

# Update from the 4th Edition of the World Health Organization Classification of Head and Neck Tumours: Tumors of the Nasal Cavity, Paranasal Sinuses and Skull Base

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**Abstract** The sinonasal tract remains an epicenter of a diverse array of neoplasia. This paper discusses changes to the WHO classification system of tumors involving this area. In particular, seromucinous hamartoma, NUT carcinoma, biphenotypic sinonasal sarcoma, HPV-related carcinoma with adenoid cystic features, SMARCB1-deficient carcinoma, and renal cell-like adenocarcinoma are discussed.

**Keywords** Nasal · Sinonasal · Sinus · Human papillomavirus · WHO · NUT carcinoma · Seromucinous hamartoma · Biphenotypic sinonasal sarcoma · Adenoid cystic · INI1

## Introduction

The sinonasal tract can be involved by a vast array of neoplasia, with phenotypic diversity surpassing what can be seen at most sites throughout the upper aerodigestive tract and even throughout most parts of the body. The 4th edition of the *World Health Organization Classification of Head and Neck Tumours* includes three new, relatively well-defined entities: seromucinous hamartoma, NUT carcinoma, and biphenotypic sinonasal sarcoma. In addition,

a handful of new, less-defined tumor types were included either as provisional entities or mentioned in the differential diagnosis of other tumors. Here, we will describe what has remained unchanged and what has changed in the new WHO classification system.

## Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) remains the most common form of neoplasia within the sinonasal tract, although it makes up a smaller proportion of neoplasia here than at other sites within the upper aerodigestive tract, approximately 65–70% of carcinomas [1]. As at most other sites, smoking of tobacco products is the greatest risk factor for disease, although other exposures such as to solvents, wood dust, and leather dusts put patients at risk. Benign sinonasal papillomas as well as high-risk human papillomavirus (HR-HPV) infection also put patients at risk.

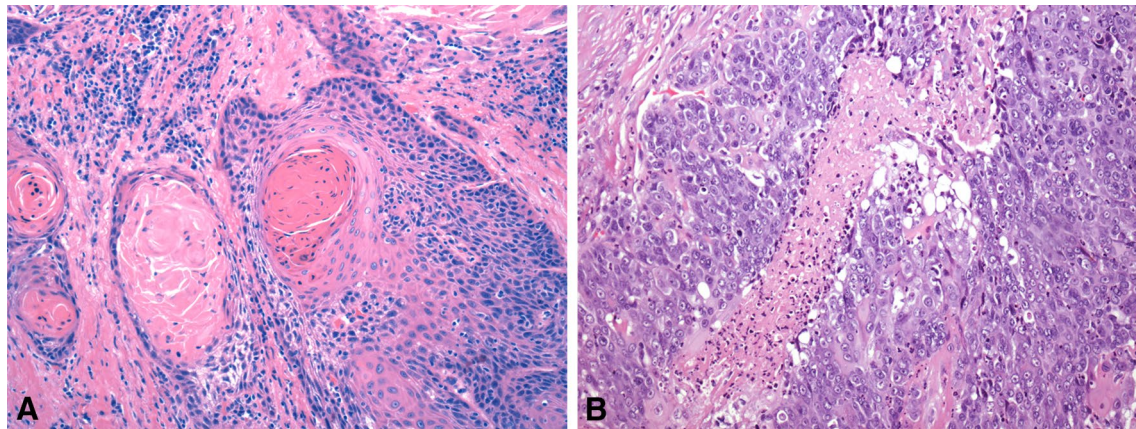
Histologic classification of SCC in the sinonasal tract remains similar to that at other sites. Most tumors are classified as either keratinizing or non-keratinizing, a distinction of possible relevance due to the fact that non-keratinizing SCC at this site is much more likely than keratinizing SCC to be secondary to HR-HPV infection (41 vs. <5%) (Fig. 1) [1–4]. Although a number of descriptive names have been applied to non-keratinizing SCC (e.g., Schneiderian carcinoma, transitional cell carcinoma, cylindrical cell carcinoma, etc.), the WHO chose to use the most accepted and straightforward terminology here. Other variants of SCC should be diagnosed as such (e.g., basaloid SCC, papillary SCC, spindle cell carcinoma, etc.). It is of note that at this site approximately 45% of basaloid SCCs and 80% of papillary SCCs are associated with HR-HPV [2, 5]. Lymphoepithelial carcinoma, a variant associated with *Epstein-Barr virus* (EBV) infection also retains its descriptive

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**Fig. 1** Squamous cell carcinoma. **a** Typical keratinizing squamous cell carcinoma of the sinonasal tract with abundant keratin formation. **b** Non-keratinizing squamous cell carcinoma with ribbons of immature squamous cells

name, actually at odds with the names used for the same entity in the nasopharynx [6].

### Other Carcinomas

Adenocarcinomas are classified as previously with the most important distinction between intestinal-type adenocarcinomas (ITACs) and non-intestinal sinonasal adenocarcinomas (SNACs) (Fig. 2). In general, this can be justified given the distinct histological and immunohistochemical features of ITAC as well as its very strong association with wood and other dust exposures [7–12].

Non-intestinal adenocarcinomas remain a group of phenotypically diverse tumors, although there is much more homogeneity with the tumors classified as low-grade. Low-grade non-intestinal SNACs are typically papillary and / or tubular and composed of monomorphic cuboidal or columnar cells with rare mitotic figures [13–16]. Tumors are free of necrosis. They uncommonly recur and do not lead to patient death. High-grade non-intestinal SNACs can show a variety of histologic features [13, 17]. Many have abundant solid growth with only focal glandular differentiation. More nested growth and cells with abundant eosinophilic cytoplasm can be seen. By definition, such tumors are high-grade and mitotic figures and necrosis are frequently present. One potentially reproducible group of tumors within the category non-intestinal SNACs has been noted that resembles conventional clear cell carcinoma of the kidney (sinonasal renal cell-like adenocarcinoma). These are discussed below.

Neuroendocrine carcinomas at this site are uncommon. As tumors similar to pulmonary carcinoid tumors or “atypical” carcinoid tumors are almost unheard of here, they are not discussed. Instead the authors use the term “neuroendocrine carcinoma” at this site to encompass high-grade

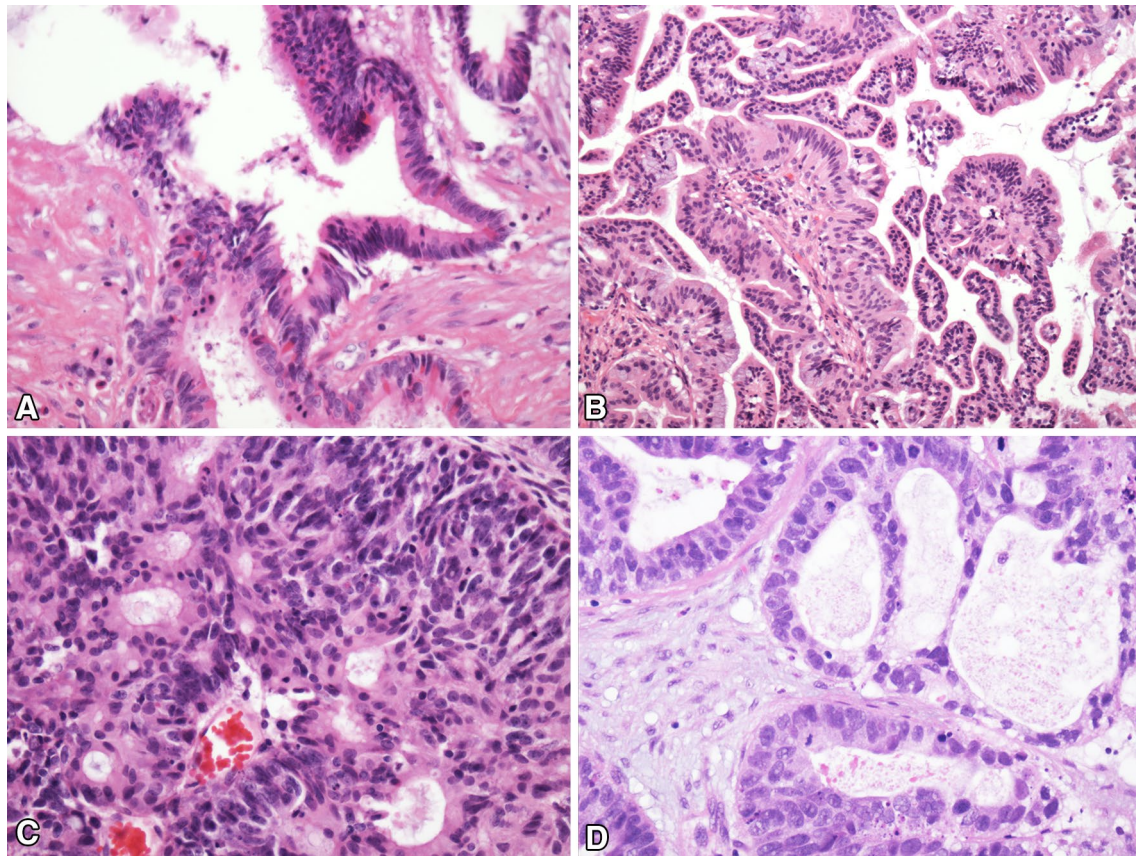
lesions, both small cell carcinoma and large cell neuroendocrine carcinoma [18, 19]. Uncommonly, either tumor may be associated with squamous cell carcinoma or adenocarcinoma [20]. There are now reports of tumors secondary to HR-HPV and previous irradiation is considered a risk factor [2, 21, 22].

Sinonasal undifferentiated carcinoma (SNUC) remains a diagnosis of exclusion. Neither overt squamous or glandular differentiation can be present [23]. Tumors associated with EBV-infection are better classified as lymphoepithelial carcinomas as mentioned above. Those tumors associated with translocations of the gene encoding nuclear protein of the testis (NUTM1) are called NUT carcinomas (see below). The absence of INI1 expression (or SMARCB1 loss) as seen with tumors of the kidney and elsewhere may come to define a unique entity as well (see also below). Finally, the definitive distinction of SNUC from large cell neuroendocrine carcinoma remains problematic, as expression of neuroendocrine markers is acceptable with tumors diagnosed as SNUCs.

### Other Tumors More or Less Distinct to the Sinonasal Tract

Teratocarcinoma is discussed within the section devoted to epithelial malignancies. By definition, the tumors must lack germ cell elements aside from those resembling teratoma. The tumors also, by definition, have carcinomatous components and sarcomatous elements [24]. They remain poorly understood other than that they do not resemble germ cell tumors at other sites of the body. Indeed, they continue to appear to be clinically, histologically, and molecularly unique lesions that seem to most resemble carcinomas [25].

Olfactory neuroblastomas (ONBs) are still considered neuroectodermal tumors and are discussed in a section



**Fig. 2** Adenocarcinoma. **a** Intestinal-type adenocarcinoma with mucin production. **b** Low-grade sinonasal adenocarcinoma with typical papillary architectures. **c, d** Two examples of high-grade sinonasal adenocarcinoma showing some of the heterogeneity that can be seen

with Ewing sarcoma/peripheral neuroectodermal tumor (PNET) and sinonasal melanoma. It remains essential to distinguish these tumors from lesions showing definite epithelial differentiation and from Ewing sarcoma/PNET. Fortunately, ONBs show little or no expression of keratins by immunohistochemistry and do not have EWSR1 rearrangements as seen with Ewing sarcomas/PNETs [26, 27]. Of note, recent papers have shown that keratin expressing Ewing sarcomas/PNETs (adamantinoma-like Ewing family tumors) do occur in the sinonasal area [28]. It is imperative to recognize such lesions and not to classify them as carcinomas.

Extranodal NK/T cell lymphoma, nasal type is so designated because of its proclivity to involve the sinonasal tract [29, 30]. It is the most common lymphoma to involve the area in eastern Asia and parts of Central and South America. The lymphomas must be distinguished from other high-grade malignancies that can affect the area and from other lymphoproliferative tumors. Fortunately, with modern immunohistochemical techniques, this is seldom a problem. Other lymphoid tumors are to be classified as per the WHO system for classification for those tumors. These lesions are all discussed in more depth elsewhere.

## Other Tumors

Mesenchymal neoplasms involving the sinonasal tract that are classified as soft tissue tumors are elsewhere. The exception here is the now well-recognized biphenotypic sinonasal sarcoma (discussed below). Of note, while glomangiopericytomas can be seen at soft tissue locations elsewhere, they are by far most often seen in the sinonasal tract [31]. Recent research has shown recurrent CTNNB1 mutations in these lesions with beta-catenin nuclear accumulation seen by immunohistochemistry [32]. Only a few other malignant lesions are discussed within the text including fibrosarcoma, a diagnosis becoming very uncommon.

Salivary neoplasms of the sinonasal tract are classified as such and the changes made within the salivary gland portion of the text should be instituted with sinonasal tumors. There are no unique salivary gland tumors of the sinonasal tract unless one regards seromucinous hamartoma (discussed below) as a salivary gland-type tumor.

## New Lesions

### Seromucinous Hamartoma

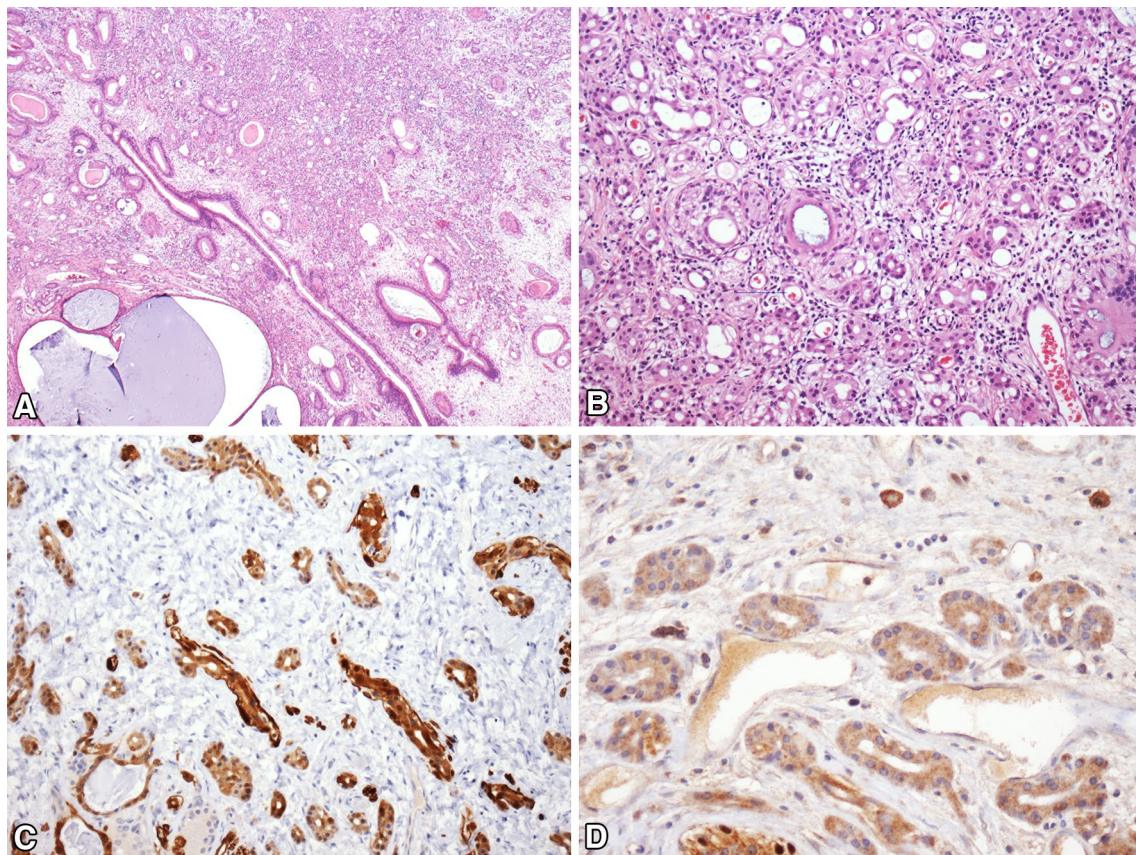
In the previous WHO classification system of tumors of the head and neck, seromucinous hamartoma (SMH) was considered synonymous with respiratory epithelial adenomatoid hamartoma (REAH). Weinreb et al. have since described 7 cases of SMH involving the sinonasal tract [33]. Patients included four men and three women and ages ranged 14–85 years. The majority of lesions occurred on the posterior nasal septum and one occurred on the lateral nasal wall. Nasal obstruction and epistaxis were the most common presenting symptoms.

The underlying glandular component of SMHs consists predominately of seromucinous glands (Fig. 3). Larger glands lined by a respiratory-type epithelium, however, are invariably present similar to what are seen with REAHs [33]. Smaller tubules, ducts and glands are present in lobular and more haphazard arrangements, lined by bland cuboidal cells that rarely contain dark, eosinophilic granular material. The smaller glands may have little intervening

stroma and can appear to be back to back. The glands may be surrounded by stromal hyalinization. A chronic lymphoplasmacellular infiltrate is typically present.

The immunohistochemical findings are similar to those seen with REAHs but reflect the disproportionate number of seromucinous glands present. Both respiratory and seromucinous glands are immunoreactive with antibodies to CK7 and CK19 and not with antibodies to CK20 [33, 34]. p63 and high molecular weight CK immunostaining can be used to highlight myoepithelial cells surrounding the large glands and some of the seromucinous glands, whereas muscle specific actin will not stain the basal cells. Of note, the seromucinous glandular proliferation typical of SMH shows little or no basal cell staining [33]. Weinreb et al. reported that the glandular cells of seromucinous hamartomas are typically immunoreactive with antibodies to S100 protein, whereas Ozolek et al., reported the larger glands of REAHs to be non-reactive [33, 34].

Good criteria do not exist for the definitive distinction between REAHs with florid seromucinous glandular proliferation, seromucinous hamartomas, and low-grade non-intestinal SNACs. In a series of 29 low-grade non-intestinal



**Fig. 3** Seromucinous hamartoma. **a** Low-power image showing abundant small seromucinous glands with occasional larger, cystically dilated glands. **b** High-power showing bland seromucinous

glands with back-to-back architecture. **c** S100 immunostain highlights the bland seromucinous glands. **d** p63 immunostain shows an absence of basal and myoepithelial cells

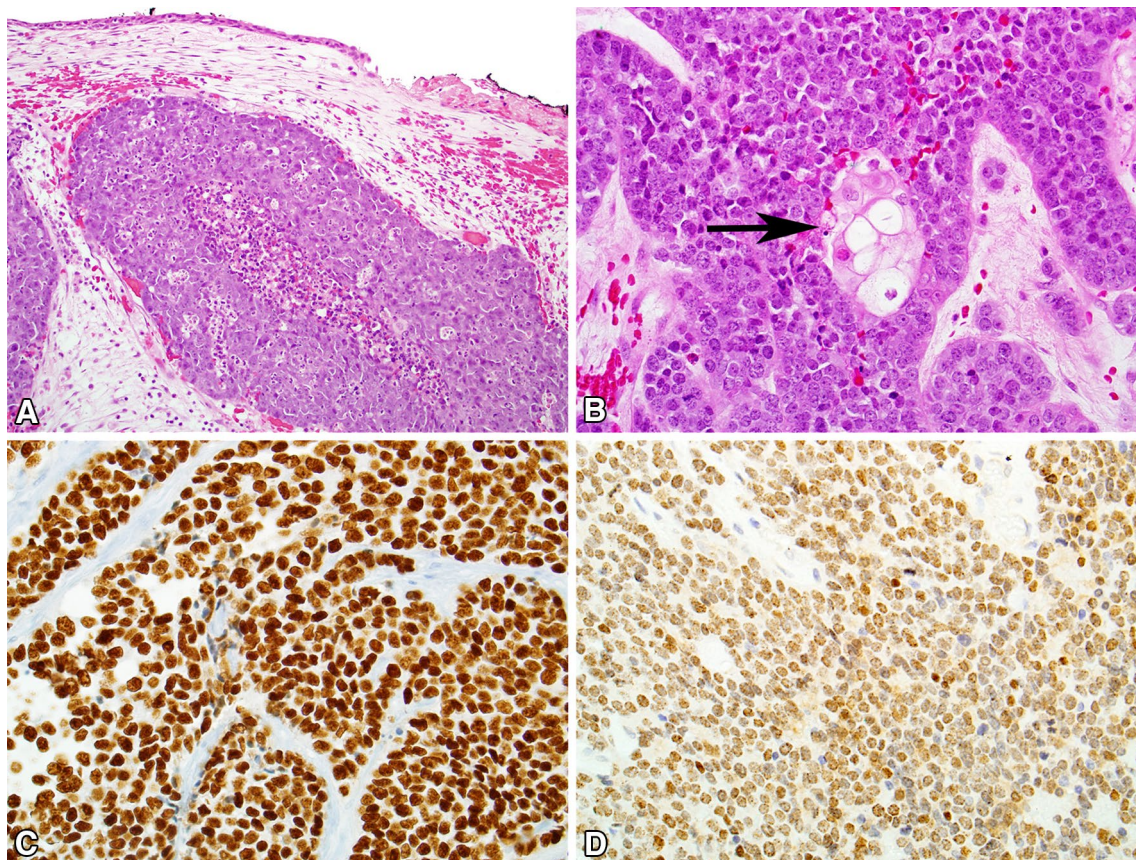
adenocarcinomas, 6 were associated with polypoid lesions that had some features similar to those of REAH [35]. That said, the seromucinous hamartomas described by Weinreb et al. have similar histologic and immunohistochemical features including a lack of myoepithelial cells surrounding the seromucinous glandular proliferations [33]. Recurrence for either lesion is uncommon (only 20% of the lesions reported by Weinreb et al. recurred) and metastases are only very rarely seen with sinonasal low-grade non-intestinal adenocarcinomas. Some authors have likened the glandular proliferation of SMH to microglandular adenosis of the breast [36]. Indeed, it may be that “adenosis” or “adenoma” is truly the best appellation for these benign glandular proliferations.

### NUT Carcinoma

NUT carcinoma, also known as NUT midline carcinoma or t(15;19) carcinoma, was initially described as a mediastinal tumor in 1991 [37, 38]. NUT carcinoma is rare, with fewer than 100 cases reported [39–43]. It can affect

patients of any age though is most common in children and young adults (median, 21.9 years), and has a slight female predominance. NUT carcinoma most often arises in the sinonasal tract and mediastinum, though it can affect virtually any site [39, 42, 44]. Patients with NUT carcinoma present with non-specific symptoms of a rapidly growing mass, including nasal obstruction, epistaxis, orbital symptoms, and pain [45, 46]. Imaging typically reveals an extensively infiltrative tumor with frequent involvement of the orbit and cranial cavity [45, 46]. About half of cases have regional and/or distant metastases on presentation [42].

Cytologic smears of NUT carcinoma are typically highly cellular, with monotonous, small to midsize, primitive-appearing cells in clusters or as single cells. The tumor cells have round to oval nuclei that appeared mostly naked and devoid of cytoplasm [47, 48]. Histologically, NUT carcinoma grows as undifferentiated cells in nests and sheets within the sinonasal submucosa (Fig. 4). There is no carcinoma-in situ component. The carcinoma is highly infiltrative, and demonstrates necrosis and high mitotic rates. An intratumoral acute inflammatory infiltrate is common. Two



**Fig. 4** NUT carcinoma. **a** NUT carcinoma grows as nests of tumor cells in the sinonasal submucosa, without a surface epithelial component. **a** neutrophilic infiltrate is seen. **b** Most cases of NUT carcinoma demonstrate focal squamous differentiation (*arrow*) in an abrupt pat-

tern. **c** NUT carcinoma is usually positive for p40. **(D)** The diagnosis of NUT carcinoma can be confirmed with diffuse immunoreactivity for NUT protein, typically with a distinctly speckled pattern

histologic hallmarks of NUT carcinoma are (1) monotonous tumor cells and (2) a peculiar pattern of keratinization often described as “abrupt.” Rarely, foci of glandular or even mesenchymal differentiation may be encountered. By immunohistochemistry, NUT carcinoma is positive for cytokeratins, often positive for squamous markers like p40, p63 and CK5/6, and occasionally positive for neuroendocrine markers, p16, or even TTF-1. The differential diagnosis of NUT carcinoma is very broad, and includes the numerous other “small round cell tumors” that occur in the sinonasal tract including olfactory neuroblastoma, melanoma, primitive neuroectodermal tumor, squamous cell carcinoma, and sinonasal undifferentiated carcinoma.

NUT carcinoma is defined by rearrangements of the NUTM1 gene on chromosome 15q14 [49]. The most common fusion partner is BRD4 (in about 70% of cases). The diagnosis of NUT carcinoma depends on demonstrating evidence of this rearrangement. While this can be done by fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR), conventional cytogenetics, or targeted next-generation sequencing approaches, it can also be confirmed immunohistochemically with >50% nuclear expression of the NUT protein by the monoclonal antibody C52 (Cell Signaling Technologies, Danvers, MA) [39, 40, 50].

The prognosis of NUT carcinoma is poor, with a median overall survival of 9.8 months [42]. There is some evidence that NUT carcinomas with variant rearrangements not involving BRD4 may have longer survival [42, 51].

### Biphenotypic Sinonasal Sarcoma

Biphenotypic sinonasal sarcoma (BSNS) was initially described in 2012 as “low-grade sinonasal sarcoma with neural and myogenic differentiation,” which remains a synonym for BSNS [52]. BSNS is rare, with fewer than 50 cases reported. BSNS tends to arise in middle-aged women (2:1 female to male ratio, mean 52 years), and although it can arise anywhere in the sinonasal tract, it has a predilection for the superior aspects of the nasal cavity and ethmoid sinuses [52–55]. Affected patients present with non-specific symptoms like nasal obstruction and facial pressure.

The histopathology of BSNS is that of an infiltrative proliferation of spindled cells arranged as fascicles or in a “herringbone” pattern (Fig. 5). Hemangiopericytoma-like (“staghorn”) vessels are common. A characteristic feature of BSNS is its propensity to entrap benign downward invaginations of sinonasal epithelium. These glands can become proliferative and undergo squamous or oncocyctic metaplasia, mimicking sinonasal papillomas. The nuclei of BSNS are pale, slender, and uniform. Mitotic figures are uncommon, and necrosis is absent. By immunohistochemistry, BSNS shows varying degrees of staining for S100, actin, and calponin. Beta-catenin is usually positive in a

nuclear distribution focally [56]. BSNS may also exhibit focal staining for desmin, myogenin, EMA, and cytokeratins [52–55]. Despite the consistent S100 positivity, SOX10 is always negative. BSNS characteristically harbors rearrangements of *PAX3*, with the most common partner being *MAML3* [54]. Studies have also identified both *PAX3-NCOA1* and *PAX3-FOXO1* fusions of alveolar rhabdomyosarcoma, which appear to be associated with focal rhabdomyoblastic differentiation in BSNS [53, 57]. Before it was recognized, BSNS was likely to be misdiagnosed as cellular schwannoma, malignant peripheral nerve sheath tumor, solitary fibrous tumor, glomangiopericytoma, and synovial sarcoma.

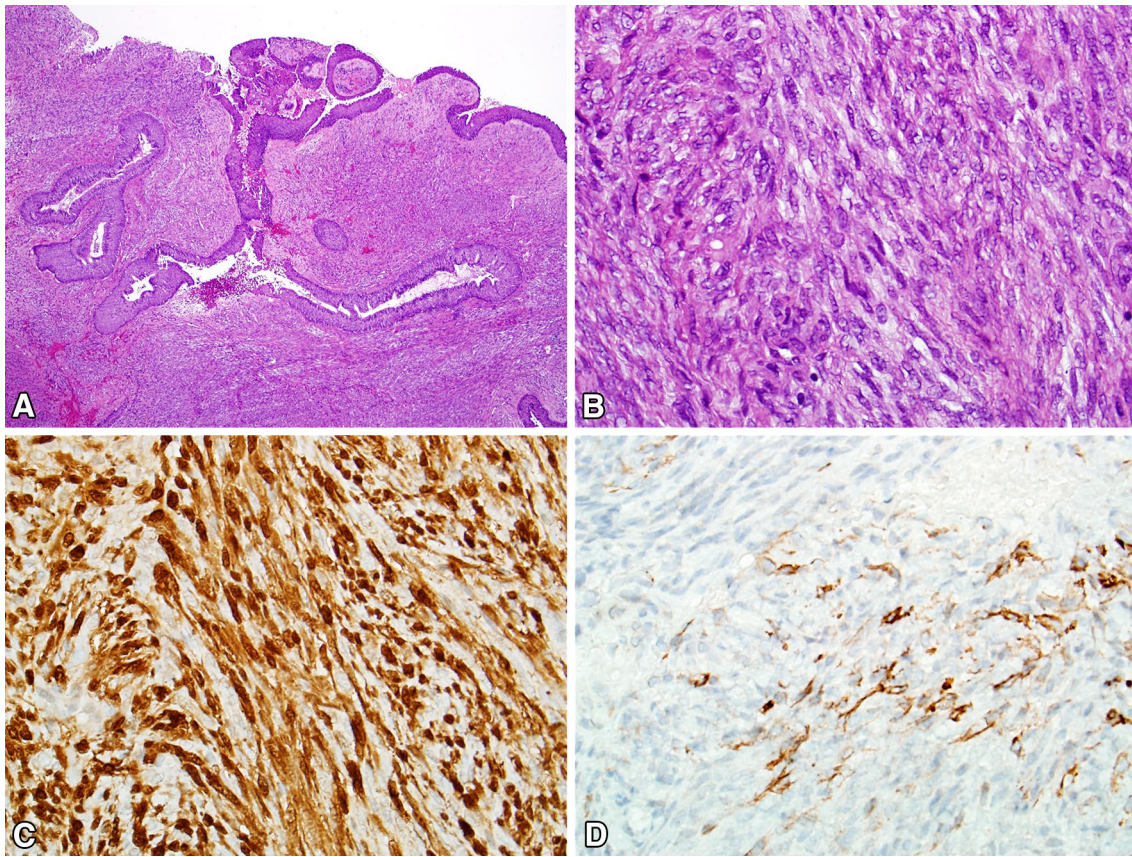
BSNS tends to demonstrate slow, progressive growth. While almost half of patients with BSNS experienced local recurrences, none of the tumors have metastasized, and only one patient to date has died of their disease [52, 54, 56].

### Emerging Entities

#### HPV-Related Sinonasal Carcinomas Including HPV-Related Carcinoma with Adenoid Cystic Features

HPV-related carcinomas of the head and neck have a striking predilection for the oropharynx, where up to 80% of carcinomas are HPV-positive compared to 5% or fewer in sites like the oral cavity and larynx [58–62]. In the oropharynx, HPV-related carcinomas are histologically and clinically distinct from their HPV-negative counterparts, and as a result, in the new edition of the WHO, squamous cell carcinomas of the oropharynx are classified by HPV status. As mentioned above, several recent papers have shown that the sinonasal tract is the second anatomic “hot spot” from which HPV-related carcinomas can arise, with 20–30% of sinonasal carcinomas harboring transcriptionally-active, high-risk forms of HPV [25–27]. In the new edition of the WHO classification, however, “HPV-related squamous cell carcinoma” is not regarded as a separate tumor entity as it is in the oropharynx, largely because it lacks clinical and pathologic distinctness. For example, while most HPV-related sinonasal carcinomas have a histologic appearance that conforms to the WHO entity of non-keratinizing squamous cell carcinoma, only about 41% of sinonasal non-keratinizing squamous cell carcinomas are HPV-positive [2–4]. Perhaps more importantly, HPV positivity has not been proven to confer the same excellent prognosis for carcinomas of the sinonasal tract as it does for carcinomas of the oropharynx, although studies have been suggestive [2, 4, 63].

The histologic variants of HPV-positive carcinoma that are encountered in the oropharynx (e.g., small cell



**Fig. 5** Biphenotypic sinonasal sarcoma. **a** Biphenotypic sinonasal sarcoma often demonstrates entrapment of downward extensions of surface epithelium, a pattern that can mimic inverted papilloma. **b** The tumor typically consists of fascicles of uniform spindled cells

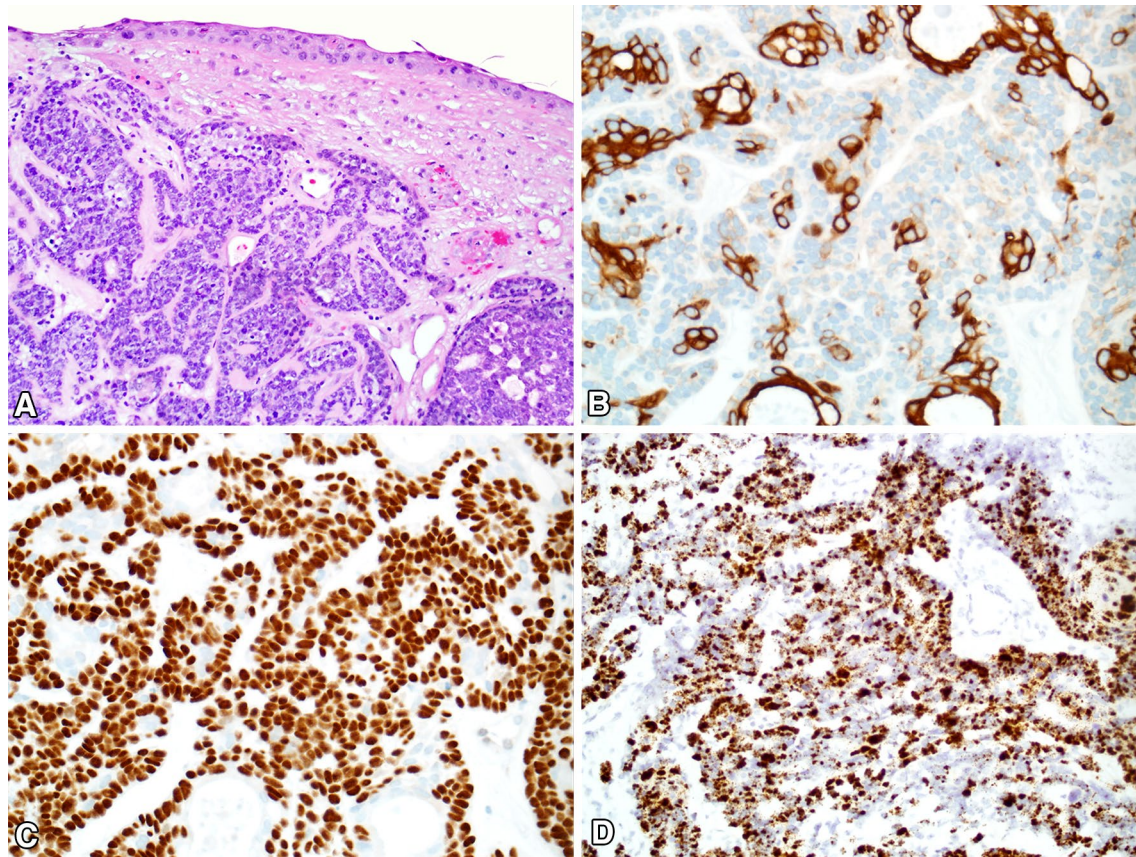
with elongated, hypo chromatic nuclei growing in a herringbone pattern. **c** Biphenotypic sinonasal sarcoma demonstrates varying degrees of immunostaining for S100. **d** Most cases are positive for smooth muscle markers like actin

carcinoma, adenosquamous carcinoma, papillary squamous cell carcinoma) have also been described in the sinonasal tract [2]. There is one histologic variant, however, that has only been described in the sinonasal tract. This variant has features of both a surface-derived and salivary gland carcinoma, and has been referred to as “sinonasal HPV-related carcinomas with adenoid cystic-like features.” [64] Nine cases of HPV-related carcinomas with adenoid cystic-like features have been published, consisting of seven women and two men ranging in age from 40 to 75 years (mean, 57) [64, 65]. Patients have presented with nasal obstruction and/or epistaxis, and often at high-stage.

At the histologic level, sinonasal HPV-related carcinoma with adenoid cystic like features consists of highly cellular proliferations of basaloid cells growing mostly as solid nests and trabeculae, with most cases also exhibiting focal cribriform structures with microcystic pseudoductal spaces, reminiscent of adenoid cystic carcinoma (Fig. 6). The predominant basaloid cells have hyperchromatic, angulated nuclei, a high nuclear-to-cytoplasmic ratio, and often demonstrate cell spindling or clearing. In addition to the

basaloid cells, these tumors also demonstrate inconspicuous ducts comprised of eosinophilic cuboidal cells. Squamous differentiation has not been seen within the invasive tumor, but most cases demonstrate squamous dysplasia of the surface epithelium. Mitotic rates are usually high, and necrosis is often present. Unlike true adenoid cystic carcinoma, perineural invasion is uncommon.

At the immunohistochemical level, sinonasal HPV-related carcinoma with adenoid cystic like features is essentially identical to true adenoid cystic carcinoma, with two cell populations. The basaloid tumor cells are myoepithelial in nature, with immunostaining for one or more of these markers: S100, calponin, p63, p40, and actin. In contrast, the tumor ducts are negative for myoepithelial immunostains but positive for c-kit and CK7. By definition, the tumor cells are positive for high-risk types of HPV. Interestingly, most reported cases have harbored the uncommon HPV type 33, and neither type 16 or 18 have been reported in this tumor [64, 65]. Unlike true adenoid cystic carcinomas, HPV-related carcinoma with adenoid cystic like features does not harbor *MYB* gene fusions. The differential



**Fig. 6** HPV-related adenoid cystic-like carcinoma. **a** Sinonasal HPV-related carcinoma with adenoid cystic-like features grows as nests and cribriform structures. Squamous dysplasia is seen in the overlying surface epithelium. **b** An immunostain for CK7 highlights

the ductal structures. **c** An immunostain for p40 highlights only the basaloid myoepithelial cells, sparing the ducts. **d** The carcinoma is strongly positive for high-risk HPV by RNA in situ hybridization

diagnosis of sinonasal HPV-related carcinoma with adenoid cystic-like features includes salivary gland neoplasms like adenoid cystic carcinoma, as well as other HPV-related variants like basaloid squamous cell carcinoma and adenosquamous carcinoma.

HPV-related carcinoma with adenoid cystic like features was considered as a possible new entity in the 4th edition of the WHO classification, but it was ultimately included as a provisional entity, listed in the differential diagnosis of non-keratinizing squamous cell carcinoma. The reservation for its inclusion focused on the low number of reported cases, its variable histology that often shows at least focal overlap with conventional non-keratinizing SCC, and its as-of-now uncertain prognostic significance.

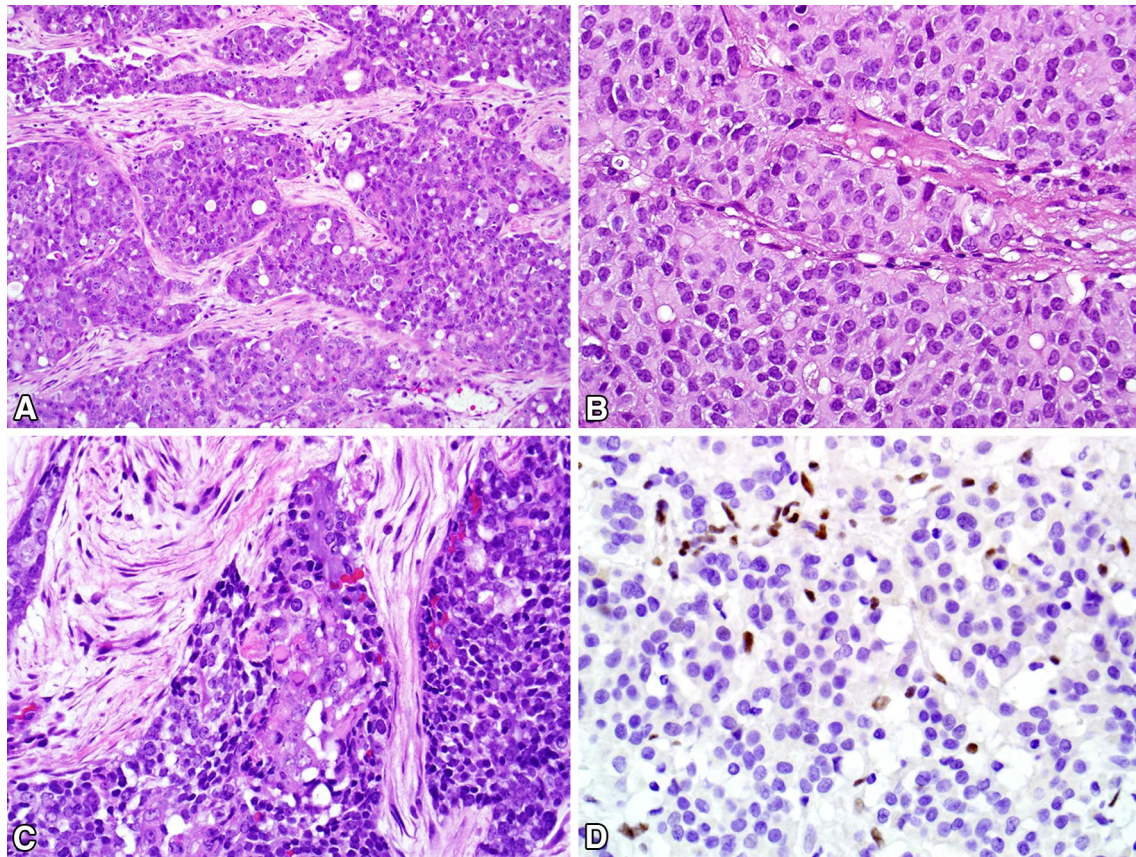
### SMARCB1 (INI-1) Deficient Sinonasal Sarcoma

*SMARCB1* (*INI-1*) is a tumor suppressor gene located on chromosome 22q11.2; its inactivation has been implicated in the pathogenesis of a family of malignant neoplasms that includes pediatric atypical teratoid/rhabdoid tumor,

rhabdoid tumors of the kidney and soft tissue [66–72], epithelioid sarcoma [73–75], renal medullary carcinoma [76], myoepithelial carcinoma of soft tissue [73, 77], epithelioid malignant peripheral nerve sheath tumor [73], and extraskeletal myxoid chondrosarcoma [78]. Recently two groups described a form of SMARCB1 (*INI-1*) deficient sinonasal carcinoma [79, 80].

The sixteen SMARCB1 (*INI-1*) deficient sinonasal carcinomas have arose in 6 men and 10 women ranging in age from 28 to 78 (mean, 54) who presented with facial pain, eye symptoms, and nasal obstruction. Histologically, the reported SMARCB1 (*INI-1*) deficient sinonasal carcinomas grew as highly infiltrative epithelioid nests with tumor necrosis and high mitotic rates (Fig. 7). While most reported SMARCB1 (*INI-1*) deficient sinonasal carcinomas have been basaloid, resembling sinonasal undifferentiated carcinoma or non-keratinizing squamous cell carcinoma, a minority were oncocytic and plasmacytoid, resembling myoepithelial carcinoma. Even in the basaloid forms, however, rare plasmacytoid or rhabdoid cells were often identified. The reported SMARCB1 (*INI-1*) deficient sinonasal





**Fig. 7** SMARCB1 Deficient carcinoma. **a** SMARCB1-deficient sinonasal carcinomas typically grow as nests and cords of undifferentiated cells. **b** Some cases exhibit prominent plasmacytoid or rhabdoid morphology. **c** Other examples are more basaloid in appearance,

with only focal plasmacytoid/rhabdoid features (*center*). **d** By definition, these tumors demonstrate a complete absence of SMARCB1 immunoreactivity, with the background stromal and inflammatory cells showing intact staining

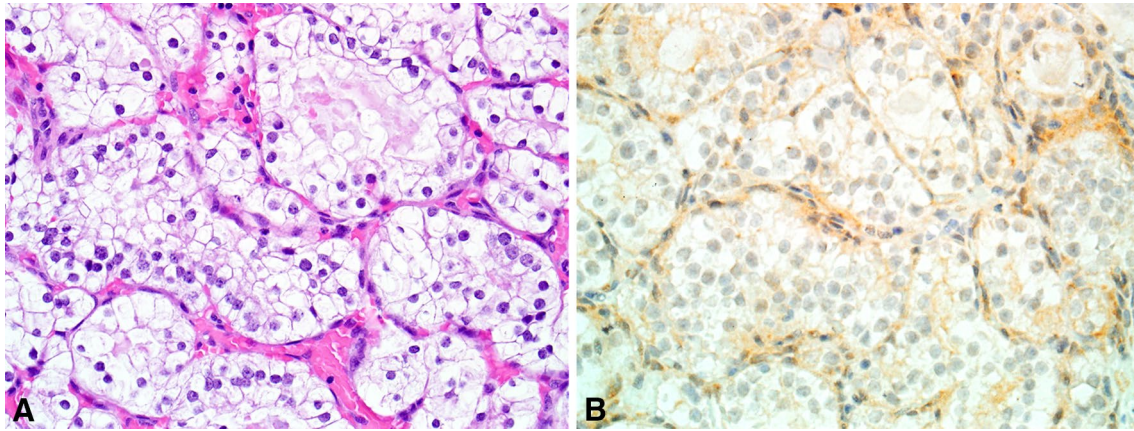
carcinomas have been consistently cytokeratin-positive and SMARCB1-negative, with variable positivity for squamous and neuroendocrine markers. All cases have been negative for HPV and NUT. In the eight cases in which *SMARCB1* (*INI-1*) FISH was successfully performed, 5 showed homozygous deletion and 1 showed a heterozygous deletion pattern. The reported SMARCB1 (*INI-1*) deficient sinonasal carcinomas have been aggressive, with frequent local invasion into the brain and/or skull base. Seven of 15 reported patients experienced local recurrence, 7 of 15 have had regional or distant metastasis, and 6 of 15 patients have died of their disease [80–82].

SMARCB1 (*INI-1*) deficient sinonasal carcinoma was given consideration for inclusion in the 4th edition of the WHO classification. It remains unclear, however, whether SMARCB1 (*INI-1*) deficient sinonasal carcinoma is a distinct entity, or rather a pattern that can be seen in a variety of tumor types. Additional publications will be needed to address this question. As a result, while in the WHO classification SMARCB1 (*INI-1*) deficient sinonasal carcinoma is mentioned in the differential diagnosis of

non-keratinizing squamous cell carcinoma, sinonasal undifferentiated carcinoma, NUT carcinoma, and melanoma, it was not regarded as a distinct tumor type.

#### Renal Cell-like Adenocarcinoma

A variant of low-grade, non-intestinal sinonasal adenocarcinoma that mimicked renal cell carcinoma was initially described as renal cell-like adenocarcinoma in 2002, and a total of 16 cases have now been reported [83–87]. Renal cell-like adenocarcinoma has occurred in 11 women and five men ranging from 22 to 89 years old (mean, 58). Patients most commonly presented with epistaxis. As the name suggests, renal cell-like adenocarcinoma histologically resembles clear cell renal cell carcinoma, with nests and follicles of polyhedral cells with abundant optically clear cytoplasm (Fig. 8). Some cases have been described as containing prominent intrafollicular hemorrhage, also a classic feature of clear cell renal cell carcinoma. Nuclear pleomorphism and mitotic activity have been minimal. Sinonasal renal cell-like adenocarcinoma has been



**Fig. 8** Renal cell-like adenocarcinoma. **a** Renal cell carcinoma-like sinonasal adenocarcinoma consists of nests and follicles of polygonal cells with small round nuclei and optically clear cytoplasm. **b** Unlike

metastatic renal cell carcinoma, renal cell carcinoma-like sinonasal adenocarcinoma is negative for PAX8

consistently positive for CK7, sometimes positive for S100, and negative for high-molecular weight cytokeratins, actin and calponin [83, 84]. More recently, it has been noted that CAIX is also positive in renal cell-like adenocarcinoma [87].

Clearly, a diagnostic consideration for renal cell-like adenocarcinoma is metastatic renal cell carcinoma, which is not uncommon in the head and neck. Sinonasal renal cell-like adenocarcinoma is consistently negative for the immunohistochemical markers PAX8, RCC, and vimentin, unlike true renal cell carcinoma. Other diagnostic considerations include the minor salivary gland tumors hyalinizing clear cell carcinoma, mucoepidermoid carcinoma, and myoepithelial carcinoma. Sinonasal renal cell-like adenocarcinoma appears to be very indolent [83, 84].

## Conclusion

There are a few new well-defined and emerging sinonasal neoplasms. Both NUT carcinomas and SMARCB1-deficient carcinomas were for the most part classified as poorly differentiated squamous cell carcinomas or SNUCs. Although the tumors have somewhat similar (very poor) prognoses, the specific molecular abnormalities seen with them may make the tumors responsive to targeted therapies in the future. The recognition of biphenotypic sinonasal sarcoma as a distinct neoplasm helps to clean up the somewhat heterogeneous group of tumors previously classified as malignant peripheral nerve sheath tumors or fibrosarcomas at the site. Finally, the recognition that some carcinomas associated with high-risk HPV can show differentiation reminiscent of salivary-gland neoplasia expands our understanding of the potential plasticity of sinonasal mucosa as it undergoes oncogenesis.

## Compliance with Ethical Standards

**Disclosure** Drs. Bishop and Stelow have no conflict of interest.

**Research Involving Animal and Human Rights** This article does not contain any studies with human participants or animals performed by any of the authors.

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