Chapter 12
Rare Sinonasal and Skull Base Tumors

Kelly R. Magliocca and Christopher C. Griffith

Teratocarcinosarcoma

Teratocarcinosarcoma (TCS) is an aggressive malignant neoplasm described in 1983 by Shanmugaratnam et al [1] as teratoid carcinosarcoma. The following year, Heffner and Hyams [2] delineated the histologic features and clinical behavior of 20 cases under the designation of teratocarcinosarcoma, a term that remains accepted to this day. TCS most commonly affects adults at a median age of 60 years and reported range of 18–79 years. An 8:1 ratio with a predilection for male patients is reported [2]. The presenting symptoms for patients with TCS are often non-specific and may include nasal obstruction, epistaxis, and headache. Depending on the anatomic site and extent of involvement, eye or facial pain, proptosis, and/or focal neurologic deficits, including loss of olfaction can occur [2–5]. Syndrome of inappropriate antidiuretic hormone secretion has been noted, but is rare [6, 7]. The nasal cavity and ethmoid sinus are most frequently reported as sites of origin, although with large destructive tumors, extension to the orbit, cranial cavity, and/or facial skin can occur [1, 2]. Histologically, tumors are heterogeneous and composed of epithelial, neuroectodermal, and mesenchymal components, with a spectrum of maturation and cellular atypia [1, 2]. The epithelial elements may be cuboidal or columnar epithelium with mucous cells arranged in irregular glandular structures and microcysts, and often appear overtly malignant (Fig. 12.1a). Keratinizing or non-keratinizing squamous epithelium in nests, or sheets may be seen in transition with glandular epithelium. Squamous epithelium exhibiting a characteristic clear

K. R. Magliocca (✉)
Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA, USA
e-mail: kmagliocca@emory.edu

C. C. Griffith
Robert J. Tomsich Pathology and Laboratory Medicine Institute Department of Pathology, Cleveland Clinic Foundation, Cleveland, OH, USA
e-mail: griffic8@ccf.edu

N. F. Saba, D. T. Lin (eds.), *Sinonasal and Skull Base Malignancies*,
https://doi.org/10.1007/978-3-030-97618-7_12

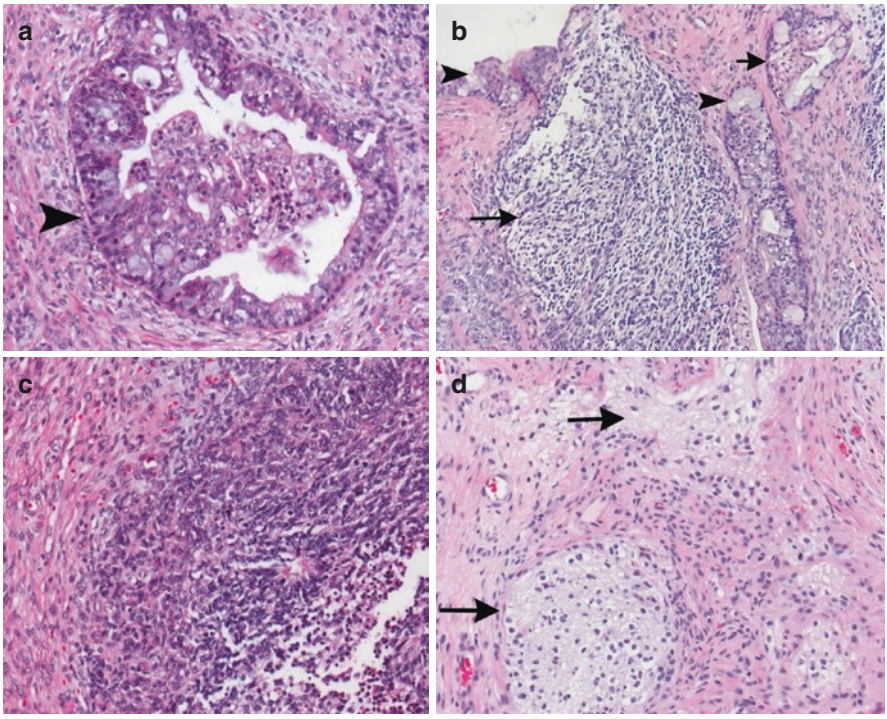

Fig. 12.1 *Teratocarcinosarcoma*: Histologic features of teratocarcinosarcoma (TCS). (**a**) TCS is characterized by glandular structures (arrow) (H&E, 200×). (**b**) Immature neuroctodermal elements (long arrow), clear "fetal-type" changes in epithelium (short arrow), and respiratory epithelium with mucous cells (arrowhead) (**c**) Rosette formation in immature neuroectodermal tissue. (**d**) Pale neurofibrillary matrix (arrow) (Hematoxylin and eosin/H&E, 200×)

cell appearance, similar to that found in fetal mucosal squamous epithelium, is thought to be a helpful diagnostic clue to TCS [2]. Neuroectodermal elements are cellular and show indistinct cell borders and a primitive appearance with rosette formation (Fig. 12.1b, c). Admixed neurofibrillary matrix may be seen (Fig. 12.1). Variable amounts of muscle (smooth or skeletal), cartilage, or rarely bone form the mesenchymal components of TCS, but moderately cellular fibrous stroma, immature adipose tissue, and/or angiomatous areas can be present and most likely represent a bland appearing mesenchymal component of TCS. Smooth muscle irregularly surrounding epithelial aggregates to impart an organoid appearance similar to primitive bronchial or intestinal structures is variably present in TCS [2]. Immunohistochemical analysis reveals the cellular primitive-appearing component in TCS expresses CD99, synaptophysin, and may express S100. While alpha-fetoprotein (AFP) has been reported to stain occasional cells [2], this result is non-specific and has been reported in other sinonasal tract neoplasms [8]. Epithelial elements show positive cytokeratin staining, neurofibrillary matrix is highlighted with GFAP, and in cases with skeletal muscle, desmin, and/or smooth muscle actin

will be positive. Recently, the recurrent immunohistochemical loss of SMARCA4 expression (partial or complete) was noted in 18 of 22 cases (82%) of sinonasal TCS, with corresponding genetic inactivation in a subset of tumors tested. The exact histogenesis of TCS remains unclear, although a neural crest or other pluripotential cell group with either the capability for multidirectional differentiation or a process of differentiation modulated by the microenvironment are hypothesized [6]. The recently identified loss of SMARCA4 and corresponding genetic inactivation of *SMARCA4* suggests that TCS is likely driven by recurrent molecular events rather than stem cell or germ cell origin [9]. From a practical point, it is worth noting that TCS can be challenging to accurately diagnose on a small incisional biopsy specimen [10].

This occurs not only because the neoplasm is extremely rare making it infrequently considered, but also occurs is in part due to partial sampling of a neoplasm known for marked histologic heterogeneity. Areas of TCS may microscopically resemble olfactory neuroblastoma, adenocarcinoma, sarcomatoid carcinoma or even rhabdomyosarcoma on limited biopsy sampling [1, 2]. Loss of SMARCA4 immunostaining may provide a helpful clue in distinguishing between a considered list of differential diagnostic entities, and in some cases may point directly to the diagnosis of TCS [9]. Radiologic features are non-specific. TCS is inherently aggressive and is surgically treated. Involvement of skull base, cranial cavity or orbit can complicate surgical management. Radiation therapy often follows surgery and some have suggested improved survival and reduced rate of metastatic disease with the combined treatment using surgery, radiation and chemotherapy, although this has not been widely studied [5]. Disease recurrence approaches 40%, with a 30–40% mortality rate [5, 6].

Biphenotypic Sinonasal Sarcoma

Sarcomas including rhabdomyosarcoma, Ewing sarcoma, chondrosarcoma, and osteosarcoma are known to occur in the sinonasal and skull base region, but they are not unique to this location. In contrast, a recently described entity, biphenotypic sinonasal sarcoma (BSNS) appears to be a site-specific neoplasm within the sinonasal tract. This monomorphic, low grade spindle cell sarcoma described in 2012 by Lewis et al. [11] was originally designated as *low-grade sinonasal sarcoma with neural and myogenic features,* until the same group renamed the entity as BSNS in 2014 [12]. BSNS is a rare sarcoma with approximately 150 cases described thus far, is of uncertain histogenetic origin, and merits separation from other sarcomas occurring in the sinonasal tract due to its relatively indolent clinical course without reports of regional or distant metastasis [13, 14]. Within the cases described, BSNS shows a predilection for involvement of the superior sinonasal tract including the upper nasal cavity and ethmoid region, singly or in combination with a notable predilection for middle aged females. A peak incidence is reported to occur in the fifth decade of life, with a range from 24 to 85 years. Clinically, patients present with

relatively non-specific mass related symptoms such as obstruction/congestion, epistaxis, or rhinorrhea [11]. These tumors are rare, though there may be a collection of imaging features that, when identified as a unilateral mass with an epicenter in the nasal cavity/ethmoid sinus of a middle aged female patient, could potentially warrant inclusion of BSNS in the radiographic differential diagnosis: hyperostosis on computed tomography (CT), combined with a magnetic resonance imaging (MRI) T2 signal isointense to cerebral gray matter and heterogenous gadolinium enhancement [15, 16]. Histologically, BSNS is an unencapsulated, cellular spindle cell neoplasm arranged in fascicles that may demonstrate a "herringbone" pattern.

Approximately 20% of tumors invade regional bone [11]. The spindled tumor cells, while elongate and overlapping, are bland and uniform in appearance, with no significant atypia or marked hyperchromasia, infrequent mitoses and no necrosis. Intercellular collagen is arranged in delicate strands. Gaping, so-called staghorn blood vessels dispersed within the tumor are not uncommon. A subset of tumors will show rhabdomyoblastic differentiation appearing as ample, brightly eosinophilic cytoplasm with cross-striations. A helpful microscopic finding is benign proliferative invagination of the surface epithelium into the underlying spindle cell sarcoma leading to the appearance of small cystic, epithelial lined spaces "inverting" into the mesenchymal neoplasm (Fig. 12.2a, b). Rarely, this proliferation is

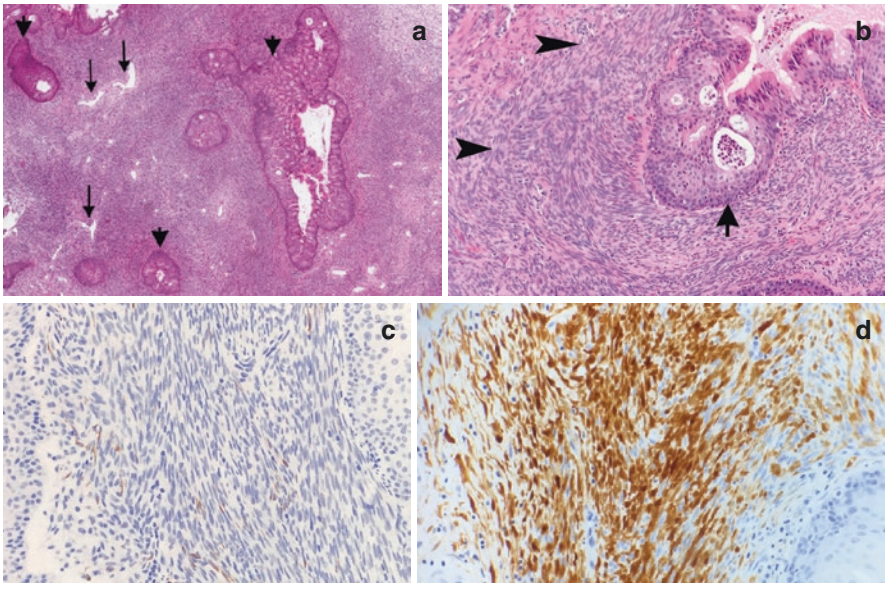

Fig. 12.2 *Biphenotypic sinonasal sarcoma:* Histologic features of biphenotypic sinonasal sarcoma (BSNS). (**a**) BSNS is characterized by spindle cells, often within a proliferative surface epithelial invagination (short arrows), and small patulous vascular channels (long arrows). (**b**) Spindle cell component (arrowheads) abutting invaginated surface epithelium (short arrow). (H&E, 200×). (**c**) Immunohistochemical stain desmin is positive in tumor cells (Desmin, 200×). (**d**) S100 immunostain is positive in tumor cells (S100, 200×)

striking and has the potential to lead to tumor misclassification as a sinonasal (inverted) papilloma on superficial biopsy.

BSNS tumor cells will characteristically demonstrate at least focal biphenotypic immunopositivity for both S100, and smooth muscle actin (Fig. 12.2c, d). Variable and focal expression of desmin, beta-catenin, CD34, EMA, cytokeratin is present. Tumors lack immunoreactivity to SOX10. Myogenin is most commonly reported as negative [11, 12], although cells with rhabdomyoblastic differentiation may react with myogenin [17]. In challenging cases, a positive nuclear reaction with monoclonal PAX3 immunohistochemistry and/or molecular testing may be required to support the diagnosis [18]. The vast majority of BSNS show *PAX3* rearrangements, most commonly with *MAML3* occurring as t(2;4)(q35;q31.1) [11]. Fusions of *PAX3* and *FOXO1, NCOA1,* or *NCOA2* occur less frequently [17]. Prior to identification of BSNS as a distinct entity in 2012, tumors had been misclassified as benign and malignant lesions including fibrosarcoma, leiomyosarcoma, low-grade malignant peripheral nerve sheath tumor, synovial sarcoma, and cellular schwannoma. The primary treatment modality for this low-grade sarcoma is surgical resection without elective neck dissection as there are no known cases with regional metastasis. Bone invasion is possible with surgical excision of involved bone required for complete excision. BSNS has rate of local recurrence that is reported in approximately 40% of cases, usually within the first 5 years. Death is rarely reported and appears to be related to intracranial extension [11, 19, 20]. The role of radiation therapy versus re-excision remains unclear, in part due to the rarity of the tumor.

Chondrosarcoma

Chondrosarcoma represents the second most common primary bone sarcoma after osteosarcoma and most commonly affects the appendicular skeleton [21]. Involvement of the head and neck region is uncommon with approximately 10–12% of all chondrosarcomas occurring in this general area [22]. Within the head and neck, chondrosarcoma can arise in the paranasal sinuses, skull base, gnathic sites, and larynx and tend to show a lower stage and improved prognosis when compared to chondrosarcoma in non-head and neck sites [23]. Conventional chondrosarcoma of the paranasal sinus and skull base shows a peak incidence in the fourth decade of life, with a wide variation in age affecting patients in the range between late childhood to the elderly. No significant male or female predominance has been demonstrated. Conventional chondrosarcoma is classified as primary when it arises de novo, that is without evidence of a pre-existing lesion. Secondary chondrosarcoma arises in the setting of a pre-existing lesion such as osteochondroma or enchondroma often in association with Ollier disease, Maffucci syndrome, or multiple hereditary exostoses/osteochondromas [24]. Secondary chondrosarcoma can rarely arise in synovial chondromatosis. In addition to conventional sarcoma (primary or secondary) several variants of chondrosarcoma exist: dedifferentiated, clear cell and mesenchymal chondrosarcoma. The vast number of chondrosarcomas are primary conventional chondrosarcoma, which represents the focus of this review.

On MRI examination, conventional chondrosarcoma appears isointense on T1, hyperintense on T2 weighted images, and chondrosarcoma usually enhances with gadolinium contrast. This pattern of MRI imaging is similar to chordoma, although in most cases chondrosarcoma is located eccentric to the midline in contrast to midline chordoma [25]. Large radiographic tumor size is not viewed as a negative prognostic factor in chondrosarcoma [26]. Computed tomography (CT) imaging will detect stippled or coarse "popcorn" calcifications, which can show organization into ring and arc calcifications [27]. Microscopically, conventional chondrosarcoma is composed of lobular abnormal hyaline cartilage but flocculent myxoid change is also possible. Chondrosarcoma infiltrates adjacent medullary bone and encases preexisting bony trabeculae. In grade 1 chondrosarcoma (also called atypical cartilaginous tumor) the neoplastic chondrocytes within lacunae are bland, show little atypia and overall these neoplasms are of low cellularity. Increase in nuclear size, hyperchromasia, degree of cellularity, and atypia are parameters used in grading chondrosarcoma, with the highest histological grade correlating with a more aggressive neoplasm [28] (Fig. 12.3a, b). Formation of metaplastic bone within cartilaginous matrix can be seen in chondrosarcoma; however, malignant osteoid would be unexpected. The latter would be indicative of chondroblastic osteosarcoma. Most chondrosarcoma in the sinonasal/skull base region represent grade 1 or 2 conventional which can recur locally but rarely metastasize [21]. A subset of recurrent chondrosarcoma will show a higher grade in the recurrent material, making it important to compare and evaluate new and old material in the case of clinical recurrence. Immunohistochemical markers are most useful in excluding mimics of chondrosarcoma, specifically chordoma in view of the clinical implications (see Chordoma). Just over half of conventional chondrosarcoma are characterized by mutations in the isocitrate dehydrogenase isoforms IDH1 and IDH2. Sequencing to detect *IDH1/2* mutations can be useful if positive in distinguishing chondrosarcoma (i.e., positive) from chondroblastic osteosarcoma [24]. Treatment of sinonasal and skull base chondrosarcoma involves surgical excision; however, an "en bloc" resection is often precluded by the critical structures in the skull base region. Low grade conventional

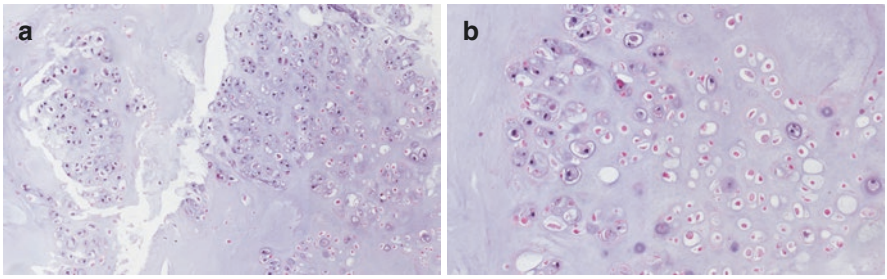

Fig. 12.3 *Chondrosarcoma:* Histologic features of chondrosarcoma. (**a**) Chondrosarcoma is characterized by cellular aggregates within chondroid matrix (H&E, 200×). (**b**) Variation in nuclear size, hyperchromasia and nuclear membrane irregularity (H&E, 400×)

chondrosarcoma, a relatively indolent tumor, is therefore treated with a maximally safe surgical resection and the extent of surgery is based upon lesion location, involvement of cranial nerves and extent of pre-existing nerve deficits, and surgical experience [29]. The use of adjuvant modern radiotherapy techniques, such as particle therapy, following excision of skull base conventional chondrosarcoma has been shown to decrease tumor recurrence and improve overall survival [30, 31]. Conventional chondrosarcoma is resistant to chemotherapy, but targeted therapy may have a role in the future. For patients with skull base chondrosarcoma, the overall 5-year survival is greater than 80%, with an 80% rate of progression free survival [32, 33].

Chordoma

Chordoma is a malignant primary bone tumor thought to originate from notochord remnants [28]. They arise in the midline anywhere along the axial skeletal from the spheno-occiput to the sacrococcygeal region, with cranial chordoma accounting for approximately 30% to 40% of cases [34]. In the recently released fifth edition of the World Health Organization Classification of Soft Tissue and Bone Tumors [28], chordoma is classified into three subtypes: conventional/chondroid, dedifferentiated and poorly differentiated. Conventional chordoma is the most common subtype representing three quarters of cases, and this subtype is the focus of the current review with respect to skull base/clival chordomas. Patients with cranial chordoma present in the 5th to 6th decades of life with headache, diplopia, and depending on location cranial nerve palsies. Either gender can be affected, although some studies describe a male predominance [34–36]. The majority of chordoma arise as isolated tumors, though a rare familial form is known [37]. CT and MRI are the methods of choice to identify the extent of the lesion, bone destruction and tumor relation to regional structures. Chordoma and chondrosarcoma have a similar appearance on these imaging modalities [34]. The primary histologic characteristic of conventional chordoma is the proliferation of highly vacuolated but otherwise uniform tumor cells (physaliferous cells) arranged in syncytial cords and/or nests with abundant mucoid intercellular material (Fig. 12.4a). Chondroid chordoma is defined by variable amounts of cartilage-like matrix supporting cords and lobules of physaliferous cells. Immunohistochemical markers cytokeratin, EMA, S100, and brachyury are positive in chordoma and this pattern of positivity aids in distinguishing chordoma from chondrosarcoma and the rare differential diagnosis of choroid meningioma, as the latter two entities are negative for brachyury [38, 39] (Fig. 12.4b). With respect to chordoma subtypes in brief: dedifferentiated chordoma demonstrates a biphasic appearance of conventional chordoma with juxtaposed high-grade sarcoma. It can occur de novo and after treatment. The dedifferentiated subtype is aggressive and associated with poorer survival outcomes, therefore in the setting of recurrent chordoma, the sample should be compared to primary tumor to assess whether the

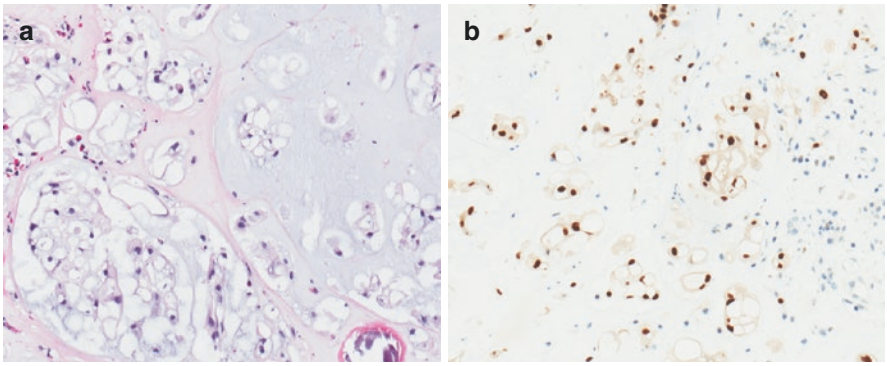

Fig. 12.4 *Chordoma:* Histologic features of Chordoma. (**a**) Chordoma characterized by the presence of highly vacuolated tumor cells (physaliferous cells) arranged in cords and nests (H&E, 400×). (**b**) Nuclear positive reaction in neoplastic cells with brachyury immunostain (Brachyury, 400×)

histologic features have changed over time [40]. Poorly differentiated chordoma (PDC) on the other hand occurs in children and young adults, histologically lacks physaliferous cells, yet highlights with brachyury. PDC is exceptionally rare, and genetically distinct, often harboring *SMARCB1* abnormalities [28]. Although the optimal treatment protocol for skull base chordoma remains controversial, surgical resection of the tumor followed by radiotherapy is accepted and most commonly performed.

Chemotherapy does not routinely form a component of standard chordoma treatment, as most are not susceptible to cytotoxic chemotherapy. In cases where loss of SMARCB1 (identified using INI-1 immunostain) is identified, the possibility of EZH2 inhibitors could potentially be considered [40]. Five-year survival for chordoma is reported at 65–70% [33, 34]. Local recurrence is the most common form of treatment failure and an important predictor of mortality, with recurrence within a biopsy site tract ("seeding") occurring only rarely [25]. Although more commonly associated with sacral chordoma, approximately 12% of patients with skull base chordoma will go on to develop distant metastases, most commonly to the lung [41].

NUT Carcinoma (Nuclear Protein in Testis)

NUT carcinoma is a rare aggressive malignancy most commonly occurring in midline structures. Mediastinum and lung are the most common primary sites closely followed by head and neck primaries. With the increasing recognition of this tumor type in the head and neck, NUT carcinoma was added to the most recent 4th edition of the World Health Organization Classification of Head and Neck Tumours [42]. In the head and neck, NUT carcinoma most commonly occurs in the sinonasal tract but

other rare head and neck sites include the larynx (particularly the supraglottis) [43] and salivary glands [44].

Head and neck NUT carcinoma occur in a wide age range (0.1–81.7 years) but continue to show a trend toward younger patients with a median age of 21.9 years [45]. NUT carcinoma tends to effect younger patients and while this continues to be true, it is increasingly being recognized in older patients as more pathologists become familiar with this entity and consider it in the differential diagnosis of high-grade carcinomas.

NUT carcinoma is defined by chromosomal rearrangement of the *NUTM1* gene, most frequently with *BRD4* as a result of a t(15;19)(q14;p13) chromosomal rearrangement. Less commonly, the *NUTM1* gene is fused to *BRD3* or other partners. One theory related to the molecular activity of these rearrangements is that the fusion product blocks transcription of pro-differentiation genes resulting in an undifferentiated phenotype which is an important histomorphologic feature that can aid in the pathologic recognition of this tumor entity [46].

By imaging, NUT carcinoma typically demonstrates a locally aggressive tumor with invasion and destruction of surrounding structures. However, this finding is not specific and can be seen with a variety of aggressive primary sinonasal tumors.

The histologic features of NUT carcinoma are fairly characteristic but not specific for the diagnosis. Tumors showing a predominant component of undifferentiated or poorly differentiated carcinoma should prompt consideration of NUT carcinoma (Fig. 12.5a, b). Foci of abrupt squamous differentiation and/or keratinization (Fig 12.5c) can be a helpful feature but are not seen in all cases and can also be seen in other tumor types. In addition to these foci of abrupt keratinization, NUT carcinoma is frequently immunophenotypically positive for markers of squamous differentiation such as p63. Given the common squamous phenotype of NUT carcinoma it is not uncommon for patients with such tumors to be initially diagnosed with poorly differentiated squamous cell carcinoma when the possibility of NUT carcinoma is not considered and investigated. Likewise, cases of NUT carcinoma may also be diagnosed as sinonasal undifferentiated carcinoma (SNUC) in some cases. Fluorescence in situ hybridization is an excellent specific and sensitive test for demonstrating the presence of a *NUTM1* gene rearrangement but NUT immunohistochemistry has emerged as a more readily available tool with high sensitivity and specificity for the diagnosis. NUT immunohistochemistry has been reported to have a sensitivity of 87% and specificity of 100% [47].

While other tumors included in the differential diagnosis of NUT carcinoma are also aggressive, it is increasingly important for patient management that the correct diagnosis of NUT carcinoma be made. NUT carcinoma is generally more aggressive with a poorer response to conventional treatments than poorly differentiated squamous cell carcinoma. NUT carcinoma has a median overall survival of only 6.7 months and a 2-year overall survival of only 19% in all sites [48]. Tumors in the head and neck are reported to have a slightly better 2-year overall survival of 27–30% compared to those in the mediastinum [45]. Surgery continues to be the mainstay of treatment with negative margins being a significant predictor of improved overall survival [45]. Most importantly though, studies are now underway

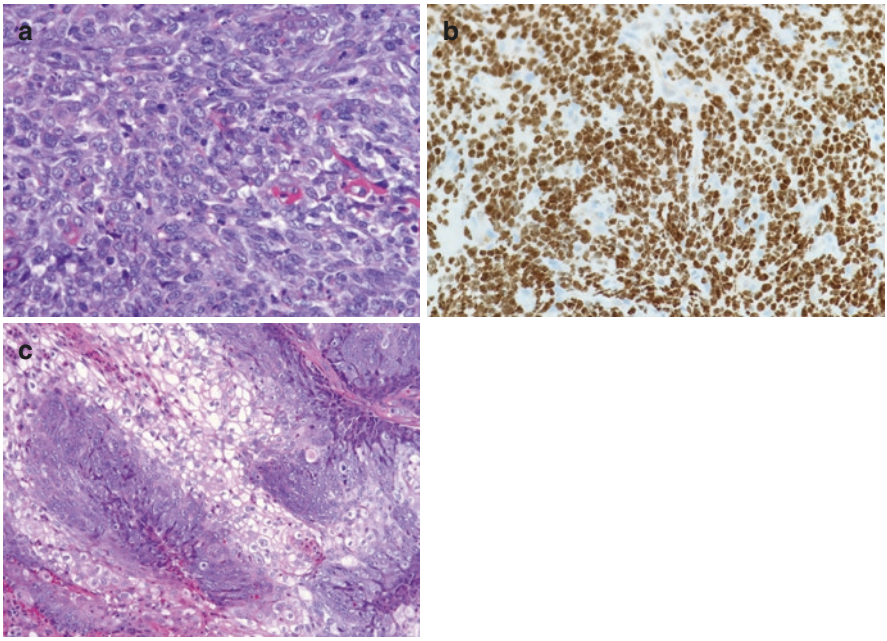

Fig. 12.5 *NUT carcinoma:* Histologic features of NUT carcinoma. (**a**) NUT carcinoma is characterized by the presence of undifferentiated tumor cells as a result of molecular pathways which block differentiation. Tumor cells in this image do not demonstrate any differentiation and have open vesicular chromatin (H&E, 400×). (**b**) Speckled nuclear pattern of NUT immunohistochemical stain (NUT immunohistochemistry, 400×). (**c**) Some cases show abrupt squamous differentiation as in this image in which more basaloid undifferentiated tumor cells are surrounded by tumor cells with abundant clear to eosinophilic cytoplasm indicative of squamous differentiation (H&E, 200×)

to examine the utility of target therapies with the hope of improving outcomes in patients with NUT carcinoma. BET inhibitors aimed at inhibiting BRD4-NUT binding to chromatin are being investigated and may be useful in patients with NUT carcinoma as well as other tumor types in which bromodomains are important in the molecular carcinogenesis [49, 50]. Histone deacetylase inhibitors are also being tested [51, 52].

SMARCB1 (INI-1)-Deficient Carcinoma

SMARCB1 is a tumor suppressor gene located on chromosome 22q11.2 and its loss of expression has been linked to carcinogenesis in several tumor types including atypical teratoid/rhabdoid tumors of the kidney and epithelioid sarcoma. Interestingly, rhabdoid morphology is a common feature for malignancies showing a loss of SMARCB1. Recently, a small subset of sinonasal tumors, many previously

classified as sinonasal undifferentiated carcinoma (SNUC), have been found to show loss of SMARCB1 [53, 54]. Fewer than 100 cases of sinonasal SMARCB1-deficient sinonasal carcinoma have been reported in the literature at the time of this writing and the entity is currently included in the WHO classification of SNUC [42]. Further study is ongoing to determine if this represents a distinct tumor entity. SMARCB1-deficient carcinomas have also been reported more rarely in other head and neck sites including oral cavity, larynx, and pharynx [55]. A case of SMARCA4 (BRG1)-deficient sinonasal carcinomas has also been reported with similar morphologic features to those with SMARCB1 loss [56].

Up to 6% of sinonasal carcinomas show loss of SMARCB1 [57]. Epidemiologically, SMARCB1-deficient sinonasal carcinoma has been reported in a wide age range (11–89 years) and affects men approximately twice as frequently as women (M:F 1.8:1).

Histologically, rhabdoid morphology is seen in most examples but basaloid tumor cells with scant cytoplasm tend to be the predominant cell type (Fig. 12.6a) [58].

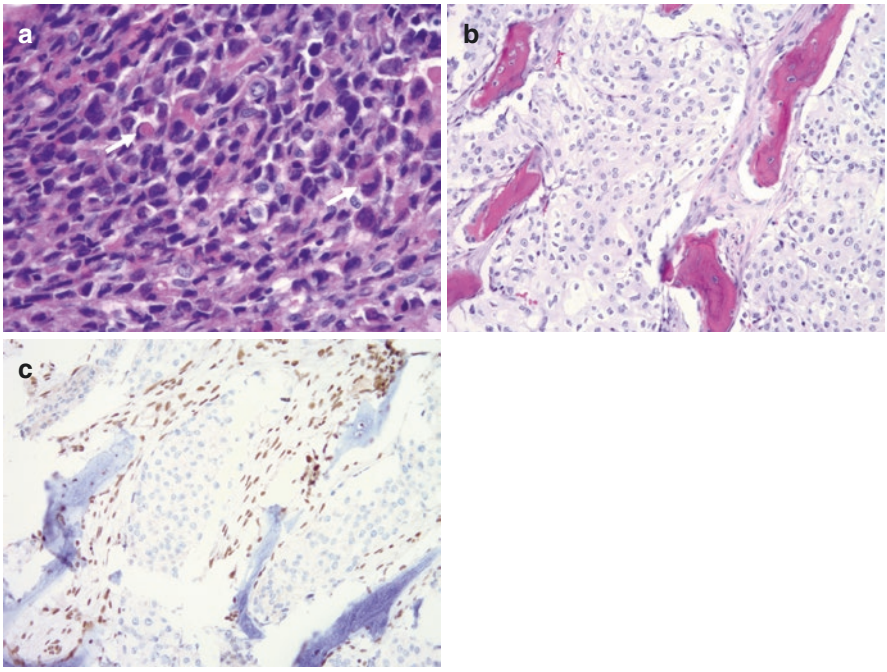

Fig. 12.6 *SMARCB1-deficient carcinoma*: Histologic features of SMARCB1-deficient sinonasal carcinoma. (**a**) SMARCB1-deficient carcinoma most commonly shows a prominence of basaloid tumor cells having scant cytoplasm. Despite the predominance of this basaloid morphology, close examination can show occasional tumor cells with rhabdoid differentiation with an eccentric nucleus and a large eosinophilic cytoplasmic inclusion (arrow) (H&E, 400×). (**b**, **c**) Loss of INI-1 expression by immunohistochemistry is a diagnostic feature of this tumor as seen in this example invading bone (**b**, H&E, 200×; **c**, INI-1 immunohistochemistry, 200×)

SMARCB1-deficient carcinomas commonly grow in a nested pattern and while they often have an exophytic papillary component they tend to be locally destructive with infiltration into surrounding structures. High-grade features including necrosis and high mitotic activity are common.

Immunophenotypically, keratin expression is present but may be weak in some cases. The squamous marker p63 is also commonly positive and neuroendocrine markers may also be expressed in some cases. A small number of SMARCB1-deficient sinonasal carcinomas have been reported with focal to prominent glandular differentiation [8]. p16 has been reported to be strong and diffuse in some cases which could cause one to consider the possibility of a human papillomavirus (HPV) associated carcinoma [58]. However, HPV and Epstein–Barr virus (EBV) have not been detected in any case that has been tested for these viral associations.

A defining feature of these carcinomas is demonstration of a loss of SMARCB1 expression by immunohistochemistry (Fig. 12.6b, c). Other immunohistochemical findings could potentially be misleading and result in a variety of other diagnoses. For example, germ cell markers such as SALL4 and AFP have been noted and reports of SMARB1-deficient sinonasal carcinomas have been described with showing yolk sac differentiation [8, 59].

SMARCB1-deficient sinonasal carcinoma is an aggressive malignancy with frequent locoregional recurrence, distant metastasis in approximately a third of patients and death due to disease in approximately half of patients [60, 61]. Loss of SMARB1 may represent a potential target in the future but currently these tumors are highly aggressive and commonly lethal. At least two patients were reported to show a good response to chemotherapy and radiation [62].

HPV-Related Multiphenotypic Sinonasal Carcinoma

High-risk human papillomavirus (HPV) infection is now linked to an increasing number of head and neck carcinomas with those of the oropharynx being most common. HPV-related multiphenotypic sinonasal carcinoma is a recently identified entity that shows histologic overlap with adenoid cystic carcinoma and an association with high-risk HPV infection. Initial descriptions of this tumor applied the term "HPV-related carcinoma with adenoid cystic-like features" to reflect the biphasic growth pattern with ductal and abluminal myoepithelial cell differentiation seen in many cases [63]. This entity was included as a provisional diagnosis under the rubric of non-keratinizing squamous cell carcinoma of the sinonasal tract in the most recent WHO but further study may result in a separate classification in the future [42].

HPV-related multiphenotypic sinonasal carcinoma most commonly presents as a large nasal mass causing nasal obstruction and epistaxis [64]. Tumors arising in the paranasal sinuses and/or involving both nasal cavity and sinuses also occur. There is a slight female predominance and a wide age range (28–90 years; mean 54 years).

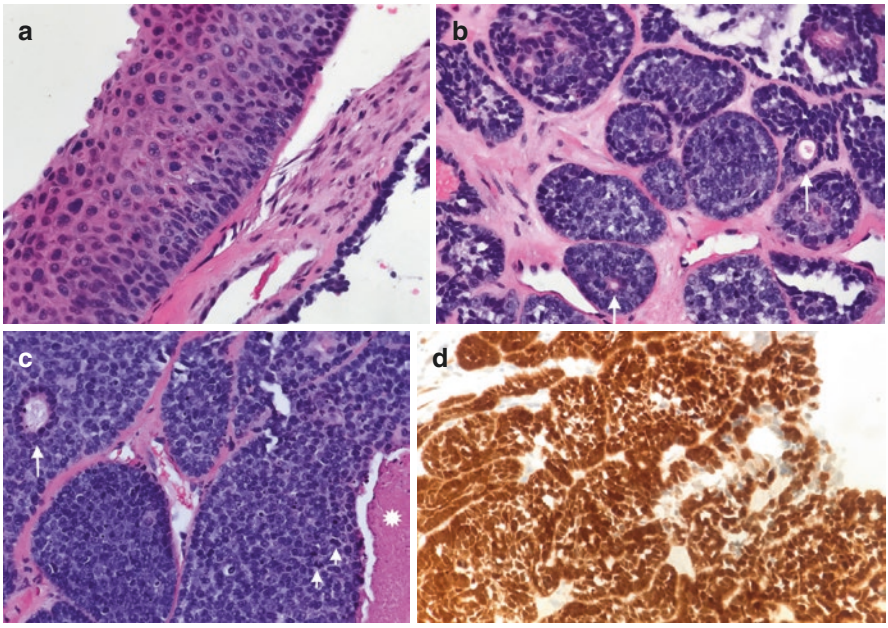

Fig. 12.7 *HPV-related multiphenotypic sinonasal carcinoma:* Histologic features of HPV-related multiphenotypic sinonasal carcinoma (HMSC): (**a**) HMSC carcinoma is characterized by the presence of surface squamous dysplasia (H&E, 400×); (**b**) Underlying basaloid nests of tumor with solid architecture, ductal differentiation (H&E, 200×); and (**c**) Higher magnification of tumor islands in **b** (H&E, 400×); (**d**) Immunostain p16 strongly and diffusely positive in tumor cells, HPV in situ hybridization—positive not shown (p16 immunostain, 400×)

Surface squamous dysplasia is present in some cases which may represent evidence of a surface epithelial derivation or colonization by a tumor arising in underlying minor salivary glands (Fig. 12.7a). These underlying tumors grow in large, highly cellular nests of basaloid tumor cells most commonly with solid architecture. High-grade cytologic features including high nuclear to cytoplasmic ratios, increased mitotic activity, apoptosis and necrosis are usually present. Myoepithelial and ductal differentiation are common with squamous differentiation identified in some cases (Fig. 12.7b, c). Immunostains are helpful to identify the biphasic growth pattern of these tumors with myoepithelial markers (smooth muscle actin, SOX10, p40, calponin, etc.) highlighting abluminal basaloid tumor cells.

HPV-related multiphenotypic sinonasal carcinoma is associated with high-risk HPV infection, predominantly HPV type 33. Rare cases have been reported in association with other HPV types, including types 16, 35, and 52 [65–67]. As a result of this close association with high-risk HPV infection, immunohistochemistry for p16 is strongly and diffusely positive in the same manner as seen in HPV-associated squamous cell carcinoma of the oropharynx (Fig. 12.7d). However, due to the low incidence of this tumor type in the sinonasal tract there is a lower positive predictive value for p16 as a surrogate marker of HPV infection and more specific direct

testing for high-risk HPV (such as PCR or in situ hybridization) are required to confirm an association with high-risk HPV in sinonasal sites. Despite the similar appearance to adenoid cystic carcinoma, MYB rearrangements are not present in HPV-related multiphenotypic sinonasal carcinoma.

Despite the high-grade histologic appearance of these tumors, the clinical behavior has been more indolent than other high-grade sinonasal tumors in most patients. HPV-related multiphenotypic sinonasal carcinoma commonly show locally aggressive growth with a high T stage and frequent recurrences but only rare metastases. A patient with late recurrences after 30-years of a disease-free period has been reported [68]. Despite this generally indolent prognosis, rare cases have been reported with a more rapidly progressive course and metastases. One patient who was treated surgically with negative margins and adjuvant radiation suffered from lung metastases 23 months after resection and showed continued disease progress despite subsequent chemotherapy and immunotherapy [67]. Two other patients experienced distant metastases by 96 and 144 months [64]. While these occasional more aggressive tumors have been reported in the literature, some authors have reported apparent cures with surgery alone [66, 69]. No deaths due to disease have been reported.

Sinonasal Neuroendocrine Carcinoma

Sinonasal neuroendocrine carcinoma (SNEC) is a rare, aggressive malignancy of the sinonasal tract representing approximately 5% of all sinonasal cancers. Given the rarity of these tumors and the challenges in classification, demographic data is challenging to determine but SNEC appears to occur in older adults (mostly above 50 years of age). Unlike high grade neuroendocrine carcinomas in other sites, SNEC lacks a strong association with tobacco use. Rare cases are reported to show an association with high-risk HPV [70–72]. Additionally, more well differentiated neuroendocrine neoplasms, so called “carcinoid” and “atypical carcinoid” tumors, of the sinonasal tract have only been anecdotally reported. One study demonstrated better survival for patients classified as having moderately differentiated SNEC (i.e., atypical carcinoid) compared to those with poorly differentiated SNEC [73]. An association with squamous cell carcinoma or adenocarcinoma can also be seen [74]. Rare cases have been reported to result in a paraneoplastic syndrome due to hormone secretion [75].

SNEC occurs in paranasal sinuses (particularly the ethmoid sinus) and nasal cavity [76]. Location in the superior nasal cavity is not uncommon and raises the differential diagnosis of olfactory neuroblastoma. SNEC is locally aggressive with most patients presenting with stage IV tumors; however, lymph node metastases are uncommon at presentation [76].

Morphologically, SNEC is similar to high grade neuroendocrine carcinomas with small cell and large cell variants being recognized as is the case in pulmonary sites. Immunostains for neuroendocrine markers are typically positive and helpful

in the diagnosis, including the more recently introduced INSM1 stain which shows more sensitivity than traditional neuroendocrine markers such as chromogranin, synaptophysin and CD56 [77]. A challenging differential diagnosis can be presented between SNEC and high-grade olfactory neuroblastoma. Morphologically, SNEC lacks neurofibrillary stroma but such stroma is also often scant in high grade olfactory neuroblastoma. The finding of significant keratin expression can be useful to favor a diagnosis of SNEC over olfactory neuroblastoma. Sinonasal undifferentiated carcinoma (SNUC) also enters the differential diagnosis but SNUC should not demonstrate significant neuroendocrine marker expression.

SNEC is an aggressive tumor and therefore multimodality therapy with a combination of surgery, radiation, or chemotherapy is commonly used. One study demonstrated a 5-year disease specific survival of 43.8% [76].

Sinonasal Renal Cell-Like Adenocarcinoma

Sinonasal renal cell-like adenocarcinoma is a very rare tumor first described in 2002 and considered a subtype of sinonasal non-intestinal type adenocarcinoma [78]. A recent review of the literature shows a female predominance (female to male ratio of 9:4) and a wide age range (22–77 years) [79]. Most cases have been reported to arise in the nasal cavity with fewer numbers occurring in paranasal sinuses and nasopharynx.

As this entity's name implies, this tumor of the sinonasal tract demonstrates close histologic similarity with clear cell renal cell carcinoma. The tumors are composed of cells with abundant clear to slightly eosinophilic cytoplasm in follicular or solid growth patterns. Papillary architecture has rarely been reported to be prominent. Nuclei are fairly monotonous with mild to, at most, moderate nuclear pleomorphism.

Prominent vascularity and hemorrhage are commonly reported.

Due to this extensive morphologic overlap with renal cell carcinoma, one of the most challenging differential diagnoses is the possibility of metastatic renal cell carcinoma. Metastatic renal cell carcinoma is a potential source of metastasis to the sinonasal tract and can occasionally initially present with an isolated solitary sinonasal metastasis [80]. Morphologic distinction between these entities can be challenging but aided through the use of immunohistochemical stains. Sinonasal renal cell-like adenocarcinoma is typically negative for pax-8, vimentin and RCC; in contrast, clear cell renal cell carcinoma is frequently positive for these markers [79, 81]. Seromucinous markers (S100, SOX-10, and DOG-1) have been reported to be positive in primary sinonasal renal cell-like adenocarcinoma but are typically negative in renal cell carcinoma. Of note, carbonic anhydrase IX staining can be a pitfall in this differential diagnosis as it is also commonly positive in both sinonasal renal cell-like adenocarcinoma and metastatic clear cell renal cell carcinoma if other markers are not examined [82]. Variants of other primary tumors that can show clear cell morphology, such as squamous cell carcinoma, acinic cell carcinoma,

myoepithelial carcinoma, mucoepidermoid carcinoma, and hyalinizing clear cell carcinoma, should also be excluded morphologically and immunophenotypically.

Since the first description, approximately 20 cases have been reported in the English language literature. These tumors are histologically low-grade and usually lack aggressive features such as perineural and vascular invasion [81]. Surgery and/or radiation have been used for therapy in many of the reported cases. No metastases have been reported and a single case showed recurrence 35 months after resection without adjuvant therapy [83].

References

1. Shanmugaratnam K, et al. Teratoid carcinosarcoma of the paranasal sinuses. Pathology. 1983;15(4):413–9.
2. Heffner DK, Hyams VJ. Teratocarcinosarcoma (malignant teratoma?) of the nasal cavity and paranasal sinuses A clinicopathologic study of 20 cases. Cancer. 1984;53(10):2140–54.
3. Pai SA, et al. Teratocarcinosarcoma of the paranasal sinuses: a clinicopathologic and immunohistochemical study. Hum Pathol. 1998;29(7):718–22.
4. Salem F, et al. Teratocarcinosarcoma of the nasal cavity and paranasal sinuses: report of 3 cases with assessment for chromosome 12p status. Hum Pathol. 2008;39(4):605–9.
5. Misra P, et al. Management of sinonasal teratocarcinosarcoma: a systematic review. Am J Otolaryngol. 2014;35(1):5–11.
6. Smith SL, et al. Sinonasal teratocarcinosarcoma of the head and neck: a report of 10 patients treated at a single institution and comparison with reported series. Arch Otolaryngol Head Neck Surg. 2008;134(6):592–5.
7. Kleinschmidt-DeMasters BK, et al. Sinonasal teratocarcinosarcoma ("mixed olfactory neuroblastoma-craniopharyngioma") presenting with syndrome of inappropriate secretion of antidiuretic hormone. Clin Neuropathol. 2000;19(2):63–9.
8. Shah AA, 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.
9. Rooper LM, et al. Recurrent loss of SMARCA4 in sinonasal teratocarcinosarcoma. Am J Surg Pathol. 2020;
10. Yang Z, Uppaluri R, Lewis JS Jr. Ethmoid sinus mass. Sinonasal teratocarcinosarcoma. JAMA Otolaryngol Head Neck Surg. 2015;141(4):389–90.
11. Lewis JT, et al. Low-grade sinonasal sarcoma with neural and myogenic features: a clinicopathologic analysis of 28 cases. Am J Surg Pathol. 2012;36(4):517–25.
12. Wang X, et al. Recurrent PAX3-MAML3 fusion in biphenotypic sinonasal sarcoma. Nat Genet. 2014;46(7):666–8.
13. Chitguppi C, et al. Biphenotypic sinonasal sarcoma-case report and review of clinicopathological features and diagnostic modalities. J Neurol Surg B Skull Base. 2019;80(1):51–8.
14. Le Loarer F, et al. Clinicopathologic and molecular features of a series of 41 biphenotypic sinonasal sarcomas expanding their molecular spectrum. Am J Surg Pathol. 2019;43(6):747–54.
15. Cannon RB, et al. Imaging and outcomes for a new entity: low-grade sinonasal sarcoma with neural and myogenic features. J Neurol Surg Rep. 2017;78(1):e15–9.
16. Miglani A, et al. Imaging characteristics and clinical outcomes of biphenotypic sinonasal sarcoma. Laryngoscope Investig Otolaryngol. 2019;4(5):484–8.
17. Fritchie KJ, et al. Fusion gene profile of biphenotypic sinonasal sarcoma: an analysis of 44 cases. Histopathology. 2016;69(6):930–6.

18. Jo VY, et al. Expression of PAX3 distinguishes biphenotypic sinonasal sarcoma from histologic mimics. Am J Surg Pathol. 2018;42(10):1275–85.
19. Gross J, Fritchie K. Soft tissue special issue: biphenotypic sinonasal sarcoma: a review with emphasis on differential diagnosis. Head Neck Pathol. 2020;14(1):33–42.
20. Rooper LM, et al. Biphenotypic sinonasal sarcoma: an expanded immunoprofile including consistent nuclear beta-catenin positivity and absence of SOX10 expression. Hum Pathol. 2016;55:44–50.
21. Compton ML, Cates JMM. Evidence-based tumor staging of skeletal chondrosarcoma. Am J Surg Pathol. 2020;44(1):111–9.
22. Koch BB, et al. National cancer database report on chondrosarcoma of the head and neck. Head Neck. 2000;22(4):408–25.
23. Ellis MA, Gerry DR, Byrd JK. Head and neck chondrosarcomas: analysis of the surveillance, epidemiology, and end results database. Head Neck. 2016;38(9):1359–66.
24. Suster D, Hung YP, Nielsen GP. Differential diagnosis of cartilaginous lesions of bone. Arch Pathol Lab Med. 2020;144(1):71–82.
25. Almefty K, et al. Chordoma and chondrosarcoma: similar, but quite different, skull base tumors. Cancer. 2007;110(11):2457–67.
26. Ma X, et al. The differences between intracranial mesenchymal chondrosarcoma and conventional chondrosarcoma in clinical features and outcomes. World Neurosurg. 2019;122:e1078–82.
27. Awad M, Gogos AJ, Kaye AH. Skull base chondrosarcoma. J Clin Neurosci. 2016;24:1–5.
28. WHO Classification of Tumours Editorial Board, ed. *Soft tissue and bone tumours*. 5th ed. Lyon: IARC Press, 2020.
29. Simon F, et al. Surgery and protontherapy in grade I and II skull base chondrosarcoma: a comparative retrospective study. PLoS One. 2018;13(12):e0208786.
30. Holtzman AL, et al. Proton therapy for skull-base chondrosarcoma, a single-institution outcomes study. J Neuro-Oncol. 2019;142(3):557–63.
31. Guan X, et al. The preliminary results of proton and carbon ion therapy for chordoma and chondrosarcoma of the skull base and cervical spine. Radiat Oncol. 2019;14(1):206.
32. Bloch OG, et al. Cranial chondrosarcoma and recurrence. Skull Base. 2010;20(3):149–56.
33. Bohman LE, et al. Skull base chordoma and chondrosarcoma: influence of clinical and demographic factors on prognosis: a SEER analysis. World Neurosurg. 2014;82(5):806–14.
34. Chambers KJ, et al. Incidence and survival patterns of cranial chordoma in the United States. Laryngoscope. 2014;124(5):1097–102.
35. Bakker SH, et al. Chordoma: a systematic review of the epidemiology and clinical prognostic factors predicting progression-free and overall survival. Eur Spine J. 2018;27(12):3043–58.
36. Williams BJ, et al. Diagnosis and treatment of chordoma. J Natl Compr Cancer Netw. 2013;11(6):726–31.
37. Liang WS, et al. Identification of therapeutic targets in chordoma through comprehensive genomic and transcriptomic analyses. Cold Spring Harb Mol Case Stud. 2018;4(6)
38. Vujovic S, et al. Brachyury, a crucial regulator of notochordal development, is a novel biomarker for chordomas. J Pathol. 2006;209(2):157–65.
39. Oakley GJ, Fuhrer K, Seethala RR. Brachyury, SOX-9, and podoplanin, new markers in the skull base chordoma vs chondrosarcoma differential: a tissue microarray-based comparative analysis. Mod Pathol. 2008;21(12):1461–9.
40. Stacchiotti S, et al. Best practices for the management of local-regional recurrent chordoma: a position paper by the Chordoma Global Consensus Group. Ann Oncol. 2017;28(6):1230–42.
41. Di Maio S, et al. Novel targeted therapies in chordoma: an update. Ther Clin Risk Manag. 2015;11:873–83.
42. El-Naggar AK, Chan JKC, Grandis JR, Takashi Takata PJS. WHO classification of head and neck tumours. 4th ed. WHO - OMS - In IARC,. Lyon; 2017.

43. Hellquist H, French CA, Bishop JA, Coca-Pelaz A, Propst EJ, Paiva Correia A, et al. NUT midline carcinoma of the larynx: an international series and review of the literature. Histopathology. 2017; https://doi.org/10.1111/his.13143.
44. Agaimy A, Fonseca I, Martins C, Thway K, Barrette R, Harrington KJ, et al. NUT carcinoma of the salivary glands: clinicopathologic and molecular analysis of 3 cases and a survey of NUT expression in salivary gland carcinomas. Am J Surg Pathol. 2018; https://doi.org/10.1097/PAS.0000000000001046.
45. Chau NG, Hurwitz S, Mitchell CM, Aserlind A, Grunfeld N, Kaplan L, et al. Intensive treatment and survival outcomes in NUT midline carcinoma of the head and neck. Cancer. 2016; https://doi.org/10.1002/cncr.30242.
46. French C. NUT midline carcinoma. Nat Rev Cancer. 2014; https://doi.org/10.1038/nrc3659.
47. Haack H, Johnson LA, Fry CJ, Crosby K, Polakiewicz RD, Stelow EB, et al. Diagnosis of NUT midline carcinoma using a NUT-specific monoclonal antibody. Am J Surg Pathol. 2009; https://doi.org/10.1097/PAS.0b013e318198d666.
48. Bauer DE, Mitchell CM, Strait KM, Lathan CS, Stelow EB, Lüer SC, et al. Clinicopathologic features and long-term outcomes of NUT midline carcinoma. Clin Cancer Res. 2012; https://doi.org/10.1158/1078-0432.CCR-12-1153.
49. Filippakopoulos P, Qi J, Picaud S, Shen Y, Smith WB, Fedorov O, et al. Selective inhibition of BET bromodomains. Nature. 2010; https://doi.org/10.1038/nature09504.
50. Stathis A, Zucca E, Bekradda M, Gomez-Roca C, Delord JP, de Rouge TLM, et al. Clinical response of carcinomas harboring the BRD4–NUT oncoprotein to the targeted bromodomain inhibitor OTX015/MK-8628. Cancer Discov. 2016; https://doi.org/10.1158/2159-8290.CD-15-1335.
51. Maher OM, Christensen AM, Yedururi S, Bell D, Tarek N. Histone deacetylase inhibitor for NUT midline carcinoma. Pediatric Blood Cancer. 2015; https://doi.org/10.1002/pbc.25350.
52. Schwartz BE, Hofer MD, Lemieux ME, Bauer DE, Cameron MJ, West NH, et al. Differentiation of NUT midline carcinoma by epigenomic reprogramming. Cancer Res. 2011; https://doi.org/10.1158/0008-5472.CAN-10-3513.
53. Agaimy A, Koch M, Lell M, Semrau S, Dudek W, Wachter DL, et al. SMARCB1(INI1)-deficient sinonasal basaloid carcinoma: a novel member of the expanding family of SMARCB1-deficient neoplasms. Am J Surg Pathol. 2014; https://doi.org/10.1097/PAS.0000000000000236.
54. Bishop JA, Antonescu CR, Westra WH. SMARCB1 (INI-1)-deficient carcinomas of the sinonasal tract. Am J Surg Pathol. 2014; https://doi.org/10.1097/PAS.0000000000000285.
55. Neves-Silva R, Almeida LY, Silveira HA, Colturato CBN, Duarte A, Ferrisse TM, et al. SMARCB1 (INI-1) and NUT immunoexpression in a large series of head and neck carcinomas in a Brazilian reference center. Head Neck. 2019; https://doi.org/10.1002/hed.26008.
56. Agaimy A, Weichert W. SMARCA4-deficient Sinonasal Carcinoma. Head Neck Pathol. 2017; https://doi.org/10.1007/s12105-017-0783-4.
57. Kakkar A, Antony VM, Pramanik R, Sakthivel P, Singh CA, Jain D. SMARCB1 (INI1)–deficient sinonasal carcinoma: a series of 13 cases with assessment of histologic patterns. Hum Pathol. 2019; https://doi.org/10.1016/j.humpath.2018.08.008.
58. Bell D, Hanna EY, Agaimy A, Weissferdt A. Reappraisal of sinonasal undifferentiated carcinoma: SMARCB1 (INI1)-deficient sinonasal carcinoma: a single-institution experience. Virchows Archiv. 2015; https://doi.org/10.1007/s00428-015-1853-1.
59. Zamecnik M, Rychnovsky J, Syrovatka J. Sinonasal SMARCB1 (INI1) deficient carcinoma with yolk sac tumor differentiation: report of a case and comparison with INI1 expression in gonadal germ cell tumors. Int J Surg Pathol. 2018; https://doi.org/10.1177/1066896917741549.
60. Agaimy A, Hartmann A, Antonescu CR, Chiosea SI, El-Mofty SK, Geddert H, et al. SMARCB1 (INI-1)-deficient sinonasal carcinoma. Am J Surg Pathol. 2017; https://doi.org/10.1097/PAS.0000000000000797.
61. McHugh KE, Policarpio-Nicolas MLC. Metastatic SMARCB1 (INI-1)-deficient sinonasal carcinoma diagnosed by endobronchial ultrasound-guided fine-needle aspiration (EBUS-FNA): a potential diagnostic pitfall and review of the literature. Acta Cytologica. 2019; https://doi.org/10.1159/000500351.

62. Wasserman JK, Dickson BC, Perez-Ordonez B, de Almeida JR, Irish JC, Weinreb I. INI1 (SMARCB1)-deficient sinonasal carcinoma: a clinicopathologic report of 2 cases. Head Neck Pathol. 2017; https://doi.org/10.1007/s12105-016-0752-3.
63. Bishop JA, Ogawa T, Stelow EB, Moskaluk CA, Koch WM, Pai SI, Westra WH. Human papillomavirus-related carcinoma with adenoid cystic-like features: a peculiar variant of head and neck cancer restricted to the sinonasal tract. Am J Surg Pathol. 2013; https://doi.org/10.1097/PAS.0b013e31827b1cd6.
64. Bishop JA, Andreasen S, Hang J-F, Bullock MJ, Chen TY, Franchi A, et al. HPV-related multiphenotypic Sinonasal carcinoma HPV-related carcinoma with adenoid cystic carcinoma-like features. Am J Surg Pathol. 2017;
65. Adamane SA, Mittal N, Teni T, Pawar S, Waghole R, Bal M. Human papillomavirus-related multiphenotypic sinonasal carcinoma with unique HPV type 52 association: a case report with review of literature. Head Neck Pathol. 2019; https://doi.org/10.1007/s12105-018-0969-4.
66. Chouake RJ, Cohen M, Iloreta AM. Case report: HPV-related carcinoma with adenoid cystic-like features of the sinonasal tract. Laryngoscope. 2018; https://doi.org/10.1002/lary.26957.
67. Rodarte AI, Parikh AS, Gadkaree SK, Lehmann AE, Faquin WC, Holbrook EH, Lin DT. Human papillomavirus related multiphenotypic Sinonasal carcinoma: report of a case with early and progressive metastatic disease. J Neurol Surg Rep. 2019;80(4):e41–3.
68. 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; https://doi.org/10.1007/s12105-018-0895-5.
69. Hwang SJI, 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; https://doi.org/10.1016/j.anl.2014.07.005.
70. Bishop JA, Guo TW, Smith DF, Wang H, Ogawa T, Pai SI, Westra WH. Human papillomavirus-related carcinomas of the sinonasal tract. Am J Surg Pathol. 2013; https://doi.org/10.1097/PAS.0b013e3182698673.
71. Laco J, Sieglová K, Vošmiková H, Dundr P, Němejcová K, Michálek J, et al. The presence of high-risk human papillomavirus (HPV) E6/E7 mRNA transcripts in a subset of sinonasal carcinomas is evidence of involvement of HPV in its etiopathogenesis. Virchows Arch. 2015; https://doi.org/10.1007/s00428-015-1812-x.
72. Thompson ED, Stelow EB, Mills SE, Westra WH, Bishop JA. Large cell neuroendocrine carcinoma of the head and neck: a clinicopathologic series of 10 cases with an emphasis on HPV status. Am J Surg Pathol. 2016; https://doi.org/10.1097/PAS.0000000000000580.
73. Likhacheva A, Rosenthal D, Hanna E, Kupferman M, Demonte F, El-Naggar A. Sinonasal neuroendocrine carcinoma: impact of differentiation status on response and outcome. Head Neck Oncol. 2011; https://doi.org/10.1186/1758-3284-3-32.
74. Franchi A, Rocchetta D, Palomba A, Innocenti DRD, Castiglione F, Spinelli G. Primary combined neuroendocrine and squamous cell carcinoma of the maxillary sinus: report of a case with immunohistochemical and molecular characterization. Head Neck Pathol. 2015; https://doi.org/10.1007/s12105-013-0513-5.
75. Vasan NR, Medina JE, Canfield VA, Gillies EM. Sinonasal neuroendocrine carcinoma in association with siadh. Head Neck. 2004; https://doi.org/10.1002/hed.10345.
76. Mitchell EH, Diaz A, Yilmaz T, Roberts D, Levine N, Demonte F, et al. Multimodality treatment for sinonasal neuroendocrine carcinoma. Head Neck. 2012; https://doi.org/10.1002/hed.21940.
77. Rooper LM, Bishop JA, Westra WH. INSM1 is a sensitive and specific marker of neuroendocrine differentiation in head and neck tumors. Am J Surg Pathol. 2018; https://doi.org/10.1097/PAS.0000000000001037.
78. Zur KB, Brandwein M, Wang B, Som P, Gordon R, Urken ML. Primary description of a new entity, renal cell-like carcinoma of the nasal cavity: Van meegeren in the house of vermeer. Arch Otolaryngol Head Neck Surg. 2002; https://doi.org/10.1001/archotol.128.4.441.
79. Kubik M, Barasch N, Choby G, Seethala R, Snyderman C. Sinonasal renal cell-like carcinoma: case report and review of the literature. Head Neck Pathol. 2017; https://doi.org/10.1007/s12105-016-0774-x.

80. Bastier PL, Dunion D, De Bonnecaze G, Serrano E, De Gabory L. Renal cell carcinoma metastatic to the sinonasal cavity: a review and report of 8 cases. Ear Nose Throat J. 2018; https://doi.org/10.1177/014556131809700902.
81. Storck K, Hadi UM, d., Simpson, R., Ramer, M., & Brandwein-Gensler, M. Sinonasal renal cell-like adenocarcinoma: a report on four patients. Head Neck Pathol. 2008; https://doi.org/10.1007/s12105-008-0047-4.
82. Shen T, Shi Q, Velosa C, Bai S, Thompson L, Simpson R, et al. Sinonasal renal cell-like adenocarcinomas: robust carbonic anhydrase expression. Human Pathol. 2015; https://doi.org/10.1016/j.humpath.2015.06.017.
83. Wu J, Fang Q, He YJ, Chen WX, Qi YK, Ding J. Local recurrence of sinonasal renal cell-like adenocarcinoma: a CARE compliant case report. Medicine (United States). 2019; https://doi.org/10.1097/MD.0000000000014533.