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Review

Translational genomics of sinonasal cancers

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ABSTRACT

The sinonasal cavities harbor a wide variety of histologically distinct cancers, the majority very aggressive with 5-year survival rates between 30–60% and local recurrence as the main cause of death. This is a complex anatomic area, close to structures such the eyes and the brain, which is of special relevance for surgery and postoperative radiotherapy. The low incidence of these rare tumors hampers accumulation of experience with diagnosis and clinical managment as well as knowledge on recurrent genetic aberrations or testing of new treatment strategies. However, recent years have seen a growing number of publications on genetic aberrations providing data that can aid or fine-tune classification and provide molecular targets for treatment with specific inhibitors. In addition, new sinonasal cancer models are created that enable preclinical testing of candidate inhibitor drugs. With more and more novel targeted therapies being developed, options for personalized treatment of sinonasal cancer patients are now opening up.

1. Introduction

The sinonasal cavities comprise an anatomical area from which a large number of histologically diverse epithelial, neuroectodermal and mesenchymal neoplasms arise [1], representing approximately 3–5% of all head and neck tumors [2–5]. According to Rarecare, sinonasal tumors occur with an incidence of approximately 0.5–1.0 patients/100.000 inhabitants (www.rarecare.eu/rarecancers). The most common affected subsites are the nasal cavity, the ethmoid and the maxillary sinus, less frequent are the frontal and sphenoid sinus [2,3]. Squamous cell carcinoma (SNSCC) and intestinal-type adenocarcinoma (ITAC) make up approximately 70% of sinonasal cancers, the other 30% include malignant mucosal melanoma (MMM), olfactory neuroblastoma (ONB), undifferentiated carcinoma (SNUC), NUT carcinoma, SMARCB1-deficient carcinoma, HPV-related multiphenotypic carcinoma (HMSC), neuroendocrine carcinoma (SNEC), non-intestinal-type adenocarcinoma (SNAC), teratocarcinosarcoma (TCS) and many other subtypes (Table 1). Mesenchymal tumors in the sinonasal cavities may not be distinct from other anatomical localizations and are therefore not included in this review.

Based on their anatomical site of origin but also their distinctive etiology, epidemiology, clinical and genetic characteristics, sinonasal tumors should be considered unique entities, apart from other head and neck cancers affecting the nasopharynx, pharynx, larynx and oral cavity [1–3]. Neighboring organs as eyes and brain are a challenge for clinical management, however, recent years have seen advances in endoscopic surgical approaches and precision radiotherapy and imaging techniques. The low incidence of sinonasal tumors and their histological diversity prevents accumulation of clinical experience in diagnosis, classification, staging and treatment at individual hospitals. In addition, as with many rare tumors, the development of new therapeutic options is hampered by the relative scarcity of genetic data and of tumor models for preclinical testing. However, recent years have seen a growing number of genetic studies of sinonasal tumors. This article will present an up-to-date overview of genetic aberrations reported in sinonasal cancer subtypes with an emphasis on those having clinical usefulness in diagnosis, prognosis or therapy.

2. Clinical features

Diagnosis of sinonasal tumors is generally late due to nonspecific symptoms similar to inflammatory diseases. The average age of onset is 50–70 years although SNUC, NUT carcinoma, SNAC and ONB also occur at younger ages [1]. Clinical examination should include a complete ear, nose and throat exploration and when malignancy is suspected also imaging tests. Computed Tomography (CT) is better for observing the bone and Magnetic Resonance Imaging (MRI) for soft tissues [6]. Especially in high-grade tumors CT may be replaced by PET-

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Table 1
Incidence and survival rates of sinonasal tumors.

Histological subtype	Proportion of sinonasal cancers	Overall survival
Squamous cell carcinoma	50%	5y: 50%
Intestinal-type adenocarcinoma	13%	5y: 36–80%*
Malignant mucosal melanoma	4%	5y: 31%
Olfactory neuroblastoma	3%	5y: 40%**
Undifferentiated carcinoma	5%	5y: 35%
SMARCB1-deficient carcinoma	< 1%	15 months
NUT carcinoma	< 1%	10 months
Neuroendocrine carcinoma	3%	5y: 43%
HPV-related multiphenotypic carcinoma	< 1%	5y: 100%
Non-intestinal-type adenocarcinoma	< 1%	5y: 38%**
Teratocarcinosarcoma	< 1%	5y: 50%
Other	± 20%	

Legend. 5y: 5-year; *worst survival for solid and mucinous types, intermediate for colonic and best for papillary type ITAC; **Survival rate of the high grade tumors.

CT to assess both the primary tumor and possible distant metastases (Fig. 1). Tumor staging of sinonasal tumors is based on location and extent, according to the current Union for International Cancer Control (UICC) classification system [7]. Lymph node metastasis is infrequent at diagnosis. After treatment of the primary tumor, 10% of patients with sinonasal tumors develop distant metastasis, however, this seldom occurs in absence of locoregional recurrence which in fact is the main cause of sinonasal cancer mortality [8–11].

ITAC and SNSCC are etiologically related to occupational exposure to wood and leather dust, but also industrial compounds such as glues, formaldehyde, chrome, nickel, and various products used in the textile industry. Tobacco smoking, an important etiological factor in most head and neck cancers, does not seem to have a key role in the development of sinonasal tumors [12–14]. Oncogenic human papillomavirus and Epstein-Barr virus have been implicated in SNSCC and HMSC and will be discussed in the section on genetic characterization. There is a male predominance in SNSCC (2:1), ITAC (6:1) and TCS (7:1) which may be related to the occupational exposure but also to defects in genes residing on the X chromosome. Chronic inflammation, a recognized mechanism of tumorigenesis, may also play a role in sinonasal cancer development through continuous irritation by inhaled dust particles stimulating the production of reactive oxygen species (ROS) and NFkB expression [15]. NFkB can upregulate COX2 expression and the canonical WNT pathway through inhibition of GSK-3b. In turn, aberrant WNT signalling can stimulate the production of ROS and chronic inflammation [15,16]. Preliminary evidence in sinonasal carcinomas indeed indicated elevated NFkB, COX2 and TNF**α** expression [17,18] and a dominance of the G > A nucleotide transition inflammatory signature in TP53 and KRAS [19–21]. Future sequencing studies should be able to shed more light on tumorigenic processes in sinonasal cancer by in-depth evaluation of mutational signatures.

Complete surgical resection with postoperative radiotherapy is the mainstay of sinonasal cancer management, although treatment should be adjusted individually according to tumor stage, histology, patient age, and previous treatments. Minimally invasive endoscopic approaches are increasingly used as they can reduce the number of complications and morbidity associated with surgery [6,22,23]. The close proximity of cranial nerves, eyes, internal carotid artery and brain makes resection of sinonasal tumors with wide margins is not always possible. Therefore, there is a role for systemic therapy in the management of sinonasal cancer [24]. While patients with recurrent disease appear to respond better to salvage surgery than chemotherapy, a multimodal treatment strategy with induction chemotherapy, surgery and radiotherapy may offer the strongest clinical benefit [25]. With the exception of low grade ONB, low grade SNAC and HMSC that appear to

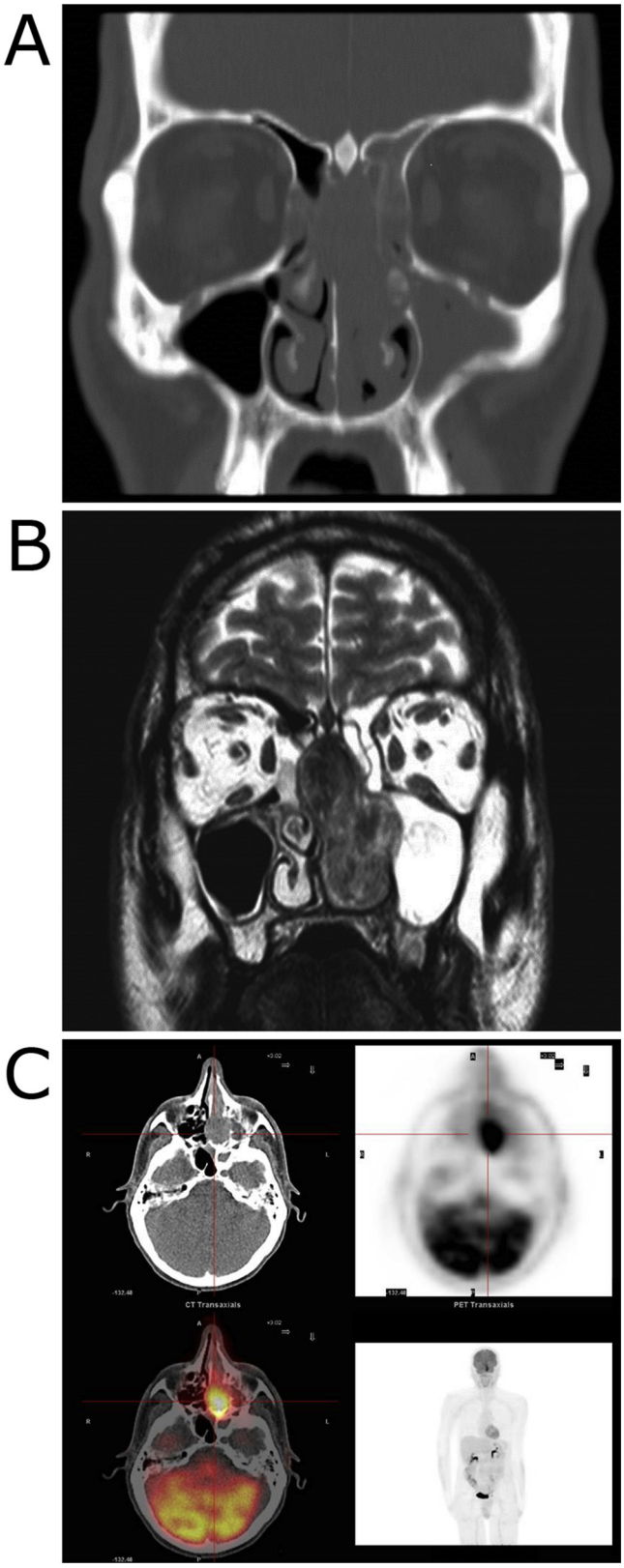

Fig. 1. Imaging tests for sinonasal cancer. A) CT scan of a tumor in the nasal fossa with frontal and maxillary sinus occupation. B) MRI scan of the same patient with better delimitation of what is tumor and and what is mucous; the tumor occupies the nasal fossa but there is no involvement of the orbit or the brain and the frontal and maxillary sinus are occupied by retained mucous. C). ET-CT scan of the same patient showing the tumor in the nasal fossa and absence of metastases in the rest of the body.

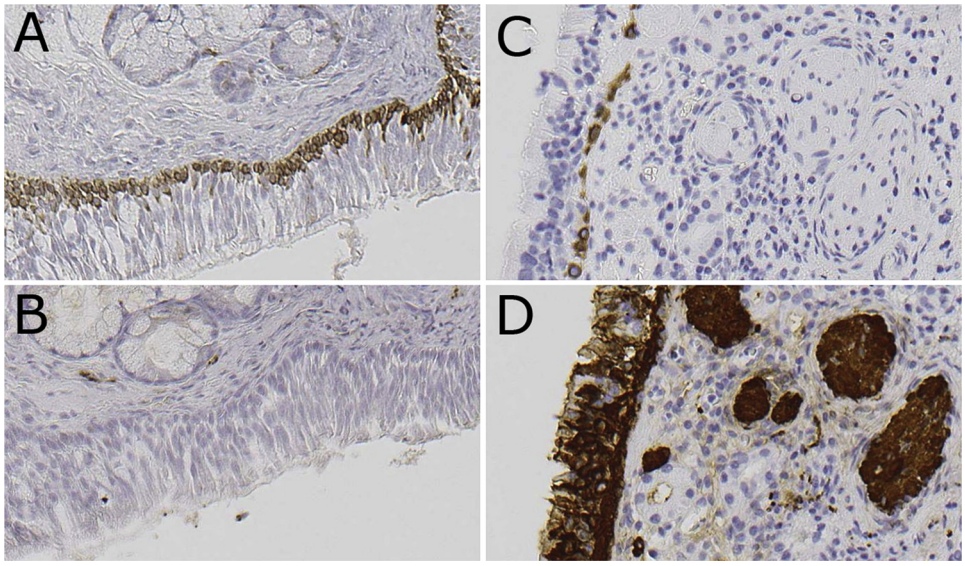

Fig. 2. Histological features of normal respiratory (A and B) and olfactory mucosa (C and D) both containing basal, ciliated, and goblet cells as well as occasional melanocytes. Seromucous secretory glands lie below the surface in the lamina propria. Immunohistochemical staining with a CK17 antibody shows the horizontal basal cells in both types of mucosa (A and C). Premature and mature olfactory neurons stained with a βIII-tubulin antibody are absent in respiratory (B) and present in olfactory mucosa.

be fairly indolent [26–29], all sinonasal tumors decribed in this review carry a dismal prognosis, down to a median of 10 months survival for NUT carcinoma [30], or 15 months for SMARCB1-deficient carcinoma [31]. Reported 5-year overall survival rates (Table 1) vary from 31% for MMM, 35% for SNUC, 38% for high-grade SNAC, 41% for high grade ONB, 43% for SNEC, 50% for TCS, 50% for SNSCC and 36–80% for ITAC, depending on the subtype [1,32–38].

3. Histological features

All of the sinonasal cavities are lined with pseudostratified respiratory mucosa. Secretory glands in the submucosa produce mucous that captures bacteria and foreign matter which ciliated cells on the surface sweep toward the pharynx. Immunological defence mechanisms include antimicrobial peptides in the mucous layer and leucocytes, lymphocytes and mononuclear cells in the stroma. The roof of the nasal cavity has pseudostratified olfactory epithelium which is similar to the respiratory mucosa except for the presence of olfactory neurons whose axons traverse the cribiform plate and transmit signals to the olfactory bulb (Fig. 2). Normal stem cells in the basal layer of the olfactory epithelium have been studied extensively, especially for their capacity to form new olfactory neurons after tissue damage [39]. Apart from generating new neurons, these same stem cells are also precursors of non-neuronal, epithelial cell types. In the respiratory epithelium, stem cells have been shown capable of differentiating into cells with either neuroectodermal or mesodermal phenotypes [40].

Sinonasal tumors could be hypothesized to derive from stem cells capable of undergoing differentiation into various cell types, rather than from differentiated, lineage-specific cells that acquire stem-cell properties. Supporting this suggestion, many sinonasal tumors with more than one histological appearance have been described, for example adenoid cystic carcinoma with ITAC or SNUC, or SNSCC with SNEC [41,42]. Furthermore, recurrent tumors sometimes are of a different histological type than the original primary tumor, for instance ITAC recurring as SNUC or ONB [43]. Abnormal cell differentiation may be an early event in malignant transformation, however, to date only two premalignant lesions have been described to precede sinonasal tumors: inverted papilloma in 10–25% of SNSCC [44] and 8–28% of ITAC may develop from intestinal metaplasia [45,46].

A common characteristic of all sinonasal epithelial and neuroendocrine malignant tumors is the fact that a large proportion of cases show very poor differentiation (Fig. 3), making their diagnosis a challenge for the pathologist, even with the aid of immunohistochemical markers as pan-cytokeratin, synaptophysin, chromogranin, enolase, CD56, desmin, S-100 and melan-A [47–50]. Many of the tumors described in this review are known as 'small round blue cell' tumors, including MMM, ONB, SNUC, SNSCC, NUT carcinoma and SNEC. These tumors show several overlapping histologic features like growth in sheets or nests, high mitotic rates and necrostic areas, and also exhibit great variation within and between cases [1,50]. Distinguishing features include melanotic pigmentation in MMM, absence of pancytokeratin and presence of neuroendocrine immunohistochemical markers in low grade ONB, abrupt foci of squamous differentiation within poorly differentiated areas in NUT carcinoma, basaloid or sometimes rhabdoid features in SMARCB1-deficient carcinoma and cribriform areas resembling adenoid cystic carcinoma in HMSC. ITAC by definition displays intestinal differentiation, indeed the four recognized subtypes, papillar, colonic, solid and mucinous (including signet ring cells) are also known in gastro-intestinal adenocarcinomas. Also SNAC is an adenocarcinoma but shows neither salivary gland nor intestinal-type features. Low grade SNAC is composed of cilindrical cells in tubular and cribriform formations while high-grade SNAC (also named high grade non-ITAC), predominantly have a solid growth with occasional glandular structures. Typical for TSC is the admixture of epithelial, mesenchymal and neuroepithelial elements (Fig. 3).

4. Genetic characteristics

'Diagnostic contamination' in published sinonasal cancer studies occurs and hampers the advancement of genetic and translational research. Increasingly, cancer types are being diagnosed and sub-classified by specific molecular-genetic features [49–51]. Among sinonasal tumors, examples are NUT carcinoma defined by a chromosomal translocation involving the Nuclear protein in testis gene (NUT1) on 15q14, SMARCB1-deficient carcinoma defined by the absence of SMARCB1/INI1 immunohistochemical staining, both formerly diagnosed as SNUC [30,31], and HMSC defined by the presence of high-risk HPV in the absence of the t(6;9) MYB-NFIB rearrangement, previously often misclassified as high grade adenoid cystic carcinoma [26]. Also in other sinonasal cancer subtypes frequent genetic alterations have been described. Their usefulness in diagnsosis, prognosis and therapy will be discussed below.

Squamous cell carcinoma (SNSCC). Genome-wide genetic studies have shown that SNSCC generally carry a wide variety and a large number of chromosomal aberrations [37,52]. Recurrent high-level amplifications at 7p12, 11p13, 11q13, and 17q21 may indicate a role for oncogenes EGFR, CD44, CCND1/CTTN, and ERBB2, respectively

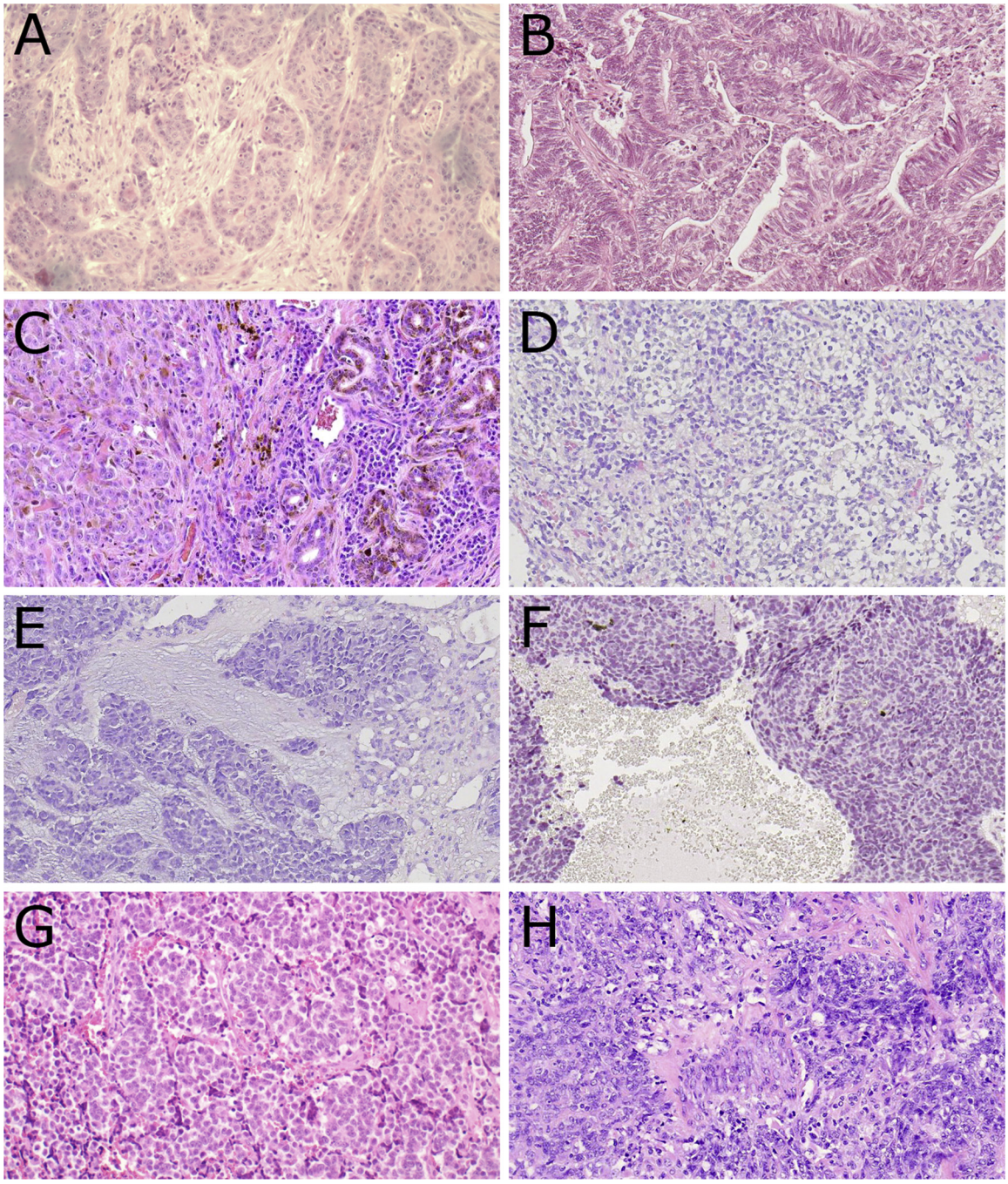

Fig. 3. Standard haematoxylin and eosin staining showing the histological features of various sinonasal tumor tissues. A) squamous cell carcinoma (SNSCC), B) colonic type intestinal-type adenocarcinoma (ITAC), C) malignant mucosal melanoma (MMM), D) olfactory neuroblastoma (ONB), E) undifferentiated carcinoma (SNUC), F) neuroendocrine carcinoma (SNEC), G) high grade non-intestinal-type adenocarcinoma (SNAC) and H) teratocarcinosarcoma (TCS). Magnification was 10× in all images.

[37,52–54]. TP53 mutation has been reported in 70% of tumors [55]. In a study on a small series of SNSCC, microsatellite instability was found in 21% (5/21) of cases [56]. A number of recent publications have described EGFR mutations, especially affecting exon 20, in 30–91% of SNSCC associated with inverted papilloma [44,57–60]. These studies also indicate that EGFR-mutated cases carry a better prognosis than wildtype tumors. Mutations in KRAS and HRAS, encoding downstream factors in the EGFR in the EGF signalling pathway, are almost absent in SNSCCs, while no BRAF mutations have been detected [61,62]. HPV infection has been described in 38% of benign and 31% malignant tumors [57,58,63–66]. In 10–24% of inverted papilloma only non-oncogenic HPV types were found [57,58]. Possibly EGFR mutation and HPV infection represent two different pathways of progression from inverted papilloma to SNSCC; indeed they appear to occur in a mutually exclusive manner [57,58]. Finally, Doescher et al reported an incidence 45% (20/44) of EBV in SNSCC associated with more frequent lymph node or distant metastases [67].

Intestinal-type adenocarcinoma (ITAC). Microarray CGH studies generally found aneuploid cases with complex chromosomal copy number changes, with the exception of papillary-type ITAC, which appeared predominantly diploid with few genetic aberrations [68–72]. Gains at 1q22–23, 3q28–29, 6p22 and 13q31–33, and losses at 4p15–16, 4q32–35 and 10q24 have been associated with worse overall survival [71,69–72]. Mutation of the TP53 gene with a frequency of

40–50% may be associated with exposure to wood dust [19,21,24,73–75]. Being a tumor histologically similar to intestinal adenocarcinoma, microsatellite instability and the Wnt pathway have been suspected and studied in ITAC. Based on mononucleotide markers, microsatellite instability was observed in 1 of 41 ITAC, suggesting that this mechanism of genomic instability does not play an important role, in contrast to intestinal adenocarcinoma [56]. Neither were mutations observed in the key Wnt components APC encoding adenomatous polyposis coli protein or CTNNB1 encoding β-catenin [74]. However, nuclear expression of β-catenin has been reported in 31–53% of cases [73,76,77], indicating that activation of the Wnt pathway probably does contribute to the development of ITAC. Mutations in EGFR were not found but KRAS and HRAS were mutated in approximately 15% of ITACs, and BRAF mutations were absent [54,61,74,77–81].

Malignant mucosal melanoma (MMM). Mucosal and uveal melanomas are more than cutaneous melanoma frequently aneuploid and carry more copy number alterations and chromosomal rearrangements [82]. Whole chromosome arm gains of 1q, 6p and 8q occurred respectively in 100%, 93% and 57%, and losses of whole arms 9p and 6q in 50% and 10 in 43%. A third of MMM appeared near-diploid and carried very few copy number changes [83]. A relatively large number of mutation studies focused on genes known to play a role in cutaneous melanoma, reporting the following frecuencies: 7–30% NRAS, 0–25% KIT, 8–11% TERT, 3–10% BRAF (in one study 36%), and 7% SF3B1 [84–89]. Mutations affecting the TERT promoter are frequent in all melanoma types [82]. In addition, MAPK signalling pathway activating translocations involving BRAF with fusion partners ZNF767, NFIC, TMEM178B and DGKI have been described in mucosal melanoma (including head and neck) and may define a new molecular subset [90].

Olfactory neuroblastoma (ONB). In a Affymetrix microarray CGH study of 11 ONB, López-Hernández et al reported a markedly low frequency of CNAs, with gains in > 35% of cases at 7q, 14q, 18q and 20 and losses at 1p, 2p, 3 and 4. Losses were more frequent than gains. Eight of 11 cases carried only whole chromosome CNAs, whereas gains or losses of segments of chromosomes were rare (Fig. 4). Markedly, gains at 8q, perhaps the most frequent alteration in all solid tumors, was completely absent in ONB [91]. Similar copy number data were obtained with analyses by conventional microarray CGH on 12 ONB and methylation microarrays on 42 ONB [92,93]. Lazo de la Vega et al also reported focal gains involving CCDN1 at 11q13 and FGFR3 at 4p16 [94]. Contrary to these results, three previous works had claimed ONB to be tumors with a high level of chromosomal instability involving deletions of 1p, 3p/q, 9p, and 10p/q and amplifications of 17q, 17p13, 20p, and 22q [95–98]. It is difficult to find a common denominator in these data, except perhaps for the frequent finding of whole chromosome events. The heterogeneous map of copy number alterations may be explained by the difficulty to diagnose ONB correctly, especially the high grade tumors. ONB also appear to carry few mutations. Two sets of sequencing data, both on 20 tumors using 400/560 cancer-related gene panels revealed only two cases with TP53 and two cases with DNMT3A mutation in one study and no recurrent mutations whatsoever in the other [93,94]. Gay et al studied 41 refractory or recurrent ONB samples, many of which treated previously by radio/chemotherapy. Their results showed TP53 mutation in 17% of cases while mutations in PIK3CA, NF1, and IDH2 were noted in two cases (5%) each [99]. Genome-wide methylation studies revealed a subgroup of cases with low-grade histology defined by low level CpG methylation [93,100].

Undifferentiated carcinoma (SNUC). Similar to SNSCC and ITAC, most SNUC carry multiple gains and losses involving all chromosomes. Gains and amplifications at 3q26 and 17q23–24 are especially frequent and may indicate a role for transcription factors SOX2 and SOX9 involved in cellular differentiation processes in these tumors [91,101–103]. Other hotspots of amplification concern chromosomal bands 8p11 and 8q24 (Fig. 4) with possible candidate oncogenes FGFR1 and cMYC [91,104]. An analysis of hotspot cancer related mutations in 12 genes (AKT, BRAF, CDK4, CTNNB1, EGFR, FBXW7, JAK2, c-KIT, KRAS, PDGFR, PI3K, VEGF) in 13 tumors revealed no mutations [103]. More recently, a study sequencing all coding exons of 300 cancer-related genes in 11 cases showed recurrent genes mutations in IDH2, TP53, PIK3CA, ARID1A, CREBBP, KMT2D, SETD2 and TET2 [101]. A

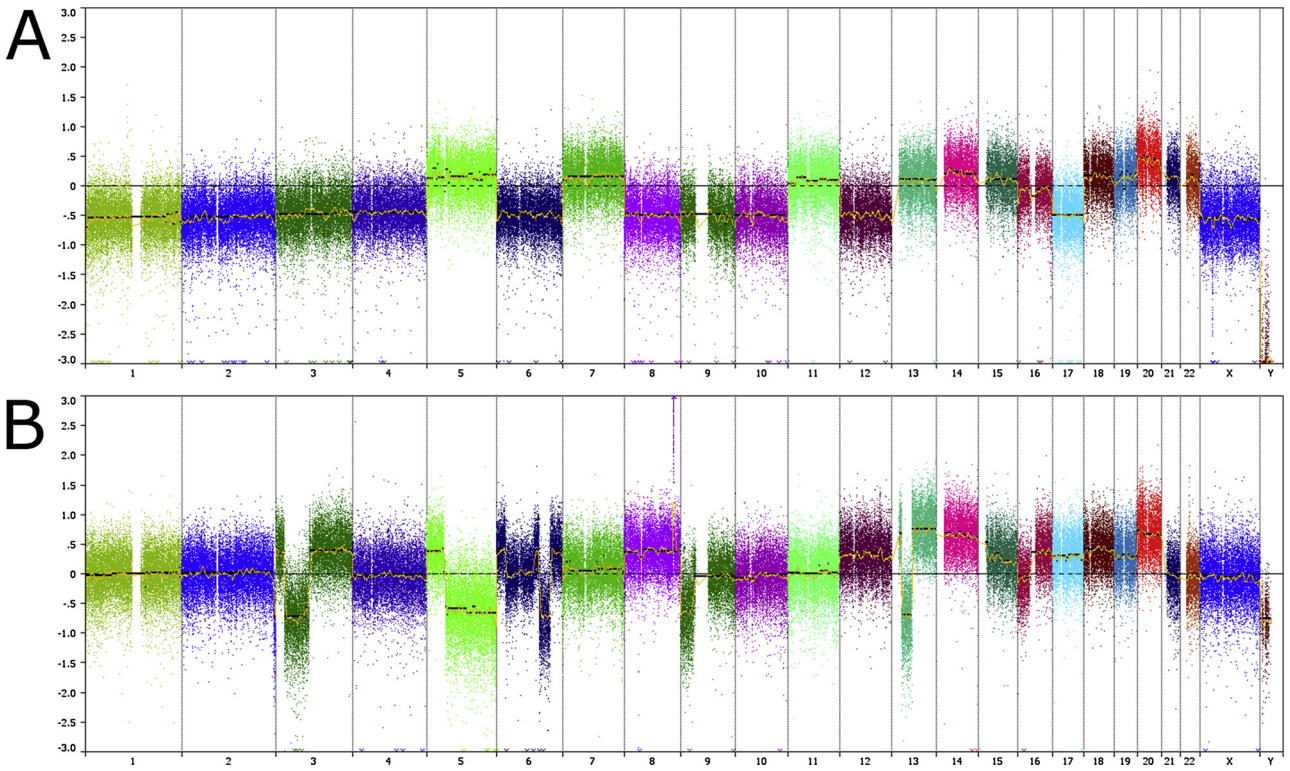

Fig. 4. Chromosomal copy number profiling. A) Olfactory neuroblastoma exclusively showing gains and losses of whole chromosomes. B) Undifferentiated carcinoma showing a complex karyotype with copy number gains and losses affecting almost all chromosomes and a high-level amplification at chromosome band 8q24.

Table 2
Actionable mutations in sinonasal cancer.

Tumors	Alteration	Therapeutic options
Squamous cell carcinoma	EGFR, ERBB2 mutation, amplification	irreversible EGFR inhibitors
	PD-L1 expression, Microsatellite instability	Immune checkpoint inhibitors
Intestinal-type adenocarcinoma	b-catenin nuclear expression	COX2, PPAR-gamma inhibitors, NSAIDs
	KRAS mutation	MEK, PDEδ, KRAS inhibitors
	PD-L1 expression	Immune checkpoint inhibitors
Malignant mucosal melanoma	NRAS, BRAF mutation	MEK, PDEδ, KRAS inhibitors
	c-KIT mutation	dasatinib, imatinib, sorafenib
Olfactory neuroblastoma	CD8+ TILs	Immune checkpoint inhibitors
Undifferentiated carcinoma	IDH2 mutation	IDH inhibitors and demethylating agents
	ARID1A, CREBBP, SETD2, TET2, KMT2D mutation	demethylating agents
SMARCB1-deficient carcinoma	SMARCB1 loss expression	EGFR-HER2-FGFR1-MET inhibitors
NUT carcinoma	NUT1 translocation	Bromodomain inhibitors
Neuroendocrine carcinoma	IDH2 mutation	IDH inhibitors and demethylating agents
HPV-related multiphenotypic carcinoma	ETV6-NTRK3 translocation	crizotinib
High grade non-intestinal-type adenocarcinoma	IDH2 mutation	IDH inhibitors and demethylating agents
	APC mutation	porcupine, tankryase, YES1 inhibitors
Teratocarcinosarcoma	CTTNB1 mutation	porcupine, tankryase, YES1 inhibitors

similar study including 10 cases reported recurrent mutations in SOX17, cKIT, SETD2 and IDH2 [102]. The most outstanding mutation concerned IDH2, in 55% (5/11) of cases, and subsequent publications confirmed the importance of this gene, presenting 49% (26/53) up to 82% (14/17) of cases with IDH2 mutation [101,102,105]. It is thought that the abnormal activity of mutated IDH2 causes an accumulation of the (R)-2-hydroxygluuotarate (2-HG) oncometabolite thus inducing global DNA hypermethylation and interruption of the differentiation of lineage-specific progenitor cells into terminally differentiated cells [106]. Capper et al have recently claimed 'sinonasal IDH2 carcinoma' as a new entity apart from IDH2 mutation characterized by high levels of methylation [93], however, whether or not IDH2 mutation is a characterizing event for a subset of SNUC remains to be seen, because they have also been detected in SNEC and high-grade SNAC [102,105].

SMARCB1-deficient carcinoma and NUT carcinoma. These former SNUC variants appear to have relatively simple diploid karyotypes [30,91,107,108]. SMARCB1 inactivation can be caused by a variety of mechanisms, including deletions, LOH and mutations, although in sinonasal tumors no mutations have been reported yet [31]. Four signalling pathways have been reported to be affected by SMARCB1: the p16INK4a-Rb-E2F pathway regulating chromosomal stability, the WNT signaling pathway shown by WNT/β-catenin overexpression, the Shh signaling pathway through regulation of GLI1, and repression of Polycomb genes through elevated expression and recruitment of EZH2 [109]. NUT carcinoma harbors a defining chromosomal translocation alteration involving the Nuclear protein in testis gene (NUT1 on 15q14), in 70% of cases creating a fusion protein with BRD4 (19p13), and in 6% with BRD3 (9q34.2), NSD3 (8p12), ZNF532 (18q21.32), ZNF592 (15q25.3) and CIC (19q13.2) [30,110,111]. A diffuse NUT1 protein expression of > 50% is also accepted for diagnosis [1].

Neuroendocrine carcinoma (SNEC). Copy number profiles with frequent gains and losses were found in SNEC. Microarray CGH analysis of 18 cases showed hotspot gains occuring in > 50% of cases at 1q, 6p, 7, 8q, 12, 14, 17q, 18q and 20, and > 35% losses occurred at 5q, 16p and 22q [91]. Very little is published on gene mutations in SNEC. The only recurrent mutations presented so far occurred in IDH2 and TP53 [102,105,112]. In a tumor showing mixed SNEC and SNSCC differentiation, TP53 mutation was only present in the SNEC compartment [41].

HPV-related multiphenotypic carcinoma (HMSC). Also named HPV-related sinonasal adenoid-cystic-like carcinoma, these tumors are defined by HPV infection in the absence of the t(6;9) MYB-NFIB rearrangement. However, variable immunohistochemical staining of cMYB has been reported [114]. Interestingly, not the well-known oncogenic HPV types 16 and 18 are involved, but in two thirds of cases HPV 33 and further HPV types 35, 56, 26, and 52 [26,113–115]. To date, there are no studies that have analyzed genetic abnormalities additional to HPV infection.

Non-intestinal-type adenocarcinoma (SNAC). Recurrent translocations involving ETV6 have been described in low grade SNAC. Andreasen et al first described a recurrent translocation t(12;15)(p13;q25) involving the genes ETV6 and NTRK3 in four cases and another translocation between ETV6 and RET [27,116]. This latter translocation was previously described in mammary analog of secretory carcinoma of the salivary gland and in sinonasal secretory carcinoma, however, these are distinct tumor entities [28,117]. Yet another translocation fusing SYN2 and PPARG genes was described by Soon et al [118]. The t(3;3) SYN2-PPARG fusion was previously observed in pulmonary small cell carcinoma. Villatoro et al detected CTNNB1 mutations in two cases of SNAC with morular metaplasia and CDX2/β-catenin nuclear expression [119]. Finally, Franchi et al reported BRAF mutations in 2 of 12 low-grade SNAC [78]. It remains to be clarified whether or not all these cases with specific genetic characteristic could be considered unique tumor entities, distinct from the SNAC subtype. High-grade SNAC (high grade non-ITAC) have been shown to carry IDH2 mutation in approximately 25% of cases [102,105,112]. Additional recurrent mutations were found in CREBBP, APC and NOTCH1 [102].

Teratocarcinosarcoma (TCS). This sinonasal tumor is very rare and hardly any genetic studies are available. Trisomy chromosome 12 was reported in two publications [120,121]. Birkeland et al found a pathogenic mutation in CTNNB1 and accumulation of accumulation of β-catenin protein in the nucleus, particularly in the mesenchymal component [122].

5. Actionable genetic alterations and preclinical models

With the development of novel inhibitors targeted to specific genetic alterations, personalized therapeutic opportunities are becoming increasingly available, also for sinonasal cancer patients. The fact that these are rare tumors makes the recruitment of a sufficient number of patients for clinical testing difficult, however, targeted therapies could be based on the results of ongoing or completed trials in patients with other, more-common tumors carrying the same actionable genetic aberrations. The genetic data obtained to date on sinonasal tumors already provide a rationale for targeted therapies for a substantial proportion of patients (Table 2).

EGFR mutation with absence of KRAS and BRAF mutations in SNSCC and its precursor lesion inverted papilloma indicate the usefulness of specific exon 20 insertion-specific inhibitors. In a preclinical setting, SNSCC cell lines have been demonstrated to respond very well to inhibitors as neratinib, afatinib and dacomitinib [44]. Perhaps the

most promising compound being tested in an ongoing phase II clinical trial on non-small-cell lung cancer is poziotinib [123], which may also be effective against exon 20 insertion mutations in ERBB2.

IDH inhibitors may be applied in SNUC, SNEC and high grade SNAC. The FDA recently approved anti-IDH agents Enasidenib and Ivosidenib for patients with relapsed or refractory acute myeloid leukemia [124]. IDH mutations have an impact on global and gene methylation, and so do other methylation-related genes recurrently mutated in SNUC, such as ARID1A, CREBBP, SETD2, TET2 and KMT2D. Therefore, demethylation-agents such as Decitabine that inhibits DNA methyltransferase to re-activate silent genes and that is approved for treatment of myelodysplastic malignancies [125], may also be effective in SNUC.

Wnt pathway activation through alterations in APC or β-catenin occur in ITAC, low grade SNAC and TCS. There are significant challenges in targeting the Wnt pathway and downstream effectors as they may not be selective. Porcupine is a Wnt pathway target that is amenable to inhibition while sparing Wnt-dependent tissues. Inhibitors of porcupine have been shown to block Wnt signaling and tumor growth in vivo [126,127] and in metastatic colorectal cancer phase 1/2 trials are underway [126,128]. Preclinical studies with tankyrase inhibitors which target the β-catenin-destruction-complex are promising, but there are currently no trials. Cancers with β-catenin patway activation are dependent on YES-associated protein 1 (YAP1), a transcription factor involved in stem cell differentiation. Tumor cell line and animal model studies have shown sensitivity to the multi-kinase inhibitor dasatinib through the inhibition of YES1 [129]. Mediated by NFkB signalling, the canonical WNT pathway is also related to chronic inflammation, a process that most likely plays a role in sinonasal cancer [17–21]. Therefore, compounds that can reduce ROS production and chronic inflammation could also decrease WNT/β-catenin signalling; candidate drugs are NSAIDs and PPAR-gamma inhibitors [16].

KRAS, NRAS and BRAF mutations have been found in ITAC, MMM and low grade SNAC and may be targets for inhibitors that target downstream MEK signalling. Other possibilities include interfering with binding of mammalian PDEδ to KRAS by means of small molecules [130]. In addition, it may be possible to directly inhibit the RAS(G12C) mutant [131]. Other genetic alterations that may be targeted by specific inhibitors are c-KIT (dasatinib, sorafenib, imatinib), NUT1 (bromodomain inhibitors), ETV6-NTRK3 fusion (crizotinib) and SMARCB1 (EGFR-HER2-FGFR1-MET inhibitors) [30,132,133].

Finally, a number or recent studies on sinonasal cancer have indicated a role for anticancer treatment by immune checkpoint inhibitors. PD-L1 expression on tumor cells has been detected in 32% SNSCC and 17% ITAC [134,135]. Moreover, microsatellite instability, now directly directly eligible for immunotherapy for all cancer types, was shown in 21% of SNSCC [56,77,79]. High numbers of both stromal and intra-tumoral CD8+ tumor infiltrating lymphocytes have been demonstrated in ONB, especially in high grade tumors, and their presence may serve as response markers for immunotherapeutic strategies [136].

To date, we are unaware of clinical trials involving sinonasal cancer patients, however, candidate gene targets can first be tested in a preclinical setting. In recent years, a number of immortalized sinonasal tumor cell lines have been established and characterized, including ITAC, SNSCC, ONB and SNUC [53,75,137,138]. In addition, mouse orthotopic sinonasal cancer models have been created by implanting SNUC or SNSCC cells into the maxillary sinus of the mouse [138–140]. These models retain the biological properties of sinonasal cancer and are important tools for functional studies on processes such as proliferation, differentiation, invasion, and metastasis in sinonasal tumors, and might facilitate the development and testing of new therapeutic agents.

6. Conclusion

Sinonasal cancers comprise a large number of histological subtypes that are difficult to diagnose correctly. In addition, their low incidence hamper the accumulation of experience with surgical, radiotherapeutic and oncological treatment, reason why for best clinical care patients should be treated in specialized referral hospitals. The same is true for molecular-genetic research, which would benefit greatly from international collaboration. Genetic characterization can aid classification and moreover, identify molecular targets for treatment with specific inhibitors. With next-generation sequencing every year more accessible and economic, knowledge on the genetic characteristics of sinonasal tumors is likely to increase considerably in the coming years, while new sinonasal cancer models are created that enable preclinical testing of candidate inhibitor drugs. As more and more novel targeted therapies are being developed, new options for personalized treatment of sinonasal cancer patients are becoming available.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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References

[1] A.K. El-Naggar, et al., WHO Classification of Tumors Pathology and Genetics of Head and Neck Tumors, Vol, 4th ed., IARC Press, Lyon, 2017.
[2] J.H. Turner, D.D. Reh, Incidence and survival in patients with sinonasal cancer: a historical analysis of population-based data, Head Neck 34 (2012) 877–885.
[3] B. Ansa, et al., Paranasal sinus squamous cell carcinoma incidence and survival based on Surveillance, Epidemiology, and End Results data, 1973 to 2009, Cancer 119 (2013) 2602–2610.
[4] D.R. Youlden, et al., International comparisons of the incidence and mortality of sinonasal cancer, Cancer Epidemiol. 37 (2013) 770–779.
[5] S. Sanghvi, et al., Epidemiology of sinonasal squamous cell carcinoma: a comprehensive analysis of 4,994 patients, Laryngoscope 124 (2014) 76–83.
[6] V.J. Lund, et al., European position paper on endoscopic management of tumors of the nose, paranasal sinuses and skull base, Rhinol. Suppl. 22 (2010) 1–143.
[7] L.H. Sobin, et al., International Union Against Cancer (UICC) TNM Classification of Malignant Tumors, 7th ed., Wiley-Blackwell, 2009.
[8] G. Cantu, et al., Anterior craniofacial resection for malignant paranasal tumors: a monoinstitutional experience of 366 cases, Head Neck 34 (2012) 78–87.
[9] F. López, et al., The impact of histologic phenotype in the treatment of sinonasal Cancer, Adv. Ther. 34 (2017) 2181–2198.
[10] S.K. Haerle, et al., Sinonasal carcinomas: epidemiology, pathology, and management, Neurosurg. Clin. N. Am. 24 (2013) 39–49.
[11] J.L. Llorente, et al., Genetic and clinical aspects of wood dust related intestinal-type sinonasal adenocarcinoma: a review, Eur. Arch. Otorhinolaryngol. 266 (2009) 1–7.
[12] IARC working group on the evaluation of carcinogenic risks to humans. arsenic, metals, fibres, and dusts, IARC Monogr. Eval. Carcinog. Risks Hum. 100 (2012) 11–465.
[13] C. Mensi, et al., Sinonasal cancer and occupational exposure in a population-based registry, Int. J. Otolaryngol. 2013 (2013) 672621.
[14] M. Bonzini, et al., Prevalence of occupational hazards in patients with different types of epithelial sinonasal cancers, Rhinology 51 (2013) 31–36.
[15] K. Taniguchi, M. Karin, NF-κB, inflammation, immunity and cancer: coming of age, Nat. Rev. Immunol. 18 (2018) 309–324.
[16] A. Vallée, Y. Lecarpentier, Crosstalk between peroxisome proliferator-activated receptor gamma and the canonical WNT/β-Catenin pathway in chronic inflammation and oxidative stress during carcinogenesis, Front. Immunol. 9 (2018) 745.
[17] R. Holmila, et al., COX-2 and p53 in human sinonasal cancer: COX 2 expression is associated with adenocarcinoma histology and wood-dust exposure, Int. J. Cancer 122 (2008) 2154–2159.
[18] J. Määttä, et al., Characterization of oak and birch dust-induced expression of cytokines and chemokines in mouse macrophage RAW 264.7 cells, Toxicology 215 (2005) 25–36.
[19] F. Perrone, et al., TP53, p14ARF, p16INK4a and H-ras gene molecular analysis in intestinal-type adenocarcinoma of the nasal cavity and paranasal sinuses, Int. J. Cancer 105 (2003) 196–203.
[20] R. Holmila, et al., Mutations in TP53 tumor suppressor gene in wood dust-related sinonasal cancer, Int. J. Cancer 127 (2010) 578–588.
[21] J. Pérez-Escuredo, et al., Wood dust-related mutational profile of TP53 in

intestinal-type sinonasal adenocarcinoma, Hum. Pathol. 43 (2012) 1894–1901.
[22] S.Y. Su, et al., Endoscopic resection of sinonasal cancers, Curr. Oncol. Rep. 16 (2014) 369.
[23] P. Castelnuovo, et al., Endoscopic endonasal skull base surgery: past, present and future, Eur. Arch. Otorhinolaryngol. 267 (2010) 649–663.
[24] P. Bossi, et al., TP53 status as guide for the management of ethmoid sinus intestinal-type adenocarcinoma, Oral Oncol. 49 (2013) 413–419.
[25] E. Orlandi, et al., Locally advanced epithelial sinonasal tumors: the impact of multimodal approach, Laryngoscope (August 1) (2019), https://doi.org/10.1002/lary.28202 [Epub ahead of print].
[26] J.A. Bishop, 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. 41 (2017) 1690–1701.
[27] S. Andreasen, et al., ETV6 gene rearrangements characterize a morphologically distinct subset of sinonasal low-grade non–intestinal-type adenocarcinoma: a novel translocation-associated carcinoma restricted to the sinonasal tract, Am. J. Surg. Pathol. 41 (2017) 1552–1560.
[28] M. Baneckova, et al., Mammary analog secretory carcinoma of the nasal cavity, Am. J. Surg. Pathol. 42 (2018) 735–743.
[29] A. Shay, et al., Survival in low-grade and high-grade sinonasal adenocarcinoma: a national cancer database analysis, Laryngoscope (May 13) (2019), https://doi.org/10.1002/lary.28052 [Epub ahead of print].
[30] C. French, NUT midline carcinoma, Nat. Rev. Cancer 14 (2014) 149–150.
[31] A. Agaimy, 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. 41 (2017) 458–471.
[32] K.J. Chambers, et al., Incidence and survival patterns of sinonasal undifferentiated carcinoma in the United States, J. Neurol. Surg. B Skull Base 76 (2015) 94–100.
[33] M.K. Bhayani, et al., Sinonasal adenocarcinoma: a 16-year experience at a single institution, Head Neck 36 (2014) 1490–1496.
[34] Wenig BM Undifferentiated malignant neoplasms of the sinonasal tract, Arch. Pathol. Lab. Med. 133 (2009) 699–712.
[35] M. Turri-Zanoni, et al., The clinicopathological spectrum of olfactory neuroblastoma and sinonasal neuroendocrine neoplasms: refinements in diagnostic criteria and impact of multimodal treatments on survival, Oral Oncol. 74 (2017) 21–29.
[36] T.P. Van der Laan, et al., Meta-analysis of 701 published cases of sinonasal neuroendocrine carcinoma: the importance of differentiation grade in determining treatment strategy, Oral Oncol. 63 (2016) 1–9.
[37] J.L. Llorente, et al., Sinonasal carcinoma: clinical, pathological and genetic advances for new therapeutic opportunities, Nat. Rev. Clin. Oncol. 11 (2014) 460–472.
[38] F. Lopez, et al., Current management of sinonasal undifferentiated carcinoma, Rhinology 53 (2015) 212–220.
[39] C.T. Leung, et al., Contribution of olfactory neural stem cells to tissue maintenance and regeneration, Nat. Neurosci. 10 (2007) 720–726.
[40] S. Hauser, et al., Isolation of novel multipotent neural crest-derived stem cells from adult human inferior turbinate, Stem Cells Dev. 21 (2012) 742–756.
[41] A. Franchi, et al., Primary combined neuroendocrine and squamous cell carcinoma of the maxillary sinus: report of a case with immunohistochemical and molecular characterization, Head Neck Pathol. 9 (2015) 107–113.
[42] S. La Rosa, et al., Mixed exocrine-neuroendocrine carcinoma of the nasal cavity: clinico-pathologic and molecular study of a case and review of the literature, Head Neck Pathol. 7 (2013) 76–84.
[43] S.Y. Kang, et al., Sinonasal undifferentiated carcinoma and esthesioneuroblastoma recurring as nonintestinal adenocarcinoma, Laryngoscope 23 (2013) 1121–1124.
[44] A.M. Udager, et al., High frequency targetable EGFR mutations in inverted sinonasal papilloma and associated sinonasal squamous cell carcinoma, Cancer Res. 75 (2015) 2600–2606.
[45] B. Vivanco, et al., Benign lesions in mucosa adjacent to intestinal-type sinonasal adenocracinoma, Patholog. Res. Int. 2011 (2011) 230147.
[46] A. Franchi, et al., Intestinal metaplasia of the sinonasal mucosa adjacent to intestinal-type adenocarcinoma. A morphologic, immunohistochemical, and molecular study, Virchows Arch. 466 (2015) 161–168.
[47] S.Y. Su, et al., Esthesioneuroblastoma, neuroendocrine carcinoma, and sinonasal undifferentiated carcinoma: differentiation in diagnosis and treatment, Int. Arch. Otorhinolaryngol. 18 (2014) S149–S156.
[48] D. Bell, et al., Neuroendocrine neoplasms of the sinonasal region, Head Neck 38 (Suppl 1) (2016) E2259–E2266.
[49] J.A. Bishop, Recently described neoplasms of the sinonasal tract, Semin. Diagn. Pathol. 33 (2016) 62–70.
[50] L.D. Thompson, Small round blue cell tumors of the sinonasal tract: a differential diagnosis approach, Mod. Pathol. 30 (2017) S1–S26.
[51] S. Andreasen, et al., An update on head and neck cancer: new entities and their histopathology, molecular background, treatment, and outcome, APMIS 127 (2019) 240–264.
[52] F. López, et al., Genomic profiling of sinonasal squamous cell carcinoma, Head Neck 33 (2011) 145–153.
[53] C. García-Inclán, et al., Establishment and genetic characterization of six unique tumor cell lines as preclinical models for sinonasal squamous cell carcinoma, Sci. Rep. 4 (2014) 4925.
[54] F. López, et al., Gene amplification and protein overexpression of EGFR and ERBB2 in sinonasal squamous cell carcinoma, Cancer 118 (2012) 1818–1826.
[55] R. Holmila, et al., Mutations in TP53 tumor suppressor gene in wood dust-related sinonasal cancer, Int. J. Cancer 127 (2010) 578–588.
[56] J.G. Martínez, et al., Microsatellite instability analysis of sinonasal carcinomas, Otolaryngol. Head. Neck Surg. 140 (2009) 55–60.
[57] A.M. Udager, et al., Human papillomavirus (HPV) and somatic EGFR mutations are essential, mutually exclusive oncogenic mechanisms for inverted sinonasal papillomas and associated sinonasal squamous cell carcinomas, Ann. Oncol. 29 (2018) 466–471.
[58] N. Sahnane, et al., Comprehensive analysis of HPV infection, EGFR exon 20 mutations and LINE1 hypomethylation as risk factors for malignant transformation of sinonasal-inverted papilloma to squamous cell carcinoma, Int. J. Cancer 144 (2019) 1313–1320.
[59] E. Sasaki, et al., Sinonasal squamous cell carcinoma and EGFR mutations: a molecular footprint of a benign lesion, Histopathology 73 (2018) 953–962.
[60] Cabal V.N., et al. EGFR mutation and HPV infection in sinonasal inverted papilloma and squamous cell carcinoma. Submitted 2019.
[61] J. Bornholdt, et al., K-ras mutations in sinonasal cancers in relation to wood dust exposure, BMC Cancer 8 (2008) 53.
[62] F. López, et al., KRAS and BRAF mutations in sinonasal cancer, Oral Oncol. 48 (2012) 692–697.
[63] K. Syrjänen, S. Syrjänen, Detection of human papillomavirus in sinonasal papillomas: systematic review and meta-analysis, Laryngoscope 123 (2013) 181–192.
[64] J.A. Bishop, et al., Human papillomavirus-related carcinomas of the sinonasal tract, Am. J. Surg. Pathol. 37 (2013) 185–192.
[65] A.B. Larque, et al., High-risk human papillomavirus is transcriptionally active in a subset of sinonasal squamous cell carcinomas, Mod. Pathol. 27 (2014) 343–351.
[66] J. Laco, 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. 467 (2015) 405–415.
[67] J. Doescher, et al., Epstein-Barr virus infection is strictly associated with the metastatic spread of sinonasal squamous-cell carcinomas, Oral Oncol. 51 (2015) 929–934.
[68] M. Ariza, et al., Comparative genomic hybridization of primary sinonasal adenocarcinomas, Cancer 100 (2004) 335–341.
[69] D. Korinth, et al., Chromosomal imbalances in wood dust-related adenocarcinomas of the inner nose and their associations with pathological parameters, J. Pathol. 207 (2005) 207–215.
[70] M.A. Hermsen, et al., Genome-wide analysis of genetic changes in intestinal-type sinonasal adenocarcinoma, Head Neck 31 (2009) 290–297.
[71] J. Pérez-Escuredo, et al., Recurrent DNA copy number alterations in intestinal-type sinonasal adenocarcinoma, Rhinology 54 (2016) 278–286.
[72] A. López-Hernández, et al., Genomic profiling of intestinal-type sinonasal adenocarcinoma reveals subgroups of patients with distinct clinical outcomes, Head Neck 40 (2018) 259–273.
[73] A. Franchi, et al., Immunohistochemical investigation of tumorigenic pathways in sinonasal intestinal-type adenocarcinoma. A tissue microarray analysis of 62 cases, Histopathology 59 (2011) 98–105.
[74] S.S. Yom, et al., Genetic analysis of sinonasal adenocarcinoma phenotypes: distinct alterations of histogenetic significance, Mod. Pathol. 18 (2005) 315–319.
[75] J. Pérez-Escuredo, et al., Establishment and genetic characterization of an immortal tumor cell line derived from intestinal-type sinonasal adenocarcinoma, Cell. Oncol. Dordr. (Dordr) 34 (2011) 23–31.
[76] J.P. Díaz-Molina, et al., Wnt-pathway activation in intestinal-type sinonasal adenocarcinoma, Rhinology 49 (2011) 593–599.
[77] B. Perez-Ordonez, et al., Expression of mismatch repair proteins, β-catenin, and cadherin in intestinal-type sinonasal adenocarcinoma, J. Clin. Pathol. 57 (2004) 1080–1083.
[78] A. Franchi, et al., Low prevalence of K-RAS, EGFR and BRAF mutations in sinonasal adenocarcinomas. Implications for anti-EGFR treatments, Pathol. Oncol. Res. 20 (2014) 571–579.
[79] M. Frattini, et al., Phenotype-genotype correlation: challenge of intestinal-type adenocarcinoma of the nasal cavity and paranasal sinuses, Head Neck 28 (2006) 909–915.
[80] C. García-Inclán, et al., EGFR status and KRAS/BRAF mutations in intestinal-type sinonasal adenocarcinomas, Cell. Oncol. Dordr. (Dordr) 35 (2012) 443–450.
[81] F. Projetti, et al., Epidermal growth factor receptor expression and KRAS and BRAF mutations: study of 39 sinonasal intestinal-type adenocarcinomas, Hum. Pathol. 44 (2013) 2116–2125.
[82] N.K. Hayward, et al., Whole-genome landscapes of major melanoma subtypes, Nature 545 (2017) 175–180.
[83] M. Van Dijk, et al., Distinct chromosomal aberrations in sinonasal mucosal melanoma as detected by comparative genomic hybridization, Genes Chromosomes Cancer 36 (2003) 151–158.
[84] A. Zebary, et al., KIT, NRAS and BRAF mutations in sinonasal mucosal melanoma: a study of 56 cases, Br. J. Cancer 109 (2013) 559–564.
[85] M. Amit, et al., Mutation status among patients with sinonasal mucosal melanoma and its impact on survival, Br. J. Cancer 116 (2017) 1564–1571.
[86] M. Colombino, et al., Unexpected distribution of cKIT and BRAF mutations among southern Italian patients with sinonasal melanoma, Dermatology 226 (2013) 279–284.
[87] M. Jangard, et al., TERT promoter mutations in sinonasal malignant melanoma: a study of 49 cases, Melanoma Res. 25 (2014) 185–188.
[88] M. Turri-Zanoni, et al., Sinonasal mucosal melanoma: molecular profile and therapeutic implications from a series of 32 cases, Head Neck 35 (2013) 1066–1077.
[89] J.P. Wroblewska, et al., SF3B1, NRAS, KIT, and BRAF mutation; CD117 and cMYC expression; and tumoral pigmentation in Sinonasal Melanomas: an analysis with

newly found molecular alterations and some population-based molecular differences, Am. J. Surg. Pathol. 43 (2019) 168–177.
[90] H.S. Kim, et al., Oncogenic BRAF fusions in mucosal melanomas activate the MAPK pathway and are sensitive to MEK/PI3K inhibition or MEK/CDK4/6 inhibition, Oncogene 36 (2017) 3334–3345.
[91] A. López-Hernández, et al., Genetic profiling of poorly differentiated sinonasal tumors, Sci. Rep. 8 (2018) 3998.
[92] U. Bockmuhl, et al., CGH pattern of esthesioneuroblastoma and their metastases, Brain Pathol. 14 (2004) 158–163.
[93] D. Capper, et al., DNA methylation-based reclassification of olfactory neuroblastoma, Acta Neuropathol. 136 (2018) 255–271.
[94] L. Lazo de la Vega, et al., Comprehensive molecular profiling of olfactory neuroblastoma identifies potentially targetable FGFR3 amplifications, Mol. Cancer Res. 15 (2017) 1551–1557.
[95] H. Holland, et al., Comprehensive cytogenetic characterization of an esthesioneuroblastoma, Cancer Genet. Cytogenet. 173 (2007) 89–96.
[96] S.H. Riazimand, et al., Analysis of cytogenetic aberrations in esthesioneuroblastomas by comparative genomic hybridization, Cancer Genet. Cytogenet. 136 (2002) 53–57.
[97] M. Guled, et al., Array comparative genomic hybridization analysis of olfactory neuroblastoma, Mod. Pathol. 21 (2008) 770–778.
[98] R. Valli, et al., Comparative genomic hybridization on microarray (a-CGH) in olfactory neuroblastoma: analysis of ten cases and review of the literature, Genes Chromosomes Cancer 54 (2015) 771–775.
[99] L.M. Gay, et al., Comprehensive genomic profiling of esthesioneuroblastoma reveals additional treatment options, Oncologist 22 (2017) 834–842.
[100] M. Classe, et al., Integrated multi-omic analysis of esthesioneuroblastomas identifies two subgroups linked to cell ontogeny, Cell Rep. 25 (e5) (2018) 811–821.
[101] V.Y. Jo, et al., Recurrent IDH2 R172X mutations in sinonasal undifferentiated carcinoma, Mod. Pathol. 30 (2017) 650–659.
[102] S. Dogan, et al., Frequent IDH2 R172 mutations in undifferentiated and poorly-differentiated sinonasal carcinomas, J. Pathol. 242 (2017) 400–408.
[103] A. Gelbard, et al., Molecular profiling of sinonasal undifferentiated carcinoma, Head Neck 36 (2014) 15–21.
[104] A. Schröck, et al., Fibroblast growth factor receptor-1 as a potential therapeutic target in sinonasal cancer, Head Neck 36 (2014) 1253-7.
[105] J.K. Mito, et al., Immunohistochemical detection and molecular characterization of IDH-mutant sinonasal undifferentiated carcinomas, Am. J. Surg. Pathol. 42 (2018) 1067–1075.
[106] C. Lu, et al., IDH mutation impairs histone demethylation and results in a block to cell differentiation, Nature 483 (2012) 474–478.
[107] E.M. Jackson, et al., Genomic analysis using high-density single nucleotide polymorphism-based oligonucleotide arrays and multiplex ligation-dependent probe amplification provides a comprehensive analysis of INI1/SMARCB1 in malignant rhabdoid tumors, Clin. Cancer Res. 15 (2009) 1923–1930.
[108] J.K. Lee, et al., Complex chromosomal rearrangements by single catastrophic pathogenesis in NUT midline carcinoma, Ann. Oncol. 28 (2017) 890–897.
[109] K. Kohashi, et al., Reduced expression of SMARCB1/ INI1 protein in synovial sarcoma, Mod. Pathol. 23 (2010) 981–990.
[110] A.A. Alekseyenko, et al., Ectopic protein interactions within BRD4-chromatin complexes drive oncogenic megadomain formation in NUT midline carcinoma, Proc. Natl. Acad. Sci. U.S.A. 114 (2017) E4184–E4192.
[111] I.M. Schaefer, et al., CIC-NUTM1 fusion: a case which expands the spectrum of NUT-rearranged epithelioid malignancies, Genes Chromosomes Cancer 57 (2018) 446–451.
[112] S. Dogan, et al., DNA methylation-based classification of sinonasal undifferentiated carcinoma, Mod. Pathol. (June 11) (2019), https://doi.org/10.1038/s41379-019-0285-x [Epub ahead of print].
[113] A.A. Shah, et al., Human papillomavirus-related multiphenotypic sinonasal carcinoma: a case report documenting the potential for very late tumor recurrence, Head Neck Pathol. 12 (2018) 623-8.
[114] S.A. Adamane, et al., Human papillomavirus-related multiphenotypic sinonasal carcinoma with unique HPV type 52 association: a case report with review of literature, Head Neck Pathol. 13 (2019) 331–338.
[115] J.F. Hang, et al., Human papillomavirus-related carcinoma with adenoid cysticlike features: a series of five cases expanding the pathological spectrum, Histopathology 71 (2017) 887–896.
[116] S. Andreasen, et al., The ETV6-RET gene fusion is found in ETV6- rearranged low-grade sinonasal adenocarcinoma without NTRK3 involvement, Am. J. Surg. Pathol. 42 (2018) 985–988.
[117] A. Skalova, 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. 42 (2018) 234–246.
[118] G.S.T. Soon, et al., A case of nasal low-grade non-intestinal-type adenocarcinoma with aberrant CDX2 expression and a novel SYN2-PPARG gene fusion in a 13-year-old girl, Virchows Arch. 474 (2019) 619–623.
[119] T.M. Villatoro, S.K. Mardekian, Two cases of sinonasal nonintestinal-type adenocarcinoma with squamoid morules expressing nuclear β-catenin and CDX2: a curious morphologic finding supported by molecular analysis, Case Rep. Pathol. 2018 (2018) 8741017.
[120] S. Vranic, et al., Hamartomas, teratomas and teratocarcinosarcomas of the head and neck: report of 3 new cases with clinico-pathologic correlation, cytogenetic analysis, and review of the literature, BMC Ear Nose Throat Disord. 8 (2008) 8.
[121] J. Thomas, et al., Sinonasal teratocarcinosarcoma with yolk sac elements: a neoplasm of somatic or germ cell origin? Ann. Diagn. Pathol. 15 (2011) 135-9.
[122] A.C. Birkeland, et al., Pathogenetic analysis of sinonasal teratocarcinosarcomas reveal actionable β-catenin overexpression and a β-catenin mutation, J. Neurol. Surg. B Skull Base 78 (2017) 346–352.
[123] S. Vyse, P.H. Huang, Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer, Signal Transduct. Target. Ther. 4 (2019) 5.
[124] E.M. Stein, et al., Enasidenib (AG-221), a potent oral inhibitor of mutant isocitrate dehydrogenase 2 (IDH2) enzyme, induces hematologic responses in patients with myelodysplastic syndromes (MDS), Blood 128 (22) (2016).
[125] S. Turcan, et al., Efficient induction of differentiation and growth inhibition in IDH1 mutant glioma cells by the DNMT inhibitor decitabine, Oncotarget 4 (2013) 1729–1736.
[126] N. Krishnamurthy, R. Kurzrock, Targeting the Wnt/beta-catenin pathway in cancer: update on effectors and inhibitors, Cancer Treat. Rev. 62 (2018) 50–60.
[127] J. Liu, et al., Targeting wnt-driven cancer through the inhibition of porcupine by LGK974, Proc. Natl. Acad. Sci. U.S.A. 110 (2013) 20224-9.
[128] B.K. Koo, et al., Porcupine inhibitor suppresses paracrine wnt-driven growth of Rnf43; Znrf3-mutant neoplasia, Proc. Natl. Acad. Sci. U.S.A. 112 (2015) 7548–7550.
[129] J. Rosenbluh, et al., β-Catenin-driven cancers require a YAP1 transcriptional complex for survival and tumorigenesis, Cell 151 (2012) 1457–1473.
[130] G. Zimmermann, et al., Small molecule inhibition of the KRAS-PDEδ interaction impairs oncogenic KRAS signalling, Nature 497 (2013) 638–642.
[131] J.P. O'Bryan, Pharmacological targeting of RAS: recent success with direct inhibitors, Pharmacol. Res. 139 (2019) 503–511.
[132] Roberts, et al., Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia, N. Engl. J. Med. 371 (2014) 1005-15.
[133] P.H. Huang, Targeting SWI/SNF mutant cancers with tyrosine kinase inhibitor therapy, Expert Rev. Anticancer Ther. 17 (2017) 1–3.
[134] C. Riobello, et al., Programmed death ligand-1 expression as immunotherapeutic target in sinonasal cancer, Head Neck 40 (2018) 818–827.
[135] H. Quan, et al., Clinical relevance and significance of programmed death-ligand 1 expression, tumor-infiltrating lymphocytes, and p16 status in sinonasal squamous cell carcinoma, Cancer Manag. Res. 11 (2019) 4335–4345.
[136] M. Classe, et al., Evaluating the prognostic potential of the Ki67 index and tumor infiltrating lymphocytes in olfactory neuroblastoma, Histopathology (July 15) (2019), https://doi.org/10.1111/his.13954 [Epub ahead of print].
[137] P.H. Sorensen, et al., Olfactory neuroblastoma is a peripheral primitive neuroectodermal tumor related to ewing sarcoma, Proc Natl Acad Sci U. S. A. 93 (1996) 1038–1043.
[138] Y. Takahashi, et al., Establishment and characterization of novel cell lines from sinonasal undifferentiated carcinoma, Clin. Cancer Res. 18 (2012) 6178–6187.
[139] M. Costales, et al., Orthotopic murine model of squamous cell carcinoma of the sinonasal cavities, Head Neck 37 (2015) 1769–1775.
[140] Y. Takahashi, et al., Human epidermal growth factor receptor 2/neu as a novel therapeutic target in sinonasal undifferentiated carcinoma, Head Neck 38 (Suppl 1) (2016) E1926-34.