Sinonasal carcinoma: clinical, pathological, genetic and therapeutic advances

José Luis Llorente, Fernando López, Carlos Suárez and Mario A. Hermsen

Abstract | The sinonasal cavities represent an anatomical region affected by a variety of tumours with clinical, aetiological, pathological, and genetic features distinct from tumours at the main head and neck cancer localizations. Together, squamous-cell carcinoma and adenocarcinoma account for 80% of all sinonasal tumours, and are aetiologically associated with professional exposure to wood and leather dust particles and other industrial compounds, and therefore, are officially recognized as an occupational disease. Owing to their distinctive characteristics, sinonasal tumours should be considered as separate entities, not to be included in the miscellany of head and neck cancers. Sinonasal tumours are rare, with an annual incidence of approximately 1 case per 100,000 inhabitants worldwide, a fact that has hampered molecular-genetic studies of the tumorigenic pathways and the testing of alternative treatment strategies. Nevertheless, the clinical management of sinonasal cancer has improved owing to advances in imaging techniques, endoscopic surgical approaches, and radiotherapy. Genetic profiling and the development of *in vitro* cell lines and animal models currently form the basis for future targeted anticancer therapies. We review these advances in our understanding and treatment of sinonasal tumours.

Llorente, J. L. *et al. Nat. Rev. Clin. Oncol.* **11**, 460–472 (2014); published online 17 June 2014; doi:10.1038/nrclinonc.2014.97

Introduction

Although the sinonasal cavities occupy a relatively small anatomical space (Figure 1), they are the site of origin of one of the most histologically diverse group of tumours observed in the entire human body. The sinonasal region is a complex anatomical area, close to structures that include the eyes and the brain, which is of special relevance to surgery and postoperative treatment, as mutilation and aesthetic deformities are difficult to avoid. Epithelial tumours are the predominant form of malignancy affecting the sinonasal cavities, representing >80% of all sinonasal tumours.[1] The most-common subtypes of epithelial tumour are sinonasal squamous-cell carcinoma (SNSCC), which predominantly occur in the maxillary sinus and nasal cavity, and intestinal-type adenocarcinoma (ITAC), which almost exclusively arise in the ethmoid sinus (Figure 1; Table 1).[1] Tumours of the frontal and sphenoid sinuses are rare.[1] Despite the anatomical proximity of the nasopharynx to the sinonasal cavities (behind the nasal cavities and above the soft palate), tumours in these regions are considered separately. Indeed, the aetiology, epidemiology, clinical features, and genetic profile of sinonasal tumours are distinct from those of the main head and neck cancer localizations, such as larynx, pharynx, and oral cavity cancers. Thus, sinonasal tumours should be considered unique malignancies not to be included in the miscellany of head and neck cancers.

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Competing interests
The authors declare no competing interests.

This article focuses on SNSCC and ITAC, which have been the subjects of an increasing number of publications on multiple oncological aspects. In particular, the advances in endoscopic surgical approaches, radiotherapy and imaging techniques that have improved the clinical management of patients with sinonasal cancer are reviewed. In addition, the progress in genetic profiling and the development of *in vitro* and animal models of sinonasal cancers, which is laying the foundations for future targeted anticancer therapies, are discussed.

The epidemiology of sinonasal tumours

Sinonasal cancers comprise 5% of all cancers of the head and neck, with a worldwide incidence of approximately 1 case per 100,000 inhabitants, annually.[2–4] The average age at which patients present with sinonasal tumours is between 50–60 years.[5] In general, SNSCCs account for 50–80% of all sinonasal malignancies, while ITAC represents 10–20%, although these proportions vary geographically;[4,6] for both these tumour types, the highest incidences are reported in European countries.[5]

SNSCC and ITAC occur more commonly in men, with a male-to-female ratio of 2:1 in SNSCC, and up to 6:1 in ITAC.[1,4,7] The male predominance of sinonasal tumours is probably a result of the aetiological involvement of occupational hazards;[1,4,7] occupational exposure to several industrial compounds has been attributed to tumorigenesis in around 40% of all sinonasal cancers, and 30% of SNSCC and 90% of ITAC specifically.[7–10] Professionals working with wood have up to 500–900-times and 20-times increased risk of developing ITAC

Key points

- A variety of tumour types can develop in the sinonasal cavities; most common are sinonasal squamous-cell carcinoma (SNSCC) and intestinal-type adenocarcinoma (ITAC), which arise in separate sinonasal sublocalizations
- Patients with sinonasal tumours often present with nonspecific clinical symptoms and with advanced-stage tumours, and therefore, have a poor prognosis
- Exposure to wood and leather dusts is a strong aetiological factor associated with the development of SNSCC and especially ITAC, possibly through tumorigenic pathways of chronic inflammation
- SNSCC and ITAC have aneuploid genomes—harbouring multiple genetic aberrations—that are distinct from each other and from histologically similar tumours (head and neck squamous-cell carcinoma and colorectal adenocarcinoma, respectively)
- Genetic profiling of sinonasal tumours and studies in relevant *in vitro* cell culture and animal models are laying the foundations for future targeted therapies
- The clinical management of sinonasal cancer has improved greatly owing to developments in endoscopic surgery and precision radiotherapy

and SNSCC, respectively, compared with the general population.[10] In individuals who present with these diseases, exposure to such environmental insults usually began at an early age and often persisted for longer than 20 years.[3,11] On the basis of this evidence, in many European countries ITAC is officially considered a professional disease.[12] Indeed, the International Agency for Research on Cancer (IARC) designated wood dust as a human carcinogen in 1995,[13] and in 2002, the NIH identified wood dust as a "known human carcinogen".[14] Outside of Europe, however, only 20% of patients with ITAC have a history of exposure to wood.[15] This geographical variation might reflect the existence of currently unidentified genetic susceptibility factors, or exposure to different types of wood or other compounds. Apart from wood and leather dust, chemical substances such as glues, formaldehyde, chrome, nickel, and various compounds used in the textile industry have been associated with sinonasal carcinomas, mainly SNSCC.[16]

In contrast to most head and neck cancers, tobacco smoking does not seem to have a key role in the development of sinonasal tumours; nevertheless, evidence suggests that smoking tobacco can increase the risk of SNSCC twofold to threefold.[5] In addition, human papilloma virus (HPV) type 16 and HPV-18 have been implicated in the development of SNSCC,[17,18] mainly in cases of malignant transformation, which occurs in 3–16% of inverted papillomas.[17]

Clinical presentation

The typical clinical symptoms of sinonasal cancer, such as nasal obstruction, facial pain, or persistent rhinorrhoea ('runny nose'), or epistaxis (nosebleed), are nonspecific, and indeed are often indistinguishable from symptoms of patients with benign sinonasal disease. Proptosis (bulging of the eyes), diplopia (double vision), or neurological symptoms can be present in patients with advanced-stage tumours. Owing to the nonspecific and the often relatively mild nature of the symptoms at early stages of disease, sinonasal malignancies have a prolonged diagnostic latency.[7,19] As such, lymphatic metastasis at diagnosis occurs in 10–20% of patients

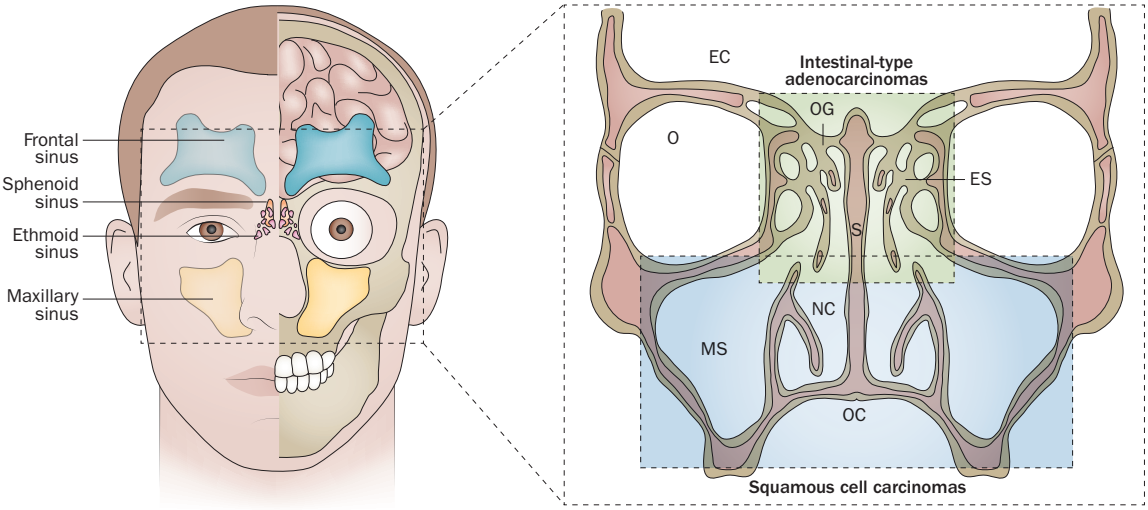

Figure 1 | Schematic view of the sinonasal cavities and distribution of the main sinonasal tumour types. Sinonasal malignancies comprise mostly tumours of epithelial origin, mainly SNSCCs and ITACs, but also esthesioneuroblastomas, SNUCs, and ACCs.[1] Other malignancies affecting the sinonasal region include melanomas, soft-tissue tumours, tumours of bone and cartilage, haematolymphoid tumours, germ-cell tumours, and metastases from primary tumours in other parts of the body. Almost all ITACs are located in the olfactory groove of the ethmoid sinuses, whereas SNSCCs occur mainly in the nasal cavity and the maxillary sinuses.[1] Apart from esthesioneuroblastomas, which originate in the olfactory epithelium, the other types of sinonasal tumours can occur anywhere within the sinonasal cavities, although tumours with frontal and sphenoid sinus localizations are rare.[1] Given the close proximity of these anatomical areas and the fact that tumours frequently present at advanced stages,[7,19] identifying the exact anatomical localization from which they developed is often difficult. Of note, the regions affected by sinonasal tumours are situated close to the eyes and brain. Abbreviations: ACCs, adenoid cystic carcinomas; EC, endocraneum; ES, ethmoid sinuses; ITACs, intestinal-type adenocarcinomas; MS, maxillary sinus; NC, nasal cavity; O, orbit; OC, oral cavity; OG, olfactory groove; S, septum; SNSCCs, sinonasal squamous-cell carcinomas; SNUCs, sinonasal undifferentiated carcinomas.

Table 1 | Summary of sinonasal tumour subtypes*

Histological subtype	Proportion of sinonasal cancers (%)	5-year overall survival rate (%)
Sinonasal squamous-cell carcinoma	50	50
Intestinal-type adenocarcinoma	13	60
Mucosal melanoma	7	35
Esthesioneuroblastoma	7	70
Adenoid cystic carcinoma	7	70
Sinonasal undifferentiated carcinoma	3	35
Other	13	Variable

*These data come from a study of patients with sinonasal cancer in the USA;[1] however, similar data have been obtained in patient populations in Europe and other regions.[5]

with SNSCC (especially if the tumour erodes through the maxillary gingiva), but is a rare occurrence in patients presenting with ITAC,[20,21] perhaps because the pattern of tumour spread is largely dependent of the sinus origin and lymphatic drainage. During the follow-up period after treatment of the primary tumour, 10% of patients with sinonasal tumours develop distant metastasis; however, this seldom occurs in absence of locoregional recurrence.[19–21]

Clinical examination of patients with suspected sinonasal tumour should begin with a thorough medical history and a complete ear, nose, and throat (ENT) exploration, including assessment of the cranial nerves and neck. Anterior rhinoscopy generally provides limited information and, therefore, rigid nasal endoscopy with optics at 0° or 45° is mandatory. Nasofibroscopy can also provide useful data, but the image quality is usually worse than with rigid endoscopes. Noninvasive imaging tests are also essential because they enable the complete extent of the tumour to be established and can potentially provide information on the benign or malignant nature of the tumour. Currently, when malignancy is suspected, both CT imaging and MRI must be performed to obtain precise anatomical details regarding the tumour localization and extension, which are critical in determining operability or in planning radiotherapy (Figure 2). MRI is considered the standard imaging modality for postoperative surveillance. The value of PET–CT in the assessment of sinonasal tumours has not been clearly defined, but this imaging modality is especially important in evaluating patients with suspected metastasis or tumour recurrence; up to one-third of sinonasal tumours might be accurately upstaged because of neck or distant-site involvement discovered using PET–CT.[22] Once the appropriate imaging data have been obtained, clinical staging of sinonasal tumours is performed based on location and extent, according to the current Union for International Cancer Control (UICC) classification system.[23]

Tumour histology

The sinonasal cavities are lined with a pseudostratified respiratory epithelium, which changes into pseudostratified olfactory epithelium at the roof of the nasal cavity (Figure 3a–b); the main difference between these epithelia is the presence of olfactory neurons in the latter, with the axons of these neurons forming unmyelinated nerve bundles that traverse the cribiform plate and transmit signals to the olfactory bulb. Goblet cells and submucosal secretory glands within these epithelia produce mucous that captures bacteria and other foreign matter, and is moved toward the pharynx by coordinated

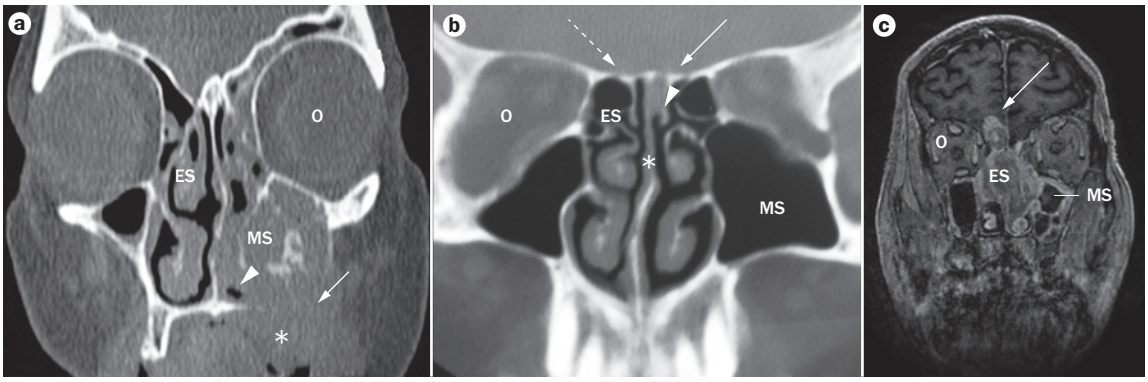

Figure 2 | Imaging approaches for diagnosis of sinonasal tumours. CT imaging in axial and coronal sections, preferably with contrast enhancement, enables accurate assessment of sinonasal cancers, especially in terms of bone destruction. Features of malignancy are invasion of soft tissue and the presence of reactive osteogenesis. MRI is generally indicated for assessing extension beyond the sinonasal cavities (orbital, intracranial or infratemporal fossa invasion), evaluating perineural tumour spread, and differentiating tumour from postobstructed secretions. MRI protocols generally include axial and coronal T_1-weighted, T_2-weighted, STIR and T_1-weighted gadolinium-enhanced scans. **a** | Coronal CT image showing an aggressive left maxillary SNSCC with destruction of the maxillary sinus walls. Erosion of the floor of the maxillary sinus and extension of the tumour into the maxillary alveolus (arrow), buccal space (asterisk), and hard palate (arrowhead) is evident. **b** | Coronal CT image of a woodworker, which led to the early diagnosis of a small ITAC of the left olfactory cleft (arrow). The left olfactory cleft is closed by a slight bulging of the corresponding nasal septum (asterisk) to the right and of the conchal lamina (arrowhead) to the left. Note the thinning of the left cribiform plate (dotted arrow). **c** | 3D IR-prepared gradient-echo sequence coronal MRI image demonstrating a large, heterogeneous ITAC occupying the nasal cavity and ethmoid sinuses bilaterally, with extension into the anterior cranial fossa (arrow). Abbreviations: ES, ethmoid sinuses; IR, inversion recovery; ITAC, intestinal-type adenocarcinoma; MS, maxillary sinus; O, orbit; SNSCC, sinonasal squamous-cell carcinoma; STIR, short tau inversion recovery.

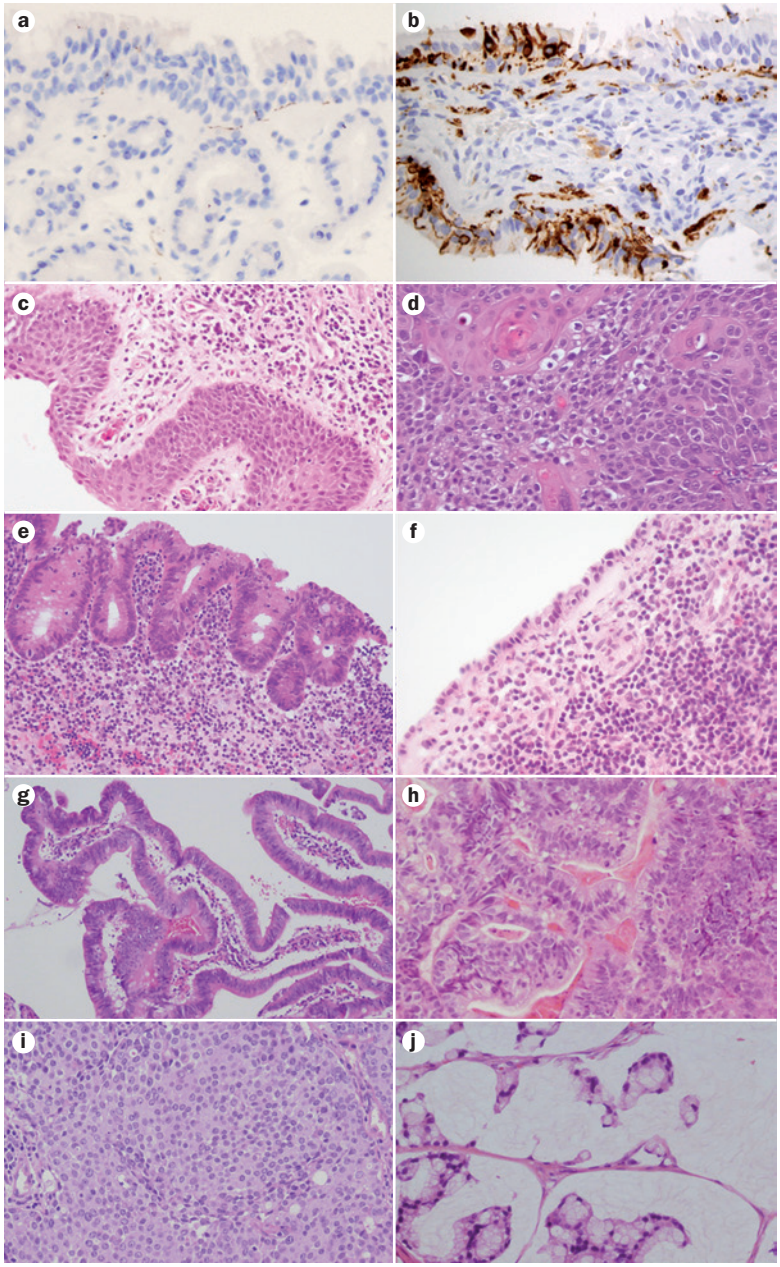

Figure 3 | Histological features of normal, benign metaplastic and various sinonasal tumour tissues. **a** | The sinonasal cavities are lined with pseudostratified respiratory epithelium containing occasional melanocytes, and basal, ciliated, and goblet cells. Seromucous secretory glands and lobular ducts lie below the surface epithelium in the lamina propria. **b** | The roof of the nasal cavity is lined with the olfactory epithelium, which differs from the respiratory epithelium mainly by the presence of olfactory neurons (brown stain). In the olfactory epithelium, basal cells are thought to produce olfactory neurons as well as sustentacular and ensheathing cells, and tubuloalveolar Bowman's glands below the surface epithelium. **c** | Abnormal cell differentiation can lead to squamous metaplasia, a precursor to SNSCC. **d** | SNSCCs are graded as well-differentiated, moderately differentiated, and poorly differentiated tumours, all of which are characterized by extracellular or intracellular keratin fibres and intercellular bridges. **e** | Abnormal cell differentiation can also lead to intestinal metaplasia. **f** | Cuboidal metaplasia is also possible. These histological samples demonstrating intestinal and cuboidal metaplasia come from patients with occupational exposure to wood dust, which is a known risk factor for sinonasal cancer, and particularly ITAC. Indeed, intestinal and cuboidal metaplasia are both precursors to ITAC, which occurs in four main subtypes: **g** | well-differentiated papillary-type ITAC, characterized by tall columnar monomorphic cells and a low number of mitotic figures; **h** | moderately differentiated colonic-type ITAC, which is associated with a mixed tubulopapillary pattern and increased mitotic rate; **i** | poorly differentiated solid-type ITAC, in which tubules are infrequent and highly hyperchromatic nuclei are common; **j** | mucinous-type ITAC, comprising alveolar goblet cells or signet-ring cells and mucin lakes. In parts a and b, immunohistochemical staining with anti-βIII-tubulin antibodies with haematoxylin counterstain was used to identify neurons. In parts c–j standard haematoxylin and eosin staining was performed. Magnification was 20× in all images, except parts g and j in which a magnification of 10× was used. Abbreviations: ITAC, intestinal-type adenocarcinoma; SNSCC, sinonasal squamous-cell carcinoma.

sweeping of ciliated cells on the surface of the epithelium. This protective layer of mucous also contains antimicrobial peptides and factors that regulate the local immunological defence mechanisms. In the stroma, leukocytes, lymphocytes and mononuclear cells lie ready and form a second line of defence.

Aberrant cell differentiation in the sinonasal epithelia can result in various forms of metaplasia, some of which might subsequently evolve to malignant transformation to form SNSCC (Figure 3c–d), or ITAC (Figure 3e–f). Similar to other mucosal sites in the head and neck, SNSCCs are graded into well-differentiate, moderately differentiated (Figure 3d), and poorly differentiated tumours according to the WHO tumour classification system,[24] although histological grade does not seem to have any clinical relevance.[25,26] Four histological subtypes of ITAC are recognized (Figure 3g–j), the most frequent type is colonic (40%), followed by mucinous (22%), solid (20%), and papillary (18%).[24] ITACs can also show mixtures of two or more of these four histological subtypes.[24] Irrespective of the histological type, ITACs demonstrate elevated production of intracellular or extracellular mucins, and might also contain argyrophilic, endocrine, enterochromaffin, and Paneth cells.[24]

Tumorigenesis of sinonasal tumours

Chronic inflammation

The pathogenic molecular pathways that result in sinonasal cancer remain unknown. The organic dusts associated with tumour development are not considered directly mutagenic, but these materials might—through continuous irritation of the mucosa—illicit chronic inflammation, which is a recognized mechanism of tumorigenesis in several types of cancer.[27]

A role for chronic inflammation in sinonasal tumorigenesis is supported by the findings of various studies. *In vitro,* phagocytosis of inhaled organic dust, mineral fibres, or fungal spores induced activated alveolar

macrophages to secrete a variety of cytokines and chemokines involved in the development and maintenance of the inflammatory response, including tumour necrosis factor (TNF).[28] The cytokines TNF and IL-1β can result in activation of the transcription factor nuclear factor κB (NFκB), which is implicated in tumorigenesis, thus connecting inflammation with cancer development.[27] Of note, expression of both NFκB and downstream prostaglandin G/H synthase 2 (also known as cyclooxygenase-2 [COX2]) have been found to be elevated in sinonasal carcinomas.[29] In addition, upon stimulation by wood dust, alveolar macrophages released reactive oxygen species (ROS) and reactive nitrogen species (RNS), such as peroxynitrites and nitrogen oxides, which can generate mutagenic DNA adducts.[30,31] Under acute inflammatory conditions, these free radicals are released to combat pathogenic organisms, but in chronic inflammatory conditions, they can have detrimental effects on the host tissues. A strong relationship between nitric oxide (NO) production through inducible nitric oxide synthase (iNOS) activity and G>A nucleotide transitions in the *TP53* gene was demonstrated in colorectal cancer.[31] Likewise, a dominance of *TP53* G>A transitions has been observed almost exclusively in nonsmoking woodworkers, whereas G>T transversions associated with tobacco smoking were considerably less frequently observed.[32–34] Furthermore, G>A transition in *KRAS* was the most-frequent mutation found in patients with ITAC who had a history of exposure to wood and leather dust.[35]

Together, these data implicate chronic inflammatory processes as a causal or promoting factor in the tumorigenesis of both SNSCC and ITAC, particularly in individuals exposed to industrial compounds. However, more studies are needed to confirm this relationship, and also to explain why none of the known sinonasal cavity inflammatory pathologies, such as rhinitis and polyps, seem to be associated with an increased cancer risk.

Precursor lesions

Multistep carcinogenesis through various histological changes accompanied by accumulating genetic alterations has not been demonstrated for sinonasal carcinomas. However, any premalignant histological changes might be obscured by growth of the tumour mass, which is often detected at advanced stages of progression. At an early stage of development of both SNSCCs and ITACs, the normal respiratory or olfactory epithelium undergoes metaplasia, redirecting the normal cell differentiation pathways toward tissue types that do not normally exist in the sinonasal cavities. One could speculate that such metaplasia is a histopathological change reflecting cellular and tissue responses to a chronic inflammatory microenvironment.

Squamous metaplasia and subsequent dysplasia are histological changes that precede the development of SNSCC (Figure 3c–d).[24] In addition, inverted papilloma is associated with a small proportion of SNSCCs; HPV-16 infection has been described in 38% of benign and 31% malignant tumours,[17,18] suggesting that inverted papilloma is a precursor to this subset of SNSCCs.

Differentiation or reprogramming the sinonasal epithelium towards an intestinal-type epithelium, incorporating resorptive, goblet, neuroendocrine, and Paneth cells, occurs before the development of ITAC (Figure 3e–f),[24] but is not unique to the sinonasal cavities: this process has been reported to precede the development of tumours at a number of locations, including the stomach, oesophagus, and lung.[36,37] Both cuboidal and intestinal metaplasia have been proposed to be a precursor to ITAC, as these metaplastic tissues have been observed adjacent to such tumours and in sinonasal mucosa of individuals with exposure to aetiological risk factors (Figure 3e–f).[38–40] Immunohistochemically, this metaplasia can be detected as a switch from a normal cytokeratin-7 (CK-7)$^+$/CK-20$^-$/CDX-2$^-$/villin$^-$ sinonasal epithelial cell phenotype to an abnormal CK-7$^-$/CK-20$^+$/CDX-2$^+$/villin$^+$ intestinal epithelial cell phenotype.[41] Expression of p53, which is absent in the normal respiratory epithelium, has been also been observed, mainly in squamous metaplasia, and seems to be related to wood-dust exposure.[39,40] This observation might be indicative of upregulated expression of functional p53 in response to inflammatory signals in the wood-dust-exposed sinonasal epithelium, rather than of *TP53* gene mutation.

Cancer stem cells

Another method of investigating the origin of sinonasal cancer is the analysis of cancer stem cells (CSC), as proposed for other head and neck tumours.[42,43] To our knowledge, no research has been published on the role of CSC in sinonasal cancer. Nevertheless, normal stem cells in the olfactory epithelium have captured the attention of stem-cell researchers, especially with regard to the ability of these cells to form new olfactory neurons after tissue damage sustained during adulthood.[44] The same olfactory neuroepithelium stem cells were also found to be precursors of non-neuronal, epithelial cell types.[44] In addition to the olfactory epithelium, stem cells have been isolated from respiratory epithelium of the lower and middle turbinate, and these cells were capable of differentiating into cells with either neuroectodermal or mesodermal phenotypes.[45] On the basis of specific neuronal markers, esthesioneuroblastoma is the only type of sinonasal tumour demonstrated to derive from the olfactory epithelium. Clinical and radiological evidence suggests that ITACs also originate from the olfactory epithelium lining the olfactory cleft (Figure 1 and Figure 2), whereas SNSCCs might develop in other sinonasal areas, such as respiratory mucosa in the maxillary sinus or in the pterigopalatine fossa.[46,47] Thus, these tumour types could potentially result from expansion of CSCs localized in these particular regions.

Sinonasal tumours could be hypothesized to derive from CSCs 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 tumours have been described that demonstrate more than one histological appearance; for example, adenoid cystic carcinoma with adenocarcinoma or undifferentiated carcinoma, or

Table 2 | Genetic alterations in SNSCCs/ITACs, and possible targeted therapies

Genetic aberration	ITAC	SNSCC	Targeted therapeutic agents*
EGFR overexpression[59,66–68]	20–33%	40%	Cetuximab and TKIs
ERBB2 overexpression[59,68]	ND	3–7%	Trastuzumab and TKIs
KRAS mutation[35,58,71,72]	15%	1%	Deltarasin
Overexpression of VEGFR-encoding genes[59,116]	ND	50%	Sunitinib and TKIs
Overexpression of NFκB-encoding genes[29]	36%	ND	Solithromycin
FGFR1 amplification[73]	ND	20%	Dovitinib
PTGS2 (also known as *COX2*) overexpression[29]	40–60%	8%	NSAIDs

*The list of drugs is not exhaustive and only provides examples of specific agents or classes of agents that target the druggable genetic alterations demonstrated in SNSCC and ITAC to date. Abbreviations: ITAC, intestinal-type adenocarcinoma; ND, not determined; NFκB, nuclear factor κB; NSAIDs, non-steroid anti-inflammatory drugs; SNSCC, sinonasal squamous cell carcinoma; TKIs, tyrosine kinase inhibitors; VEGFR, vascular endothelial growth factor receptor.

SNSCC with neuroendocrine carcinoma.[48,49] Furthermore, recurrent tumours can have a different histological type than the original primary tumour, with reports of ITAC recurrence as undifferentiated carcinoma or esthesioneuroblastoma.[50]

The CSC hypothesis provides a model that accommodates the multiple causes of tumour heterogeneity.[51] According to this hypothesis, tumorigenesis can be considered as a dynamic and plastic process regulated by microenvironmental factors, rather than as a hierarchical or static concept.[52] The study of CSCs and the tumour microenvironment might, therefore, have clinical implications for sinonasal cancer, particularly as these cells have been implicated in disease recurrence and resistance to chemotherapy,[53–56] which are both notable characteristics of sinonasal carcinomas.[19–21]

Genetic characterization

Sinonasal-cancer-related genes

Studies of the involvement of specific genes in SNSCC and ITAC have often been guided by findings from more-frequent and better-studied tumours with similar histology, such as head and neck squamous-cell carcinoma and colorectal carcinoma, respectively. Mutation of the *TP53* gene has been associated with exposure to wood dust, with frequencies of *TP53* mutation ranging from 70% in SNSCC and up to 86% in ITAC.[33,34,57,58] Overexpression of p53 has also been reported in around 50% of SNSCCs and 72% of ITACs.[29,33,58–60] Interestingly, the frequency of p53 overexpression seems to be markedly lower in mucinous-type ITAC compared with the other ITAC subtypes.[60]

Aberration of the canonical Wnt signalling pathway has also been implicated in sinonasal cancer. Activation of this pathway, detected as nuclear expression of β-catenin, has been reported in 31–53% of ITACs, with a higher proportion of activation of Wnt signalling observed in papillary and colonic ITAC subtypes than in solid-type and mucinous-type ITAC.[60–62] This proportion is, however, substantially lower than the 90% of sporadic colorectal adenocarcinoma that demonstrate activation of the Wnt pathway, but is similar to the 40% frequency in colorectal adenocarcinomas that arise in patients with inflammatory bowel disease.[63,64] Furthermore, mutations in *APC* (encoding adenomatous polyposis coli protein) or *CTNNB1* (encoding β-catenin), key components of the Wnt cascade that are frequently mutated in colorectal cancer,[65] have not been identified in sinonasal carcinomas.[58] Thus, although activation of the Wnt pathway probably contributes to the development of certain ITACs, the specific mechanisms remain to be identified and are likely to differ from those underlying the histologically similar spontaneous colorectal adenocarcinomas. In SNSCC, nuclear β-catenin expression is rare and the Wnt pathway is unlikely to have a role in the development of this tumour type (unpublished data, M. A. Hermsen).

Several studies have demonstrated EGFR overexpression in about 40% of SNSCCs and in 20–33% of ITACs (Table 2).[59,66–68] Again, these frequencies are lower than those reported for the histologically similar head and neck and colorectal cancers.[69,70] Interestingly, *EGFR* mutations that have been observed in lung adenocarcinoma were not found in ITAC.[66] Overexpression of HER2 (also known as ErbB2) has also been detected in <10% of SNSCCs.[59,68] Mutations in *KRAS* and *HRAS*, which encode proteins downstream of EGFR in the EGF signalling pathway, have been found in approximately 1% in SNSCCs and 15% of ITACs,[35,58,71,72] whereas *BRAF* mutations have not been detected in these tumours.[71]

In SNSCC, 21% of tumours overexpressed $p16^{INK4A}$ (also known as cyclin-dependent kinase inhibitor 2A), and high expression levels of this protein were a surrogate marker of a subset of HPV-positive cases.[18,73] Conversely, epigenetic silencing of $p16^{INK4A}$ was reported in 67% and loss of heterozygosity at the 9p21 locus—which harbours the gene encoding this protein—in 45% of ITAC cases studied.[33] Furthermore, microsatellite instability can occur in a small proportion of SNSCCs, but does not seem to have a role in ITAC oncogenesis.[62,72,74] In addition, using fluorescence *in situ* hybridization, gene amplification of *FGFR1* and *SOX2* was demonstrated in 20% and 37% of SNSCC cases, respectively, whereas 0% and 8% of ITACs had amplification of these genes, respectively (Table 2).[73,75] Several studies have also reported NFκB and COX2 overexpression in sinonasal carcinomas, particularly in ITAC, suggesting a role for chronic inflammation in tumorigenesis.[29]

Genomic profiling of ITAC and SNSCC

Genome-wide genetic studies have shown that both SNSCC and ITAC generally have complex, aneuploid genomes that carry a wide variety and a large number of chromosomal aberrations (Figure 4),[76–79] similarly to most solid tumours. An exception is papillary-type ITAC, which seems to be predominantly diploid with few genetic aberrations.[76,77] SNSCC and ITAC each have both shared and unique genetic abnormalities compared with other head and neck tumours, such as larynx, pharynx, or oral cavity squamous-cell carcinomas, but have a considerably different genetic profile compared with salivary gland tumours, which have characteristic chromosomal translocations and relatively few genetic changes.[48,80,81]

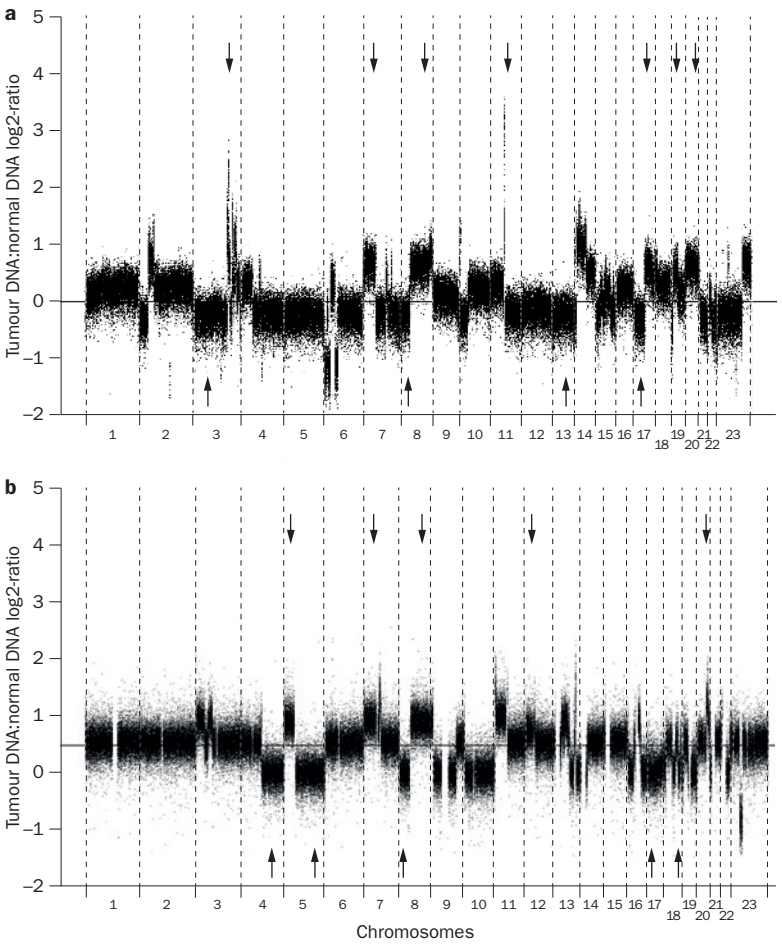

Figure 4 | Microarray CGH analysis demonstrating profiles characteristic of SNSCC and ITAC. The data for each chromosome are ordered continuously from left to right, pter to qter, as chromosomes 1 up to chromosomes X and Y (numbered as 23 and 24, respectively), with the boundaries between chromosomes defined by dashed vertical lines. All data points are expressed as tumour DNA:normal DNA log2-ratios; a log2-ratio of 0 is interpreted as a normal copy number, and log2-ratios of >0 and <0 indicate copy-number gains and losses, respectively. **a** | CGH analysis profile of a DNA aneuploid, stage T4aN2bM0, poorly differentiated SNSC§C of the right maxillary sinus with copy-number alterations for most chromosomes. This case demonstrates many of the recurrent alterations observed in SNSCC (arrows): high-level amplification at 3q26–3qter (including *SOX2*) and at 11q13 (including *CCDN1*, *EMS1*), copy-number gains at 7p, 8q, 17q, 19p, and 20q, and losses at 3p, 8p, 13q, and 17p. **b** | CGH profile of a DNA aneuploid, stage T3N0M0, colonic-type ITAC of the right ethmoid sinus with copy-number alterations in many chromosomes. This case demonstrates many of the recurrent alterations observed in ITAC (arrows): copy-number gains at 5p, 7p, 8q, 12p, and 20q, and losses at 4q, 5q, 8p, 17p, and 18q. Abbreviations: CGH, competitive genomic hybridization; ITAC, intestinal-type adenocarcinoma; SNSCC, sinonasal squamous-cell carcinoma.

In SNSCC, DNA copy number gains are found frequently at chromosomal regions 3q, 7p, 8q, 11q13, 17q, 19p, and 20q, with losses at 3p, 8p, 9p, 13q, 17p, 17q, and 18q, whereas recurrent DNA copy number gains in ITAC genomes include 5p, 6p, 7p, 7q, 8q, 12p, and 20q, and losses are commonly seen at 4q, 5q, 8p, 17p, and 18q (Figure 4).[76–79] Recurrent high-level amplifications of chromosomal loci detected in SNSCC include 7p12, 11p13, 11q13, and 17q21, which contain the suggested candidate oncogenes *EGFR*, *CD44*, *CCND1*/*CTTN*, and *ERBB2*, respectively;[78] in ITAC high-level amplifications are less frequent, but some have been reported at 1q, 5p, 7q, 8q23–24, 12p, 13q14, and 20q.[76,77]

Using an expression array of 6,864 genes, and validated by RT-PCR and immunohistochemistry, two genes with marked differential expression compared with matched normal nontumour sinusal tissue were identified in nine ITACs.[82] Specifically, *LGALS4*—encoding galectin-4—was highly upregulated, particularly in well-differentiated tumours; and *CLU*, which encodes clusterin, was downregulated in all tumours.[82] However, these findings await validation and, therefore, the potential implications of these data remain unknown.

Two SNSCC, one HPV-positive and one HPV-negative, were included as part of a large exome-sequencing study of head and neck squamous-cell carcinoma, and both were discovered to be among the tumours with the lowest number of mutations.[83] *TP53* was the only mutated gene identified in the HPV-positive SNSCC, whereas the other HPV-negative tumour was found to harbour two mutated genes, *SYNE1* and *NOTCH3*, which have both been implicated in the regulation of nuclear polarity and terminal differentiation of squamous epithelia.[83]

Models of sinonasal cancer

In the past 3 years, the first immortalized ITAC cell line and a number of new SNSCC cell lines have been established and characterized.[84,85] In addition, a mouse orthotopic sinonasal cancer model has been developed by implanting cells from a human sinonasal undifferentiated carcinoma (SNUC) into the maxillary sinus of mice.[86] This model suggests that development of mouse orthotopic models of SNSCC and ITAC might also be feasible. These *in vitro* and *in vivo* models, which retain the biological properties of sinonasal cancer,[84–86] are important tools for functional studies on the role of CSCs and processes such as proliferation, differentiation, invasion, and metastasis in sinonasal tumours, and might facilitate the development and testing of new therapeutic agents.

Sinonasal-cancer prognosis

Independent of the treatment type used, the prognosis of patients with sinonasal carcinomas is poor, with an overall 5-year survival rate of 30–50% (Table 1).[1,2,5] The 5-year survival rates depend on disease stage and drops from 80% in patients with T1 disease to 30% in patients with T4 tumours.[1,2,5] Histological grade does not have prognostic value in patients with SNSCC;[25,26] among patients with ITACs, however, papillary-type and colonic-type tumours are associated with more-favourable clinical outcome than the solid or mucinous subtypes.[24] Molecular markers of poor prognosis include EGFR expression and HPV-negativity in SNSCC,[17,18,59] and p53 and nuclear β-catenin expression in ITAC.[57,61] Local recurrence often occurs within 2 years of follow-up and is the main contributor to sinonasal cancer mortality.[19,21] Lymph node and distant metastases are infrequent; however, sinonasal tumours should not be considered exclusively as a locoregional disease and wider anatomical imaging studies such as PET-CT can help proper staging.

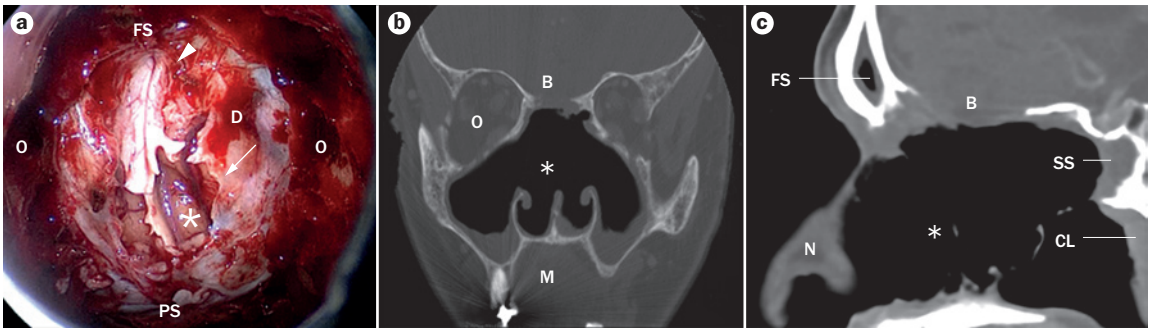

Figure 5 | Endoscopic surgery for the treatment of sinonasal tumours. **a** | Endoscopic nasal view of the anterior cranial fossa during an endoscopic craniofacial surgery in a patient with ITAC. After debulking the tumour, the cribriform plate, the dura mater (D), and the tumour implantation area are resected with proper tumour-free margins. The resection limits are: the frontal sinus (FS), the planum sphenoidale (PS), and sides of the both orbits (O). The frontal lobes (asterisk), falx cerebri (arrowhead), and dural resection margin (arrow) are indicated. **b** | Postoperative coronal CT image of a total endoscopic resection of a bilateral ITAC showing one single sinonasal cavity (asterisk) free of tumour, leaving only the two inferior turbinates and part of the septum directly below the sinonasal cavity. **c** | A postoperative sagittal CT image provides an alternate view of the same resection (asterisk). Abbreviations: B, brain; CL, clivus; D, dura mater; FS, frontal sinus; ITAC, intestinal-type adenocarcinoma; M, mouth; N, nose; O, orbit; PS, planum sphenoidale; SS, sphenoid sinus.

Treatment of sinonasal cancer

Complete surgical resection with postoperative radiotherapy is the mainstay of sinonasal-cancer management (Figure 5), although the therapeutic modality used should be tailored individually according to tumour stage, histology, patient age, and previous treatments. More-effective treatments that are also associated with less morbidity than the currently available options are needed, especially for advanced-stage tumours. Strategies to improve treatment outcome should focus on local disease control and reducing distant metastasis.

Surgery

A detailed description of the different potential surgical approaches to the treatment of the various sinonasal carcinomas is beyond the scope of this Review. However, minimally invasive endoscopic approaches are increasingly used, and deserve special attention, because they can reduce the number of complications and morbidity associated with surgery.[87–89] In addition, traditional open surgical approaches, such as maxillectomy, have become less destructive, with surgeons disguising the incisions using degloving facial approaches and regional or free-flap reconstructions.[90]

Resection of sinonasal tumours with wide margins is not always possible, as doing so would affect the cranial nerves, eyes, internal carotid artery, or brain. Thus, such attempts to remove tumour with wider surgical margins could cause unacceptable morbidity and would be technically difficult, if not impossible, either by open or endoscopic techniques. Moreover, no evidence suggests that this approach would substantially increase survival.

For decades, open craniofacial resection and maxillectomy was the mainstay treatment for sinonasal tumours.[91] In the late 1980s and early 1990s endoscopes began to be used for the removal of benign nasal tumours and this endoscopic surgery has now culminated in the resection of sinonasal malignancies, including those affecting the anterior cranial base.[89,92] The first challenge to the utility of endoscopic surgery in sinonasal malignancies was the fact that tumours could not be removed in monobloc; however, overwhelming evidence indicates that monobloc procedures are not always essential and that tumours can be fragmented if radical removal of the tumour at the end of the intervention is guaranteed.[87,89] One example is endoscopic laryngeal surgery using a CO_2 laser, which has been shown to be as effective as open approaches.[93] At the beginning of an intervention, dissection and fragmentation of the sinonasal tumour are commonly performed to facilitate its removal. In addition, the anterior skull base (dura mater and olfactory tracts), the site of ITAC origin in many cases, can be removed safely in monobloc by endoscopic approaches (Figure 5, Supplementary Video 1). The ability to control bleeding has been improved owing to the numerous haemostatic techniques that are now available.[94] Another challenge in endoscopic resection of sinonasal tumours in patients with intracranial extension has been the reconstruction of the dura mater to separate the aseptic brain area from the septic nasal cavity region and also to prevent cerebrospinal fluid leakage. The dura mater can be reconstructed with good results through inlay and overlay procedures using different tissue grafts comprising fascia lata, collagen matrix or abdominal fat (Supplementary Video 1). One improvement in the repair of dural defects after skull-base surgery was the introduction of vascularized local flaps, with the repair performed using vital tissue;[95] currently, most surgeons use the so-called septal mucosal flap, with some modifications.[95] These flaps are especially useful in pituitary pathology, but in the case of malignant tumours some safety limitations restrict use of this approach, for example when a sinonasal tumour invades or grows in proximity to tissues comprising the harvest flap, such as the septum or choanas. In such cases, for oncological reasons, this type of procedure should be avoided.

More data are needed from larger studies of endoscopic surgery with longer follow-up periods, or preferably from randomized studies directly comparing open

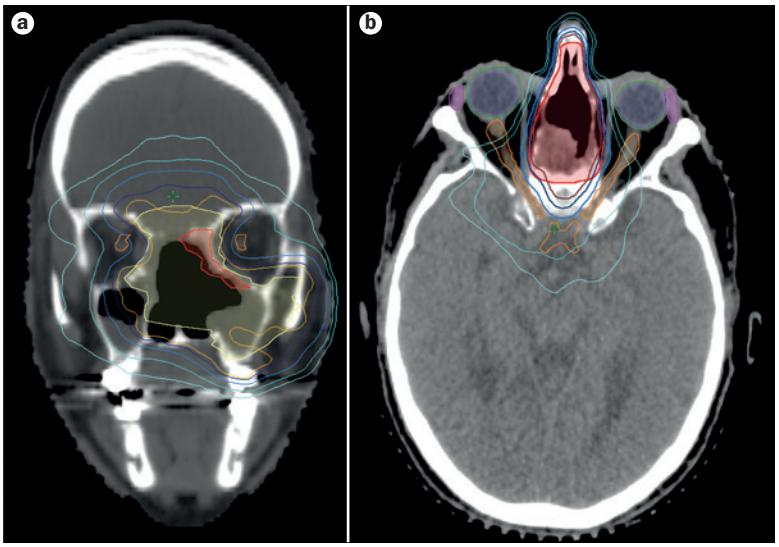

Figure 6 | Precision radiotherapy for the treatment of sinonasal tumours. **a** | Coronal CT section showing the clinical target volumes for radiotherapy with VMAT in a patient with a recurrent ITAC of the ethmoid sinus after endoscopic craniofacial resection. Clinical target volumes were 60 Gy (yellow contour) in the high-risk subclinical disease area, and 66 Gy (red contour) in the tumour implantation area; isodose lines of 57 Gy (brown), 54 Gy (dark blue), 45 Gy (mid-blue), 30 Gy (light blue), and 20 Gy (turquoise), as well as the optic nerves (orange contours), are also shown. **b** | Axial CT section showing the VMAT radiation-dose distribution in a patient with a T4bN0 ethmoid ITAC after endoscopic craniofacial resection. Note the close vicinity of the 60 Gy clinical target volume (red contour) to the optic-system apparatus (eyes and optic nerves, indicated by the green and orange contours, respectively). The lachrymal glands are shown by the pink contours. Isodose lines of 57 Gy (brown), 54 Gy (dark blue), 45 Gy (mid-blue), 30 Gy (light blue), and 20 Gy (turquoise) are also depicted. Abbreviations: ITAC, intestinal-type adenocarcinoma; VMAT, volumetric modulated arc therapy.

and endoscopic surgical approaches. However, endoscopic techniques offer a number of advantages over open surgical methodologies: the endoscope enables a more direct approach to the tumour, without altering or injuring healthy tissues; patient recovery is generally faster and less-complicated compared with open surgery; and facial incisions are avoided, resulting in better cosmetic outcomes and the potential prevention of further complications in irradiated tissues, including nasocutaneous fistula. To date, the results of many case series support the endoscopic resection of malignant sinonasal tumours, rather than open surgical treatment.[88,96,97] Despite difficulties associated with standardization of reported outcomes, a systematic review that included all types of sinonasal malignancies indicated that the 5-year overall survival rate was considerably increased among patients who underwent endoscopic surgery compared with those who were treated using open surgical approaches.[98] In some circumstances, however, an open surgical approach will be more appropriate than endoscopy, in particular, when the tumour (especially SNSCC) has infiltrated the orbital fat or extraocular muscles, orbital apex, the brain, or the facial skin, in which case special reconstructive surgery is needed. It must also be recognized that, when properly indicated, open surgery can be performed with limited subsequent morbidity—certainly without the 'mutilation' erroneously suggested in many papers—and low mortality.

In summary, most surgeons agree that in experienced hands and for selected patients, endoscopic surgery in adherence with the general principles of oncological surgery, with adequate exposure, margins, and reconstruction, is suitable for the treatment of sinonasal tumours.[87,99] Contrary to false assumptions, choosing an endoscopic approach to surgical management of sinonasal tumours does not mean that a radical resection cannot be achieved (Figure 5). In fact, improvements in instrumentation and the introduction of robotic technology, together with generalization of navigation systems, are expected to expand the indications of endoscopic approaches.[100]

Precision radiotherapy

Another aspect of sinonasal-cancer therapy that has witnessed undoubted improvements in the past decade is radiotherapy.[8,101] The main difficulty facing radiotherapy for the treatment of sinonasal tumours, whether used instead of surgery or postoperatively, is the low radiation tolerance of the nearby optical structures (eyes, and optic nerves and chiasm) and other adjacent organs, such as the lachrymal glands, the cochlea, the pituitary gland, the frontal and temporal brain lobes, the brainstem, the spinal cord, the parotid glands, the mandible, and the oral cavity (Figure 1). New radiation techniques such as intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), tomotherapy, and proton-beam therapy enable the achievement of well-defined and steep dose gradients close to the target volumes.[102–105] The greater conformality of these new techniques also results in a lower rate of radiation-induced toxicity and increases therapeutic efficiency compared with conventional approaches.[102] Image-guided radiation therapy (IGRT) has also been introduced to complement these approaches in ensuring the safe delivery of a highly conformal treatment, by facilitating convenient and frequent imaging of the patient anatomy throughout the treatment course.[106]

Indeed, the precision of these sophisticated radiation techniques stresses the importance of proper target delineation during the planning process. Thus, a good understanding of the patterns of tumour spread and recurrence by the multidisciplinary teams involved in the management of patients with sinonasal tumours is required. Such knowledge facilitates not only surgical planning, but also the delineation of the treatment volumes for postoperative radiotherapy to avoid undertreatment of areas at risk of microscopic tumour invasion, while minimizing the radiation dose applied to the unaffected tissues and vital organs (Figure 6). With IMRT and VMAT, microscopic tumour spread can be targeted around the site of the primary tumour and throughout the lymphatic channels to the lymph nodes in the neck, as well as along other routes of dissemination.[101] In tumours with risk of perineural spread, the nerves at risk can be safely treated.[101] Endoscopic surgery and CT imaging can precisely define the tumour implantation site. For example, an ethmoid ITAC involving the whole nasal cavity on CT scans could be pedicled at only a small implantation area on the olfactory surface.

Given the new possibilities to deliver different doses of radiation simultaneously to different anatomical areas while minimizing the dose at adjacent normal tissues, further studies are need to address a number of clinical questions. Firstly, would a higher dose delivered to the tumour implantation area improve local control and patient survival? Secondly, would irradiation of the hypothetical location of the CSC niches, possibly responsible for tumour maintenance and recurrence, increase the therapeutic efficiency? Finally, could precision radiotherapy be applied to modify the microenvironment in the surgical field in a way that blocks or reduces the chance of residual tumour regrowth or reseeding of circulating tumour cells?

Chemotherapy

Owing to the low incidence of these tumours, few clinical trials have been performed specifically in patients with sinonasal carcinomas; therefore, chemotherapy or chemoradiotherapy protocols are usually administered by extrapolation of the approaches taken in similar, more-common tumours, such as laryngeal-preservation protocols. In addition, several institutions have experimented with regional chemotherapy for sinonasal cancer, mainly SNSCC, to try and minimize the complications of radical surgical treatments.

The classic indication for chemotherapy in sinonasal malignancies is the palliative treatment of patients with locally advanced or metastatic tumours when surgery and radiotherapy are contraindicated or no longer control the disease effectively. However, new developments in radiotherapy techniques have renewed interest in the use of chemotherapy as a primary therapy for sinonasal tumours. Chemotherapy can be used before, concurrent with, or as an adjuvant to radiotherapy, depending on the tumour histology or the radiotherapy and chemotherapy protocol used. Currently, patients with advanced-stage SNSCC have been shown to respond to neoadjuvant chemotherapy, and the response to this initial treatment might be predictive of the ultimate outcome of therapy and prognosis.[107] Evidence also suggests that concomitant radiotherapy and chemotherapy increases survival and enables locoregional control,[108,109] but comparative studies have not been performed and are, therefore, a requirement in the future; thus, at present, no clear statistically significant survival benefit has been demonstrated for concomitant chemoradiotherapy versus neoadjuvant chemotherapy protocols.

The choice of chemotherapy regimen should be individualized based on patient characteristics and disease presentation. Among the varied regimens used in the treatment of sinonasal tumours, induction chemotherapy usually involves docetaxel, cisplatin, or 5-fluorouracil protocols.[107,110–112] Following induction therapy, weekly carboplatin is used in concurrent chemoradiation protocols.[107,110–112] In addition, targeted therapy with cetuximab every 2 weeks in patients overexpressing *EGFR* has been described after induction therapy.[113] Cisplatin-based induction chemotherapy followed by chemoradiotherapy with high-dose cisplatin administered every 3 weeks is not recommended because of toxicity concerns.[107,110–112] Alternative therapeutic schemes for the treatment of sinonasal carcinoma are weekly intra-arterial infusions of cisplatin delivered rapidly to the tumour bulk with conventional external-beam irradiation in patients with SNSCC. Despite encouraging organ-preservation rates, these approaches have been associated with substantial toxicity, particularly those using intra-arterial cisplatin and conventional intravenous chemotherapy.[107,110] Good results have been reported for patients with ITAC by combining surgical debulking and repeated topical chemotherapy with 5-fluorouracil.[114] Nevertheless, safer and more-effective adjuvant therapies for sinonasal tumours—or induction therapies for unresectable tumours—are clearly needed.

The use of molecular markers predictive of response to adjuvant treatment in patients with sinonasal tumours would represent an important therapeutic advance. For instance, chemotherapy was demonstrated to be highly effective in patients with ITACs carrying wild-type *TP53*, but ineffective in those carrying *TP53* mutations.[57] Some biomarkers, such as low DNA excision repair protein ERCC1 scores, have been shown to reflect favourable responses to chemotherapy.[115] In addition, genetic profiling of SNSCCs and ITACs have indicated a number of frequently altered genes, such as those encoding COX2, EGFR, ErbB2, FGFR1, NFκB, and VEGFR proteins,[29,58,59,66–73,116] that could potentially be targets for treatment with specific antibodies or small-molecule inhibitors (Table 1). At present, however, no relevant case studies or clinical trials of such approaches to the treatment of sinonasal cancer have been published.

Future directions

As technology improves, robot-assisted surgery might be the next breakthrough in sinus and skull-base surgery. With increasing miniaturization of instrumentation to fit the sinonasal area and skull base, imaging-guided, robot-assisted surgery will become more useful, less invasive, and more precise. Improved radiation therapy techniques, such as proton-beam and light ions radiotherapy, could potentially—owing to their physical characteristics—reduce toxicity and achieve better quality-of-life, and might improve survival outcomes compared with the current standard methodologies; these possibilities might be especially relevant in patients with tumours that have dural involvement or that affect structures such as the optic nerves and/or chiasm, cavernous sinus, or carotid artery. The development of novel approaches to systemic chemotherapy, intra-arterial chemotherapy, and molecular targeted therapy (guided by genomic profiling of tumours), alone or in combination with other therapeutic modalities (neoadjuvant, concomitant or adjuvant), might contribute to improve disease control and minimize the associated morbidity if vital organs are affected.

Conclusions

Sinonasal tumours arise in an anatomically complex region of the body. Furthermore, the low incidence of such tumours and their histological diversity have hampered

diagnosis, genetic analyses, classification, and staging, and prevented the accumulation of clinical experience at individual institutions. Nevertheless, the clinical management of these cancers has improved due to advances in surgery and radiotherapy, although limited progress has been made in chemotherapy, partly owing to the difficulty of recruiting a sufficient number of patients for clinical trials. Importantly, however, because of their distinctive characteristics, sinonasal tumours should not be included in the miscellany of head and neck cancers, as occurs in many published case series. Moreover, SNSCCs and ITACs originate in different sinonasal sublocalizations, and both tumour types have different clinical management options. Many of the advances, improvements, and strategies discussed in this Review can be applied to other sinonasal tumours, such as SNUCs, adenoid cystic carcinomas, neuroendocrine carcinomas, or esthesioneuroblastomas; however, these tumours have different clinicopathological and molecular genetic features, hence, the therapeutic strategies used might have some peculiarities that would demand a separate review.

Currently, increasing knowledge of the genomics of sinonasal cancer enables a new approach to tumour classification, which is more-refined than classic anatomical and histological grouping. Furthermore, genetic analyses comprising at least of a panel of druggable gene products, if not genome-wide, would be a promising addition to open up possibilities for targeted anticancer therapy. On the basis of these advances, combined with the development of novel targeted therapies, personalized therapeutic opportunities are becoming available. In this context, the low numbers of patients with sinonasal tumours such as SNSCC and ITAC who are available for clinical trials might not be an issue, as targeted therapy could be based on the results of ongoing or completed trials in patients with other more-common tumours that have the same druggable genetic aberrations. In addition, *in vitro* and mouse models of sinonasal tumours have been developed and are now available for preclinical studies.[84–86]

Occupational exposure to wood and leather dust is a strong aetiological factor for SNSCC and especially ITAC, possibly through tumorigenic pathways of chronic inflammation. Further investigation of this field is needed and might yield tools for chemoprevention (such as anti-inflammatory drugs) and for early detection of tumours in individuals at risk. In the case of SNSCC, routine HPV-testing in biopsies of patients with inverted papilloma might also be advisable.

To provide the best possible care, patients with sinonasal cancer should be treated in clinical referral centres specialized in skull-base pathologies; such centres should include a multidisciplinary team consisting of ENT surgeons, neurosurgeons, radiotherapists, medical oncologists, and pathologists. Local hospital ENT physicians need to be aware of the possibility of sinonasal tumours despite their nonspecific symptoms. Outside of local clinical and referral centres, the study of molecular tumorigenic pathways and the testing of alternative treatment strategies would greatly benefit from wider multi-institutional collaboration, and we strongly support such collaborative efforts.

Review criteria

Data for this manuscript were obtained by searching the PubMed database for papers published before 27 January 2014; the search terms used were “sinonasal cancer”, “sinonasal squamous cell”, “sinonasal adenocarcinoma”, “paranasal sinuses cancer”, and “nasal cavity”. Only English-language articles were considered.

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Acknowledgements

The authors thank R. Cabanillas for his assistance with radiotherapy issues and images, B. Vivanco for preparing the pathological images shown herein, and J. Pérez-Escuredo, C. García-Inclán and C. Álvarez-Marcos for their active collaboration.

Author contributions

J.L.L., F.L. and M.A.H. contributed to all stages of the preparation of the manuscript. C.S. made substantial contributions to discussion of content and review/editing of the manuscript before submission.

Supplementary information is linked to the online version of the paper at www.nature.com/nrclinonc.