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Nasal and paranasal sinus carcinoma: how can we continue to make progress?

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Purpose of review

New developments in the nasal and paranasal sinus cancers are reviewed.

Recent findings

In addition to woodworking, several risk factors for nasal and paranasal sinus cancers have been identified, most notably smoking. Progress in the differential diagnosis of small round cell nasal and paranasal sinus cancers allows the precise diagnosis of esthesioneuroblastoma. Despite recent improvements, T staging for ethmoid and nasal cavity needs refinement. An association of surgery and radiation therapy remains the best treatment modality. Major developments include endoscopic resection of nasal and paranasal sinus cancers, high-precision radiotherapy techniques such as intensity-modulated radiotherapy, and proton-beam radiotherapy. There is probably no role for chemotherapy in esthesioneuroblastoma. Although chemotherapy is important for aggressive neoplasms, its generalized use for nasal and paranasal sinus cancers awaits the application/development of newer drugs. These drugs might be applied locally since the majority of recurrences remain local.

Summary

Progress in the treatment of nasal and paranasal sinus cancers could be achieved through better prevention and the developments of more selective treatments such as endoscopic resection, high-precision radiotherapy, and new chemotherapy drugs.

Keywords

adenocarcinoma, cancer, craniofacial resection, chemotherapy, esthesioneuroblastoma, epidemiology, endoscopic surgery, neuroectodermal, paranasal sinus, radiotherapy, undifferentiated sinonasal carcinoma

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Abbreviations

CT	computer tomography
MRI	magnetic resonance imaging
NPSCa	nasal and paranasal sinus carcinoma
OR	odds ratio

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Introduction

Cancers of the nasal cavity and paranasal sinuses remain a challenging disease because of their rarity, the great variety of histological types [1••], and the complexity of the surrounding vital structures, which render radical surgery and radiation therapy delicate and associated with numerous complications. This review builds up on a recent meta-analysis of publications on nasal and paranasal sinus carcinoma (NPSCa) from 1960 to 2000 [2], which demonstrated a progressive improvement of treatment results over the past few decades. In order to continue improving the outcome of NPSCa patients, we can focus on prevention, early and exact diagnosis, as well as more efficient treatments that result on fewer side effects. New developments are reviewed and areas of controversies discussed.

Etiology

The role of employment in the wood and to a lesser extent in the leather industries as a risk factor for ethmoidal adenocarcinoma has been documented for quite some time [3,4]. While the majority (96% according to one study [5]) of adenocarcinoma occurs in woodworkers, the exact role of wood dust and chemical agents used in the wood industry has remained elusive. An interesting study by Wolf *et al.* [6] demonstrates that both factors play a role: hardwood dust such oak and beech contains toxic substances and resulted in dysplasia of the nasal mucosa. Chemicals, such as lindane and pentachlorophenol, are present in most wood-preserving agents and are also toxic for the nasal mucosa. Nasal dysplasia, however, was only found in cases of exposure to both wood dust and chemicals.

For squamous cell carcinoma, there is mounting evidence that smoking should be considered as a risk factor [7–10]. Another risk factor is inverted sinonasal papilloma that exhibits malignant transformation into squa-

mous cell carcinoma in about 5% of patients [11]. In lymphoepithelial carcinoma, a rare NPSCa epidemiologically related to nasopharyngeal carcinoma, an Epstein–Barr virus association is present in the majority of reported cases [1,12].

Beyond wood and leather, a recent meta-analysis of 12 studies [13] found other significant associations. The incidence of adenocarcinoma was elevated in men employed as salespersons (odds ratio (OR) 5.0), in food processing (OR 3.3), or as motor-vehicle drivers (OR 2.5). Women working in the textile industry also showed a higher incidence of adenocarcinoma (OR 2.6). The incidence of squamous cell carcinoma was elevated for men employed in the production of food preservatives (OR 13.9), as fiber preparers (OR 5.1), as rubber or plastic product makers (OR 3.2), as bleachers (OR 3.0), as 'artists' such as sculptors, painters, photographers, and so on (OR 2.8), as hairdressers (OR 2.8), as orchard farmers (OR 2.5), and as cooks (OR 2.0). No such associations were found for squamous cell carcinoma in women, although women accountants and managers seem to have a higher risk, which might be explained by higher smoking rates.

Progress in this area is hampered by the rarity of NPSCa, the time lag between exposure and diagnosis, obvious ethical reasons that prevent experimentation, and dissimilarities between human and animal nasal carcinogenesis. The rate of observance of protective masks in wood workers is unknown. Regular nasal examinations in exposed workers [14] might detect NPSCa at earlier stages and improve the outcome. Further animal studies are required to characterize the specific chemicals used in the wood industries and their carcinogenic effects. Possibly noncarcinogenic substitutes could be elaborated and employed. The implication of viral agents and the molecular genetics of NPSCa have been recently reviewed by Götte and Hörmann [15•]; while there is certainly a potential role in the future, the present evidence demonstrates few direct clinical implications.

Diagnostic evaluation

The diagnosis of NPSCa is rare at an early stage probably because tumor expansion remains asymptomatic and early symptoms differ little from common nasal complaints. Unilateral persisting symptoms, such as recurrent epistaxis and nasal obstruction, mandate a thorough sinonasal examination to rule out malignancy. When more alarming symptoms such as dental problems (tooth pain, loose teeth, ill-fitting dentures), ocular complaints (epiphora, diplopia, proptosis, vision loss), cranial nerve deficits, cheek mass, or trismus are apparent, the outcome tends to be less favorable. It is unclear if the recent widespread use of nasal endoscopes and radiological studies will result in an earlier diagnosis of nasal and paranasal sinus carcinoma.

The safe approach for NPSCa is to obtain a computer tomography (CT) scan prior to biopsy because some lesions can bleed profusely and could rarely contain intracranial pathologies [16]. Ample amount of fresh tissue should be sent for pathological evaluation. Additional magnetic resonance imaging (MRI) is undertaken prior to staging and treatment planning. CT and MRI provide complementary information: CT delineates best bony erosion, while MRI is useful for the accurate assessment of intracranial or orbital extension, as well as perineural spread. T2-weighted MRI is essential to distinguish between the intermediate-signal-intensity tumor from the high signal of edematous mucosa and mucoid secretions. MRI fat-saturated sequences help distinguish tumor from orbital fat and muscle [17]: a smooth bowing of the tumor–fat interface suggests that the lesion is contained by periorbital fascia, while an irregular margin favors frank invasion of the orbit. It is unclear whether new MRI sequences can improve the delineation of the involved structures. Often definitive diagnosis of invasion of dura and periorbit is possible only at surgery.

The World Health Organization (WHO) histological classification of tumors of the nasal cavity and paranasal sinuses [1••] recognizes malignant epithelial tumors, malignant soft tissue tumors, malignant tumors of bone and cartilage, haematolymphoid tumors, neuroectodermal tumors, as well as secondary tumors (Table 1). Whereas histopathologic diagnosis of squamous cell carcinoma is quite straightforward, the correct differential diagnosis of small round-cell neoplasms of the nose and paranasal sinuses could be extremely difficult [1,18,19]. Immunostaining is an essential step but molecular techniques are increasingly used and nowadays esthesioneuroblastoma can be reliably distinguished from other small-cell NPSCa [20••]. Advances in molecular biology and genetics of NPSCa remain sparse with limited direct clinical implications [15•] and further research in this area is paramount, as the choice of treatment modalities will depend on the exact pathological diagnosis.

Staging

Recent modifications of the T staging according to the American Joint Cancer Committee (AJCC) and Union Internationale Contre le Cancer (UICC) [21] include the subdivision of stage T4 in T4a and T4b, the introduction of a staging system for the nasal cavity, and a modification of the staging for the ethmoid sinus. There is no

Table 1 World Health Organization (WHO) classification of cancers of the nasal cavity and paranasal sinuses

1. Malignant epithelial tumors
1.1. Squamous cell carcinoma
Verrucous carcinoma
Papillary squamous cell carcinoma
Basaloid squamous cell carcinoma
Spindle cell carcinoma
Adenoid squamous cell carcinoma
1.2. Lymphoepithelial carcinoma
1.3. Adenocarcinoma
Intestinal type adenocarcinoma
Sinonasal non-intestinal type adenocarcinoma
1.4. Salivary gland-type carcinoma
Acinic cell carcinoma
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Polymorphic low-grade adenocarcinoma
Carcinoma in pleomorphic adenoma
Malignant myoepithelioma
Epithelial-myoepithelial carcinoma
Clear cell carcinoma
1.5. Neuroendocrine tumors
Carcinoid tumors
Small cell carcinoma, neuroendocrine type
2. Malignant soft tissue tumors
2.1. Fibrosarcoma
2.2. Malignant fibrous histiocytoma
2.3. Leiomyosarcoma
2.4. Rhabdomyosarcoma
2.5. Angiosarcoma
2.6. Malignant peripheral nerve sheath tumor
3. Malignant tumors of bone and cartilage
3.1. Chondrosarcoma
3.2. Osteosarcoma
3.3. Chordoma
4. Haematolymphoid tumors
4.1. Non-Hodgkin lymphoma
4.2. Diffuse large B-cell lymphoma
4.3. Extramedullary plasmocytoma
4.4. Extramedullary myeloid sarcoma
4.5. Histiocytic sarcoma
4.6. Langerhans cell histiocytosis
5. Neuroectodermal tumors
5.1. Ewing sarcoma
5.2. Primitive neuroectodermal tumor
5.3. Esthesioneuroblastoma
5.4. Melanotic neuroectodermal tumor of infancy
5.5. Mucosal malignant melanoma

Modified from Barnes *et al.* [1].

staging for frontal and sphenoid carcinomas, but several studies classify them as T4 ethmoid tumors [2]. While the evolution of TNM staging is a work in continuous progress, the T staging of ethmoid and nasal primaries needs an urgent revision, because the notion of subsites for the nasal cavity has the size of the tumor as its sole basis, with little clinical evidence to support it. In a previous study [2], using the 1997 version of the UICC staging system, there was little difference between stages T2 and T3. The major modification of stage T3 for the ethmoid sinus puts it more in line with the previously proposed staging for esthesioneuroblastoma [22], later adapted by Cantu *et al.* for NPSCa [23]. The future version should address a better delineation in the current T1 and T2 nasal cavity and ethmoid sinus stages.

Treatment modalities

Our recent meta-analysis [2] confirms that the local control and cure rates are better with surgery (70%) and combined surgery and radiation (56%) than radiotherapy alone (33%). Despite the inherent patient selection bias of retrospective studies, most notably the selection of patients with favorable lesions for surgery leaving patients with large lesions and those treated for palliation in the exclusive radiation or chemoradiation modalities, the available data suggest that surgery should be included in the treatment strategy for NPSCa treated with a curative intent [24]. Except for a few publications, the results of radiation alone are poorer than treatments including surgery. The sequence of surgery and radiotherapy in the management has remained open to debate since the work of Jesse [25] showed no clear difference. As a high incidence of residual cancer is found after primary radiation [26–28], the main goal of primary radiation is often to shrink the tumor so that the surgical resection is less extensive and vital structures such as the eye can be spared [29–31]. The soundness of this approach has yet to be demonstrated.

Surgical approaches

When discussing surgery for NPSCa, one should distinguish the approach and the actual resection [2]. Surgical approaches can be divided [32] into intracranial, which are variations of the classical frontal craniotomy, transfacial, consisting of lateral rhinotomy, midfacial degloving, and transnasal endoscopy, and various lateral approaches such as infratemporal fossa or facial disassembly. The resections can be divided into six types [2]: inferior, median, or total maxillectomy, orbital exenteration, craniofacial resection, and infratemporal fossa resection with different combinations according to the extent of disease.

We have abandoned lateral rhinotomy not only because of the facial scar but mostly because the exposure of the lower midface is better through a midfacial degloving. The access to the cribriform plate and base of the skull is limited with both approaches and requires a bicoronal flap, which could be taken to the lower extent of the nasal bones [33] and is adequate for the majority of ethmoid NPSCa. A recent multi-institutional review of 1193 patients having undergone a craniofacial resection [34•] concluded at a surprisingly high mortality rate of 4.7% and a complication rate of 36% (wound complications in 20%, central nervous system complications in 16%, systemic complications in 5%, and orbital complications in 2%). Factors associated with complications included comorbidity, prior radiation, and dural and brain invasion.

Major developments in the surgery of NPSCa will be to determine the exact indications for transnasal endoscopic resection [35]. Present experience is mostly limited to less aggressive tumors such as esthesioneuroblastoma [36,37]. The entire resection can be performed endoscopically, or the endoscope can be used for the lower nasal extension, while a standard frontal craniotomy is used for resection at the skull base [37]. While oncologic data are still preliminary [38•], the extent of resections undertaken [39••,40] is an indication of future potential.

Advances in radiotherapy techniques

Radiation doses above 60 Gy, that are needed even to eradicate residual postsurgical disease, exceed the tolerance of nervous structures and the eye [41]. Furthermore, the classical anterior plus one or two lateral wedged beam fields encompass part of the optic pathways, and radical radiotherapy protocols for ethmoid NPSCa have resulted in 20% [42] to 30% [43] unilateral and 6% [42] to 10% [43] bilateral blindness. While the incidence of retinopathy might be reduced by hyperfractionation [44], intense efforts have been made to promote 'high precision' in the delivery of radiotherapy by either three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT) with the main aim of increasing the therapeutic ratio. With 3D-CRT and particularly IMRT, it is now possible to optimize the delivery of radiation to complex target volumes including tumors of the nasal and paranasal sinuses [45]. These techniques, however, are based on multiple-field arrangements and consequently lead to an increase of the body area receiving small doses, potentially doubling the incidence of second malignancies compared with conventional radiotherapy for patients surviving at 10 years [46]. The ultimate solution might be the use of proton therapy [47]. Owing to their physical advantages, protons can provide a clear improvement in dose distribution compared with photons [48•], and improved outcomes may be attainable by maximizing the dose delivered to the tumor area while minimizing normal tissue irradiation without enhancing the integral body dose. So far, the clinical experience using any of these techniques still remains sparse and most publications deal with dose geometry models rather than patient survival figures.

Role of chemotherapy

While chemotherapy is more often used in squamous carcinoma of the head and neck in general, there is little definitive data to recommend its general use in NPSCa. The controversial points are the histologic types that might benefit from chemotherapy, its role in the more common squamous cell carcinoma, the role of induction chemotherapy in reducing the structures that might be resected, most importantly the eye, the route of administration – intravenous or intra-arterial, and finally the specific drugs that could be of benefit.

It appears that chemotherapy is useful for certain histologic types of NPSCa, namely sinonasal undifferentiated carcinoma (SNUC) [49], lymphoma [50], certain sarcoma, and possibly neuroendocrine carcinoma and esthesioneuroblastoma. A recent article from Anderson [51••] helps to clarify some issues: among 31 esthesioneuroblastoma (almost exclusively treated locally without chemotherapy) no distant metastasis was observed and the local control rate was 96%. In contrast, higher rates of distant metastasis and lower survival rates were found for neuroendocrine carcinoma (12% metastasis and 64% 5-year survival), undifferentiated sinonasal carcinoma (25% metastasis and 62% 5-year survival), and small-cell carcinoma (75% metastasis and 28% 5-year survival). Hopefully, this work will settle the controversy on the role of chemotherapy in esthesioneuroblastoma [19]. This further emphasizes the need for exact pathologic diagnosis of these cancers [19,20••], since most probably some of the esthesioneuroblastoma of other series include misdiagnosed neuroendocrine histologies.

No study provides convincing evidence for the use of chemotherapy in squamous cell carcinoma or other glandular types of nasal cancer. In one study [52] the response of adenocarcinoma to cisplatin and 5-Fluorouracil chemotherapy was predicted by the p53 protein in the pretreatment biopsy: 80% compared with 0% response in functional and mutated p53, respectively. Similar predictive factors are needed for other histologic types and, because the majority of treatment failures of NPSCa are local [2], we favor a local treatment without chemotherapy for most patients.

The recent trend has been to avoid orbital exenteration, and induction chemotherapy with or without radiotherapy has been promoted to achieve this goal. While this conservative approach might be sound, we failed to find any study that convincingly points to chemotherapy as effective in this setting.

Intra-arterial chemotherapy has the theoretical advantage of increased drug concentration and lower systemic toxicity. Recent studies show disease-free survival around 60% with this approach [53,54], although the associated toxicity was high [55]. Of note, local chemotherapy has been applied with some success in Japan and might warrant further evaluation.

In the future, the question might not be whether chemotherapy is useful but the specific drug to be used. Newer molecules used in other head and neck cancers should be evaluated for NPSCa.

Outcome

In our systematic review [2], the average overall survival was 41% and the overall result for the 1990s was 51%. Better survival figures were found for 'glandular' carcinoma (~60%) than for squamous cell or adenocarcinoma (~50%), while undifferentiated carcinoma had the poorest survival (28%). Nasal primaries (~65%) had better survival than ethmoid (50%) or maxillary (45%) primaries. Figures for T1 (94%) were better than T2 (55%) and for T3 (50%), and much better than those for T4 (27%). An analysis of the National Cancer Institute database [56] has confirmed that age, T stage, N stage, histology, and treatment modality are statistically related to outcome.

Neck lymph metastasis remains rare in NPSCa, either at presentation (12%) or following treatment (13%). Isolated neck lymph node recurrence is present in about 5% [2]. For advanced-stage maxillary squamous cell carcinoma, the rate of neck metastasis at presentation is around 20–25% and prophylactic treatment of the neck should be considered [57,58]. Several studies [59,60] have indicated a higher incidence of neck recurrence with involvement of the alveolus and cheek. The results of treatment of metastatic neck disease are disappointing, with about 20–25% 5-year survival for either primary or post-treatment neck metastasis.

The most frequent recurrence in NPSCa remains local (about 35%), with relatively rare isolated regional (5%) or distant metastasis (5%) when the primary is controlled [2]. Local extension sites associated with worse prognosis include the pterygomaxillary fossa for maxillary primaries, and invasion of the frontal sinus, sphenoid sinus, cribriform plate, dura, and brain for ethmoid primaries [2]. A recent study confirms most of these findings, with poor prognosis associated with sphenoid, 'deep orbit', and brain involvement [61].

Conclusion

NSPCa remains a challenging problem because of its rarity and the proximity of vital structures. Care of patients with NPSCa requires a team of experts with diverse competences, mainly in radiodiagnosis, histopathology, surgery, radiotherapy, and chemotherapy. The exact pathological diagnosis is essential to select the proper treatment modality. The role of newer techniques such as endoscopic transnasal surgery and high-precision radiotherapy awaits formal trials. Except for aggressive neoplasms, a widespread role for chemotherapy is yet to be defined.

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