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REVIEW

The Impact of Histologic Phenotype in the Treatment of Sinonasal Cancer

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ABSTRACT

The management of sinonasal cancer is a challenge due to its low occurrence and anatomical and significant diversity of histological types. The therapeutic modality used should be tailored individually according to the histology, tumour stage, molecular profile and previous treatments. The clinical management of sinonasal cancer has improved greatly owing to developments in endoscopic surgery and precision radiotherapy. Complete surgical resection is the mainstay of sinonasal malignancies' management but multimodality therapy is associated with improved outcomes in certain histologies. The recognition of various histological types with biological behaviours more suitable for non-surgical modalities has allowed treatment protocols to become more tailored to the disease. In this review we aim to describe

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and to summarise the current data guiding the management of sinonasal cancer with emphasis on phenotypic variation.

Keywords: Endoscopic surgery; Histology; Oncology; Paranasal cavities; Radiotherapy; Sinonasal cancer

INTRODUCTION

Sinonasal cancers (SNCs) are rare and aggressive neoplasms, accounting for 5% of head and neck malignancies and less than 1% of all tumours [1]. Although the sinonasal cavities occupy a small anatomical space, they house a great variety of histological subtypes [2]. Exposure to several industrial compounds is a strong aetiological factor associated with the development of SNC [3]. Epithelial tumours are the predominant form of SNC, representing >80% of all sinonasal tumours [1]. The most common subtypes of epithelial tumour are squamous cell carcinoma (SCC) with more than 60% of cases followed by intestinal-type adenocarcinoma (ITAC) (15–25% of cases) [1, 4–6]. According to Alvarez et al. SCC is the most frequent histological type of malignant tumour in the maxillary antrum (59%), whereas ITAC is the predominant histological type in the ethmoid sinus (68%) [7]. Other epithelial SNCs are undifferentiated carcinoma (UC), neuroendocrine carcinoma (NEC), adenoid cystic carcinoma (ACC), olfactory neuroblastoma (ONB) and mucosal melanoma (MM). Non-epithelial malignancies arising from soft tissue, bone, cartilage, lymphatic system and metastases from primary tumours in other parts of the body comprise a smaller proportion of cases [8, 9]. Most SNCs arise in the nasal cavity and the majority of the other tumours originate in the maxillary or ethmoid sinuses, while tumours of the frontal and sphenoid sinuses are rare.

The management of SNC is a challenge due to their low occurrence, anatomical location in proximity of cranial nerves, the brain and orbit, and the significant diversity of histological types. In this review we aim to describe and to summarise the current data guiding the management of SNC with emphasis on phenotypic variation.

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

GENERAL PRINCIPLES OF MANAGEMENT

Despite advanced-stage tumours, patients with SNC often present with nonspecific clinical symptoms and have a poor prognosis [1]. Tumours usually have significant invasion of neighbouring organs and tissues. A correct histological diagnosis is critical because of the impact on the therapeutic approach and prognosis and highlights the need for both a high index of clinical suspicion and adequate representative biopsies. Biopsy should be performed at the time of diagnosis, ideally after imaging, but it should not delay the treatment. It should be sufficient to be representative of the tumour. A specialised pathologist with considerable experience may be required for proper diagnosis. The grading of tumours (e.g. ONB) is subjective and is not routinely performed in all centres [10].

Clinical examination of patients with suspected SNC should begin with a thorough medical history and a complete ear, nose and throat (ENT) exploration, including assessment of the cranial nerves and neck. Rigid nasal endoscopy is mandatory. When malignancy is suspected, computed tomography (CT) imaging is performed and then the biopsy is made, which confirms the diagnosis. Finally, magnetic resonance imaging (MRI) is performed. Both imaging techniques are valuable for obtaining precise anatomical details regarding the tumour localisation and extension, which are critical in determining operability or in planning radiotherapy (RT).

The proximity of SNC to the neurological structures and orbit makes their treatment difficult and complex, often leading to significant morbidity and mortality. Complete surgical resection is the mainstay of SNC management. Nevertheless, multimodality therapy is associated with improved overall survival (OS) with certain histologies, such as UC [11–15]. Maximum safe surgical resection produces the best OS results. A detailed description of the

different potential surgical approaches to the treatment of the various SNCs is beyond the scope of this review. Most cases of SNC are amenable to purely endonasal endoscopic approaches, which reduce the number of complications and morbidity associated with surgery while maintaining oncological safety [16–27]. Consequently the endoscopic endonasal approach has become accepted for the treatment of selected SNC with precise indications. According to Nicolai and Castelnuovo [28] endoscopic surgery can be classified as endonasal endoscopic resection (EER), EER plus transnasal craniectomy (ERTC) or cranioendoscopic resection (CER) depending on the extent of the resection. Snyderman et al. [29] described the expanded endonasal approach as a series of modular approaches in the sagittal (midline) and coronal (paramedian, lateral to the carotid arteries) planes. These approaches provide access to the sinonasal cavities and to the entire ventral skull base. Anatomical limits include major neural and vascular structures. Traditional open surgical approaches, such as maxillectomy or craniofacial resection, have become less destructive, with surgeons internalising the incisions with facial degloving approaches [30]. The expanded use of regional and free flaps has also improved surgical outcomes. External approaches still have their indications for the following situations: tumours invading the falx and/or frontal lobe, extension lateral to the midpoint of the orbital roof, wide dural extension, invasion of superficial structures and extensive involvement of the frontal sinus. In these cases external or a combination of endoscopic technique with subfrontal craniectomy is an effective option. Likewise, in those tumours growing through the periosteum and involving orbital contents, orbital clearance may be necessary. Both endoscopic and external approaches should always be performed to achieve clear margins and with curative intent. It is important to note that the tumour size does not dictate the limit of the resection, but rather the intra-operative histological assessment of the resection margins. If margins cannot be safely cleared, conversion to an endoscopic-assisted or open approach should be considered [17, 25].

Although RT seems to play a critical role in the treatment of SNC, its role is less defined in some histological subtypes and therapeutic decisions are made on the basis of retrospective studies. Nevertheless, the fact that local recurrence drives the prognosis of SNC emphasises the necessity for the optimisation of local treatments and supports the rationale for combining maximal surgery with post-operative RT, mainly for T3-T4 disease [31]. While some authors found no benefit in survival with the administration of adjuvant RT [12, 22], others have observed that the combination of surgery and RT leads to better outcomes in certain histological sub-types [11, 32–34]. In older series, unattainability of modern imaging and the use of suboptimal RT techniques probably contributed to the lack of therapeutic advantage due to poor target visibility, coverage and dosage and high rates of severe toxicity [35]. The main difficulty facing RT is the low radiation tolerance of the nearby optical and neural structures. Less treatment-related toxicity and improved outcomes are associated with modern RT techniques such as intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), tomotherapy and heavy particle therapy [36–47]. With these sophisticated radiation techniques, higher and homogeneous doses to the target can be delivered, minimising the doses for organs at risk. Proton beam RT, if available, is ideal to treat SNC because of the ability to adequately treat the clinical target volume (CTV) to high dose while reducing the dose to the organs at risk (OAR) because of the ability to treat more conformal target volumes with a steeper dose gradient thereby reducing the risk of damage to the visual apparatus and central nervous system [40]. 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. In tumours with risk of perineural spread, such as SCC or ACC, the nerves at risk should be treated [48]. As a general rule, in early-stage tumours post-operative RT is indicated when the surgical margin is close or positive, in cases of histological aggressiveness or in SNC with unfavourable histology [27].

However, due to the inherent difficulty in obtaining clear margins in SNC, in locally advanced disease, post-operative RT with or without chemotherapy is the usual approach. In some SNCs like in UC, chemoradiation is usually the primary treatment, followed by endoscopic surgery for staging purposes or salvage.

Due to the low incidence of SNC, the use of chemotherapy is infrequent and remains controversial [49, 50]. Systemic therapy could offer improvement of locoregional control and reduction of the frequency of distant metastasis, as well as better survival for patients with unresectable disease. The classic indication for chemotherapy in SNC is the palliative treatment of patients with locally advanced or metastatic tumours when surgery is contraindicated or can no longer control the disease effectively. However, some authors have advocated its use before surgery to increase the chance for complete tumour removal to try minimising the complications of radical surgical treatments, ameliorate distant metastasis and improve local control [14, 36, 51–58]. The response to this initial treatment might be predictive of the ultimate outcome of therapy and long-term prognosis [53]. Definitive concurrent chemoradiotherapy has been less studied although evidence suggests that these regimens may yield acceptable survival and locoregional control rates [37, 47, 59, 60] but comparisons with radical surgical resection have not been performed and are, therefore, a requirement in the future, although low incidence and histological heterogeneity of SNC preclude classical randomised comparison. The small cohorts of these series and the heterogeneous histologies limit the feasibility for prospective trials. Recently, Robin et al. [11] have performed a comparative analysis of treatment modalities for SNC in a total of 11,160 patients from the National Cancer Data Base. Compared with surgery alone, patients who received adjuvant RT, adjuvant chemoradiotherapy or neoadjuvant therapy had improved OS. Patients who received RT alone or chemotherapy alone had worse outcomes. Such studies are hampered by an obvious section bias for treatment, however [11, 61].

The sinonasal structures are thought to have limited capillary lymphatics [48]. Hence, the frequency of nodal involvement is low, unless the tumour involves adjacent areas with extensive lymphatic supply [48]. Lymphatic drainage from the sinonasal cavities is mainly to the upper jugular, perifacial and retropharyngeal nodes [62]. Nevertheless, the sentinel lymph node concept is yet to be determined in SNC [63]. The risk of lymphatic metastasis is dependent on the site, extent and histology and varies widely between 8 to 50% of cases. Invasion into the orbit, oral cavity, skin and infratemporal fossa increase the rate of neck metastasis. Although the incidence of regional metastasis is low at the time of diagnosis, 25–35% of patients will develop them during follow-up, particularly in certain tumours such as ONB and MM [22, 64]. Moreover, the incidence could become higher with improved imaging of the retropharyngeal nodes [62].

Distant metastases are uncommon and depend on the histology. Overall, during the course of disease up to 13% of cases develop distant metastases [31, 65, 66].

Despite improvements in treatment, some patients can still face a very unfavourable prognosis, with a 5-year survival rate of approximately 30% in advanced disease [67]. However, with earlier diagnosis and careful patient selection, the 5- and 10-year OS for many SNC has been transformed [6, 21, 28]. The therapeutic modality used should be tailored individually according to the histology, tumour stage, molecular profile and previous treatments. More effective treatments that are also associated with less morbidity than the currently available options are still needed, especially for advanced stage tumours. Strategies to improve treatment outcome should focus on local control of disease and reduction of distant metastases [31, 68]. Recently, the recognition of various histological types and variants (phenotypes) with biological behaviours more suitable for non-surgical modalities has allowed treatment protocols to become more tailored to the disease.

TREATMENT PROTOCOLS BASED ON SPECIFIC PHENOTYPES

Squamous Cell Carcinoma

SCC is the most common SNC. Keratinising SCC (70% of cases), non-keratinising SCC (20% of cases) and other less frequent variants (10% of cases) can be distinguished [9].

For early-stage, resectable tumours, the mainstay of treatment of SCC is radical surgery followed by adjuvant RT [24, 69]. While most cases are suitable for an endoscopic approach, in the case of advanced tumours, open or combined approaches may be indicated. Adjuvant chemoradiotherapy is generally used only in cases of positive margins after surgery and for pathological evidence of neural or lymphovascular invasion. Induction chemotherapy followed by surgery and adjuvant (chemo)radiation or by definitive (chemo)radiation is advocated in cases of poorly differentiated SCC in advanced stages (T3–T4) [53]. RT as a radical treatment should only be considered in early-stage ethmoid SCC.

Orbital exenteration is required when extraocular muscles, the ocular globe, or the orbital apex are involved [57]. In all other cases, eye preservation does not seem to significantly decrease OS, although several analyses show that once the orbital periosteum has been breached, the OS is much lower [70–73].

Cervical dissection and post-operative RT are recommended for all patients with cervical lymph node involvement, either at diagnosis or if recurrence occurs in cervical lymph nodes. Elective neck dissection or irradiation of the neck is controversial, but it should be considered for locally advanced lesions (T3–T4) because of the frequency of cervical lymph node metastases [6, 19, 22]. The issue of sentinel node biopsy has not been elucidated in these tumours [63]. The 5-year regional failure rate with observation management is about 40% [73] whereas elective neck irradiation decreases regional relapse significantly to 5–10% [57, 74].

Tumours in advanced stages are associated with poor OS. Thus, the involvement of critical structures, such as the orbit, the soft tissues, the infratemporal fossa and the skull base and lymphatic and distant metastases, is a factor of poor prognosis [57, 72, 75, 76]. About 15–20% of SCCs could harbour transcriptionally active human papilloma virus (HPV), mainly non-keratinising tumours. These forms may have improved survival compared to HPV-negative tumours [77]. The main cause of death is local recurrence because of difficulties in treating recurrent disease [78, 79]. Surgical salvage is often followed by disease progression. To achieve a good long-term local control an adequate resection with the widest surgical margins is required [57]. The prognosis of patients with SCC is considered poor, with a reported 5-year OS rate of around 30–50%. This in part reflects the fact that in many series no distinction was made between prognostically more favourable non-keratinising carcinoma and poor prognosis conventional SCC [67, 76, 80]. However, in recent series, 5-year OS increases up to 60% [19, 21, 57, 69, 78, 81, 82].

Intestinal-Type Adenocarcinoma

ITAC occurs predominantly in the ethmoid sinuses (85%) [68]. Exposures to wood and leather dusts are strong aetiological factors associated with the development of these tumours, possibly through tumorigenic pathways of chronic inflammation [68, 83]. Four histological subtypes of ITAC are recognised, with colonic being the most frequent type (40%), followed by mucinous (22%), solid (20%) and papillary (18%). ITACs can also show mixtures of two or more of these four histological subtypes [8].

Despite the recognition of these phenotypes, surgery remains the first treatment of choice for most of these variants [78, 81, 84]. Endoscopic surgery seems to be effective for most ITACs with low morbidity and external surgical techniques now have a role only in a minority of patients [31, 85]. Usually, ITAC is a multifocal tumour that frequently involves the ethmoid bilaterally; therefore a bilateral resection of the ethmoid labyrinth is usually recommended though recent studies have not supported this [31, 83]. While some authors argue that if the dura is not invaded, craniofacial resection is not

necessary, others argue that, since the possible origin of the tumour is located in the olfactory groove, a craniofacial resection is mandatory in all cases [86]. EER or ERTC is effective as a single treatment modality for early-stage low-grade lesions (papillary-type and colonic-type tumours) [22, 87, 88]. By contrast, adjuvant RT is widely accepted for advanced-stage tumours in the presence of positive surgical margins or with high-grade tumours (solid-type and mucinous-type tumours) [43, 44, 89].

Chemotherapy has been demonstrated to be a valid option in patients with ITACs carrying wild-type TP53, but ineffective in those carrying *TP53* mutations [52]. Unfortunately the majority of patients with ITAC (86%) have a mutated *TP53* [90]. Choussy et al. reported that pre-operative chemotherapy including cisplatin or oxaliplatin in combination with 5-FU or capecitabine may help select lesions with a good response to medical treatment, resulting in good outcomes for some patients [91]. Moreover, some authors have reported good results for patients by combining surgical debulking and repeated topical chemotherapy with 5-fluorouracil [92], but these results have not been reproduced and this is consequently not a standardised method.

Elective treatment of the neck lymph nodes is not routinely performed in ITAC because the risk of regional metastases is low (7%) [19, 22].

Papillary- and colonic-type tumours are associated with a more favourable clinical outcome than the solid or mucinous subtypes. Moreover, advanced-stage and positive surgical margins are independently predictive of poor survival [93]. The high incidence of tumour recurrences requires a thorough follow-up. The 5-year OS for patients with ITAC is around 60–70% [31, 85, 94].

Adenoid Cystic Carcinoma

ACC is a high-grade salivary gland tumour arising in minor salivary glands of the sinonasal region [95]. It accounts for 5–15% of SNC with the maxillary sinus being the most frequent site (60%) followed by the nasal cavity (25%) and the ethmoids (15%).

ACC is characterised by multiple local recurrences and a high propensity for perineural spread and distant metastases, especially to the lung, bone and liver. Significant skull base involvement and intracranial extension, including the cavernous sinus and anterior and middle cranial fossae, are frequently observed. ACC is classified into three histological subtypes: cribriform, tubular and solid [95, 96].

The mainstay of treatment of the primary tumour is surgery followed by RT [95, 97–99]. The aim of surgery is to resect the lesion whenever feasible or at least debulking of the gross volume of the tumour. Currently, endoscopic approaches may be considered in selected cases but the difficulty in obtaining negative margins and the propensity for submucosal and perineural spread means that irradiation of the potential pathways of perineural dissemination is obligatory [95, 100].

Although they are radiosensitive tumours [99], conventional RT as a solitary treatment does not appear to be successful and local recurrence is common. However, it is the only option in cases that are considered unresectable or where surgery would generate high morbidity. In recent years, it appears that the use of heavy-particle RT using protons or carbon ions has improved local control, as both an adjuvant treatment to surgery and a primary treatment modality [60, 101, 102]. Chemotherapy and biological therapies may obtain responses, but do not appear to be useful except as part of a palliative regimen [103], and as reported recently also as a part of adjuvant therapy, concurrently with RT [104]. However, chemoradiation has recently been reported to be effective among patients with unresectable disease [60].

Elective neck treatment does not appear to be justified because regional lymph node metastases are conventionally regarded as rare [97, 105].

Sinonasal ACCs are associated with a poor long-term prognosis because high local (60%) and distant (40%) rates of recurrence are observed irrespective of the treatment modality and most, if not all patients, will eventually die of the disease. Deceptively 5-year OS of up to 60% may be reported, which exceeds that of the

other SNCs [96, 99]. The 5-year OS varies as a function of stage, histological subtype, treatment options and local control but is meaningless in terms of cure [98]. As the clinical course of ACC is characterised by late recurrences, a follow-up of at least >15 years is mandatory [95].

Olfactory Neuroblastoma

ONB usually arises in the olfactory groove from the neural-epithelial olfactory mucosa. It accounts for only 6% of all malignant nasal tumours.

The mainstay of treatment for ONB includes complete surgical resection followed by RT [106–109]. Open or endoscopic craniofacial resection is the surgery of choice. Surgical excision should include the dura of the anterior skull base together with the ipsilateral olfactory bulb in every case [110], though the necessity of this has been recently challenged [111]. For bilaterally extended cancers, the removal of both olfactory bulbs is performed. Endoscopic approaches should be used whenever possible since these have higher complete resection rates compared to open surgery approaches [20, 110–113]. Adjuvant RT is generally recommended for most ONB [106, 108, 109]. Surgery alone may be an option for early-stage tumours (Kadish stage A). It has been observed that RT reduces local recurrence rates and improves survival. Although ONBs are sensitive to chemotherapy, its use alone is only justified for palliative care. In high-grade tumours (Hyams III and IV) or with advanced disease (significant intracranial extension), neoadjuvant chemotherapy followed by surgery and RT may be considered [55, 114, 115].

Approximately 5–8% of ONBs have cervical nodal metastasis at the time of presentation. Combined modality therapy with surgery and RT is recommended for these patients [64]. Nevertheless, elective neck treatment in cN0 necks is not routinely indicated, although in advanced states (Kadish C) or in high-grade (Hyams III and IV) tumours, prophylactic cervical irradiation may be considered given the high reported rates of delayed regional failures (up to 25%) and limited morbidity associated with precision RT [64, 116, 117]. Positive margins with the primary resection are associated with a higher risk of delayed cervical metastases [118].

Proven prognostic factors are Kadish staging, lymph node and distant metastasis, age and Hyams grading [114, 116]. Following treatments, ONB requires lifelong follow-up given its tendency for late recurrence, even beyond 10 years after the initial diagnosis [109, 119]. Overall recurrence and distant metastasis rates of 46% and 15%, respectively, have been reported [108]. Previously the 5-year OS ranged from 45% [106] to 75% [107] but with careful patient selection, 5- and 10-year OS rates of 97% can be obtained with endoscopic resection [20]. Data from an international collaborative study on 151 patients who underwent craniofacial resection showed that, with a median follow-up of 56 months, the 5-year OS, disease-specific and recurrence-free survival rates were 78%, 83% and 64%, respectively [120].

Mucosal Melanoma

MM is a very aggressive and capricious tumour that accounts for less than 5% of all SNCs. It usually arises in the nasal cavity (lateral walls, septum). MMs are characterised by early and repeated recurrences.

The treatment of choice is surgery with free margins, whenever possible. Minimally invasive endoscopic approaches are generally associated with better survival rates than those obtained with external surgeries [121, 122]. Although MMs are considered radio-resistant, it has been observed that radiosensitive areas exist and RT is indicated after surgery in cases of involved or nearby margins or as treatment alone in unresectable tumours [121]. RT seems to improve only local control of disease without affecting survival [121–123]. Systemic therapy should be considered only for patients with metastatic or unresectable locoregional disease [124]. Regardless, all patients should be evaluated in conjunction with a medical oncologist for consideration of systemic immunotherapy or participation in clinical trials.

At diagnosis, lymph node metastases are present in 10–20% of patients and less than 10% of patients have evidence of distant metastases. An additional 20% can expect to develop nodal metastases during the course of the disease and 40–50% will develop distant metastases (in the lungs, brain, bone and liver). Although cervical metastases confer a dramatically worse outcome, elective neck treatment is not indicated since it does not alter the prognosis [124]. Currently, the role of sentinel node biopsy for MM is being studied to improve detection of regional metastasis and improve long-term outcomes of this aggressive malignancy [125, 126].

MM is one of the most aggressive tumours and, despite radical resection and adjuvant RT, patients with MM still face a very unfavourable prognosis (5-year OS <30%) with high rates of locoregional recurrence and distant metastasis [124]. For this reason, endoscopic techniques offer an attractive alternative to conventional approaches without any evidence of compromising cure [121]. The high risk of failure for MM is independent of the T and N stage although patients with distant metastasis or unresectable disease have a dismal prognosis [127]. It is interesting to remark that although 5-year disease-specific survival in a series of 39 localised lymph node-negative (stage I) primary sinonasal mucosal melanomas reached 38%, the median survival was found to decrease significantly with increasing level of invasion: level I (melanoma in situ): 138 months; level II (invasion into the lamina propria only): 69 months; level III (invasion into bone or cartilage): 17 months [128].

Recently, a range of biological drugs based on the genetic profiling of patients was used with some success in selected cases (e.g. ipilimumab), which potentiates antitumour T cell response in HLA-A*0201-positive patients [129]. However, these drugs are not without their cost and side effects. Unlike cutaneous melanoma, MMs have infrequent BRAF mutations and do not seem sensitive to therapies targeting BRAF [130].

Undifferentiated Carcinoma

UC is a highly aggressive carcinoma, with or without neuroendocrine differentiation, typically presenting with locally extensive disease (up to 80% of cases have spread beyond the sinonasal tract to adjacent sites such as the orbit, skull base and brain) [131]. It accounts for 3–5% of all SNCs. In the 4th edition of the World Health Organisation (WHO) classification of head and neck tumours, it remains a diagnosis of exclusion, requiring separation from several other epithelial and non-epithelial high-grade sinonasal malignancies [8, 9]. UC is an undifferentiated carcinoma without glandular or squamous features and not otherwise classifiable. The refinement of diagnostic techniques may lead to reclassification of tumours originally diagnosed as UC as specific genetically or immunophenotypically definable entities such as NUT carcinoma or SMARCB1-deficient carcinoma.

UC often presents with advanced local and regional disease with brain invasion and bulky cervical metastases. Given its chemosensitivity, advanced stage of disease at presentation and the high incidence of distant failure, neoadjuvant chemotherapy followed by either chemoradiation or surgery followed by post-operative RT shows optimal outcomes [132–134]. For earlier stage lesions without cervical metastases, gross tumour resection followed by post-operative RT or chemoradiotherapy should be considered [135]. Endoscopic surgery is suitable following the principles of oncological surgery with adequate exposure and margins and can be used to stage response after chemoradiotherapy.

UC has the ability to spread regionally (30%) and with distant metastasis [131]. Elective neck irradiation would be advocated in all patients with locally advanced disease.

The prognosis of UC is generally considered poor. Nevertheless, aggressive treatment with multimodality therapy can achieve 5-year OS rates of 75% [136].

Neuroendocrine Carcinoma

NEC is a high-grade malignant epithelial neoplasm showing morphological as well as immunohistochemical features of neuroendocrine differentiation. According to the 4th edition of the WHO classification of head and neck tumours, NEC is separated into small and large cell types [8]. The upper and posterior regions of the nasal cavity are the most frequent sites of origin of NEC. It accounts for less than 3% of SNCs and usually presents at an advanced stage, while distant metastases develop in 50% of patients in a short period of time, without significant possibilities for cure and a dismal prognosis, especially in small cell carcinoma [137–139].

Aggressive multimodal therapy seems to be the most effective approach [137, 138]. Whenever feasible, gross total resection and post-operative chemoradiotherapy yielded the most favourable outcomes for NEC [138]. Nevertheless, neoadjuvant chemotherapy followed by surgical resection and adjuvant RT or chemoradiation alone can be effective [138, 140, 141]. The response to induction chemotherapy can also represent a strong prognostic factor [138].

The 5-year overall survival (OS) rate for NEC is up to 65% [138, 139, 141]. The local recurrence rate is around 40–50% [138, 142] and the distant metastasis rates range between 35% and 42% [138, 140].

Mesenchymal Tumours: Soft Tissue Sarcomas and Ewing Sarcoma

Sarcomas arising in the sinonasal region are rare and often aggressive malignant tumours. There are several histological subtypes, with rhabdomyosarcoma being the most frequent, followed by other types such leiomyosarcoma, osteosarcoma, malignant fibrous histiocytoma, fibrosarcoma, angiosarcoma, synovial sarcoma or malignant peripheral nerve sheath tumours [143]. Nevertheless, the WHO classification continues to evolve because of the development of molecular biology techniques [9].

Surgery should be always considered in sinonasal sarcoma treatment, even if wide resection cannot be obtained. However RT and chemotherapy do play a major role in the treatment [143]. For some subsets of sarcomas (e.g. Ewing sarcoma) neoadjuvant chemotherapy followed by radical surgery and adjuvant irradiation (brachytherapy or external RT) seems to be the best treatment option [144, 145].

Compared to superficial sarcomas, sinonasal sarcomas have a worse survival rate. Altogether, the 5-year OS rate was 62% [143]. The tumour grade and histology have a crucial impact on the metastatic risk and OS in sinonasal sarcomas. Rhabdomyosarcoma is considered a systemic disease and it seems to be the most aggressive and to progress more rapidly. There is an overall poor prognosis of alveolar rhabdomyosarcoma (5-year OS of 30–40%) although young patients (5-year OS 62%) tend to have a better prognosis. The 5-year OS of sinonasal Ewing sarcoma is much better than for other sites, with rates around 50–75%; local recurrence and metastases, when they develop, are usually soon (2 years) after initial presentation [146].

Chondrosarcoma

Chondrosarcomas of the sinonasal tract are rare tumours arising in hyaline cartilage. They affect older adults, with a male predilection. Biological behaviour is dependent on the grade of the tumour. Low-grade tumours can be indolent with slow growth over many years. However, a particularly aggressive histological variant is the mesenchymal chondrosarcoma, which is a malignant small round cell neoplasm with focal cartilaginous differentiation, and often with a pericytomatous vascular pattern. Overall, their pattern of growth and scarcity of cartilaginous matrix result in frequent misdiagnosis [147]. The maxillary sinus is the most common site of involvement followed by the ethmoid sinuses and the nasal cavity [147].

Radical surgery appears to yield the best clinical outcome. The use of adjuvant RT for prevention of local recurrence after subtotal or total resection may be indicated but the tumours are

generally regarded as radioresistant though there may be a role for proton beam therapy in this histology [148]. Chondrosarcomas are associated with an excellent prognosis in the short term if the lesions are completely resected [148]. Adjuvant radiation therapy is indicated for high-grade tumours. The use of heavy particle RT may be associated with improved local control and less morbidity. Nevertheless, recurrence develops in approximately one-third of patients, possibly because of multifocal disease and ultimately patients with chondrosarcoma have a poor prognosis due to late local recurrence and need life-time surveillance. Mesenchymal chondrosarcoma has a very poor prognosis irrespective of treatment with virtually no long-term survivors [147].

Haematolymphoid Tumours

The most common haematolymphoid tumours in the sinonasal area are non-Hodgkin lymphomas and plasmacytomas. In addition, clinicians should be aware of NK-T cell lymphomas, which may present as midline destructive lesions. These may prove difficult to diagnose without careful representative biopsy and specialist histopathology.

The haematologist will be in charge of the treatment of lymphomas and the main role of surgery for such tumours is to obtain a proper histological diagnosis to guide the appropriate regimen of chemotherapy and/or RT [149]. Standard treatment for plasmacytoma consists of RT to the tumour. However, in the case of localised tumours, endoscopic surgery may be considered in addition to post-operative RT. Local control and survival outcomes are higher with this treatment [150].

Surgery may also be indicated to exclude persistence of disease after treatment, whenever imaging studies including PET suggest possible persistent disease [27].

Metastatic Tumours

Metastatic tumours to the nasal cavity and paranasal sinuses are far less common than primary cancer. The most common tumour metastatising to the sinonasal tract is renal cell carcinoma. Tumour from other origins such as the thyroid, breast, lung and prostate may also metastasise to the sinonasal cavities. The prognosis for these patients is generally poor.

The aim of treatment of these patients is palliative in order to improve or maintain their quality of life. Treatment should be tailored according to the tumour location, local symptoms and the general status of the patient. Endoscopic surgery is an optional treatment for patients with single resectable sinonasal metastases. For local symptomatic control of unresectable tumours, RT, chemotherapy and immunotherapy should be considered [151].

New Tumour Phenotypes

The 4th edition of the Classification of Head and Neck Tumours published by the WHO has updated the classification and characterisation of SNC [8]. Three new entities have been added: NUT carcinoma, seromucinous hamartoma and biphenotypic sinonasal sarcoma. Other emerging entities are the SMARCB1-deficient carcinomas, the sinonasal adamantinoma-like Ewing sarcoma and HPV-related carcinoma with adenoid cystic-like features and have been included as provisional diagnoses [9, 152].

So far, no documented regional or distant metastasis from HPV-related carcinoma with adenoid cystic-like features has been reported [153]. However, the number of study cases of this tumour is small and clinical follow-up is limited.

NUT carcinoma is an aggressive and highly lethal tumour with an average survival of <1 year. It affects people of all ages without sex predilection and the sinonasal area is the most frequent location in the head and neck [154]. The true incidence of NUT carcinoma is unknown because it is morphologically indistinguishable from other poorly differentiated carcinomas. However, a thorough histopathological study will display unique features, the immunohistochemistry will show a diffuse nuclear staining with the NUT antibody and NUT rearrangement is observed by molecular

analysis. NUT carcinoma shows poor response to conventional chemotherapy and aggressive local treatment with gross total resection and RT might be associated with enhanced survival. Bromodomain inhibitors may prove useful [155].

SMARCB1-deficient carcinoma does not have specific differentiation and it could be misdiagnosed like SCC non-keratinising, UC or ITAC [156]. It is an aggressive tumour, presenting with advanced T stage and with frequent local recurrences and/or distant metastases.

Biphenotypic sinonasal sarcoma is a low-grade spindle cell sarcoma with distinctive histological, immunohistochemical and molecular features. It is frequently characterised by PX3-MAML3 gene fusion [157]. This tumour involves multiple sinonasal locations, mainly the roof of the ethmoid with possible extension into the orbit or the cribriform plate. Nearly 50% of patients experience local recurrences as long as 9 years after initial treatment. Neither metastatic disease nor death from this tumour has been reported [158].

The treatment and biological behaviour of these new entities has not yet been elucidated. Therefore, treatment must follow established guidelines for the most frequent CNS.

Recurrent Sinonasal Cancer

Many of the SNCs described here have a high risk of local recurrence throughout their lifetime. There is a paucity of literature regarding the optimal management of patients with local recurrence. For patients with ITAC, a substantial number of patients with local recurrence can still be cured using an EER or a CER [31]. For this reason different authors propose a rigid follow-up scheme including frequent MR imaging [19, 27, 31, 86, 94]. Primary considerations include the histology (biological behaviour) and location of the recurrence and level of aggressiveness of prior therapies [159]. The potential for cure and quality of life should both be considered before proceeding with surgery. Patients with the best prognosis include recurrences in the ethmoid region. Recurrence of a high-grade neoplasm at other skull base sites has a poor prognosis and palliative options should be considered. Surgery remains an option for low-grade malignancies that recur at all sites.

SUMMARY AND CONCLUSIONS

SNCs, in general, are rare tumours and prognosis varies widely depending on histology. Prognosis remains poor for many types, despite advances in surgical techniques and RT and systemic therapy. An accurate histopathological diagnosis is necessary because of differences in management. Distinctive histological, immunohistochemical and molecular features allow these tumours to be correctly diagnosed. Surgery has an important role in management of both the primary tumour and recurrences. Currently, whenever possible, endoscopic approaches should be used to minimise the surgical morbidity for the patients. Nevertheless, in certain situations open approaches are still indicated. Post-operative RT is indicated in the majority of cases. New radiation techniques such as IMRT, VMAT, tomotherapy and particle therapy are key to the improvement of local control. The development of novel approaches to systemic chemotherapy and molecular targeted therapy (guided by genomic profiling of tumours), alone or in combination with other therapeutic modalities, might contribute to improved disease control and minimise the associated morbidity if vital organs are affected.

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