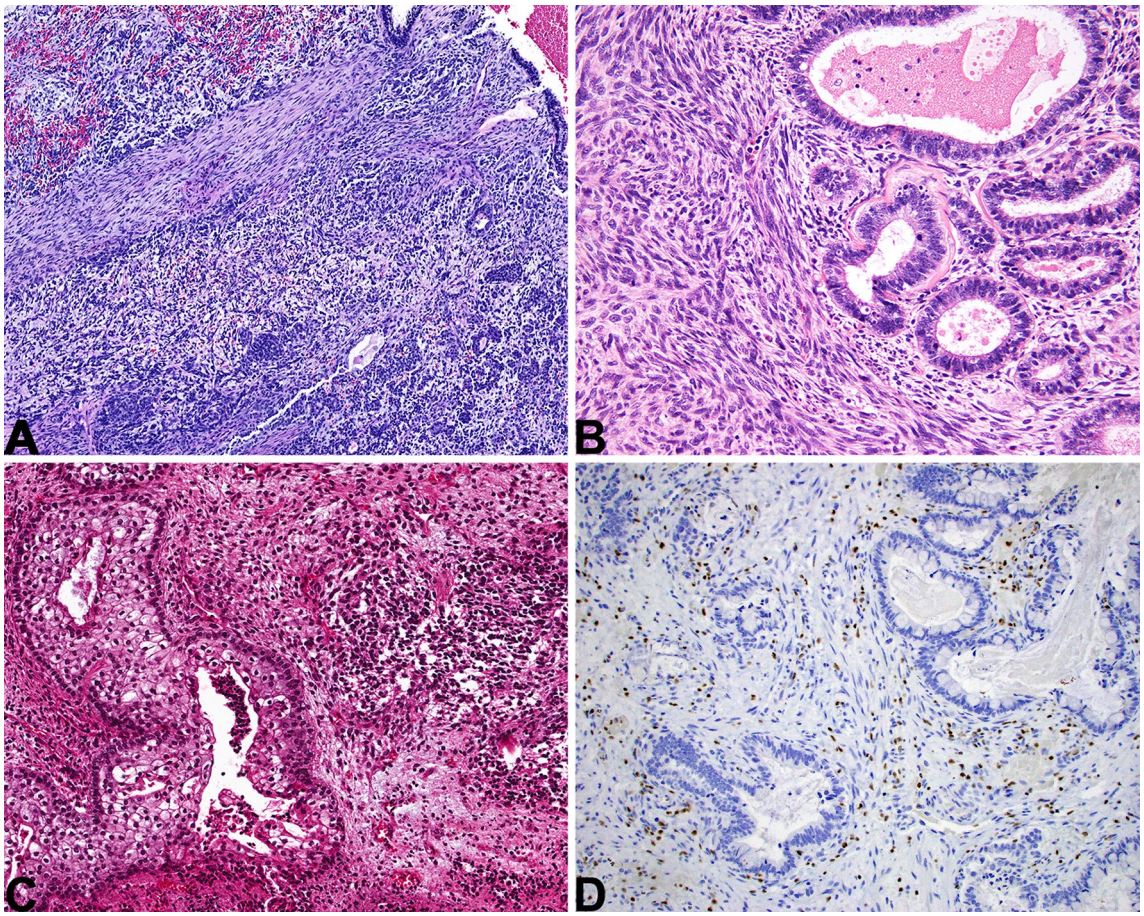

Fig. 5 Teratocarcinosarcoma. A) There is a blend of spindled cells, epithelial elements and primitive cells. B) The mesenchymal spindled cell component is juxtaposed with malignant glandular elements. C) An area of squamoid differentiation shows clear cell change, while the primitive neuroectodermal component has a high nuclear to cytoplasmic ratio. **D** SMARCA4 is lost as reflected by a negative BRG1 stain. Note retained expression in lymphocytes, a helpful internal control

malignant and sometimes with clear cell change, combined with hypercellular mesenchymal elements, while primitive neuroepithelial cells are seen in sheets and nests (Fig. 5). Many immunohistochemical markers are reactive, each highlighting a specific constituent, potentially resulting in a complex immunoprofile. However, germ cell markers are negative, while a majority of cases will show some degree of SMARCA4 (BRG1) loss [69], with aberrant nuclear ß-catenin in a few cases [68].

HPV-Related Multiphenotypic Sinonasal Carcinoma

HPV-related multiphenotypic sinonasal carcinoma (HMSC) is a very unique neoplasm that is seemingly restricted to the sinonasal area. Previously known as HPV-related carcinoma with adenoid cystic-like features, HMSC has histologic and immunophenotypic features of both a salivary-type carcinoma (biphasic ductal and myoepithelial differentiation, often in a cribriform arrangement resembling adenoid cystic carcinoma) and a squamous cell carcinoma (frequent squamous cell carcinoma in situ, occasional squamous differentiation within the invasive tumor) [70–72] (Fig. 6). HMSC harbors high-risk HPV, with the rare type 33 being the most common type isolated. HMSC has a favorable prognosis despite often-aggressive appearing histologic features (e.g., necrosis, high mitotic rates). [70, 72].

Because of the prognotic significance to making an HMSC diagnosis, a sensitive threshold is needed. The main diagnostic considerations are squamous cell carcinoma (which lacks myoepithelial differentiation) and a true salivary-type carcinoma (which does not harbor high-risk HPV). Notably, basaloid squamous cell carcinoma is often positive for SOX10 and occasionally positive for S100 protein; these markers, by themselves, do not reliably establish a salivary-type phenotype [73]. Moreover, while p16 immunohistochemistry is also always positive in HMSC, this marker is not sufficiently specific by itself to make the diagnosis as it

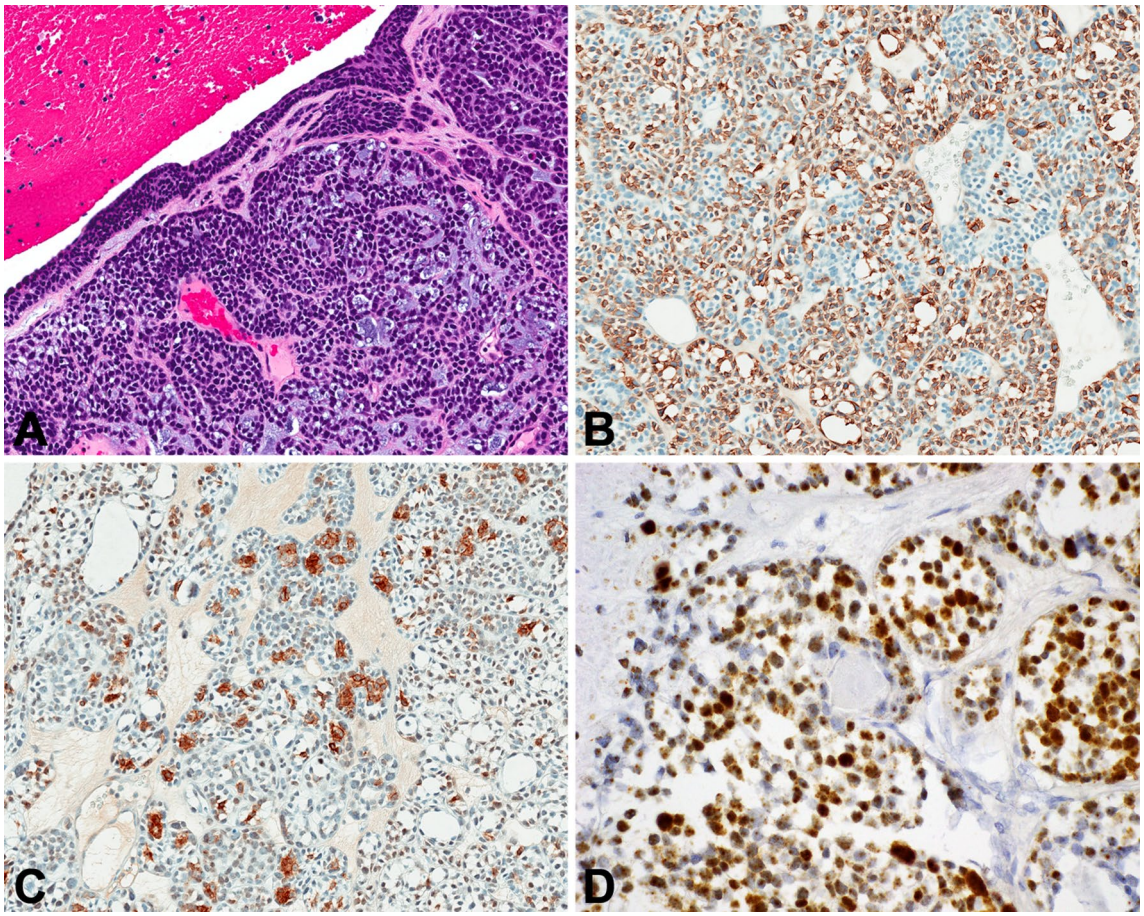

Fig. 6 HPV-related multiphenotypic sinonasal carcinoma. **A** The tumor infiltrates as basaloid nests and strands within a myxoid stroma. Surface epithelial dysplasia is seen overlying the tumor. **B** Myoepithelial cell markers like SMA are positive in an abluminal pattern. **C** CD117 highlights tumor ducts which are often subtle on routine microscopy. **D** The presence of high-risk HPV required for a diagnosis of HPV-related multiphenotypic sinonasal carcinoma. In this case, it was demonstrated by RNA in situ hybridization

is also positive in adenoid cystic carcinoma and other tumors [29, 74].

Adenocarcinoma

Intestinal-Type Adenocarcinomas of Sinonasal Tract

Intestinal-type adenocarcinoma (ITAC) is morphologically and immunophenotypically nearly identical to primary intestinal type adenocarcinomas. Distinction from other glandular-type neoplasms is important as there is a strong etiologic relationship with occupational exposures to wood and leather dusts and because of well recognized aggressive biologic behavior [75–77]. Arranged in various patterns (papillary, tubular, solid), the cells show a cuboidal to columnar appearance, often with nuclear stratification, while a signet-ring pattern is uncommon [78]. Neoplastic cells are typically positive for markers of intestinal differentiation, including cytokeratin 20, CDX2, MUC2 and villin [79, 80]. Because ITAC is essentially identical to intestinal adenocarcinomas, the distinction from a distant metastasis to the sinonasal tract must be made on clinical and radiographic grounds.

The genetic alterations in ITAC are similar to those observed in colorectal adenocarcinoma [81]. *TP53* is most frequently mutated (40–50%) [82–84], while *APC*, *KRAS*, and *BRAF* mutations are found in a subset [81, 85–87].

Non-intestinal-Type sinonasal Adenocarcinoma

Non-intestinal-type adenocarcinoma (non-ITAC) is a heterogenous group of tumors that demonstrate glandular differentiation but are otherwise a diagnosis of exclusion. They

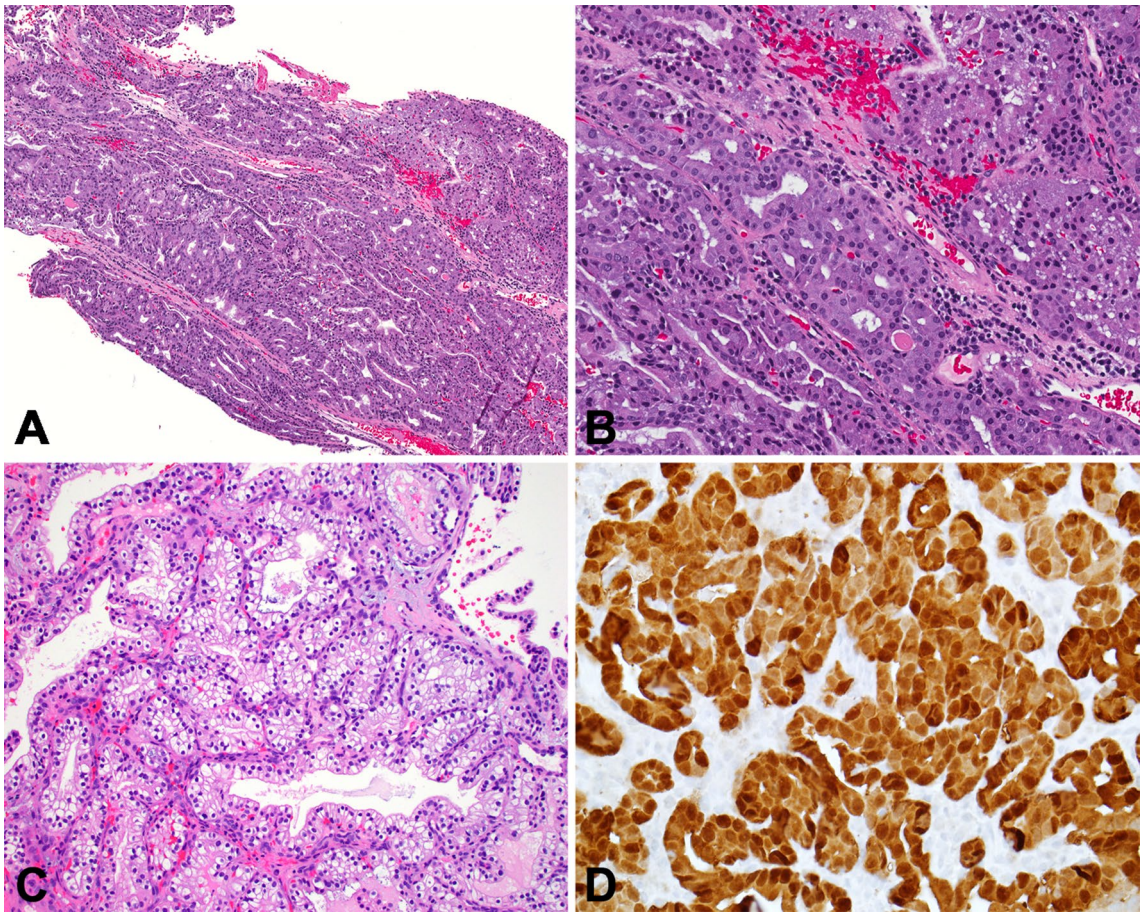

Fig. 7 Low-grade non-intestinal-type sinonasal adenocarcinoma. **A** At low-power, there is a markedly increased number of seromucinous glands within the nasal submucosa. **B** The tumor glands have minimal cellular atypia, but demonstrate architectural atypia in the form of fusion and cribriforming with no intervening stroma. **C** A rare variant known as renal cell carcinoma-like adenocarcinoma has water-clear cytoplasm and prominent cell membranes. **D** S100 protein is usually positive, supporting seromucinous differentiation

not only lack intestinal differentiation but also cannot be better classified as any specific salivary gland-type tumor. Non-ITAC is dichotomous, subdivided into low-grade and high-grade tumors. Low-grade non-ITAC is very indolent and defined by seromucinous-type gland with architectural atypia (fused glands, cribriforming, and papillary formations) in spite of very bland cellular features [88–90] (Fig. 7a, b). Renal cell carcinoma-like adenocarcinoma is a low-grade subtype with optically clear cytoplasm resembling renal cell carcinoma [91, 92] (Fig. 7c). In contrast, high-grade non-ITAC is an aggressive tumor that is histologically poorly differentiated, sometimes showing only focal evidence of glandular differentiation [93]. Low-grade non-ITAC tends to show seromucinous gland-like differentiation, with frequent staining with S100 protein (Fig. 7d), SOX10, and DOG1, while high-grade non-ITAC is variable by immunohistochemistry [94].

Emerging molecular studies suggest that low-grade non-ITAC is heterogeneous with some cases harboring distinctive mutations (e.g., *CTNNB1*) or fusions (e.g., *ETV6::NTRK3*) [95, 96]. The molecular underpinnings of high-grade non-ITAC are not well studied.

Mesenchymal Tumors of the Sinonasal Tract

Sinonasal Tract Angiofibroma

The specific site of origin is known to include the posterolateral wall and roof of the nasal cavity along with lateral nasopharynx, and so the tumor name has been more correctly designated as sinonasal tract angiofibroma, moved out of the nasopharynx chapter in this edition. The pathogenesis is defined by somatic mutations in *CTNNB1*, the ß-catenin encoding gene in the majority of tumors, while nuclear ß-catenin localization is seen immunophenotypically in nearly all cases [97–99]. The tumor is characterized by numerous vessel types and sizes, with variable smooth

muscle wall content, stellate stromal fibroblasts and a variably collagenized stroma. Androgen receptor immunoreactivity in the stromal cells is common [98–100].

Sinonasal Glomangiopericytoma

The unique sinonasal tract origin of this tumor has permitted this soft tissue tumor to remain in the sinonasal tract chapter. The tumor shows a perivascular myoid phenotype, with recurrent missense mutations within *CTNNB1* exon 3, leading to aberrant nuclear translocation and accumulation of ß-catenin, detected immunohistochemically [101–103]. The tumor is composed of an ovoid to spindled syncytium of myoid-type cells set within a richly vascularized stroma, showing a peritheliomatous hyalinization, extravasated erythrocytes, eosinophils, and mast cells [104]. In addition to SMA or MSA reactivity, CD34 reactivity has been showed to be clone dependent, with absent staining with clone My10 [104, 105].

Biphenotypic Sinonasal Sarcoma

Biphenotypic sinonasal sarcoma (BSNS) was originally described as low-grade sinonasal sarcoma with neural and myogenic features. BSNS characteristically arises in the nasal cavity or ethmoid sinus of middle-aged women (Fig. 8a). It is an infiltrative tumor that often entraps invaginations of surface epithelium and is made up of uniform spindled cells arranged as fascicles, often in a herringbone pattern (Fig. 8b, c). Dilated, hemangiopericytoma-like vessels are common. Tumor nuclei are elongated, wavy, and hypochromatic, with few mitotic figures. Rhabdomyoblasts can occasionally be encountered (Fig. 8d).

By immunohistochemistry, BSNS expresses S100 and SMA, although the extent and intensity of the staining varies. EMA, CK-pan, and desmin are variable, and myogenin/MyoD1 highlights rhabdomyoblasts, when present. SOX10 is always negative. Most cases show focal nuclear beta-catenin, and pan-TRK is also often positive. Most

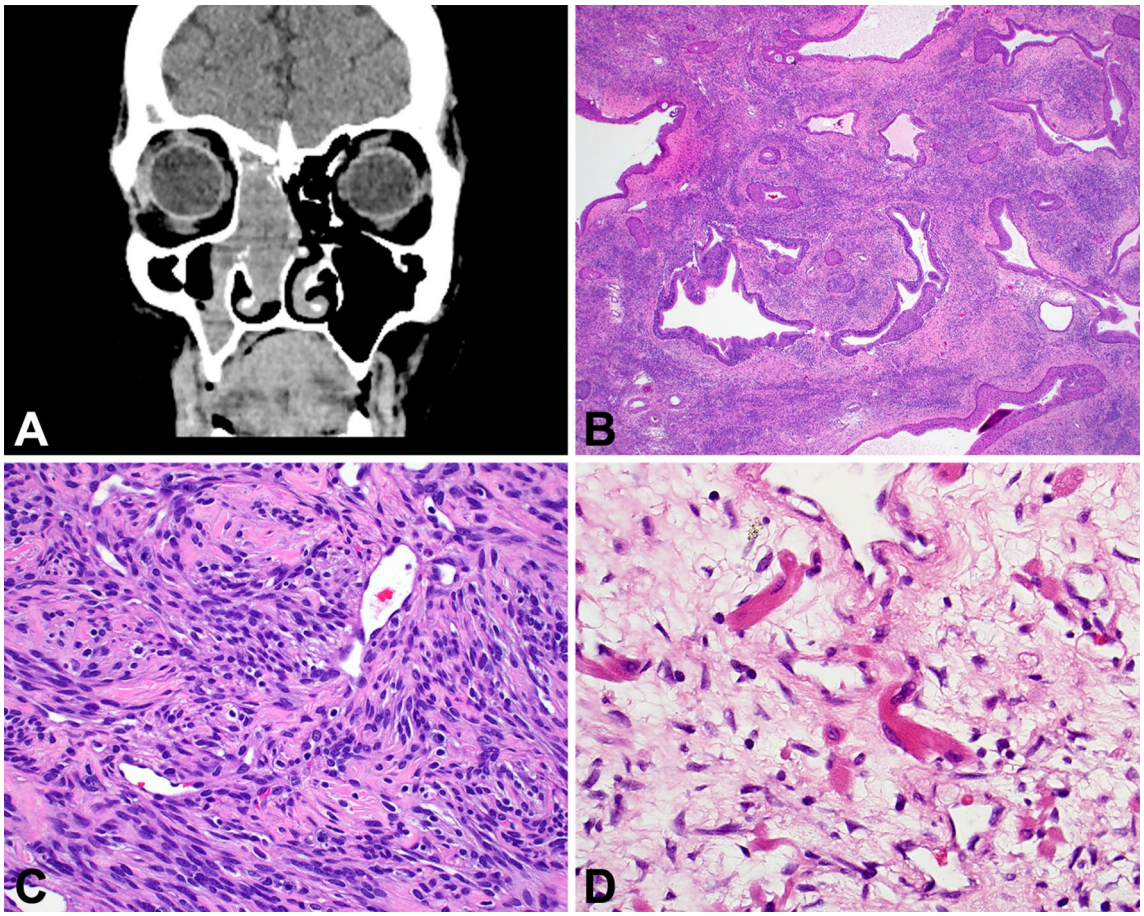

Fig. 8 Biphenotypic sinonasal sarcoma. **A** The right-sided tumor involves the nasal cavity with bone erosion. **B** The tumor is infiltrative and often entraps downward invaginations of surface respiratory-type epithelium. **C** The tumor grows as fascicles of uniform spindle cells with minimal mitotic activity or atypia. Slit-like vessels are common. **D** In some cases the tumor can show overt rhabdomyoblastic differentiation in the form of strap cells

cases of BSNS harbor a fusion involving *PAX3*, most often *PAX3*::*MAML3*. PAX3 immunohistochemistry has been reported to be positive in BSNS, but it can be technically challenging to optimize.

Chordoma

This malignant bone tumor recapitulating notochordal differentiation is a neoplasm that affects the skull base and upper mobile spine, and as such was included in the sinonasal tract chapter rather than the nasopharynx chapter, recognizing it may present in either location. The tumors are usually large and destructive, lytic midline masses. The aberrant expression of TBXT is recognized in the pathogenesis of chordomas, with associated brachyury expression by immunohistochemistry. *PBRM1* and *SETD2* alterations, members of the SWI/SNF complex are frequently identified [106, 107], while homozygous deletion of *SMARCB1* with loss of protein expression is seen in poorly differentiated tumors [108]. Lobules of large epithelioid cells with bubbly cytoplasm are suspended in a myxoid or chondroid matrix, separated by fibrous septa. The co-expression of pancytokeratin, EMA, and S100 protein, along with brachyury (TBXT) are considered characteristic [109, 110].

Other Sinonasal Tumors

Sinonasal Ameloblastoma

Morphologically indistinguishable from gnathic counterparts, sinonasal tract ameloblastoma must be centered in the sinonasal tract, with imaging showing a solid soft tissue-density mass associated with bone remodeling or destruction of the sinus bony walls (Fig. 9). Tumors develop in older patients than jaw counterparts. *BRAF* or *RAS* mutations are detected in jaw lesions along with co-occurring *SMO*

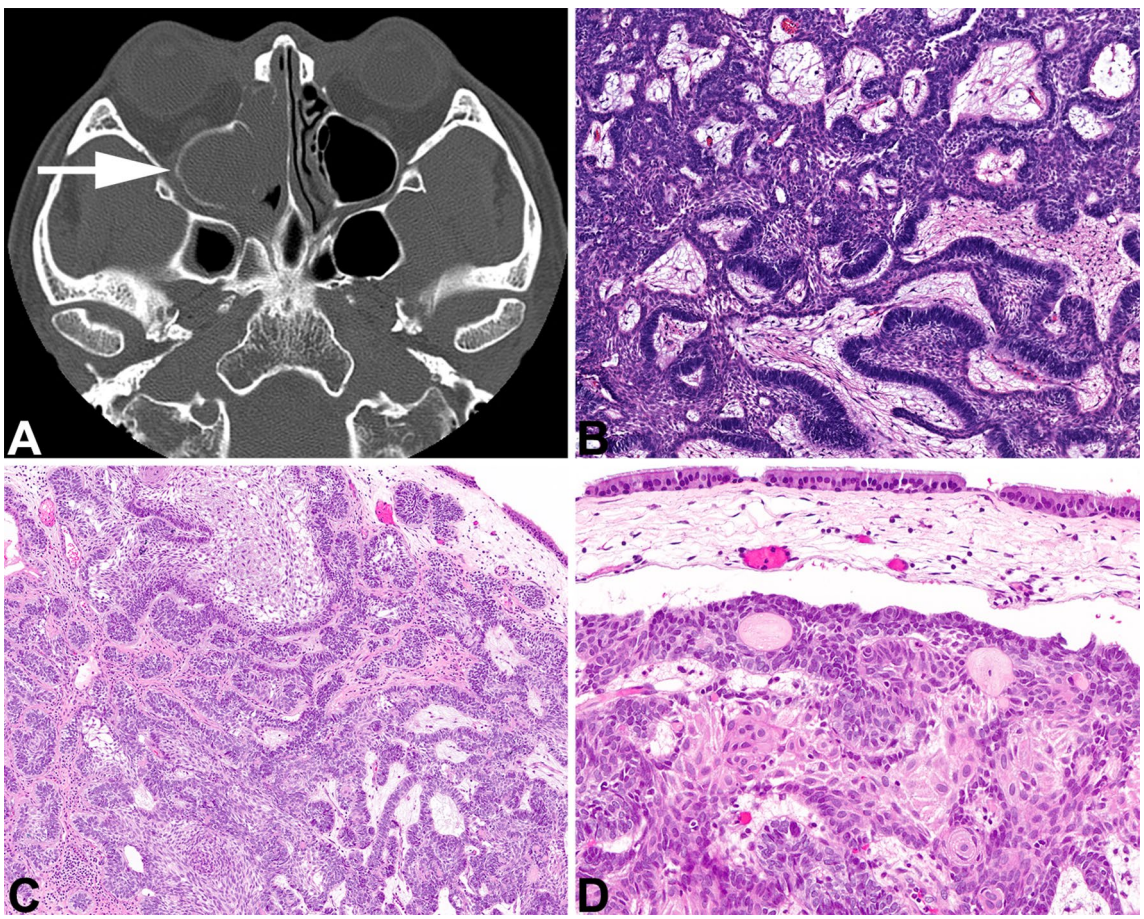

Fig. 9 Sinonasal ameloblastoma. **A** An axial CT shows an ethmoid sinus mass expanding and filling the sinus with a soft tissue-density mass. **B** A central stellate reticulum with ameloblastic palisade. **C** The surface respiratory epithelium overlies the proliferation of ameloblastoma. **D** An intact, ciliated respiratory-type epithelium is seen overlying a proliferation of columnar, basaloid cells associated with a well-developed central stellate reticulum

mutations, and are extrapolated to be similar in sinonasal tract tumors [111–113]. A central stellate reticulum is surrounded by a basaloid, reverse polarized columnar ameloblast-like component, showing well developed subnuclear vacuoles (Fig. 9).

Adamantinomatous Craniopharyngioma

Craniopharyngioma is separated into adamantinomatous and papillary, with the former documented to occasionally exclusively present in the sinonasal tract or nasopharynx. For taxonomic clarity, the tumor was included in the sinonasal tract rather than nasopharynx chapter (previously in 4th edition), since Rathke cleft origin is considered part of the nasopharynx embryologic development and this is an ectopic presentation in the sinonasal tract. The tumor shows a mixed solid and cystic benign squamous epithelium associated with a stellate reticulum and anucleated ghost-like remnants of squamous cells (referred to as "wet keratin"). There is a blending of these elements (Fig. 10), frequently showing calcification and with secondary changes to ruptured cyst content quite common. Tumor cells express p63, CK5/6, CK903, CK7 and SOX9 [114–116]. Nuclear ß-catenin expression is usually spatially restricted to small epithelial whorls, and may be detected even when *CTNNB1* mutations are not identified [117–119], although activating *CTNNB1* mutations are clonal drivers of most tumors. There are histologic and molecular parallels with odontogenic tumors, hence occasionally teeth will be seen in adamantinomatous craniopharyngioma [120].

Meningioma of the Sinonasal Tract

Imaging studies are crucial in documenting the exact extent, location, and presence or absence of intracranial involvement, as meningiomas may secondarily involve the sinonasal tract much more commonly than arising ectopically [121–123]. Further, as many meningiomas will express somatostatin receptor 2a (SSTR2a) [124–126], imaging studies based on somatostatin receptors (such

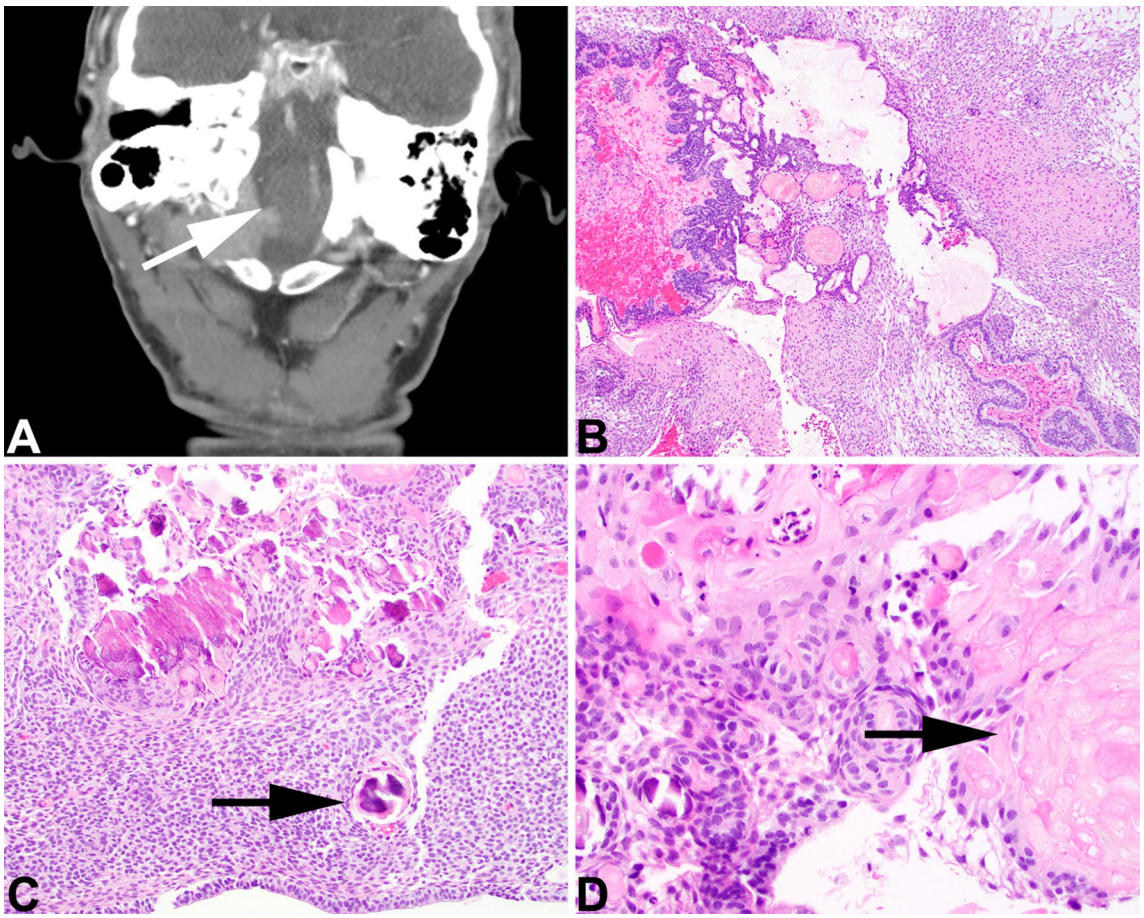

Fig. 10 Adamantinomatous craniopharyngioma. **A** A destructive skull base mass extends into the nasopharynx (white arrow). **B** A solid and cystic proliferation of stellate reticulum and anucleated squamous epithelium. **C** A cellular stellate reticulum with numerous calcifications (black arrow). **D** Wet keratin is identified as anucleated squamous cell adjacent to the epithelium

as 68 Ga-DOTATATE PET-CT) may further aid in tumor detection and potentially provide alternative treatment options [127, 128]. If atypical features are detected (increased mitoses, tumor necrosis, sheet-like growth, pleomorphism), detection of *TERT* promoter mutations may impact management as there is an associated lower overall survival [129, 130].

Olfactory Neuroblastoma

Given the unique anatomic predilection of this tumor, even though there is neuroendocrine differentiation, olfactory neuroblastoma (ONB) was retained in the sinonasal tract chapter. The derivation from the specialized sensory olfactory neuroepithelium in part dictates involvement of the cribriform plate and/or adjacent structures. As a neuroendocrine tumor, somatostatin receptor expression is seen in most ONBs, which allows for ^{68}Ga-DOTATATE PET-CT to potential aid in documenting disease, recurrence, and/or metastasis [131–134], in addition to radionuclide therapy options. The histologic features of uniform cells with a salt-and-pepper nuclear chromatin arranged in sharply demarcated lobules and nests help to make low grade tumors easily recognizable; but with greater nuclear pleomorphism, lack of neuropil, tumor necrosis, and increased mitoses, high grade tumors become more difficult to recognize. Tumor grading using the Hyams grading system is advocated as there are prognostic outcome differences [135–137]. Rare divergent differentiation (melanin, ganglion cells, rhabdomyoblasts, true glands, clear cells) may hamper recognition of the tumor type. Use of a selected panel of immunohistochemistry studies helps to support the diagnosis and to exclude tumors in the differential diagnosis [134, 138–141].

Conclusions

With two major new entities included in this edition, along with several emerging entities discussed, it is important to appreciate that for the most part, sinonasal tract tumors are still defined and recognized by their histological features, with the addition of selected ancillary tests to narrow the diagnosis for possible differences in treatment and prognostication. Further, it should be realized that classification based on tumor type (soft tissue, hematolymphoid, melanocytic, neuroendocrine) has been introduced to supplement anatomic site for tumors which are known to affect more than one site. It is hoped that this summary spurs the reader to tackle the knowledge gaps and to report new findings such that the next classification update in 5 years will continue to better the understanding of tumor biology and thereby improve treatment of patients because of it.

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Declarations

Conflict of interest All authors have contributed to this work and both authors declare they have no conflict of interest as it relates to this study.

Ethical Approval All evaluations performed in this analysis do not involve any individual patient's data, but was still performed in accordance with the ethical standards of the institutional review board (IRB #5968) of Southern California Permanente Medical Group. The opinions or assertions contained herein are the private views of the authors.

Consent Statement No personally identifiable information is included and thus informed consent is not applicable.

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