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Don't stop the champions of research now: a brief history of head and neck pathology developments☆,☆☆,

Lester D.R. Thompson MD[a,*], James S. Lewis Jr. MD[b], Alena Skálová MD, PhD[c], Justin A. Bishop MD[d]

[a]*Southern California Permanente Medical Group, Department of Pathology, Woodland Hills, CA 91365, USA*
[b]*Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, TN 37232, USA*
[c]*Sikl's Department of Pathology, Medical Faculty of Charles University, Faculty Hospital, 305 99 Plzen, Czech Republic*
[d]*Department of Pathology, University of Texas Southwestern Medical Center, Clements University Hospital, Dallas, TX 75390, USA*

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Summary The field of head and neck pathology was just developing 50 years ago but has certainly come a *long way* in a relatively short time. Thousands of developments in diagnostic criteria, tumor classification, malignancy staging, immunohistochemistry application, and molecular testing have been made during this time, with an exponential increase in literature on the topics over the past few decades: There were 3506 articles published on head and neck topics in the decade between 1969 and 1978 (PubMed source), with a staggering 89 266 manuscripts published in the most recent decade. It is daunting and impossible to narrow the more than 162 000 publications in this field and suggest only a few topics of significance. However, the *breakthrough* in this anatomic discipline has been achieved in 3 major sites: oropharyngeal carcinoma, salivary gland neoplasms, and sinonasal tract tumors. This review will highlight selected topics in these anatomic sites in which the most profound changes in diagnosis have occurred, focusing on the information that helps to guide daily routine practice of surgical pathology.

1. Introduction

It is impossible to state with any certainty *the miracle* in research that has been the most meaningful in the field of head and neck pathology over the past several decades. The song *We Are the Champions* by the rock group Queen was declared by Goldsmith University in 2011 to be the catchiest song of all time based on 1100 volunteers being asked to sing from a select list of songs, with the most "singable" songs identified by 4 specific findings: pitches that changed during the song's

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* Corresponding author at: Southern California Permanente Medical Group, Woodland Hills Medical Center, Department of Pathology, 5601 De Soto Ave, Woodland Hills, CA 91365.

E-mail addresses: Lester.D.Thompson@kp.org (L. D. R. Thompson), James.lewis@vanderbilt.edu (J. S. Lewis), skalova@fnplzen.cz (A. Skálová), Justin.Bishop@UTSouthwestern.edu (J. A. Bishop).

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hook; long and detailed musical phrases; a male singer; and, most importantly, a high-pitched male voice exhibiting palpable effort and purpose during the song (as reported via New Musical Express, www.nme.com, accessed 01AUG2019). Determining the best in music can be reduced to math, science, engineering, and technology using the physics and frequencies of sound to recognize pitch and harmony. However, the feeling you get when you listen to the music remains elusive. In this way, we hope that the presentation of what we believe to be the most significant advances in head and neck pathology will elude any rigid algorithm and instead stimulate the reader to go forward with more research in this field, ungoverned by any preconceived notions or ideas and remaining open to whatever advancement presents itself. The review will contain 3 parts, presented alphabetically, starting with oropharyngeal carcinoma, continuing with salivary gland neoplasms, and closing with sinonasal tract tumors. The *one vision* we hope to achieve is to highlight the *staying power* of methodical research combined with a dose of serendipity in the *procession* of one discovery built on another.

2. Oropharyngeal squamous cell carcinoma

Fifty years is a speck over the evolution of life on this planet, but it is essentially an "eternity" when it comes to modern medical scientific discovery. There have been enormous changes in surgical pathology since 1970, including major changes in key areas of head and neck pathology. Nowhere is this more dramatic than in oropharyngeal squamous cell carcinoma (OPSCC). A trip down *Penny Lane* to the early 1970s would show you that patients who had "oral cancer" (lumping tumors of the oral cavity and oropharynx into the same group) were poorly differentiated and thus assumed to be worse for the patient, and that metastatic carcinoma of unknown primary was frequent with an enigmatic pathophysiology. Treatment was harsh, damaging most of the head and neck mucosa with high doses of radiation and with no targeted therapeutic agents available to the medical oncologist when it recurred or metastasized. *Fast forward* to today and suddenly many tried and true traditions, of the morphologic distinction between in situ and invasive carcinoma, keratinizing versus nonkeratinizing morphology, nodal metastases being a harbinger of very poor prognosis, and smoking being the most important risk factor for throat cancer, no longer hold true. This part of the review delves into these most important issues about OPSCC (Table 1) as they have been defined; refined; or, frankly, *debunked* over the past 50 years.

Table Major changes in OPSCC

Abrogation of the term *oral cancer*
High-risk HPV and routine clinical practice testing
Tonsillar crypt anatomy and in situ *vs* invasive carcinoma
Nodal metastases and metastatic CUP
Clinical and pathologic staging

2.1. "Oral cancer"

Lumping of head and neck SCC from various sites into clinical trials, biomarker studies, and pathology series was very common in years past, but oropharynx has emerged as its own unique subsite, as is proper. The term *oral cancer* was used to denote carcinomas of the oral cavity and oropharynx, which were largely equated and considered together. This may have been historically acceptable but, over the last 3 decades with the emergence of OPSCC as a distinct entity due to high-risk human papillomavirus (HPV) and tumors arising in the tonsillar crypts, is no longer acceptable. The most recent edition of the *World Health Organization (WHO) Classification of Head and Neck Tumours* ("blue book") finally separated the oral cavity and oropharynx into separate anatomic site chapters [1]. This blanket terminology of *oral cancer* is still found occasionally in the literature [2] but should be avoided. In fact, particularly for oral cavity SCC, subsite-specific studies such as those for mobile tongue, alveolar ridge, floor of mouth, and buccal mucosa may be necessary because the pathophysiology, etiology, and pathology of SCC even at these closely approximated subsites are also subtly different. Furthermore, oropharyngeal subsite stratification of OPSCC may be necessary, as we know that tonsil and base of tongue tumors are largely very different than those arising in the soft palate, uvula, and posterior wall because of the presence of tonsillar crypts in the former and not in the latter. With the tropism of high-risk HPV for the reticulated tonsillar crypt epithelium and the peculiar anatomy that it has, as we shall see, OPSCC arising from it has unique and sometimes confusing features.

2.2. High-risk HPV

Nearly all of the changes in OPSCC are driven by the so-called epidemic [3,4] of HPV-related tumors arising in the tonsillar crypt epithelium. This story is so well told and so familiar now that it bears little use to delve into great detail here. What is clear is that this type of OPSCC is not only different but is essentially even a separate type of SCC altogether. These tumors are morphologically, molecularly, epidemiologically, pathophysiologically, and clinically different from conventional head and neck SCC [5]. The main features, many of which are still poorly understood across the medical community, include the following: (1) high-risk HPV is derived from sexual exposure; (2) tumors arise in the reticulated tonsillar crypts where HPV has ready access to the basal appearing squamous cells; (3) smoking is a major co-carcinogen, with more than 50% of patients with HPV-related OPSCC having a smoking history and 20%-25% current smokers; (4) most HPV-related OPSCCs (~85%) have a distinctive nonkeratinizing morphology; (5) mutation profiles show distinct mutations in these tumors and less gross chromosomal aberrations; and, finally, (6) nodal metastases are extremely common and have a much less negative impact on patient outcomes than for

conventional head and neck SCC. HPV-related OPSCC is usually nonkeratinizing (Fig. 1) but can show any of the described SCC variant morphologic patterns with the exception of verrucous [6] carcinoma [6–8]. It must be recognized that ~5% of HPV-related OPSCCs show a conventional (keratinizing) SCC morphology [6,9]. Although any of the dozens of high-risk HPV types can cause OPSCC, robust data show that ~90% of the time it is HPV 16 followed 2%-3% of the time by HPV 33 and 35, whereas HPV 18 is uncommon (<1%) [10-12]. The significance of individual HPV type is unclear, but HPV 16 may be prognostically more favorable compared to the non–HPV 16 type.

The prognosis is clearly much better for HPV-related OPSCC patients than for those that are negative, regardless of how they are treated. Hazard ratios for death from any cause and death from the cancer itself are from 0.2 to 0.5 with data derived from retrospective and prospective studies and from large meta-analyses [13-15]. Testing for HPV is now strongly recommended (required) for all patients with OPSCC, with p16 immunohistochemistry emerging as a standalone test recommended by the College of American Pathologists (CAP) [16] evidence-based guidelines and accepted by the American Society of Clinical Oncology [17] and major cancer staging and reporting systems such as the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control [18-20]. Because there is lingering concern about the 5% to 10% of patients with p16-positive OPSCC but negative HPV-specific testing result, the recommendations may be refined in the future to include HPV-specific test modalities such as RNA in situ hybridization [21].

2.3. Tonsillar crypt anatomy and implications for tumor spread

"Crypt" is indeed appropriate for what lies within the lymphoid rich tissue of the palatine tonsils and base of tongue. Indeed, deep in these structures lie an anatomy and a physiology that contradicts many of the classical dogmas of surgical pathology. Foremost is the anatomy. The ***surface*** of the tonsils and base of tongue are stratified squamous epithelium with an intact basement membrane and without adjacent lymphoid tissue. However, the crypts are different, comprised of a reticulated epithelium [22] (Fig. 2), which, by anatomic studies and descriptions going back to the 1950s and earlier [23], is a fenestrated and ill-defined epithelium that appears designed to facilitate exposure of lymphoid-rich inflammatory tissue to antigens present in the oropharynx [22]. Unlike squamous epithelium elsewhere, it consists primarily of high nuclear to cytoplasmic ratio "basal" appearing squamous cells, has a discontinuous basement membrane, and has intraepithelial capillaries. This implies that there is no natural barrier to tumor cell spread, which is borne out by the clinical behavior of HPV-related OPSCC. Studies show that, regardless of T classification, HPV-related OPSCC patients have nodal metastasis (clinical or pathologically proven) at the time of initial presentation 80% to 90% of the time. Primary tumors can be extremely small (1-2 mm) with large, bulky nodal metastases. As many as 50%-60% of patients present with neck symptoms [24] rather than symptoms derived from the primary tumor. Most "cancer of unknown primary" (CUP) patients with HPV-related SCC in their lymph nodes are found to have tiny primary tumors when the tonsil and base of tongue tissue are resected and thoroughly examined. Although patients can have large HPV-positive primary tumors without nodal metastases, it is an exceptionally small minority.

These data support the concept that tonsillar crypt epithelium has no natural barrier to spread, a barrier that must be overcome in larynx, oral cavity, and surface pharyngeal mucosal SCC. This concept has profound implications for the practicing pathologist. It is very common for SCC to appear limited to the lining epithelium of the tonsillar crypts on small biopsies and even on resection (Figs. 2 and 3), and yet almost all of these patients already have nodal metastatic disease. Even the more obviously downward invading tumors typically lack a desmoplastic stromal reaction. Pathologists, even today, still routinely call SCC of the oropharynx as "in situ" or "at least in situ," applying the old maxims of in situ versus invasive extrapolated from other head and neck mucosa. Experienced practitioners and a great deal of indirect evidence in the literature teach us that ***any*** SCC in the oropharynx has

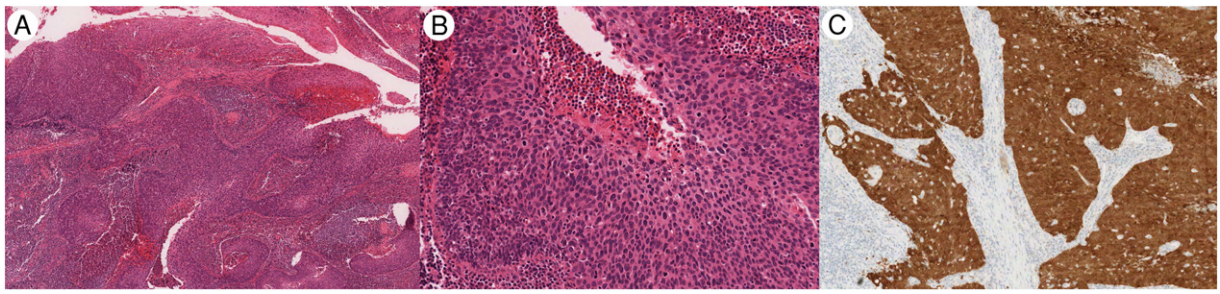

Fig. 1 Typical morphology of HPV-related OPSCC. A, A case of nonkeratinizing SCC of the oropharynx with large, rounded nests of cells in tonsillar lymphoid tissue. The nests have no stromal reaction. B, On higher power, the nonkeratinizing SCC shows cells with high nuclear to cytoplasmic ratios, round to oval nuclei lacking prominent nucleoli, and scant to only modest amounts of cytoplasm. In this tumor, there is no maturing squamous differentiation. C, Tumor showing diffuse, strong positive nuclear and cytoplasmic staining for p16.

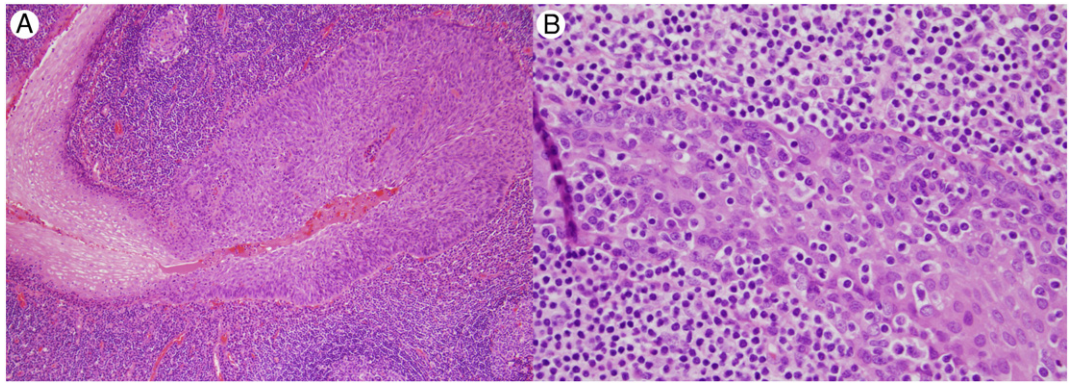

Fig. 2 Tonsillar crypt anatomy and morphology of early HPV-related OPSCC. A, A very small focus of nonkeratinizing SCC arising within a tonsillar crypt. The cells have high nuclear to cytoplasmic ratios and mitotic activity. There are smooth edges with no stromal reaction. This mimics in situ carcinoma, but the patient already had bulky cervical nodal metastases. B, The reticulated tonsillar crypt epithelium is irregular, is highly interdigitated with lymphocytes, and has squamous cells, most of which are basal in appearance with high nuclear to cytoplasmic ratios and round to oval shape, morphologically similar to the nonkeratinizing SCC cells which arise there.

the potential to spread to lymph nodes or has already done so. Thus, SCC may *truly be limited* to the crypt epithelium but still be able to spread. This would have given a *Sheer Heart Attack* to a practicing surgical pathologist in 1970!

This was logically argued and beautifully described by Westra [25] in a review article in 2012 in the following summary:

> "Until the histologic progression of HPV-related neoplasia of the tonsils is better characterized and the critical transition marking infiltrative growth is more clearly-demarcated, an aggressive approach that regards all HPV-related neoplasia of the tonsils as potentially malignant, even in the absence of those histologic features that have been traditionally used to diagnose invasion, may be warranted."

In the following years, practice guidelines have slowly started to reflect this viewpoint. CAP guidelines [16] recommend that there should be no diagnosis of in situ or invasive for HPV-related OPSCC—just diagnose it as SCC with no qualifiers. The current eighth edition AJCC and Union for International Cancer Control staging manuals have followed suit by removing the Tis category for p16-positive (HPV-related) OPSCC but retaining it, appropriately, for p16-negative (HPV-negative) OPSCC [18-20].

2.4. Nodal metastases and CUP

As previously mentioned, HPV-related OPSCC, whether inherently or due to the unique anatomy of the tonsillar crypt epithelium from which it arises, has a proclivity for early nodal metastasis from relatively small primary tumors. Given that the tumors arise deep in the crypt epithelium with no natural barrier to spread and generate little stromal reaction, it is common for patients to present with bulky, symptomatic nodal disease with no obvious primary tumor on clinical examination or imaging [24]. At least 50% of head and neck CUPs in the modern era are metastatic HPV-related OPSCCs [26]. These patients have a very favorable prognosis if treated appropriately, essentially equivalent to patients with proven oropharyngeal primary HPV-related OPSCC [26]. This certainly makes sense if one assumes that their primary tumor was so small as to be undetectable (would have to be a T1) or already had regressed spontaneously. As will be discussed more in the next section, when metastatic SCC of unknown primary is shown to be p16/HPV positive, the patients are actually now staged as if they are T0 primary OPSCC even if the primary is never detected.

The lymph node metastases are commonly cystic [27-29], sometimes exquisitely so, and approximately 90% of them are present in upper jugular (level II and III) nodes [30]. These are hallmark features of HPV-related OPSCC. Fig. 4 shows a typical example of cystic metastatic HPV-related OPSCC. What would a pathologist have thought of this in the early 1970s? Confusion with branchial cleft cysts was (and still is) very common both clinically and sometimes even on pathologic examination. In this modern (HPV) era, however, any cystic neck mass in an adult should be considered metastatic SCC until unequivocally proven to the contrary.

2.5. Staging

As HPV-related OPSCC has now been clearly recognized as a distinct entity with distinct clinical behavior, it became clear that HPV was accounting for the lack of meaningful prognostication when applying the seventh edition AJCC staging system to OPSCC patients [31]. The growth, spread, and prognosis of HPV-related OPSCC are different from HPV-negative OPSCC, and thus, a separate staging system was needed. The eighth edition AJCC staging [18,19] began the approach based on large numbers of institutional database patients. As p16 immunohistochemistry as a surrogate for HPV

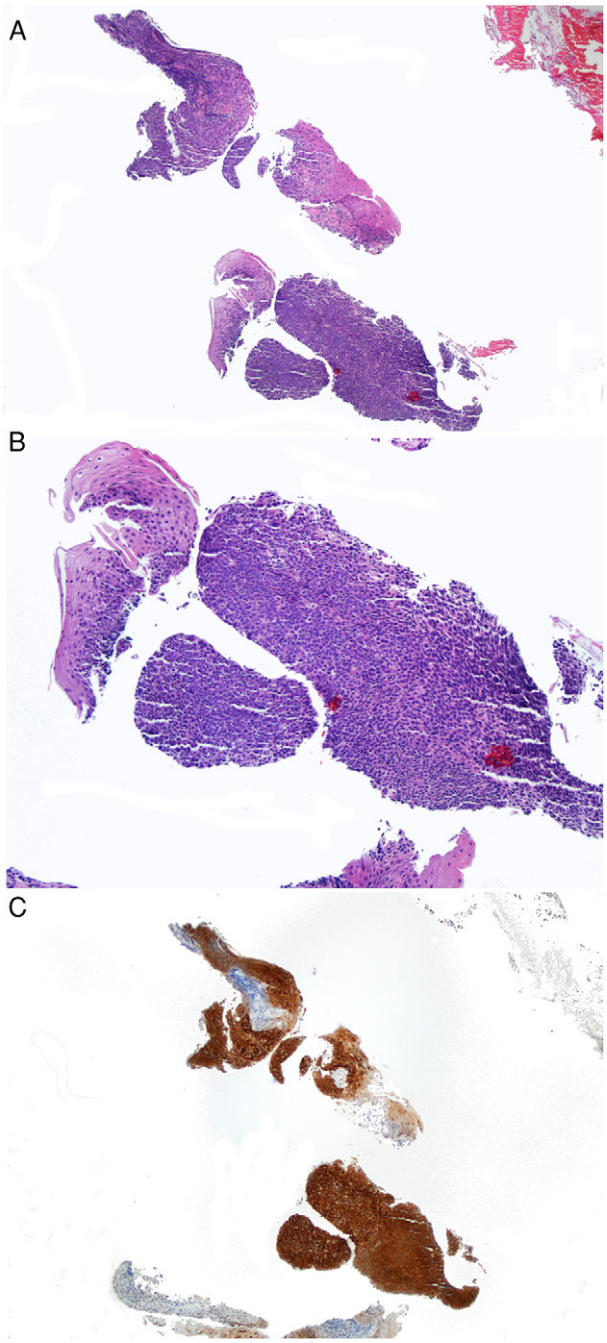

Fig. 3 Biopsies from HPV-related OPSCC. A, Minute biopsy specimen showing detached fragments of nonkeratinizing SCC. B, Higher power showing nonkeratinizing neoplastic epithelium with apoptosis and mitoses. This can mimic in situ carcinoma or at least has so little stroma that one may feel that a diagnosis of invasive carcinoma should not be rendered. However, this can and should considered invasive (ie, with potential to metastasize) by simply diagnosing it as "OPSCC." This patient already had bulky cervical nodal metastases. C, p16 immunohistochemistry on the small biopsy specimen showing strong, diffuse nuclear and cytoplasmic positivity.

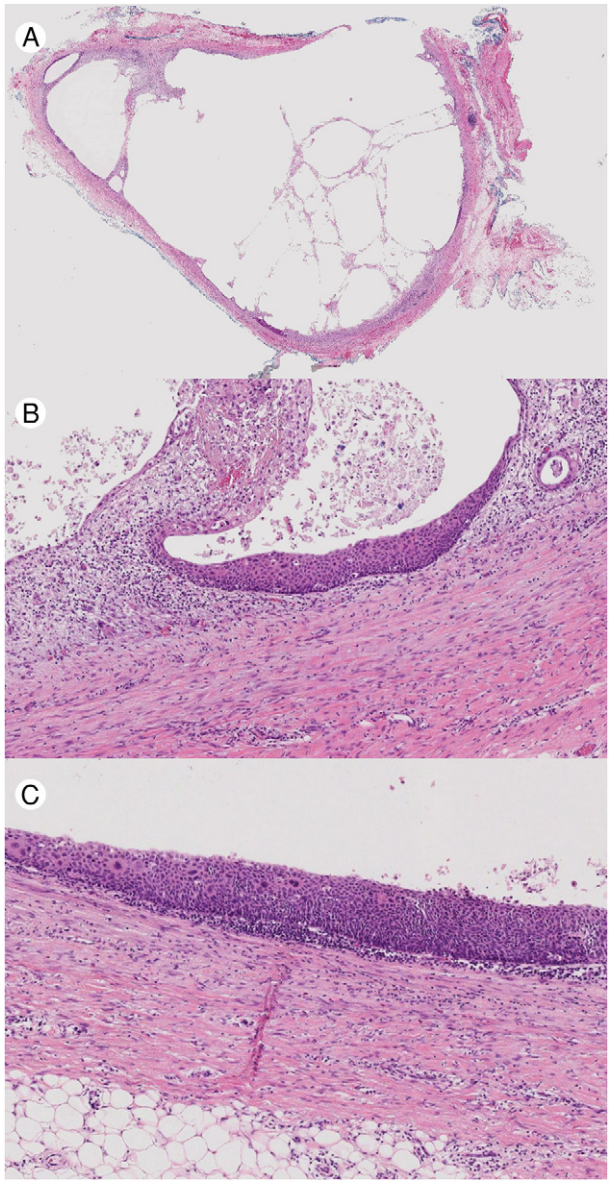

Fig. 4 Metastatic HPV-related OPSCC with extensive cystic change. A, Low power magnification shows an extensively cystic lesion with a few wispy bands of connective tissue crossing the cyst and rare areas lined by viable/intact tumor cells. B, Medium power shows the thin, flat areas of residual nonkeratinizing SCC. C, Higher power shows the tumor cells to be nonkeratinizing with minimal maturing squamous differentiation and with scattered anaplastic and multinucleated cells.

status is widely available, highly prognostic, very reproducible, cheap, and easy to perform [18,32], the staging system used p16 as a standalone test to stage patients based on "p16-positive (HPV-mediated)" OPSCC. Patients are no longer immediately stage IV based on having 1 large lymph node or multiple lymph nodes. The new classification system (1) removes Tis and T4b and (2) simplifies nodal staging with any ipsilateral node positivity ≤6 cm as N1, (3) contralateral or bilateral nodal positivity ≤6 cm as N2, and (4) any lymph node positivity >6 cm as N3 [18,33]. The improved discrimination of prognostic groups with the eighth edition system has

now been validated in numerous follow-up studies, although the overall stage II patients variably skew closer to I or III in various studies rather than being consistently smoothly in between them [34-36], and low neck disease and overt radiographic extranodal extension may need to be further evaluated [37].

Another change relevant to pathologists is that there is now a surgically resected OPSCC distinct pathologic staging for nodal staging based only on number of involved nodes (pN0 = none, pN1 = ≤4 involved lymph nodes, pN2 = >4 involved lymph nodes) [38]. Notably, histologic extranodal extension is *not* used in staging for HPV-related OPSCC. This marks the first time in history that there is a pathology-specific staging system (distinct from clinical staging) in head and neck cancer. Follow-up studies published thus far have largely validated this pathology-specific staging system as prognostic and discriminatory of outcomes [39-41].

The final key change in staging for HPV-related SCC is that for CUP. Another major breakthrough is that metastatic p16/HPV-positive SCC in a cervical node where no primary can be found is staged according the oropharynx system as a T0 lesion [18]. Because p16 positivity loses specificity in SCC not directly in the oropharynx, the CAP guidelines [16] suggested that if the positive node is not both in level II (or III) of the neck and a nonkeratinizing morphology, the HPV-specific testing should be performed (ideally RNA in situ hybridization). The subsequent American Society of Clinical Oncology review guidelines [17] and the AJCC staging manual for CUP [18,19] both suggest that, for CUP, any p16-positive SCC should also receive HPV-specific testing, with only the double-positive patients regarded as being metastases from an occult oropharyngeal primary. Whatever the case, one is reminded to be careful when performing p16/HPV testing in a cervical nodal specimen where there is clinically no apparent primary.

2.6. Summary

The changes in OPSCC in the past several decades and, indeed, in the past 50 years have been immense. HPV has taught us a lot about the anatomy of the tonsillar crypts and has blown up much of the conventional wisdom regarding head and neck pathology, including showing us that oropharyngeal tumors are very different than oral cavity ones, that transcriptionally active HPV-related tumors are very different than those where only HPV DNA is detected, that tumor limited to the epithelium can still spread to lymph nodes, that cancers of unknown primary in the head and neck are mostly HPV-related tumors obscured deep in the oropharynx, and that prognosis for HPV-related OPSCC is substantially better than for HPV-negative ones. Given the number of surprising revelations, one wonders what else we hold to now as "the way things are" will change in the coming years as we delve further into this unique cancer type and uncover more about HPV's role in this disease.

3. Enhancements in salivary gland tumor classification

Salivary gland neoplasms are a morphologically heterogeneous group of lesions that are often diagnostically challenging because of their rarity, morphological overlap between different entities, and a somewhat complicated classification scheme with a tumor diversity that is arguably unparalleled in comparison to other organs. In recent years, considerable progress in salivary gland taxonomy has been reached by the discovery of tumor type–specific fusion oncogenes generated by chromosome translocations. Although conventional morphology and immunohistochemical findings still serve as the primary tools for diagnosis, recent advances in molecular pathology offer new diagnostic tools for resolving difficult differential diagnoses, as well as identifying potentially valuable prognostic indicators and therapeutic targets.

In the past decade, many salivary gland neoplasms have been found to demonstrate characteristic tumor type–specific chromosomal rearrangements, such as (1) *ETV6-NTRK3* and *ETV6-RET*, in secretory carcinoma (also known as *mammary analogue secretory carcinoma*) [42,43]; (2) *EWSR1-ATF1* [44] and *EWSR1-CREM* [45] in hyalinizing clear cell carcinoma (HCCC); (3) *CRTC1-MAML2* and *CRTC3-MAML2* in mucoepidermoid carcinoma (MEC) [46]; (4) *ARID1A-PRKD1* and variant *PRKD1*, *PRKD2*, and *PRKD3* fusions in cribriform adenocarcinoma of minor salivary glands [47,48]; and (5) *PRKD1* somatic mutations in polymorphous adenocarcinoma [49]. The growing list of gene fusion–positive salivary gland carcinomas now includes a subset of acinic cell carcinoma (AciCC) with *HTN3-MSANTD3* fusion transcript [50], and intraductal carcinoma (IC) with an *NCOA4-RET* fusion [51,52] and a novel *TRIM27-RET* fusion in a subset of IC with apocrine morphology [52], including invasive and metastatic carcinomas [53]. This review highlights the clinicopathological features of a selected group of salivary gland carcinomas with a focus on their distinctive genomic characteristics.

3.1. Discovery of "mammary analogue secretory carcinoma"

Mammary analogue secretory carcinoma, now simplified to secretory carcinoma (SC), is a distinctive low-grade malignant salivary gland cancer that harbors a characteristic chromosomal translocation, t(12;15)(p13;q25) resulting in *ETV6-NTRK3* fusion [42]. SC was initially recognized by Skálová et al [42] as an entity distinctly different from AciCC based on 3 major findings. First, SC showed no basophilic granularity in the cytoplasm in any of the constituent cells. This is a hallmark of serous acinar cells of AciCC that represent cytoplasmic zymogen granules. Second, SC has a completely different immunohistochemical profile than AciCC, almost always strongly expressing S100 protein, SOX10, and mammaglobin, and lacking DOG1 and p63 expression. Lastly, unlike salivary or breast AciCC, most cases of SC were found to

harbor an *ETV6-NTRK3* fusion gene due to t(12;15)(p13,q25), a finding identical to breast secretory carcinoma [54] (Fig. 5). Based on the morphological similarity and sharing of the identical fusion transcript *ETV6-NTRK3*, the authors proposed "mammary analogue secretory carcinoma of salivary gland" [42]. The 2017 edition of the *WHO Classification of Head and Neck Tumours* standardized the terminology to *secretory carcinoma*, as secretory carcinomas develop in a variety of sites, such as thyroid gland [55,56], skin [57,58], and nasal cavity [59,60], with identical findings no matter where they develop.

As SCs have become more widely recognized, a small subset of cases has been reported with high-grade histologic features (Fig. 5) and aggressive clinical behavior [61-68]. These tumors tend to develop persistent local disease and extensive distant metastases despite surgical resection, radiation, and chemotherapy, making targeted therapy an attractive treatment option. Entrectinib and larotrectinib/VITRAKVI are tyrosine kinase inhibitors that have recently been developed to block the activity of TrkA, TrkB, and TrkC proteins in tumors expressing *NTRK*-rearrangements, including the *ETV6-NTRK3* fusion of secretory carcinoma [69].

Importantly, a small subset of cases demonstrates divergent molecular findings [43,58,70,71]. Notably, Skálová et al [43] recently characterized 10 cases with alternate *ETV6-RET*; and Rooper et al [70], 1 case with *ETV6-MET* fusion,

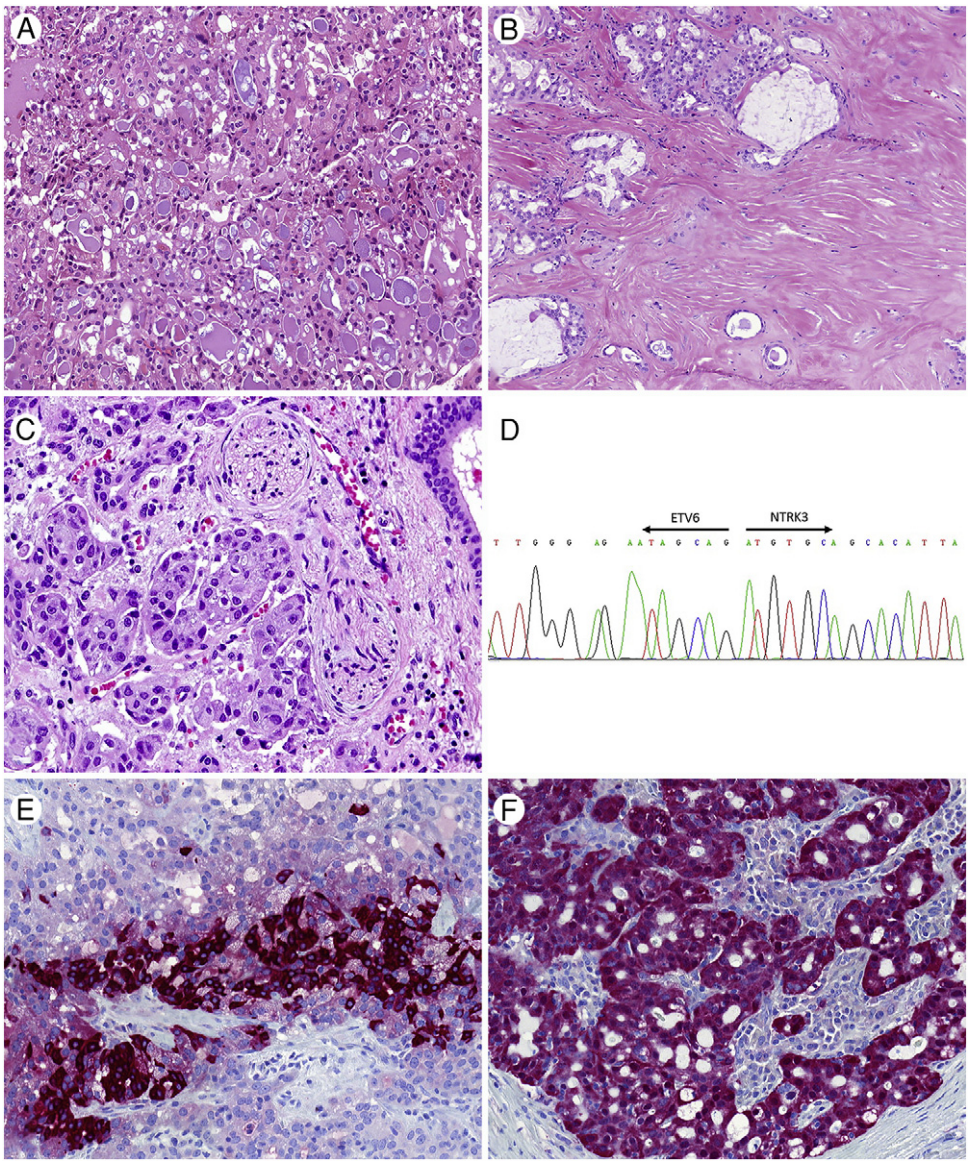

Fig. 5 Typical morphology of SC. A, Solid and microcystic growth pattern with abundant intraluminal secretory material is typical finding in SC with *ETV6-NTRK3* fusion. B, SC with *ETV6-RET* fusion characterized by abundant hyalinized stromal component. C, SC with high-grade transformation showing perineural invasive growth. D, Part of the *ETV6-NTRK3* fusion transcript sequence in SC. E, SC with mammaglobin expression. F, SC with S-100 protein expression.

respectively. Although extremely rare, these cases complicate the use of targeted therapies in SC and raise questions about the definition of this entity. Although molecular testing might not be mandatory for the diagnosis of SC with classic morphology and immunoprofile (S100 protein and mammaglobin positive and DOG1 and p63 negative) [72,73], identification of the exact *ETV6* fusion partner is essential for selecting the best targeted therapy option. Although *ETV6-NTRK3* rearranged SCs have demonstrated dramatic responses to Trk inhibitors entrectinib and VITRAKVI (larotrectinib), there is no precedent for using these drugs in cases that lack *NTRK3* fusions. Conversely, the findings of *ETV6-RET* and *ETV6-MET* translocations in SCs can offer alternate use of RET and c-Met inhibitors, respectively [74,75].

3.2. Intraductal carcinoma: defining molecular alterations and recognizing invasion and the relationship to salivary duct carcinoma

In the 2017 *WHO Classification of Head and Neck Tumours* [76], the tumor entity originally described as *low-grade salivary duct carcinoma* [77] and later called *low-grade cribriform cystadenocarcinoma* [78] was renamed as

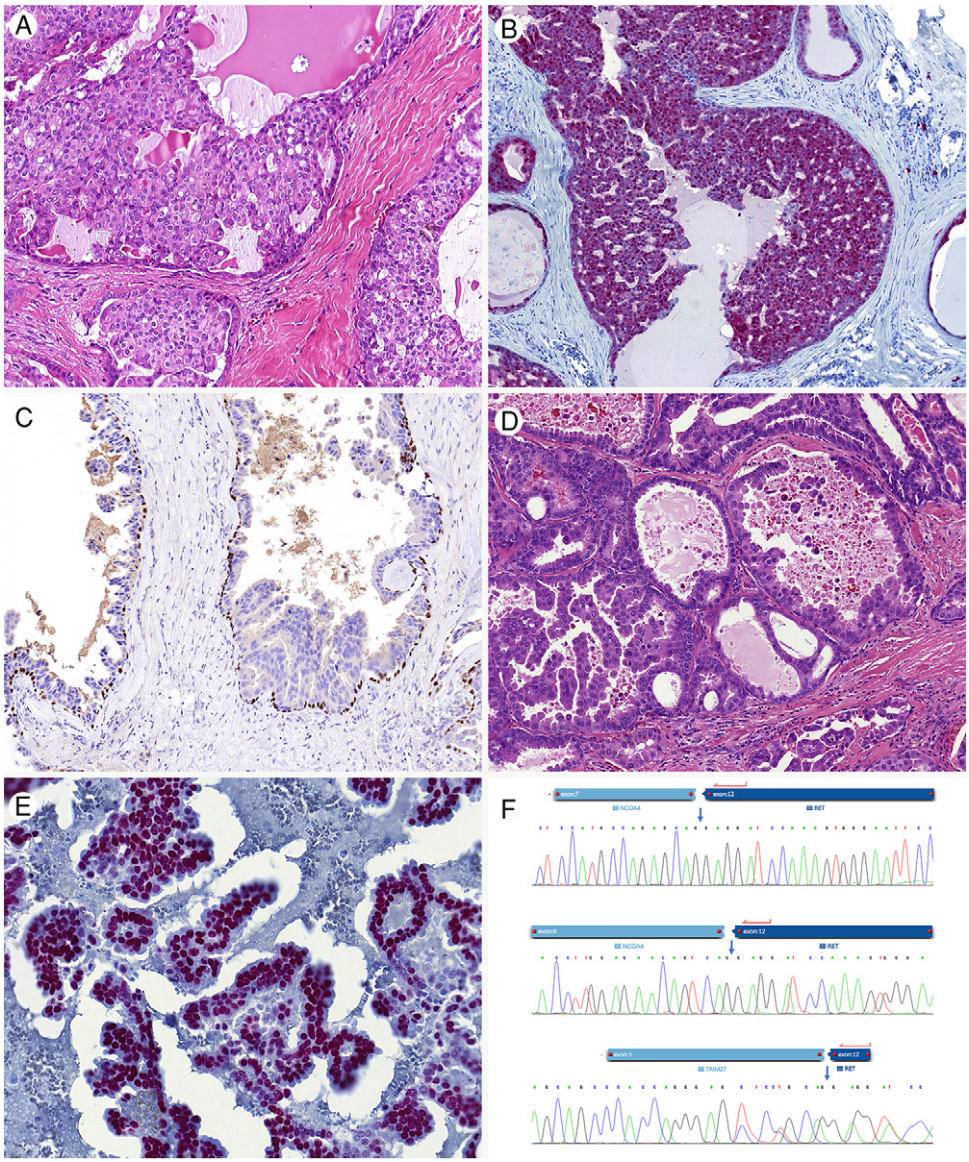

Fig. 6 Intraductal carcinoma. A, IC is characterized by intraductal and intracystic proliferation of luminal ductal cells exhibiting solid and cribriform growth pattern. The neoplastic cells are bland without atypia. B, IC typically shows an intercalated duct phenotype demonstrating S100 protein positivity of luminal cells. C, The intraductal nature of IC is demonstrated by an intact myoepithelial cell layer highlighted by antibodies to p63 protein. D, A subset of IC shows apocrine morphology. E, This is further supported by androgen receptor immunoexpression. F, Sanger sequencing analysis of reverse-transcription PCR generated fusion transcripts *NCOA4-RET* (exon joining 7-12), *NCOA4-RET* (exon joining 8-12), and *TRIM27-RET* (exon joining 3-12) (arrow shows fusion position).

intraductal carcinoma (IC). IC is a rare low-grade salivary gland malignancy with histomorphological features reminiscent of atypical ductal hyperplasia or ductal carcinoma in situ of the breast. The tumor is, in typical cases, characterized by an intraductal and intracystic proliferation of luminal ductal cells exhibiting solid, cribriform, and papillary patterns (Fig. 6). Its in situ intraductal nature is demonstrated by an intact myoepithelial cell layer highlighted by antibodies to p63 protein, calponin, and/or cytokeratin 14. IC typically shows an intercalated duct phenotype demonstrating S100 protein– and SOX10-positive luminal cells (Fig. 6), whereas a subset of IC shows apocrine morphology further supported by strong androgen receptor immunoexpression [79] (Fig. 6). Rare lesions show mixed features of the 2 (hybrid types).

Recent studies investigating the molecular genetics of IC showed recurrent rearrangements of *RET* gene with a predominant *NCOA4-RET* fusion in the intercalated duct type IC [51,52] (Fig. 6) and a *TRIM27-RET* fusion in the apocrine type IC [52,80]. *NCOA4-RET* fusion was described in noninvasive IC; and thus, *RET* was identified as an apparent early oncogenic driver [51,52]. Interestingly, rare but well-documented cases of IC with focal or widespread invasive growth have been reported [52,79]. Moreover, IC cases with *NCOA4-RET* gene fusion and an invasive component were described recently by Weinreb et al [51] and Skálová et al [53]. These findings, in particular intercalated predominant and pure apocrine carcinomas with widely invasive growth patterns and *RET* rearrangement, suggest that the term *intraductal carcinoma* should be replaced by a more appropriate designation, as it is a misnomer when widely invasive carcinoma is present with a background of in situ intraductal low-grade lesions harboring *NCOA4-RET* or *TRIM27-RET* gene fusions [51,53].

3.3. Discovery of cribriform adenocarcinoma of salivary glands

In 1999, Michal et al published a series of distinctive adenocarcinomas occurring in the posterior oral tongue and the base of tongue characterized by synchronous metastases to lateral neck lymph nodes but no distant spread [81]. The tumor was designated cribriform adenocarcinoma of the tongue and included in the 2005 *WHO Classification of Head and Neck Tumours* as a possible variant of polymorphous low-grade adenocarcinoma (PLGA) [82]. Additional cases have been reported arising in minor salivary glands other than in the

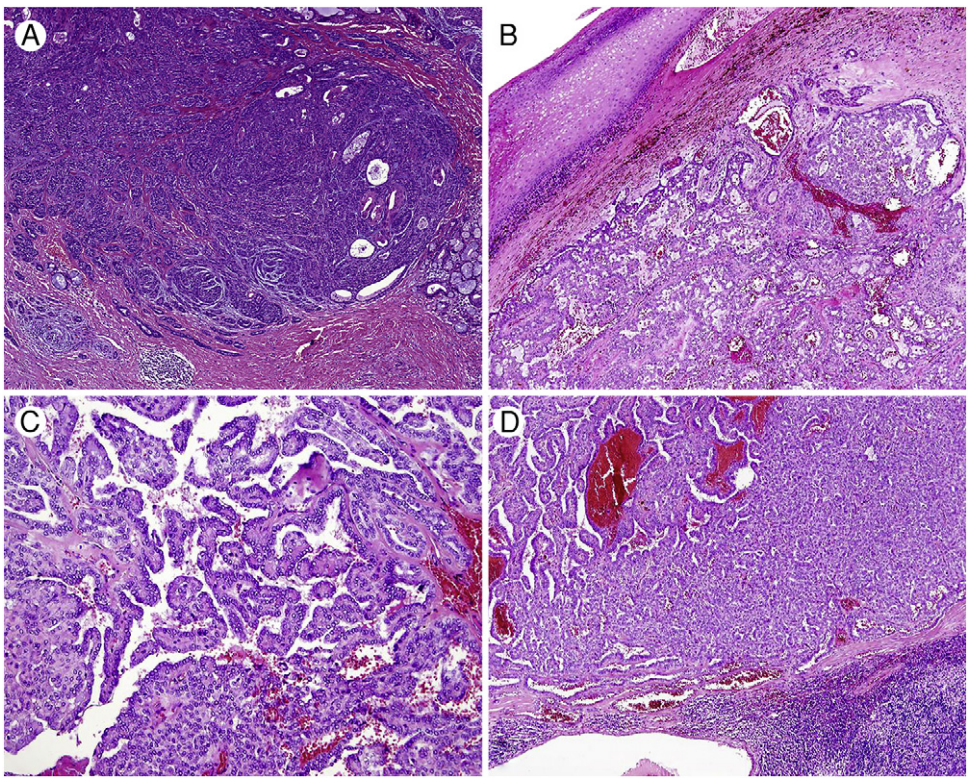

Fig. 7 PAC versus CASG. A, PAC typically has a wide range of architectural appearances, including tubule and fascicle formation. A particularly characteristic feature of PAC is the occurrence of streaming columns of single file or narrow trabeculae of cells forming concentric whorls, thereby creating a target-like appearance. B, CASG consists of a solid mass, often divided by fibrous septa into irregularly shaped and sized nodules composed of solid, cribriform microcystic and especially glomeruloid structures in variable proportions. C, The most prominent and characteristic microscopic feature is the appearance of the nuclei. They are optically clear and vesicular with a ground glass appearance, strongly resembling those in papillary thyroid carcinoma. D, CASG often presents with cervical lymph node metastasis.

tongue. These cases were published with the unwieldy title of "cribriform adenocarcinoma of minor salivary gland origin principally affecting the tongue" [47]. PLGA and cribriform adenocarcinoma of (minor) salivary gland (CASG) origin seem to be related entities with differing clinicopathological profiles despite overlap. They are the subject of an ongoing taxonomic debate. The 2017 *WHO Classification of Head and Neck Tumours* applied "polymorphous adenocarcinoma" (PAC) to cover both entities, referring to CASG as the "cribriform variant of PAC" [83]. However, CASG has differences both morphologically and behaviorally from classic PAC. Unlike classic PAC, CASGs are more frequently extrapalatal, commonly at the tongue base, and show a higher propensity for lymph node metastasis [47]. Histologically, they have more pronounced vesicular nuclei and tend to have a papillary, glomeruloid, and cribriform growth rather than a targetoid, whorled-fascicular pattern seen in classic PAC [47,81] (Fig. 7). CASGs tend to demonstrate translocations involving the *PRKD1-3* family of genes [48] rather than the *PRKD1* hotspot point mutation (E710D), which is present in >70% of cases of classic PACs [49,84].

A recent study revealed that recurrent PACs displayed the canonical alterations affecting *PRKD* genes, including *PRKD1* hotspot E710D mutations or a *PRKD2* rearrangement identified in the primary [85]. The maintenance of the highly recurrent/pathognomonic genetic alteration that characterizes these tumors in the recurrences and after the acquisition of high-grade histologic features is consistent with the observations made in other tumor types driven by pathognomonic genetic alterations [63] and is consistent with the notion that these alterations constitute drivers of the neoplasms. Thus, it seems that CASG is a distinctive tumor different from classic PAC by location (ie, most often arising within the tongue), by prominent nuclear clearing, and by differing alterations of the *PRKD* gene family and clinical behavior with frequent metastases at the time of presentation of the primary tumor. In spite of high rates of early metastatic disease in CASG, there is still overall an indolent behavior, a unique finding in low-grade salivary gland tumors.

3.4. Hyalinizing clear cell carcinoma: molecular testing aids diagnosis and separation from mucoepidermoid carcinoma

Hyalinizing clear cell carcinoma (HCCC) is a rare salivary gland malignancy with squamous differentiation and prominent clear cell morphology. The 2017 *WHO Classification of Head and Neck Tumours* included *clear cell carcinoma* (CCC) as an equivalent term, defining the tumor as a low-grade salivary gland carcinoma composed of malignant cells with clear cytoplasm, with or without hyalinization [86] (Fig. 8). Most CCCs have a recurrent t(12;22)(q13;q12) chromosomal translocation, leading to fusion of the *EWSR1* and *ATF1* genes [44]. Notably, this rearrangement was not detected in myoepithelioma, PAC, MEC, or epithelial-myoepithelial carcinoma (EMC) [87].

Immunophenotypically, CCC has similarities to SCC and MEC, with positive immunoreactivity for high–molecular weight keratins and p40/p63 but nonreactive with myoepithelial markers. The distinction from other clear cell salivary gland tumors can be challenging, especially from MEC. The emergence of molecular data in CCC now allows for a more rigorous appraisal of its morphological spectrum. The *EWSR1-ATF1* fusion was detected in clear cell odontogenic carcinoma [88]; thus, a genetic link between clear cell odontogenic carcinoma and CCC was proven. Molecularly proven CCCs have also shown that cases with overt squamous differentiation may still be true CCC [89]. In addition, the *EWSR1-ATF1*–translocated CCCs may have mucin production, and thus, mucin is not an exclusion criterion for CCC [88]. Recently, a novel *EWSR1-CREM* fusion gene was discovered in a small subset of CCCs with extensive mucinous differentiation [45] (Fig. 8).

Taken together, CCC is a rare salivary gland tumor with a specific *EWSR1-ATF1* or *EWSR1-CREM* fusion gene with possible mucin production. Therefore, MEC, particularly with a clear cell component, is a morphologic mimic of CCC [90]. In most instances, the diagnosis of CCC is readily apparent, but cases with limited biopsy material or with only focal clear cell differentiation often require additional ancillary testing. In such cases, *EWSR1* fluorescence in situ hybridization (FISH) testing may be diagnostic. The current recommendation is that *EWSR1* FISH is not necessary in classic mucin-negative cases of CCC. However, when abundant mucin is present or when there is minimal clear cell differentiation or hyalinization, confirmation can be useful. MECs showing similar features will generally be a higher-grade tumor than CCC and potentially receive different treatment [89]. This is because most CCCs lack cystic features, have highly infiltrative tumor fronts, and tend to show significant perineural invasion. With mucinous differentiation, these tumors would be considered at least intermediate grade or even high grade when using traditional MEC grading schemes [90].

MEC is associated with a clinically useful translocation involving the *MAML2* and *CRTC1* or *CRTC3* genes [46]. A recurrent t(11;19)(q21;p13) translocation, resulting in a *CRTC1-MAML2* fusion, was first described in MEC in 2003 [91]. Further study identified a small subset of MECs with t(11;15)(q21;q26) translocations generating molecularly similar *CRTC3-MAML2* fusions [92]. The use of *MAML2* FISH is a useful ancillary test in the routine clinical diagnosis of salivary gland tumors in which MEC enters the differential diagnosis [46].

Clinically, detection of a *MAML2* rearrangement using break-apart FISH probes is helpful in several situations. In cases of low-grade MEC, differential diagnostic considerations can often include benign entities, such as metaplastic variant of Warthin tumor [93,94], or more rare lesions such as lymphadenoma. In such cases, detection of *MAML2* rearrangement confirms the diagnosis of MEC. A particular scenario in which *MAML2* FISH can be extremely useful is the oncocytic variant of MEC, in which the prominent oncocytic

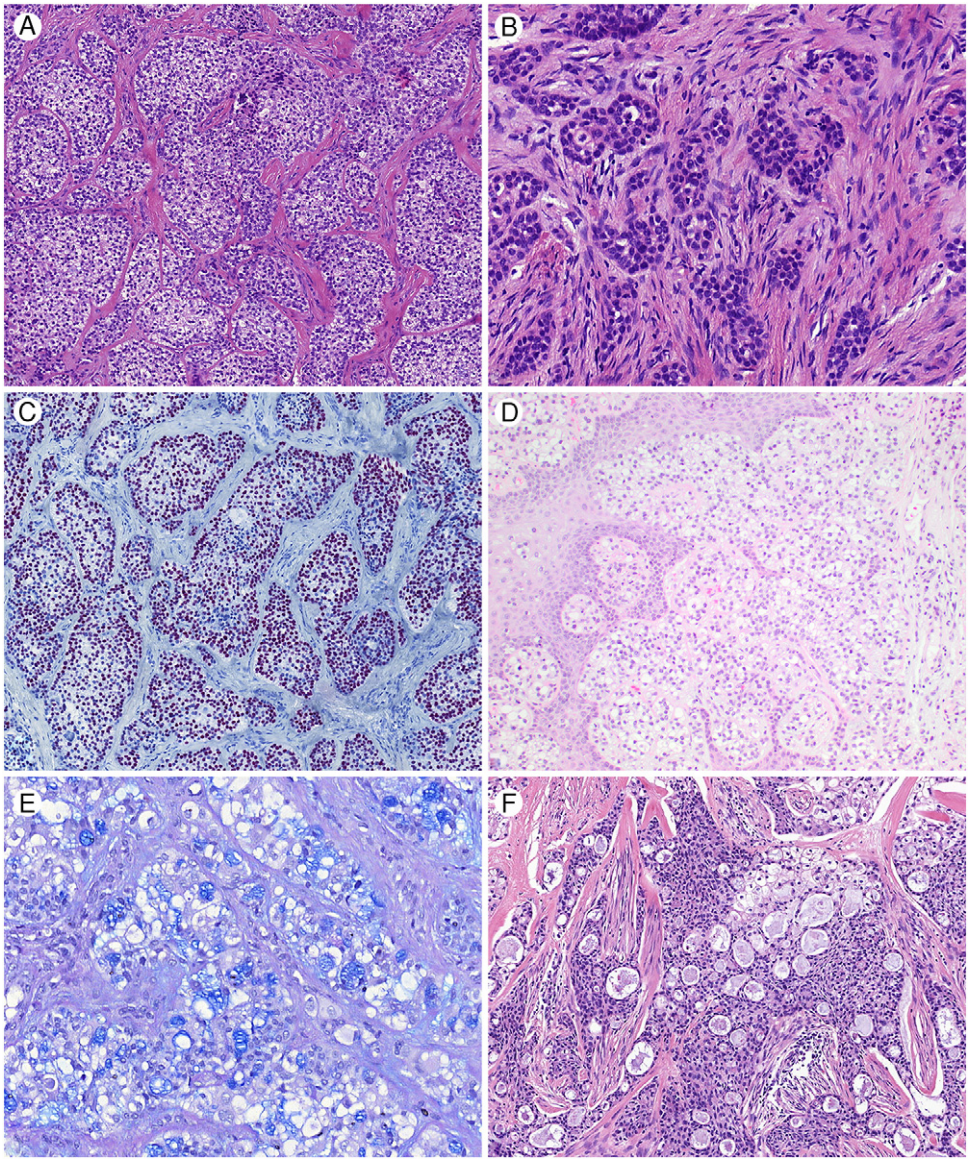

Fig. 8 Hyalinizing clear cell carcinoma. A, In typical cases, HCCC is composed of solid cords and nests of clear cells in a hyalinized and myxoid stroma. B, The stroma of HCC can be very cellular, and neoplastic cells do not have always clear cytoplasm. C, Tumor cells show nuclear staining for p63. D, Clear cell variant of mucoepidermoid carcinoma is major differential diagnostic challenge. E, Abundant intracytoplasmic mucin is demonstrated in MEC by Alcian blue/periodic acid–Schiff staining. F, Subset of HCCC with variant *EWSR1-CREM* translocation, shows sheets and nests of tumor cells with hyalinized stroma with focal mucinous differentiation.

morphology can mask the epidermoid or even mucinous phenotype and mimic Warthin tumor, oncocytic cystadenoma, oncocytoma, or AciCC. Although p63 reactivity can be useful in many cases to suggest a diagnosis of MEC, detection of *MAML2* rearrangements confirms a diagnosis of MEC [95,96].

3.5. Molecular advances in adenoid cystic carcinoma and EMC

Adenoid cystic carcinoma (AdCC) is a common salivary gland carcinoma of both major and minor glands, no matter where the latter may be found (sinonasal tract, larynx, nasopharynx). AdCC is characterized by its slow but relentless clinical progression. It is a morphologically bland but highly infiltrative and aggressive biphasic basaloid tumor composed of abluminal myoepithelial and luminal ductal cells arranged in tubular, cribriform, and solid growth patterns. The cells tend to have scant cytoplasm and angulated, hyperchromatic nuclei (Fig. 9). Perineural invasion is almost invariably present with adequate sampling.

The most significant advance in the understanding of the molecular pathology of AdCC is the discovery and characterization of the t(6;9)(q22-23;p23-24) translocation resulting in

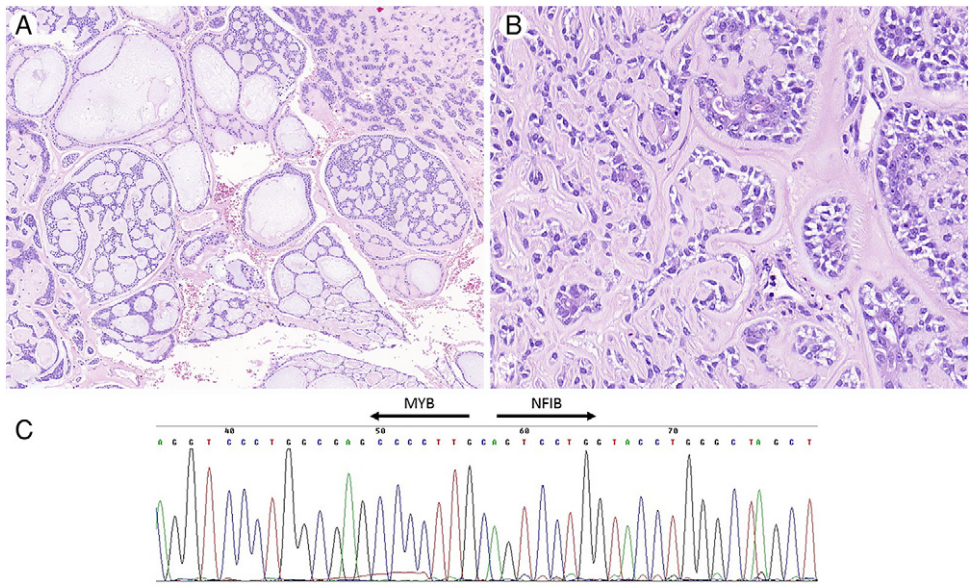

Fig. 9 Adenoid cystic carcinoma. A, AdCC is a morphologically bland but highly infiltrative biphasic basaloid tumor composed of abluminal myoepithelial and luminal ductal cells arranged in tubular, cribriform, and solid growth patterns. B, Less common growth pattern of AdCC with clear abluminal cells and resemblance to EMC. C, Part of *MYB-NFIB* transcript fusion sequence.

MYB-NFIB gene fusion, the main genomic hallmark [97] (Fig. 9). Recently, a small subset of *MYB-NFIB* negative cases was shown to have t(8;9) translocations resulting in the closely related *MYBL1-NFIB* fusion [98]. Other genomic alterations in AdCC are variable with solid tumors showing a higher number of copy number alterations, including chromosomal losses involving 1p and 6q [99]. Interestingly, recent studies have shown 1p36 locus deletion correlates with poor prognosis in AdCC [100].

AdCC is a biphasic salivary gland neoplasm consisting of a variety of architectural patterns. The abluminal myoepithelial cells often secrete a basement membrane-like material which is deposited in characteristic extracellular pseudocystic/cribriform myxoid and hyalinized extracellular matrix deposits. Although this might be a useful diagnostic clue, identical extracellular matrix deposits can be produced also by other biphasic salivary gland neoplasms, including PA, EMC, basal cell adenoma/adenocarcinoma, and PLGA/PAC. The use of *MYB* testing serves as a robust ancillary test in the routine clinical diagnosis of salivary gland tumors in which AdCC enters the differential diagnosis. Detection of *MYB-NFIB* and *MYBL1-NFIB* fusion may help in distinguishing AdCC from its histomorphologic mimics and is crucial for optimal treatment decisions.

EMC is a rare malignant salivary gland tumor that accounts for less than 1% of all salivary gland epithelial neoplasms. It is classically characterized by a biphasic glandular arrangement of inner eosinophilic ductal epithelial cells and outer clear myoepithelial cells [101]. However, many histological variants of EMC, such as sebaceous [102], oncocytic/apocrine [103], and double-clear [104], have been described. In addition, some cases undergo high-grade transformation, which is associated with a worse prognosis [101]. These histological variations make the diagnosis of EMC difficult.

Because immunohistochemical staining is of limited value in distinguishing EMC from other salivary gland tumors with biphasic differentiation, additional testing to aid diagnostic accuracy may be needed. Recently, *HRAS* mutations have been reported in salivary gland tumors, particularly in EMC [104-106]. Classic low-grade EMCs are genetically distinct from AdCCs in that they do not harbor *MYB* fusions [107]. The presence of an *MYB* fusion in EMCs showing hybrid features of AdCC or exhibiting highly infiltrative growth suggests that a subset of these tumors may be true AdCCs masquerading as EMCs [108]. The consistent absence of *MYB* fusions in classic EMC supports the current concept that EMC is genetically distinct from AdCC. There is no significant correlation between the *HRAS* mutation status and histologic indicators of tumor aggressiveness, such as nuclear grade, the presence of necrosis, lymphovascular invasion, perineural invasion, mitotic count, and Ki-67 index [106], but molecular testing of *MYB*, *MYBL1*, and *NFIB* fusions and *HRAS* mutations is useful in differential diagnosis of AdCC and EMC, respectively.

4. Classification improvements in sinonasal tract tumors

Despite its relatively small size in *a human body*, the sinonasal tract (SNT; nasal cavity and paranasal sinuses) gives rise to a dizzyingly diverse group of neoplasms. Indeed, the 2017 *WHO Classification of Tumours of the Head and Neck* included 40 unique neoplasms in the SNT chapter [109]. This diversity, combined with difficult access and often scant sample

size with procedural artifacts, results in SNT pathology representing one of the most challenging areas of pathology. SNT tumor classification has recently undergone several refinements, with a number of additional sinonasal neoplasms described. Most of these newly recognized entities were defined in part on underlying viral or genetic mechanisms, supporting their separate classification and, in some cases, offering potential therapeutic targets. General surgical pathologists come *under pressure* when approaching these unfamiliar lesions, potentially leading to misdiagnosis. To *play the game* well, the following are several of the diagnoses that are all important to recognize as part of treatment and outcome considerations.

4.1. NUT carcinoma

NUT carcinoma was first described in 1991 in 2 case reports of mediastinal tumors harboring t(15;19) translocations [110,111]. Only recently, however, have these tumors with *NUT* translocations become better recognized [112-115], and included in the 2017 *WHO Classification of Head and Neck Tumours* [116]. NUT carcinoma was originally thought to affect children and young adults exclusively, and indeed, it is most commonly encountered in children and young adults (mean, 22 years; median, 16 years). With increasing recognition, however, it is evident that NUT carcinoma can arise in patients of any age [115,116]. NUT carcinoma was previously known as *NUT midline carcinoma* because of its predilection for organs along the midline of the body; the mediastinum and sinonasal tract are most frequently affected. However, NUT carcinoma has now been reported in several nonmidline locations such as kidney and parotid gland, thus making *midline* obsolete. Patients present with nonspecific symptoms such as nasal obstruction, pain, epistaxis, and proptosis [117,118]. Imaging reveals extensive local invasion into neighboring structures like the orbit, meninges, or brain [117,118]. Metastatic disease at presentation is seen in ~50% of patients [115].

NUT carcinoma is defined by a chromosomal rearrangement involving the *NUT* gene on chromosome 15q14 [119]. The most common partner is *BRD4* on chromosome 19, but a significant subset (approximately one third) has variant translocations involving *BRD3* or other genes. These genetic alterations may be identified by FISH or polymerase chain reaction (PCR).

At the histologic level, sinonasal NUT carcinoma grows as nests and sheets of primitive but homogenous cells in the sinonasal submucosa. The neoplasm is typically highly invasive with bone, vessel, and neural invasion and exhibits a high mitotic rate with frequent comedonecrosis. Although it resembles many other tumors (see differential diagnosis below), there are histologic clues to its diagnosis. First, NUT carcinoma is often neutrophil rich. Second, despite its aggressive growth features, NUT carcinoma nuclei are paradoxically monotonous, in contrast to what is usually seen in other high-grade carcinomas. Finally, most but not all examples of NUT carcinoma exhibit squamous differentiation in the form of peculiar keratinization that is often described as "abrupt," with undifferentiated cells immediately adjacent to highly differentiated squamous cells (Fig. 10A).

NUT carcinoma is part of the so-called sinonasal small round blue cell tumor differential diagnosis that also includes sinonasal undifferentiated carcinoma (SNUC), olfactory neuroblastoma, alveolar rhabdomyosarcoma, lymphoma, and melanoma, among others. Retrospective studies have shown that NUT carcinomas were previously most often diagnosed as SNUC or SCC [117,120]. Immunohistochemistry is helpful in this differential diagnosis: NUT carcinoma is positive for cytokeratins, usually positive for p63 and p40, and usually negative for neuroendocrine markers. CD34 is positive in about half of cases. Ultimately, a definitive diagnosis of NUT carcinoma requires demonstrating the defining *NUT* rearrangement. There is a highly sensitive and specific immunohistochemical stain for NUT protein (Cell Signaling Technologies, Danvers, MA) that has greatly simplified the diagnosis [121]. Diffuse (>50%) nuclear positivity for NUT is regarded as sufficient evidence for NUT rearrangement (Fig. 10B), obviating the need for highly specialized genetic testing [112,113,121]. There is an emerging group of so-

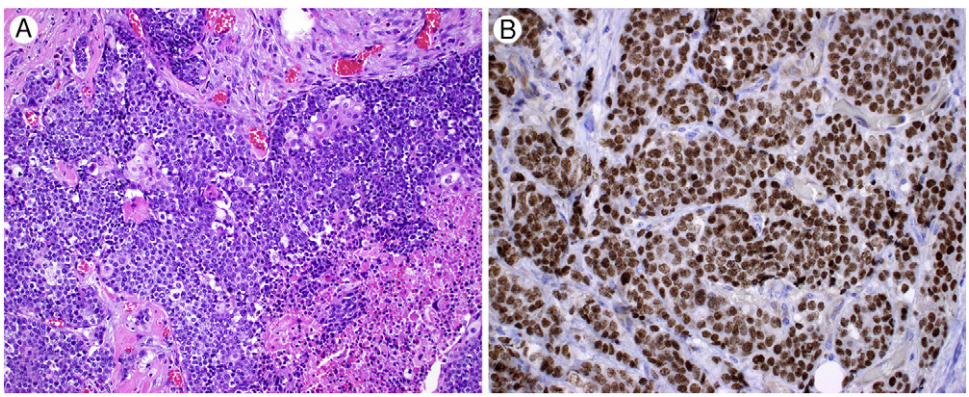

Fig. 10 A, NUT carcinoma grows as nests of undifferentiated cells with uniform nuclei, punctuated by abrupt foci of squamous differentiation. B, Diffuse nuclear labeling for NUT protein in a granular pattern confirms the diagnosis.

called NUT sarcomas that are cytokeratin negative; it is unclear whether this is a separate tumor or part of the spectrum of NUT carcinoma [122].

Correctly diagnosing NUT carcinoma is important for prognostic and therapeutic reasons [113]. NUT carcinoma is highly aggressive with a dismal prognosis; conventional chemotherapeutic agents are ineffective [115]. On the other hand, clinical trials are open investigating targeted agents including BET bromodomain inhibitors (https://clinicaltrials.gov/ct2/show/NCT02516553?cond=BI+894999). Correctly identifying NUT carcinoma allows affected patients to be enrolled into the International NUT Carcinoma Registry (www.nmcregistry.org) which follows patient outcomes and can direct them to the institutions running these trials [112,113].

4.2. HPV-related multiphenotypic sinonasal carcinoma

The rate of head and neck SCCs associated with HPV is on the rise, and the oropharynx is the anatomic site where most HPV-related SCCs originate [13,123]. Up to 80% of oropharyngeal carcinomas harbor transcriptionally active, high-risk HPV, compared to ≤5% in sites like the oral cavity and larynx [21,124-126]. However, several studies have demonstrated that the sinonasal tract is a second anatomic "hot spot" from which HPV-related carcinomas can arise. Indeed, approximately 20%-25% of carcinomas arising from the sinonasal tract harbor high-risk HPV [125,127,128]. Most HPV-related sinonasal carcinomas have the appearance of a nonkeratinizing SCC, similar to their oropharyngeal counterparts. However, a recently described variant of HPV-related sinonasal carcinomas closely resembles salivary gland carcinomas. These carcinomas were originally referred to as *sinonasal HPV-related carcinoma*s with adenoid cystic-like features [125] but are now known as *HPV-related multiphenotypic sinonasal carcinoma* (HMSC) [129].

More than 50 cases of HMSC have now been reported [130-135]. HMSC has a slight female predominance, with a peak incidence in the sixth decade (range, 28-90 years) [130-135]. Most patients present with nasal obstruction and epistaxis. The vast majority of tumors affect the nasal cavity with or without paranasal sinus involvement; only rare cases affect sinuses without nasal involvement.

Histologically, HMSC consists of hypercellular proliferations of basaloid cells growing predominantly as solid nests, sheets, and trabeculae (Fig. 11A). Most cases also demonstrate a minor component of cribriform and/or tubular growth. In the cribriform areas, basaloid tumor cells are aligned around cylindromatous spaces filled with mucoid material, a pattern reminiscent of AdCC. The basaloid tumor cells demonstrate histologic features of myoepithelial differentiation, including clear cytoplasm and eosinophilic hyaline matrix deposition. Most HMSCs also have a variably prominent subpopulation of true ducts scattered among the basaloid cells, and the

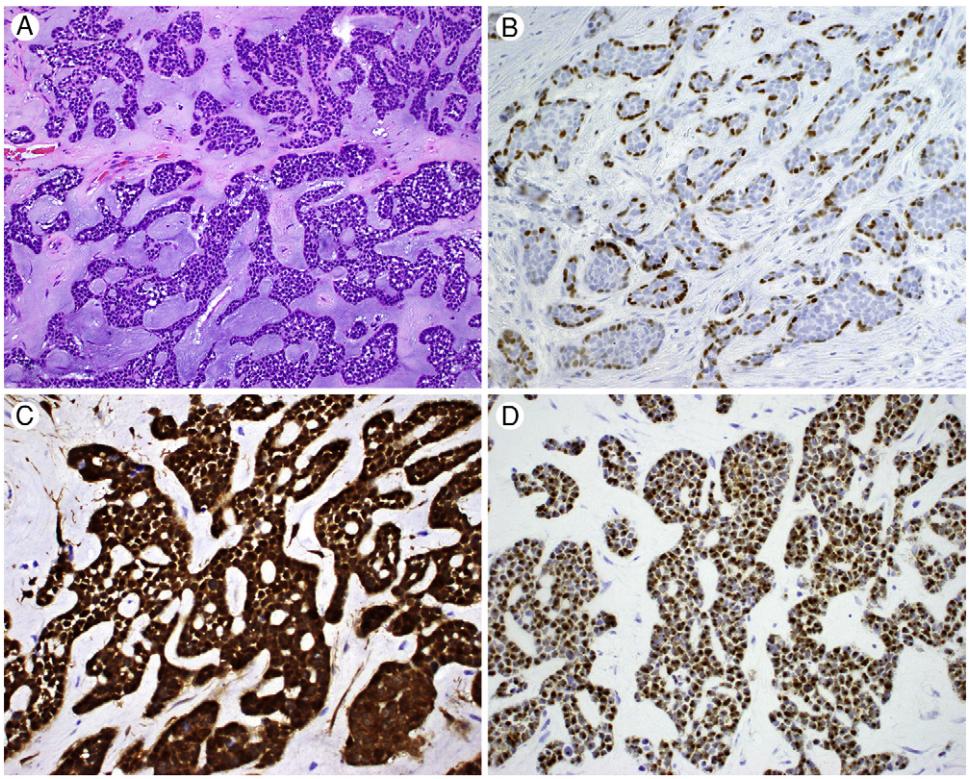

Fig. 11 A, HPV-related multiphenotypic sinonasal carcinoma growing as tubules and trabeculae of basaloid cells within a myxoid stroma. B, An abluminal pattern of p40 staining is typical. C, p16 is diffusely positive, and (D) high-risk HPV is demonstrated by RNA in situ hybridization.

majority of cases have a surface epithelial component consisting of bizarrely pleomorphic squamous epithelium. Mitotic rates are generally high, and tumor necrosis is common. Increasing experience has revealed a wider histologic spectrum than was originally realized. In some cases, HMSC does not resemble AdCC but rather other salivary tumors such as EMC or basal cell adenocarcinoma. In addition, squamous differentiation has now been reported in the invasive component of some HMSCs. Indeed, "multiphenotypic sinonasal carcinoma" seems appropriate to emphasize its broad morphologic spectrum and to draw a distinction from true AdCC.

HMSC shares immunohistochemical features with AdCC and other biphasic salivary gland carcinomas. The basaloid cells have a myoepithelial immunophenotype and are variably positive for p40 (Fig. 11B), p63, calponin, and smooth muscle actin. In contrast, the ductal cells are positive for CD117. Both cell components may be positive for S100 protein and SOX10. Pan-cytokeratin is also positive in both components, with stronger staining in ducts and weaker staining in the myoepithelial-like cells. All cell components (surface, ductal, myoepithelial) are diffusely positive for the surrogate high-risk HPV marker p16 (Fig. 11C).

One defining feature of HMSC is its positivity for high-risk HPV, which can be demonstrated by PCR-based techniques or by in situ hybridization for high-risk HPV DNA or RNA (Fig. 11D). Interestingly, HMSC is only rarely positive for HPV 16, by far the predominant HPV type in OPSCC. Instead, most cases that have been typed have harbored the uncommon HPV 33. Types 35, 52, and 56 have also been reported, whereas some HMSCs have harbored high-risk HPV types that could not be determined.

In contrast to salivary AdCC which harbors fusions of *MYB* or *MYBL1* in 60%-70% of cases, all HMSCs tested to date have been negative for these alterations. Notably, MYB protein is often expressed by immunohistochemistry despite the negative molecular results, severely limiting the usefulness of this stain for separating HMSC from AdCC [136].

HMSC may closely resemble AdCC or other salivary gland malignancies, but it differs in important ways. First, HMSC has only been encountered in the sinonasal tract, whereas salivary gland carcinomas like AdCC arise in any major or minor salivary gland sites. Second, HMSC lacks *MYB* or *MYBL1* alterations which are seen in the majority of AdCCs. Third, HMSC harbors high-risk HPV, which has not been demonstrated in genuine salivary gland malignancies. Notably, p16 immunohistochemistry is not a reliable surrogate HPV marker in this setting, as AdCC and other salivary gland carcinomas are frequently p16 positive due to mechanisms unrelated to HPV [137]. Finally, the presence of an intraepithelial component of malignant squamous cells is unexpected in AdCC or any other salivary gland neoplasm. HMSC may also be confused with SCC, especially the basaloid variant. Both tumors have a very basophilic appearance with predominantly solid growth, and both HMSC and SCC may exhibit squamous differentiation. Moreover, a significant number of sinonasal SCC are HPV related. Distinguishing these tumors rests on demonstrating myoepithelial differentiation and, in most cases, scattered tumor ducts in HMSC. This is most easily accomplished with immunohistochemistry for myoepithelial markers (eg, smooth muscle actin, calponin) and ductal markers (eg, CD117). Although p63 and p40 are positive in both SCC and HMSC, the pattern of labeling is helpful. SCC is positive for p40/p63 in virtually every cell, whereas in HMSC it is patchy. Note that SOX10 is not useful in this differential diagnosis; basaloid variant of SCC is frequently positive for this marker [138].

Most patients with HMSC have been treated with surgical resection with or without radiation therapy. Although many have recurred locally (sometimes very late), only rare patients have experienced distant metastases [129,132]. Most importantly, so far, there have been no reports of tumor-related deaths due to HMSC. Indeed, despite the high-grade histologic features of most HMSCs, they appear to display paradoxically indolent clinical behavior. This indolence underscores the need to distinguish HMSC from its more aggressive mimickers.

4.3. SMARCB1-deficient sinonasal carcinoma

SMARCB1 (also known as *INI-1* or *BAF47*) is a tumor suppressor gene on chromosome 22q11.2; its gene product is ubiquitously expressed in all normal tissues as part of the SWI/SNF nucleosome remodeling complex. *SMARCB1* inactivation has been implicated in the pathogenesis of a diverse family of neoplasms that includes pediatric atypical teratoid/rhabdoid tumor, rhabdoid tumors of the kidney and soft tissue [139], epithelioid sarcoma [140], renal medullary carcinoma [141], soft tissue myoepithelial carcinoma [140], epithelioid malignant peripheral nerve sheath tumor [140], and extraskeletal myxoid chondrosarcoma [142]. SMARCB1-deficient sinonasal carcinoma is a newly identified member of the family [143].

More than 50 SMARCB1-deficient sinonasal carcinomas have been described [144,145]. They occur over a wide age range (19-89 years, mean 52 years) with a slight male predominance. They arise primarily in the paranasal sinuses (especially ethmoid) and nasal cavity, often with extension into the orbit. Affected patients present with pain, obstruction, and eye symptoms.

Histologically, SMARCB1-deficient sinonasal carcinomas grow as highly infiltrative epithelioid nests within the sinonasal submucosa, frequently invading bone with tumor necrosis and high mitotic rates. The tumor cell nuclei tend to be uniformly round with open chromatin and a prominent nucleolus; significant nuclear pleomorphism is not typical. SMARCB1-deficient sinonasal carcinoma typically demonstrates cells that are recognizable as rhabdoid or oncocytoid, although the extent is variable. A minority of tumors are extensively oncocytoid, imparting a "pink" appearance (Fig. 12A); the remainder are basaloid appearing, with the oncocytoid cells still present but more focal (Fig. 12B). SMARCB1-deficient sinonasal carcinomas do not exhibit overt squamous differentiation, but rare

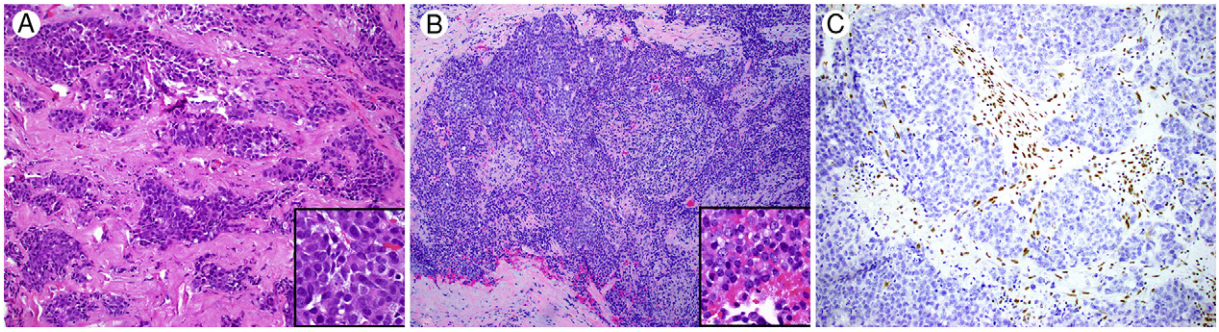

Fig. 12 A, Some SMARCB1-deficient sinonasal carcinomas have a "pink" appearance and are comprised entirely of cells with plasmacytoid or oncocytoid morphology (inset). B, Many SMARCB1-deficient sinonasal carcinomas have a more basaloid low-power appearance, but close inspection will typically reveal scattered plasmacytoid or oncocytoid tumor cells (inset). C, In all forms, SMARCB1 is entirely lost by immunohistochemistry. Stromal cells serve as a useful internal control.

cases do show glandular or even yolk sac–like differentiation [145,146]. An in situ carcinoma component is not seen, but in occasional cases, there is striking pagetoid spread of tumor cells into the overlying epithelium [145].

By immunohistochemistry, SMARCB1-deficient carcinoma demonstrates strong and diffuse cytokeratin expression along with a complete absence of SMARCB1 immunostaining (Fig. 12C). Other than these findings, the immunoprofile of this tumor is inconsistent. SMARCB1-deficient sinonasal carcinoma may be positive for p63 and p40 and may show weak or focal staining with neuroendocrine markers. Interestingly, some cases have shown diffuse positivity for p16, but all tested cases lacked high-risk HPV by in situ hybridization or PCR. Most, but not all, harbor mutations in *SMARCB1* gene on chromosome 22q11.2 [145].

SMARCB1-deficient sinonasal carcinoma may be confused with SCC, particularly if it demonstrates diffuse p63 or p40 immunolabeling, and diffuse p16 staining may erroneously suggest that the tumor is HPV related. However, SMARCB1-deficient sinonasal carcinoma does not show squamous differentiation or surface squamous dysplasia, and HPV-specific testing is negative. NUT carcinoma may also be considered due to the undifferentiated appearance of SMARCB1-deficient sinonasal carcinoma along with its relatively monomorphic tumor cell population. However, SMARCB1-deficient sinonasal carcinoma does not demonstrate the abrupt keratinization characteristic of NUT carcinoma, and it is consistently negative for NUT immunohistochemistry. SNUC may also be in the differential, although typically exhibiting more pleomorphic tumor cells than in SMARCB1-deficient sinonasal carcinomas, and SNUC is regarded as a diagnosis of exclusion, only used when other diagnoses have been removed from consideration [147]. When confronted with a basaloid carcinoma in the sinonasal tract without clear-cut squamous differentiation, a search for rhabdoid cells and a low threshold for SMARCB1 immunostaining are warranted. Finally, a single case of sinonasal carcinoma with loss of SMARCA4 (another member of the SWI/SNF complex) has been reported [145]. It is unclear how this tumor is related to SMARCB1-deficient sinonasal carcinoma.

SMARCB1-deficient sinonasal carcinoma appears to be an aggressive neoplasm, with frequent local invasion into the brain and/or skull base. The majority of patients have died of disease (mean, 15 months) [143,144,148]. Targeted EZH2 inhibitor (tazemetostat) therapy is currently being investigated for SMARCB1-deficient neoplasms, offering promise for the future treatment of this aggressive disease [149].

4.4. Biphenotypic sinonasal sarcoma

Lewis et al described a low-grade sarcoma arising exclusively in the sinonasal tract and initially referred to it as "low-grade sinonasal sarcoma with neural and myogenic differentiation" [150]. In a follow-up series, the same group renamed the entity *biphenotypic sinonasal sarcoma* (BSNS) [151]. There are more than 100 cases of BSNS reported [151-158], usually arising in the superior nasal cavity and ethmoid sinuses of women (female-male ratio is 3:1), with a peak in the fifth and sixth decades [151-158]. Affected patients present with nonspecific symptoms such as nasal congestion and facial pressure.

Histologically, BSNS grows as a poorly circumscribed and unencapsulated proliferation of highly cellular, intersecting fascicles with a frequent "herringbone" pattern. Gaping "staghorn" vessels are also common. BSNS often entraps invaginations of native, hyperplastic surface epithelium (Fig. 13A). The spindled tumor cell nuclei are uniform and pale (Fig. 13B), with few mitotic figures and no necrosis. By immunohistochemistry, BSNS is positive, to varying degrees, for S100 protein (Fig. 13C) and smooth muscle actin (Fig. 13D). BSNS may also exhibit focal staining for desmin, myogenin, EMA, and cytokeratin, whereas it is negative for SOX10. BSNS harbors rearrangements of *PAX3*, with the most frequent translocation partner being *MAML3* [151]. Several alternate fusions have been identified, including the *PAX3-NCOA1* and *PAX3-FOXO1* fusions usually detected in alveolar rhabdomyosarcoma [152,153]. PAX3 immunohistochemistry appears to be highly sensitive and specific for tumors harboring PAX3 rearrangements [156].

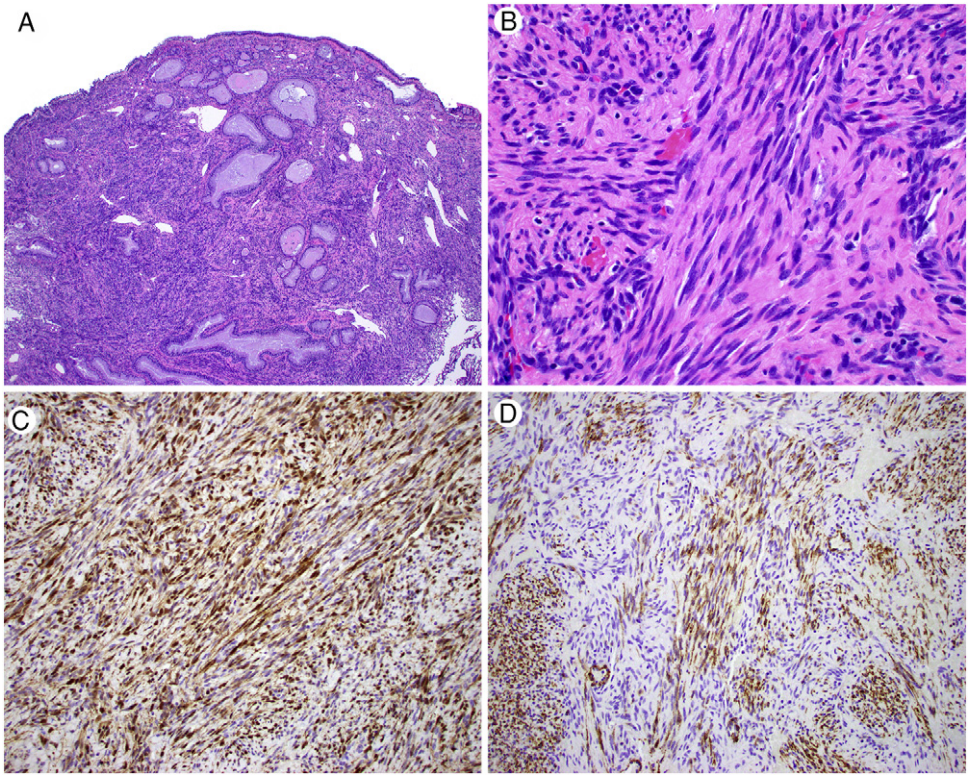

Fig. 13 A, Biphenotypic sinonasal sarcoma is an unencapsulated proliferation of spindled cells. Note the dilated vessels and entrapped invaginations of surface epithelium at low power. B, At high power, the tumor is made up of cells with elongated, wavy nuclei with minimal atypia or mitotic activity. The tumor is positive to varying degrees for (C) S100 protein and (D) smooth muscle actin.

Retrospective studies have shown that before it was recognized, BSNS was diagnosed as many different tumor types including nerve sheath tumors (either schwannoma or low-grade malignant peripheral nerve sheath tumor), solitary fibrous tumor, glomangiopericytoma, fibrosarcoma, leiomyosarcoma, and synovial sarcoma. BSNS may be distinguished from nerve sheath tumors by its immunostaining for smooth muscle markers (actin, calponin, sometimes desmin) and its absence of SOX10 immunostaining. The staghorn vasculature of BSNS raises the possibilities of glomangiopericytoma or solitary fibrous tumor. The spindled cells and S100 protein positivity of BSNS argue against glomangiopericytoma which is also typically more epithelioid than BSNS. Nuclear β-catenin is seen in both tumors and thus is not helpful in distinguishing between these tumors. BSNS lacks the characteristic ropey collagen and variable cellularity of solitary fibrous tumor, the latter S100 protein negative with a strong STAT6 nuclear immunoreaction. Given the occasional focal cytokeratin or EMA immunostaining and uniform nuclear features of BSNS, a monophasic synovial sarcoma is another diagnostic consideration. BSNS is negative for synovial sarcoma fusion transcripts [150,151] and also lacks TLE1 immunoreactivity. Finally, the presence of the *PAX3* rearrangement characteristic of BSNS is not found in any of the other diagnostic considerations, and PAX3 immunostaining is a reliable surrogate [156].

Clinically, BSNS appears to be a relatively indolent neoplasm. Although local recurrences are common, none of the tumors have metastasized, and tumor-related deaths are rare [151-158].

4.5. Adamantinoma-like Ewing sarcoma

Ewing sarcoma is well recognized to occur in the head and neck, including the sinonasal tract [159]. Around 20%-30% of Ewing sarcomas demonstrate epithelial differentiation in the form of cytokeratin immunostaining [160-162]. Although this cytokeratin labeling is usually limited to focal staining with low–molecular weight cytokeratins, rare forms of genetically confirmed Ewing sarcomas have exhibited overt squamous differentiation at histologic, immunophenotypic, and ultrastructural levels. These Ewing sarcomas were originally encountered in the bones, where their overlap with adamantinoma led to the diagnostic term *adamantinoma-like* Ewing sarcoma [160,163-165]. Adamantinoma-like Ewing sarcoma has been increasingly recognized in the head and neck, which appear to be favored sites [166-170].

In the head and neck, adamantinoma-like Ewing sarcomas have arisen in patients ranging from 7 to 77 years in age (mean, 42 years), who present with symptoms related to their anatomic location [166-170]. The patients with sinonasal

adamantinoma-like Ewing sarcomas present with epistaxis, nasal obstruction, and proptosis.

Histologically, adamantinoma-like Ewing sarcoma has similarities with conventional Ewing sarcoma: they are arranged as nests, sheets, and trabeculae of uniform, small cells with clear to eosinophilic cytoplasm. The tumor nuclei are round to oval with finely dispersed chromatin and a single, indistinct nucleolus. Cell spindling can be seen, along with focal rosettes. Tumor necrosis is common, and mitotic rates are typically high. In other respects, however, the histologic features of adamantinoma-like Ewing sarcomas depart from conventional Ewing sarcomas: they often have a basaloid appearance in tumor nests with peripheral nuclear palisading (Fig. 14A), they feature prominent intratumoral fibrosis, and occasional cases exhibit overt squamous differentiation in the form of squamous pearls (Fig. 14B). By immunohistochemistry, adamantinoma-like Ewing sarcoma is diffusely positive for pan-cytokeratin (Fig. 14C) as well as the squamous markers p63 and p40. CD99 (Fig. 14D) and NKX2.2 are consistently positive. Focal synaptophysin expression is also common.

Adamantinoma-like Ewing sarcoma is a diagnostic challenge. The prominent nesting, occasional keratinization, and immunostaining pattern strongly point to SCC, a far more common neoplasm in the sinonasal tract. The most helpful clues to the diagnosis are its nuclear monotony and consistent CD99 and NKX2.2 immunoexpression. Indeed, finding of CD99 or NKX2.2 immunoexpression in a sinonasal carcinoma should prompt molecular testing for Ewing sarcoma because sinonasal SCC is almost always negative for these antibodies [168,171]. It is also difficult to distinguish adamantinoma-like Ewing sarcoma from NUT carcinoma; both tumors commonly occur in young patients, exhibit monomorphic tumor nuclei, and may have focal squamous differentiation. CD99 can occasionally be positive in NUT carcinoma [172]. NUT immunostaining is helpful in this differential diagnosis, as it is consistently negative in adamantinoma-like Ewing sarcoma. Finally, separating adamantinoma-like Ewing sarcoma from a round cell soft tissue myoepithelial carcinoma is problematic because of overlapping histologic and immunophenotypic features. In addition, soft tissue myoepithelial carcinomas often harbor rearrangements of *EWSR1*, and as a result, a definitive diagnosis of adamantinoma-like Ewing sarcoma requires not only demonstration of *EWSR1* rearrangement but also a determination of the partner gene, usually *FLI1* or *ERG* [173-175].

Because of its rarity, the behavior of adamantinoma-like Ewing sarcoma is not yet clear. Early indications appear to indicate that it is more indolent than conventional Ewing sarcoma [168,170]. It is not clear if the adamantinoma-like variant is best managed like conventional Ewing sarcoma or whether it can be treated more conservatively.

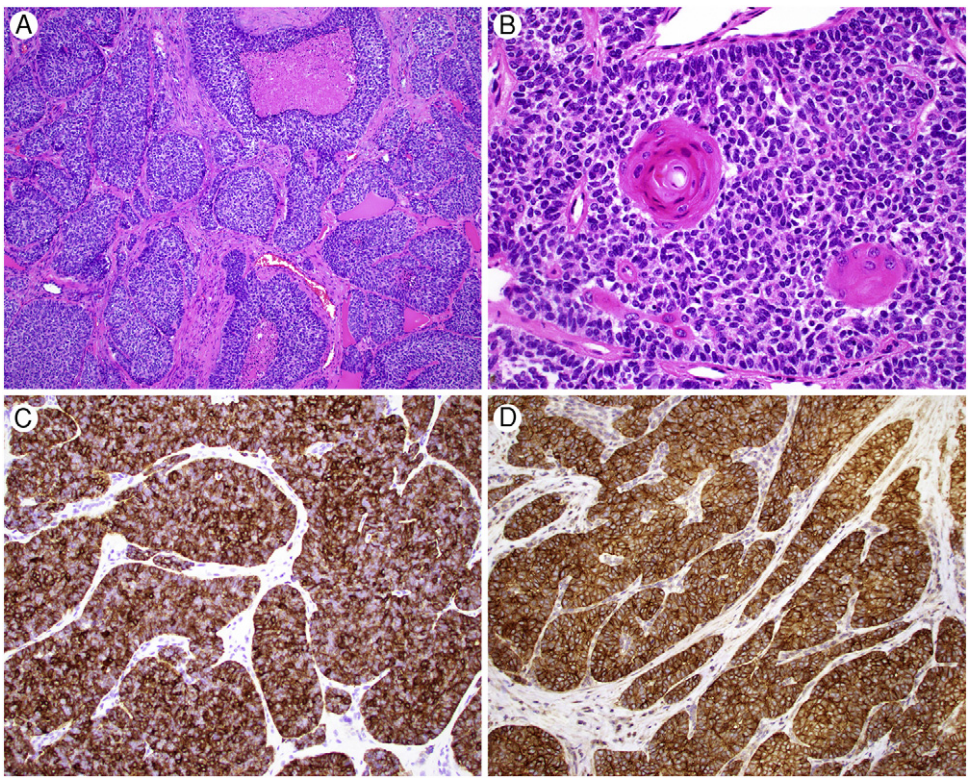

Fig. 14 A, Adamantinoma-like Ewing sarcoma grows as basaloid lobules in a fibrous stroma. Necrosis is evident. B, These tumors are composed of uniform small cells, and foci of squamous differentiation are often seen. These tumors are consistently positive for (C) pan-cytokeratin and (D) CD99.

5. Conclusions

Was it all worth it? Absolutely. The field of head and neck pathology is *doing all right*, expanding rapidly and finding itself in *good company* with advancements in other anatomic disciplines within pathology. No doubt, many additional advancements will be *coming soon*, as research in this discipline grows exponentially. There is no *lost opportunity* for any person with an interest in continuing to further development in this field, and he or she is encouraged to do so. *Now I'm here* to say: *if you can't beat them*, join them! The discipline welcomes all and trusts that the next 50 years will bring even more amazing advances letting all enjoy a favorite Queen song: *It's a Beautiful Day*.

(Hyperbaton: Pertinent italics reference Queen song titles to harmonize the commentary.)

References

[1] Westra W, Boy SC, El-Mofty SK, Gillison M, Schwartz MR, Syrjanen S. Squamous cell carcinoma, HPV-positive. In: El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ, editors. WHO classification of head and neck tumours. Lyon, France: IARC; 2017. p. 136-8.

[2] Valdez JA, Brennan MT. Impact of oral cancer on quality of life. Dent Clin N Am 2018;62:143-54.

[3] Massarelli E, Ferrarotto R, Glisson BS. New strategies in human papillomavirus-related oropharynx cancer: effecting advances in treatment for a growing epidemic. Clin Cancer Res 2015;21:3821-8.

[4] Sturgis EM, Ang KK. The epidemic of HPV-associated oropharyngeal cancer is here: is it time to change our treatment paradigms? J Natl Compr Canc Netw 2011;9:665-73.

[5] Pan C, Issaeva N, Yarbrough WG. HPV-driven oropharyngeal cancer: current knowledge of molecular biology and mechanisms of carcinogenesis. Cancers Head Neck 2018;3:12.

[6] Gondim DD, Haynes W, Wang X, Chernock RD, El-Mofty SK, Lewis Jr JS. Histologic typing in oropharyngeal squamous cell carcinoma: a 4-year prospective practice study with p16 and high-risk HPV mRNA testing correlation. Am J Surg Pathol 2016;40:1117-24.

[7] Patel KR, Chernock RD, Zhang TR, Wang X, El-Mofty SK, Lewis Jr JS. Verrucous carcinomas of the head and neck, including those with associated squamous cell carcinoma, lack transcriptionally active high-risk human papillomavirus. Hum Pathol 2013;44:2385-92.

[8] Chernock RD. Morphologic features of conventional squamous cell carcinoma of the oropharynx: 'keratinizing' and 'nonkeratinizing' histologic types as the basis for a consistent classification system. Head Neck Pathol 2012;6(Suppl. 1):S41-7.

[9] Cai C, Chernock RD, Pittman ME, El-Mofty SK, Thorstad WL, Lewis Jr JS. Keratinizing-type squamous cell carcinoma of the oropharynx: p16 overexpression is associated with positive high-risk HPV status and improved survival. Am J Surg Pathol 2014;38:809-15.

[10] Varier I, Keeley BR, Krupar R, et al. Clinical characteristics and outcomes of oropharyngeal carcinoma related to high-risk non–human papillomavirus16 viral subtypes. Head Neck 2016;38:1330-7.

[11] Gao G, Chernock RD, Gay HA, et al. A novel RT-PCR method for quantification of human papillomavirus transcripts in archived tissues and its application in oropharyngeal cancer prognosis. Int J Cancer 2013;132:882-90.

[12] Bratman SV, Bruce JP, O'Sullivan B, et al. Human papillomavirus genotype association with survival in head and neck squamous cell carcinoma. JAMA Oncol 2016;2:823-6.

[13] Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24-35.

[14] Sedghizadeh PP, Billington WD, Paxton D, et al. Is p16-positive oropharyngeal squamous cell carcinoma associated with favorable prognosis? A systematic review and meta-analysis. Oral Oncol 2016;54:15-27.

[15] Benson E, Li R, Eisele D, Fakhry C. The clinical impact of HPV tumor status upon head and neck squamous cell carcinomas. Oral Oncol 2014;50:565-74.

[16] Lewis Jr JS, Beadle B, Bishop JA, et al. Human papillomavirus testing in head and neck carcinomas: guideline from the College of American Pathologists. Arch Pathol Lab Med 2018;142:559-97.

[17] Fakhry C, Lacchetti C, Rooper LM, et al. Human papillomavirus testing in head and neck carcinomas: ASCO clinical practice guideline endorsement of the College of American Pathologists Guideline. J Clin Oncol 2018;36:3152-61.

[18] Lydiatt WM, Patel SG, O'Sullivan B, et al. Head and neck cancers—major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67:122-37.

[19] O'Sullivan B, Lydiatt WM, Haughey BH, Brandwein-Gensler M, Glastonbury CM, Shah JP. HPV-mediated (p16+) oropharyngeal cancer. Switzerland: Springer Nature; 2016.

[20] Lewis Jr JS, Adelstein DJ, Agaimy A, et al. Data set for the reporting of carcinomas of the nasopharynx and oropharynx: explanations and recommendations of the guidelines from the International Collaboration on Cancer Reporting. Arch Pathol Lab Med 2019;143:447-51.

[21] Ukpo OC, Flanagan JJ, Ma XJ, Luo Y, Thorstad WL, Lewis Jr JS. High-risk human papillomavirus E6/E7 mRNA detection by a novel in situ hybridization assay strongly correlates with p16 expression and patient outcomes in oropharyngeal squamous cell carcinoma. Am J Surg Pathol 2011;35:1343-50.

[22] Perry ME. The specialised structure of crypt epithelium in the human palatine tonsil and its functional significance. J Anat 1994;185(Pt 1):111-27.

[23] Kassay D, Sandor A. The crypt system of the palatine tonsils. Arch Otolaryngol 1962;75:144-55.

[24] McIlwain WR, Sood AJ, Nguyen SA, Day TA. Initial symptoms in patients with HPV-positive and HPV-negative oropharyngeal cancer. JAMA Otolaryngol Head Neck Surg 2014;140:441-7.

[25] Westra WH. The morphologic profile of HPV-related head and neck squamous carcinoma: implications for diagnosis, prognosis, and clinical management. Head Neck Pathol 2012;6(Suppl. 1):S48-54.

[26] Ren J, Yang W, Su J, et al. Human papillomavirus and p16 immunostaining, prevalence and prognosis of squamous carcinoma of unknown primary in the head and neck region. Int J Cancer 2019;145(6):1465-74.

[27] Huang YH, Yeh CH, Cheng NM, et al. Cystic nodal metastasis in patients with oropharyngeal squamous cell carcinoma receiving chemoradiotherapy: relationship with human papillomavirus status and failure patterns. PLoS One 2017;12:e0180779.

[28] Goldenberg D, Begum S, Westra WH, et al. Cystic lymph node metastasis in patients with head and neck cancer: an HPV-associated phenomenon. Head Neck 2008;30:898-903.

[29] Thompson LD, Heffner DK. The clinical importance of cystic squamous cell carcinomas in the neck: a study of 136 cases. Cancer 1998;82:944-56.

[30] Amsbaugh MJ, Yusuf M, Cash E, et al. Distribution of cervical lymph node metastases from squamous cell carcinoma of the oropharynx in the era of risk stratification using human papillomavirus and smoking status. Int J Radiat Oncol Biol Phys 2016;96:349-53.

[31] Dahlstrom KR, Calzada G, Hanby JD, et al. An evolution in demographics, treatment, and outcomes of oropharyngeal cancer at a major cancer center: a staging system in need of repair. Cancer 2013;119:81-9.

[32] Lewis Jr JS. p16 immunohistochemistry as a standalone test for risk stratification in oropharyngeal squamous cell carcinoma. Head Neck Pathol 2012;6(Suppl. 1):S75-82.

[33] Panwar A, Interval E, Lydiatt WM. Emergence of a novel staging system for oropharyngeal squamous cell carcinoma based on HPV status. Oncology (Williston Park) 2017;31:e33-40.

[34] Fakhry C, Zhang Q, Gillison ML, et al. Validation of NRG oncology/RTOG-0129 risk groups for HPV-positive and HPV-negative oropharyngeal squamous cell cancer: implications for risk-based therapeutic intensity trials. Cancer 2019;125:2027-38.
[35] Deschuymer S, Dok R, Laenen A, Hauben E, Nuyts S. Patient selection in human papillomavirus related oropharyngeal cancer: the added value of prognostic models in the new TNM 8th edition era. Front Oncol 2018;8:273.
[36] Wurdemann N, Wagner S, Sharma SJ, et al. Prognostic impact of AJCC/UICC 8th edition new staging rules in oropharyngeal squamous cell carcinoma. Front Oncol 2017;7:129.
[37] Bhattasali O, Thompson LDR, Schumacher AJ, Iganej S. Radiographic nodal prognostic factors in stage I HPV-related oropharyngeal squamous cell carcinoma. Head Neck 2019;41:398-402.
[38] Haughey BH, Sinha P, Kallogjeri D, et al. Pathology-based staging for HPV-positive squamous carcinoma of the oropharynx. Oral Oncol 2016;62:11-9.
[39] Zhan KY, Eskander A, Kang SY, et al. Appraisal of the AJCC 8th edition pathologic staging modifications for HPV-positive oropharyngeal cancer, a study of the National Cancer Data Base. Oral Oncol 2017;73:152-9.
[40] Gupta P, Migliacci JC, Hay A, et al. Validation and assessment of discordance of the 8th edition AJCC (American Joint Committee on Cancer) clinical and pathologic staging systems in patients with p16+ oropharyngeal cancer treated with surgery and adjuvant radiation at a single institution. Oral Oncol 2018;83:140-6.
[41] Geltzeiler M, Bertolet M, Albergotti W, et al. Staging HPV-related oropharyngeal cancer: validation of AJCC-8 in a surgical cohort. Oral Oncol 2018;84:82-7.
[42] Skálová A, Vanecek T, Sima R, et al. Mammary analogue secretory carcinoma of salivary glands, containing the ETV6-NTRK3 fusion gene: a hitherto undescribed salivary gland tumor entity. Am J Surg Pathol 2010;34:599-608.
[43] Skálová A, Vanecek T, Martinek P, et al. Molecular profiling of mammary analog secretory carcinoma revealed a subset of tumors harboring a novel ETV6-RET translocation: report of 10 cases. Am J Surg Pathol 2018;42:234-46.
[44] Antonescu CR, Katabi N, Zhang L, et al. EWSR1-ATF1 fusion is a novel and consistent finding in hyalinizing clear-cell carcinoma of salivary gland. Genes Chromosomes Cancer 2011;50:559-70.
[45] Chapman E, Skalova A, Ptakova N, et al. Molecular profiling of hyalinizing clear cell carcinomas revealed a subset of tumors harboring a novel EWSR1-CREM fusion: report of 3 cases. Am J Surg Pathol 2018;42:1182-9.
[46] Jee KJ, Persson M, Heikinheimo K, et al. Genomic profiles and CRTC1-MAML2 fusion distinguish different subtypes of mucoepidermoid carcinoma. Mod Pathol 2013;26:213-22.
[47] Skalova A, Sima R, Kaspirkova-Nemcova J, et al. Cribriform adenocarcinoma of minor salivary gland origin principally affecting the tongue: characterization of new entity. Am J Surg Pathol 2011;35:1168-76.
[48] Weinreb I, Zhang L, Tirunagari LM, et al. Novel PRKD gene rearrangements and variant fusions in cribriform adenocarcinoma of salivary gland origin. Genes Chromosomes Cancer 2014;53:845-56.
[49] Weinreb I, Piscuoglio S, Martelotto LG, et al. Hotspot activating PRKD1 somatic mutations in polymorphous low-grade adenocarcinomas of the salivary glands. Nat Genet 2014;46:1166-9.
[50] Andreasen S, Varma S, Barasch N, et al. The HTN3-MSANTD3 fusion gene defines a subset of acinic cell carcinoma of the salivary gland. Am J Surg Pathol 2019;43(4):489-96.
[51] Weinreb I, Bishop JA, Chiosea SI, et al. Recurrent RET gene rearrangements in Intraductal carcinomas of salivary gland. Am J Surg Pathol 2018;42:442-52.
[52] Skalova A, Vanecek T, Uro-Coste E, et al. Molecular profiling of salivary gland intraductal carcinoma revealed a subset of tumors harboring NCOA4-RET and novel TRIM27-RET fusions: a report of 17 cases. Am J Surg Pathol 2018;42:1445-55.
[53] Skalova A, Ptakova N, Santana T, et al. NCOA4-RET and TRIM27-RET are characteristic gene fusions in salivary intraductal carcinoma, including invasive and metastatic tumors: is "intraductal" correct? Am J Surg Pathol; 2019.
[54] Tognon C, Knezevich SR, Huntsman D, et al. Expression of the ETV6-NTRK3 gene fusion as a primary event in human secretory breast carcinoma. Cancer Cell 2002;2:367-76.
[55] Reynolds S, Shaheen M, Olson G, Barry M, Wu J, Bocklage T. A case of primary mammary analog secretory carcinoma (MASC) of the thyroid masquerading as papillary thyroid carcinoma: potentially more than a one off. Head Neck Pathol 2016;10:405-13.
[56] Dettloff J, Seethala RR, Stevens TM, et al. Mammary analog secretory carcinoma (MASC) involving the thyroid gland: a report of the first 3 cases. Head Neck Pathol 2017;11:124-30.
[57] Bishop JA, Taube JM, Su A, et al. Secretory carcinoma of the skin harboring ETV6 gene fusions: a cutaneous analogue to secretory carcinomas of the breast and salivary glands. Am J Surg Pathol 2017;41:62-6.
[58] Kastnerova L, Luzar B, Goto K, et al. Secretory carcinoma of the skin: report of 6 cases, including a case with a novel NFIX-PKN1 translocation. Am J Surg Pathol 2019;43:1092-8.
[59] Wu B, Loh TKS, Vanecek T, Michal M, Petersson F. (Mammary analogue) secretory carcinoma of the nasal cavity: report of a rare case with p63 and DOG1 expression and uncommon exon 4-exon 14 ETV6-NTRK3 fusion diagnosed with next generation sequencing. Head Neck Pathol 2019. https://doi.org/10.1007/s12105-019-01051-z.
[60] Baneckova M, Agaimy A, Andreasen S, et al. Mammary analog secretory carcinoma of the nasal cavity: characterization of 2 cases and their distinction from other low-grade sinonasal adenocarcinomas. Am J Surg Pathol 2018;42:735-43.
[61] Jung MJ, Song JS, Kim SY, et al. Finding and characterizing mammary analogue secretory carcinoma of the salivary gland. Korean J Pathol 2013;47:36-43.
[62] Luo W, Lindley SW, Lindley PH, Krempl GA, Seethala RR, Fung KM. Mammary analog secretory carcinoma of salivary gland with high-grade histology arising in hard palate, report of a case and review of literature. Int J Clin Exp Pathol 2014;7:9008-22.
[63] Skalova A, Vanecek T, Majewska H, et al. Mammary analogue secretory carcinoma of salivary glands with high-grade transformation: report of 3 cases with the ETV6-NTRK3 gene fusion and analysis of TP53, beta-catenin, EGFR, and CCND1 genes. Am J Surg Pathol 2014;38:23-33.
[64] Drilon A, Li G, Dogan S, et al. What hides behind the MASC: clinical response and acquired resistance to entrectinib after ETV6-NTRK3 identification in a mammary analogue secretory carcinoma (MASC). Ann Oncol 2016;27:920-6.
[65] Baghai F, Yazdani F, Etebarian A, Garajei A, Skalova A. Clinicopathologic and molecular characterization of mammary analogue secretory carcinoma of salivary gland origin. Pathol Res Pract 2017;213:1112-8.
[66] Cipriani NA, Blair EA, Finkle J, et al. Salivary gland secretory carcinoma with high-grade transformation, CDKN2A/B loss, distant metastasis, and lack of sustained response to Crizotinib. Int J Surg Pathol 2017;25:613-8.
[67] Wu EY, Lebastchi J, Marqusee E. Lorch JH. Barletta JA. A case of primary secretory carcinoma of the thyroid with high-grade features. Histopathology: Krane JF; 2017.
[68] Xu B, Aryeequaye R, Wang L, Katabi N. Sinonasal secretory carcinoma of salivary gland with high grade transformation: a case report of this under-recognized diagnostic entity with prognostic and therapeutic implications. Head Neck Pathol 2018;12:274-8.
[69] Khotskaya YB, Holla VR, Farago AF, Mills Shaw KR, Meric-Bernstam F, Hong DS. Targeting TRK family proteins in cancer. Pharmacol Ther 2017;173:58-66.
[70] Rooper LM, Karantanos T, Ning Y, Bishop JA, Gordon SW, Kang H. Salivary secretory carcinoma with a novel ETV6-MET fusion: expanding the molecular spectrum of a recently described entity. Am J Surg Pathol 2018;42:1121-6.

[71] Guilmette J, Dias-Santagata D, Nose V, Lennerz JK, Sadow PM. Novel gene fusions in secretory carcinoma of the salivary glands: enlarging the ETV6 family. Hum Pathol 2019;83:50-8.
[72] Shah AA, Wenig BM, LeGallo RD, Mills SE, Stelow EB. Morphology in conjunction with immunohistochemistry is sufficient for the diagnosis of mammary analogue secretory carcinoma. Head Neck Pathol 2015;9:85-95.
[73] Bishop JA, Yonescu R, Batista D, Begum S, Eisele DW, Westra WH. Utility of mammaglobin immunohistochemistry as a proxy marker for the ETV6-NTRK3 translocation in the diagnosis of salivary mammary analogue secretory carcinoma. Hum Pathol 2013;44:1982-8.
[74] Drilon A, Hu ZI, Lai GGY, Tan DSW. Targeting RET-driven cancers: lessons from evolving preclinical and clinical landscapes. Nat Rev Clin Oncol 2018;15:151-67.
[75] Mo HN, Liu P. Targeting MET in cancer therapy. Chronic Dis Transl Med 2017;3:148-53.
[76] Loening T, Leivo I, Simpson RHW, Weinreb I. Tumours of the salivary glands: malignant tumours: intraductal carcinoma. In: El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ, editors. WHO classification of head and neck tumours. Lyon, France: IARC; 2017. p. 170-1.
[77] Delgado R, Klimstra D, Albores-Saavedra J. Low grade salivary duct carcinoma. A distinctive variant with a low grade histology and a predominant intraductal growth pattern. Cancer 1996;78:958-67.
[78] Brandwein-Gensler MS, Gnepp DR. Low-grade cribriform cystadenocarcinoma. In: Barnes EL, Eveson JW, Reichart PA, Sidransky D, editors. Pathology and genetics of head and neck tumours. Lyon: IARC Press; 2005. p. 233.
[79] Weinreb I, Tabanda-Lichauco R, Van der Kwast T, Perez-Ordonez B. Low-grade intraductal carcinoma of salivary gland: report of 3 cases with marked apocrine differentiation. Am J Surg Pathol 2006;30:1014-21.
[80] Lu H, Graham RP, Seethala R, Chute D. Intraductal carcinoma of salivary glands harboring TRIM27-RET fusion with mixed low grade and apocrine types. Head Neck Pathol 2019. https://doi.org/10.1007/s12105-018-0996-1.
[81] Michal M, Skalova A, Simpson RH, et al. Cribriform adenocarcinoma of the tongue: a hitherto unrecognized type of adenocarcinoma characteristically occurring in the tongue. Histopathology 1999;35:495-501.
[82] Luna MA, Wenig BM. Polymorphous low-grade adenocarcinoma. In: Barnes EL, Eveson JW, Reichart PA, Sidransky D, editors. Pathology and genetics of head and neck tumours. Lyon: IARC Press; 2005. p. 223-4.
[83] Fonseca I, Assaad A, Katabi N, Seethala R, Weinreb I, Wenig BM. Tumours of the salivary glands: malignant tumours: polymorphous adenocarcinoma. In: El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ, editors. WHO classification of head and neck tumours. Lyon, France: IARC; 2017. p. 167-8.
[84] Piscuoglio S, Fusco N, Ng CK, et al. Lack of PRKD2 and PRKD3 kinase domain somatic mutations in PRKD1 wild-type classic polymorphous low-grade adenocarcinomas of the salivary gland. Histopathology 2016;68:1055-62.
[85] Sebastiao APM, Pareja F, Kumar R, et al. Genomic analysis of recurrences and high-grade forms of polymorphous adenocarcinoma. Histopathology 2019;75:193-201.
[86] Wenig BM, Bell D, Chiosea S, Inagaki H, Seethala RR. Tumours of the salivary glands: malignant tumours: clear cell carcinoma. In: El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ, editors. WHO classification of head and neck tumours. Lyon, France: IARC; 2017. p. 168-9.
[87] Shah AA, LeGallo RD, van Zante A, et al. EWSR1 genetic rearrangements in salivary gland tumors: a specific and very common feature of hyalinizing clear cell carcinoma. Am J Surg Pathol 2013;37:571-8.
[88] Bilodeau EA, Weinreb I, Antonescu CR, et al. Clear cell odontogenic carcinomas show EWSR1 rearrangements: a novel finding and a biological link to salivary clear cell carcinomas. Am J Surg Pathol 2013;37:1001-5.
[89] Tanguay J, Weinreb I. What the EWSR1-ATF1 fusion has taught us about hyalinizing clear cell carcinoma. Head Neck Pathol 2013;7:28-34.
[90] Hsieh MS, Wang H, Lee YH, Ko JY, Chang YL. Reevaluation of MAML2 fusion-negative mucoepidermoid carcinoma: a subgroup being actually hyalinizing clear cell carcinoma of the salivary gland with EWSR1 translocation. Hum Pathol 2017;61:9-18.
[91] Tonon G, Modi S, Wu L, et al. t(11;19)(q21;p13) translocation in mucoepidermoid carcinoma creates a novel fusion product that disrupts a Notch signaling pathway. Nat Genet 2003;33:208-13.
[92] Fehr A, Roser K, Heidorn K, Hallas C, Loning T, Bullerdiek J. A new type of MAML2 fusion in mucoepidermoid carcinoma. Genes Chromosomes Cancer 2008;47:203-6.
[93] Di Palma S, Simpson RH, Skalova A, Michal M. Metaplastic (infarcted) Warthin's tumour of the parotid gland: a possible consequence of fine needle aspiration biopsy. Histopathology 1999;35:432-8.
[94] Skalova A, Vanecek T, Simpson RH, et al. CRTC1-MAML2 and CRTC3-MAML2 fusions were not detected in metaplastic Warthin tumor and metaplastic pleomorphic adenoma of salivary glands. Am J Surg Pathol 2013;37:1743-50.
[95] Weinreb I, Seethala RR, Perez-Ordonez B, Chetty R, Hoschar AP, Hunt JL. Oncocytic mucoepidermoid carcinoma: clinicopathologic description in a series of 12 cases. Am J Surg Pathol 2009;33:409-16.
[96] Bishop JA, Cowan ML, Shum CH, Westra WH. MAML2 rearrangements in variant forms of mucoepidermoid carcinoma: ancillary diagnostic testing for the ciliated and Warthin-like variants. Am J Surg Pathol 2018;42:130-6.
[97] Persson M, Andren Y, Mark J, Horlings HM, Persson F, Stenman G. Recurrent fusion of MYB and NFIB transcription factor genes in carcinomas of the breast and head and neck. Proc Natl Acad Sci U S A 2009;106:18740-4.
[98] Mitani Y, Liu B, Rao PH, et al. Novel MYBL1 gene rearrangements with recurrent MYBL1-NFIB fusions in salivary adenoid cystic carcinomas lacking t(6;9) translocations. Clin Cancer Res 2016;22:725-33.
[99] Stephens PJ, Davies HR, Mitani Y, et al. Whole exome sequencing of adenoid cystic carcinoma. J Clin Invest 2013;123:2965-8.
[100] Steiner P, Andreasen S, Grossmann P, et al. Prognostic significance of 1p36 locus deletion in adenoid cystic carcinoma of the salivary glands. Virchows Arch 2018;473:471-80.
[101] Seethala RR, Bell D, Fonseca I, Katabi N. Tumours of the salivary glands: malignant tumours: epithelial-myoepithelial carcinoma. In: El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ, editors. WHO classification of head and neck tumours. Lyon, France: IARC; 2017. p. 175-6.
[102] Seethala RR, Barnes EL, Hunt JL. Epithelial-myoepithelial carcinoma: a review of the clinicopathologic spectrum and immunophenotypic characteristics in 61 tumors of the salivary glands and upper aerodigestive tract. Am J Surg Pathol 2007;31:44-57.
[103] Seethala RR. Oncocytic and apocrine epithelial myoepithelial carcinoma: novel variants of a challenging tumor. Head Neck Pathol 2013;7(Suppl. 1):S77-84.
[104] Chiosea SI, Miller M, Seethala RR. HRAS mutations in epithelial-myoepithelial carcinoma. Head Neck Pathol 2014;8:146-50.
[105] Rupp NJ, Brada M, Skalova A, et al. New insights into tumor heterogeneity: a case of solid-oncocytic epithelial-myoepithelial carcinoma of the parotid gland harboring a HRAS and heterogeneous terminating ARID1A mutation. Head Neck Pathol 2019. https://doi.org/10.1007/s12105-019-01055-9.
[106] Urano M, Nakaguro M, Yamamoto Y, et al. Diagnostic significance of HRAS mutations in epithelial-myoepithelial carcinomas exhibiting a broad histopathologic spectrum. Am J Surg Pathol 2019;43:984-94.
[107] Bishop JA, Westra WH. MYB translocation status in salivary gland epithelial-myoepithelial carcinoma: evaluation of classic, variant, and hybrid forms. Am J Surg Pathol 2018;42:319-25.
[108] Hellquist H, Skalova A, Azadeh B. Salivary gland hybrid tumour revisited: could they represent high-grade transformation in a low-grade neoplasm? Virchows Arch 2016;469:643-50.

[109] El-Naggar AK, Chan JKC, Grandis JR. WHO classification of head and neck tumours. Lyon, France: IARC Press; 2017.
[110] Kees UR, Mulcahy MT, Willoughby ML. Intrathoracic carcinoma in an 11-year-old girl showing a translocation t(15;19). Am J Pediatr Hematol Oncol 1991;13:459-64.
[111] Kubonishi I, Takehara N, Iwata J, et al. Novel t(15;19)(q15;p13) chromosome abnormality in a thymic carcinoma. Cancer Res 1991;51:3327-8.
[112] French C. NUT midline carcinoma. Nat Rev Cancer 2014;14:149-50.
[113] French CA. The importance of diagnosing NUT midline carcinoma. Head Neck Pathol 2013;7:11-6.
[114] Stelow EB. A review of NUT midline carcinoma. Head Neck Pathol 2011;5:31-5.
[115] Bauer DE, Mitchell CM, Strait KM, et al. Clinicopathologic features and long-term outcomes of NUT midline carcinoma. Clin Cancer Res 2012;18:5773-9.
[116] French CA, Bishop JA, Lewis JS, Muller S, Westra WH. NUT carcinoma. In: el-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ, editors. WHO classification of head and neck tumours. Lyon, France: IARC Press; 2017. p. 20-1.
[117] Bishop JA, Westra WH. NUT midline carcinomas of the sinonasal tract. Am J Surg Pathol 2012;36:1216-21.
[118] Fang W, French CA, Cameron MJ, Han Y, Liu H. Clinicopathological significance of NUT rearrangements in poorly differentiated malignant tumors of the upper respiratory tract. Int J Surg Pathol 2013;21:102-10.
[119] French CA, Ramirez CL, Kolmakova J, et al. BRD-NUT oncoproteins: a family of closely related nuclear proteins that block epithelial differentiation and maintain the growth of carcinoma cells. Oncogene 2008;27:2237-42.
[120] Stelow EB, Bellizzi AM, Taneja K, et al. NUT rearrangement in undifferentiated carcinomas of the upper aerodigestive tract. Am J Surg Pathol 2008;32:828-34.
[121] Haack H, Johnson LA, Fry CJ, et al. Diagnosis of NUT midline carcinoma using a NUT-specific monoclonal antibody. Am J Surg Pathol 2009;33:984-91.
[122] Dickson BC, Sung YS, Rosenblum MK, et al. NUTM1 gene fusions characterize a subset of undifferentiated soft tissue and visceral tumors. Am J Surg Pathol 2018;42:636-45.
[123] Marur S, D'Souza G, Westra WH, Forastiere AA. HPV-associated head and neck cancer: a virus-related cancer epidemic. Lancet Oncol 2010;11:781-9.
[124] Singhi AD, Westra WH. Comparison of human papillomavirus in situ hybridization and p16 immunohistochemistry in the detection of human papillomavirus–associated head and neck cancer based on a prospective clinical experience. Cancer 2010;116:2166-73.
[125] Bishop JA, Guo TW, Smith DF, et al. Human papillomavirus–related carcinomas of the sinonasal tract. Am J Surg Pathol 2013;37:185-92.
[126] Lewis Jr JS, Ukpo OC, Ma XJ, et al. Transcriptionally-active high-risk human papillomavirus is rare in oral cavity and laryngeal/hypopharyngeal squamous cell carcinomas—a tissue microarray study utilizing E6/E7 mRNA in situ hybridization. Histopathology 2012;60:982-91.
[127] Lewis Jr JS, Westra WH, Thompson LDR, et al. The sinonasal tract: another potential "hot spot" for carcinomas with transcriptionally-active human papillomavirus. Head Neck Pathol 2013:1-9.
[128] Larque AB, Hakim S, Ordi J, et al. High-risk human papillomavirus is transcriptionally active in a subset of sinonasal squamous cell carcinomas. Mod Pathol 2014;27:343-51.
[129] Bishop JA, Andreasen S, Hang JF, et al. HPV-related multiphenotypic sinonasal carcinoma: an expanded series of 49 cases of the tumor formerly known as HPV-related carcinoma with adenoid cystic carcinoma-like features. Am J Surg Pathol 2017;41:1690-701.
[130] Hwang SJ, Ok S, Lee HM, Lee E, Park IH. Human papillomavirus-related carcinoma with adenoid cystic-like features of the inferior turbinate: a case report. Auris Nasus Larynx 2015;42:53-5.
[131] Bishop JA, Westra WH. Human papillomavirus-related multiphenotypic sinonasal carcinoma: an emerging tumor type with a unique microscopic appearance and a paradoxical clinical behaviour. Oral Oncol 2018;87:17-20.
[132] Shah AA, Lamarre ED, Bishop JA. Human papillomavirus-related multiphenotypic sinonasal carcinoma: a case report documenting the potential for very late tumor recurrence. Head Neck Pathol 2018;12:623-8.
[133] Ahn B, Kim E, Oh H, et al. Human papillomavirus-related multiphenotypic sinonasal carcinoma with late recurrence. J Pathol Transl Med 2019. https://doi.org/10.4132/jptm.2019.04.02.
[134] Chen CC, Yang SF. Human papillomavirus-related carcinoma with adenoid cystic-like features of the sinonasal tract (also known as human papillomavirus-related multiphenotypic sinonasal carcinoma). Arch Pathol Lab Med 2019. https://doi.org/10.5858/arpa.2018-0027-RS.
[135] Hsieh MS, Lee YH, Jin YT, Huang WC. Strong SOX10 expression in human papillomavirus-related multiphenotypic sinonasal carcinoma: report of 6 new cases validated by high-risk human papillomavirus mRNA in situ hybridization test. Hum Pathol 2018;82:264-72.
[136] Shah AA, Oliai BR, Bishop JA. Consistent LEF-1 and MYB Immunohistochemical expression in human papillomavirus–related multiphenotypic sinonasal carcinoma: a potential diagnostic pitfall. Head Neck Pathol 2019;13:220-4.
[137] Jour G, West K, Ghali V, Shank D, Ephrem G, Wenig BM. Differential expression of p16(INK4A) and cyclin D1 in benign and malignant salivary gland tumors: a study of 44 cases. Head Neck Pathol 2013;7:224-31.
[138] Rooper LM, McCuiston AM, Westra WH, Bishop JA. SOX10 Immunoexpression in basaloid squamous cell carcinomas: a diagnostic pitfall for ruling out salivary differentiation. Head Neck Pathol 2018. https://doi.org/10.1007/s12105-018-0990-7.
[139] Biegel JA, Kalpana G, Knudsen ES, et al. The role of INI1 and the SWI/SNF complex in the development of rhabdoid tumors: meeting summary from the workshop on childhood atypical teratoid/rhabdoid tumors. Cancer Res 2002;62:323-8.
[140] Hornick JL, Dal Cin P, Fletcher CD. Loss of INI1 expression is characteristic of both conventional and proximal-type epithelioid sarcoma. Am J Surg Pathol 2009;33:542-50.
[141] Cheng JX, Tretiakova M, Gong C, Mandal S, Krausz T, Taxy JB. Renal medullary carcinoma: rhabdoid features and the absence of INI1 expression as markers of aggressive behavior. Mod Pathol 2008;21:647-52.
[142] Kohashi K, Oda Y, Yamamoto H, et al. SMARCB1/INI1 protein expression in round cell soft tissue sarcomas associated with chromosomal translocations involving EWS: a special reference to SMARCB1/INI1 negative variant extraskeletal myxoid chondrosarcoma. Am J Surg Pathol 2008;32:1168-74.
[143] Agaimy A, Koch M, Lell M, et al. SMARCB1(INI1)-deficient sinonasal basaloid carcinoma: a novel member of the expanding family of SMARCB1-deficient neoplasms. Am J Surg Pathol 2014;38:1274-81.
[144] Bishop JA, Antonescu CR, Westra WH. SMARCB1 (INI-1)-deficient carcinomas of the sinonasal tract. Am J Surg Pathol 2014;38:1282-9.
[145] Agaimy A, Hartmann A, Antonescu CR, et al. SMARCB1 (INI-1)-deficient sinonasal carcinoma: a series of 39 cases expanding the morphologic and clinicopathologic spectrum of a recently described entity. Am J Surg Pathol 2017;41:458-71.
[146] Shah AA, Jain D, Ababneh E, et al. SMARCB1 (INI-1)-deficient adenocarcinoma of the sinonasal tract: a potentially under-recognized form of sinonasal adenocarcinoma with occasional yolk sac tumor-like features. Head Neck Pathol 2019. https://doi.org/10.1007/s12105-019-01065-7.
[147] Frierson Jr HF, Mills SE, Fechner RE, Taxy JB, Levine PA. Sinonasal undifferentiated carcinoma. An aggressive neoplasm derived from schneiderian epithelium and distinct from olfactory neuroblastoma. Am J Surg Pathol 1986;10:771-9.
[148] Bell D, Hanna EY, Agaimy A, Weissferdt A. Reappraisal of sinonasal undifferentiated carcinoma: SMARCB1 (INI1)-deficient sinonasal carcinoma: a single-institution experience. Virchows Arch 2015;467:649-56.
[149] Gounder MM, Zhu G, Roshal L, et al. Immunologic correlates of the abscopal effect in a SMARCB1/INI1-negative poorly differentiated

chordoma after EZH2 inhibition and radiotherapy. Clin Cancer Res 2019;25:2064-71.
[150] Lewis JT, Oliveira AM, Nascimento AG, et al. Low-grade sinonasal sarcoma with neural and myogenic features: a clinicopathologic analysis of 28 cases. Am J Surg Pathol 2012;36:517-25.
[151] Wang X, Bledsoe KL, Graham RP, et al. Recurrent PAX3-MAML3 fusion in biphenotypic sinonasal sarcoma. Nat Genet 2014;46:666-8.
[152] Wong WJ, Lauria A, Hornick JL, Xiao S, Fletcher JA, Marino-Enriquez A. Alternate PAX3-FOXO1 oncogenic fusion in biphenotypic sinonasal sarcoma. Genes Chromosomes Cancer 2016;55:25-9.
[153] Huang SC, Ghossein RA, Bishop JA, et al. Novel PAX3-NCOA1 fusions in biphenotypic sinonasal sarcoma with focal rhabdomyoblastic differentiation. Am J Surg Pathol 2016;40:51-9.
[154] Rooper LM, Huang SC, Antonescu CR, Westra WH, Bishop JA. Biphenotypic sinonasal sarcoma: an expanded immunoprofile including consistent nuclear beta-catenin positivity and absence of SOX10 expression. Hum Pathol 2016;55:44-50.
[155] Andreasen S, Bishop JA, Hellquist H, et al. Biphenotypic sinonasal sarcoma: demographics, clinicopathological characteristics, molecular features, and prognosis of a recently described entity. Virchows Arch 2018;473:615-26.
[156] Jo VY, Marino-Enriquez A, Fletcher CDM, Hornick JL. Expression of PAX3 distinguishes biphenotypic sinonasal sarcoma from histologic mimics. Am J Surg Pathol 2018;42:1275-85.
[157] Kakkar A, Rajeshwari M, Sakthivel P, Sharma MC, Sharma SC. Biphenotypic sinonasal sarcoma: a series of six cases with evaluation of role of beta-catenin immunohistochemistry in differential diagnosis. Ann Diagn Pathol 2018;33:6-10.
[158] Le Loarer F, Laffont S, Lesluyes T, et al. Clinicopathologic and molecular features of a series of 41 biphenotypic sinonasal sarcomas expanding their molecular Spectrum. Am J Surg Pathol 2019;43:747-54.
[159] Hafezi S, Seethala RR, Stelow EB, et al. Ewing's family of tumors of the sinonasal tract and maxillary bone. Head Neck Pathol 2011;5:8-16.
[160] Folpe AL, Goldblum JR, Rubin BP, et al. Morphologic and immunophenotypic diversity in Ewing family tumors: a study of 66 genetically confirmed cases. Am J Surg Pathol 2005;29:1025-33.
[161] Gu M, Antonescu CR, Guiter G, Huvos AG, Ladanyi M, Zakowski MF. Cytokeratin immunoreactivity in Ewing's sarcoma: prevalence in 50 cases confirmed by molecular diagnostic studies. Am J Surg Pathol 2000;24:410-6.
[162] Collini P, Sampietro G, Bertulli R, et al. Cytokeratin immunoreactivity in 41 cases of ES/PNET confirmed by molecular diagnostic studies. Am J Surg Pathol 2001;25:273-4.
[163] Bridge JA, Fidler ME, Neff JR, et al. Adamantinoma-like Ewing's sarcoma: genomic confirmation, phenotypic drift. Am J Surg Pathol 1999;23:159-65.
[164] Hauben E, van den Broek LC, Van Marck E, Hogendoorn PC. Adamantinoma-like Ewing's sarcoma and Ewing's-like adamantinoma. The t(11; 22), t(21; 22) status. J Pathol 2001;195:218-21.
[165] Fujii H, Honoki K, Enomoto Y, et al. Adamantinoma-like Ewing's sarcoma with EWS-FLI1 fusion gene: a case report. Virchows Arch 2006;449:579-84.
[166] Weinreb I, Goldstein D, Perez-Ordonez B. Primary extraskeletal Ewing family tumor with complex epithelial differentiation: a unique case arising in the lateral neck presenting with Horner syndrome. Am J Surg Pathol 2008;32:1742-8.
[167] Kikuchi Y, Kishimoto T, Ota S, et al. Adamantinoma-like Ewing family tumor of soft tissue associated with the vagus nerve: a case report and review of the literature. Am J Surg Pathol 2013;37:772-9.
[168] Bishop JA, Alaggio R, Zhang L, Seethala RR, Antonescu CR. Adamantinoma-like Ewing family tumors of the head and neck: a pitfall in the differential diagnosis of basaloid and myoepithelial carcinomas. Am J Surg Pathol 2015;39:1267-74.
[169] Alexiev BA, Tumer Y, Bishop JA. Sinonasal adamantinoma-like Ewing sarcoma: a case report. Pathol Res Pract 2017;213:422-6.
[170] Rooper LM, Jo VY, Antonescu CR, et al. Adamantinoma-like Ewing sarcoma of the salivary glands: a newly recognized mimicker of basaloid salivary carcinomas. Am J Surg Pathol 2019;43:187-94.
[171] McCuiston A, Bishop JA. Usefulness of NKX2.2 immunohistochemistry for distinguishing Ewing sarcoma from other sinonasal small round blue cell tumors. Head Neck Pathol 2018;12:89-94.
[172] Teo M, Crotty P, O'Sullivan M, French CA, Walshe JM. NUT midline carcinoma in a young woman. J Clin Oncol 2011;29:e336-9.
[173] Antonescu CR, Zhang L, Chang NE, et al. EWSR1-POU5F1 fusion in soft tissue myoepithelial tumors. A molecular analysis of sixty-six cases, including soft tissue, bone, and visceral lesions, showing common involvement of the EWSR1 gene. Genes Chromosomes Cancer 2010;49:1114-24.
[174] Brandal P, Panagopoulos I, Bjerkehagen B, Heim S. t(19;22)(q13;q12) Translocation leading to the novel fusion gene EWSR1-ZNF444 in soft tissue myoepithelial carcinoma. Genes Chromosomes Cancer 2009;48:1051-6.
[175] Agaram NP, Chen HW, Zhang L, et al. EWSR1-PBX3: a novel gene fusion in myoepithelial tumors. Genes Chromosomes Cancer 2015;54:63-71.