Malignant Tumours

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Introduction

Sinonasal malignancies are rare tumours, accounting for 0.2–0.8% of all malignancies and 3–5% of head and neck cancers. Their prognosis is extremely variable, being influenced by the local extension of the disease, possible involvement of noble structures such as brain, orbit or internal carotid artery and tumour histology, itself critically influencing the biological aggressiveness [1].

The management of these uncommon diseases is handled by a multidisciplinary oncologic skull base team composed of head and neck surgeons, neurosurgeons, radiologists, radiotherapists, medical oncologists and pathologists.

The spectrum of treatment strategies is wide, from various surgical approaches to multimodal management, and is driven by the tumour histotype and its extension.

Craniofacial resection, firstly described by Ketcham in 1964 [2], has represented the gold standard in the treatment of sinonasal malignant tumours for decades, even though it is burdened by invasive transfacial approaches, significant functional sequelae and a complication and mortality rate of 36.3% and 4.7%, respectively [3].

The endoscopic endonasal approach, which was initially developed in the 1970s for the treatment of inflammatory sinonasal conditions, following progressive refinements in surgical techniques and technologies, has been gradually

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applied to selected cases of sinonasal malignancies since 1990 [4], with results comparable to those ones of traditional external approaches.

Epidemiology

In Western countries the incidence varies between 0.8 and 1 per 100,000 people, whereas it is greater in Africa and Eastern countries, where it can reach 2.6 per 100,000 people as reported in Japan [5].

The average age at diagnosis is 60 years; men are more affected than females (58.6%), which is probably due to environmental or occupational exposure. Children can be affected by different histotypes, rhabdomyosarcoma being the most prevalent type [6].

The most common site of origin is the maxillary sinus (50–70%), followed by the nasal cavity (15–30%) and ethmoid sinus (10–20%); frontal and sphenoid sinuses are rarely the primary site, yet they are generally involved by locally advanced tumours with dismal prognosis.

The role of different work-related chemical hazards in determining sinonasal cancers has been widely investigated by epidemiological studies, and the evaluation of the occupational exposure can be very challenging, because of the potential long latency period.

Workers exposed to wood dust, leather, aluminium and other chemicals (such as formaldehyde and solvents) have an increased risk for developing sinonasal malignancies. The strong association between intestinal-type adenocarcinoma (ITAC) and former exposure to wood or leather dust, as demonstrated by Bonzini et al. (87% of patients with ITAC were exposed), is noteworthy [7].

In addition to occupational hazards, other risk factors include previous head and neck irradiation, smoking, genetic alterations and inverted papilloma.

Two thirds of sinonasal malignancies have an epithelial origin and the most common histologies are adenocarcinoma (ADC) in European countries and squamous cell carcinoma (SCC) in North America; other epithelial histotypes include adenoid cystic carcinoma (ACC) and sinonasal undifferentiated carcinoma (SNUC) [8].

Paranasal sinuses may be the site of metastases from other cancers and almost half of all cases is represented by renal cellular carcinoma, followed by breast, prostate, lungs, gastrointestinal tract and thyroid carcinoma [9].

Clinical Features

Sinonasal malignancies commonly present with non-specific signs and symptoms, therefore making the diagnosis difficult and generally delayed. Initial findings can often be misleading because they may mimic more common and benign conditions such as inflammatory diseases.

In our institution, among 565 patients treated in the last 20 years, the most common complaints were respiratory nasal obstruction (71%), epistaxis (51%), olfactory dysfunction (36%), rhinorrhoea (29%), headache (17%), facial pain (13%), epiphora (6%), swelling (4%), visual disturbance (4%) and diplopia (4%).

Symptoms may be an indicator of the local extension of the disease because of the mass effect on surrounding tissues.

Maxillary tumours may present with facial swelling, if extending anteriorly, or palatal swelling and loosening of teeth, in cases with inferior extension; diplopia and proptosis may be the result of orbital invasion, whereas a posterior spread, towards the infratemporal/pterygoid palatine fossa, may cause trismus or facial neuralgia or occasionally altered sensation/numbness because of the involvement of masticatory muscles or maxillary nerve. Ethmoidal malignancies may extend laterally into the orbit, thus causing visual symptoms or proptosis, or intracranially with potential neurological symptoms (Fig. 32.1).

Among this broad spectrum of clinical findings, unilateral persistent symptoms unresponsive to medical treatment must draw clinicians' attention and should prompt a thorough further investigation.

On initial presentation cervical lymph node metastases occur within a range variable from 3 to 30%, whereas distant metastases are less frequent, with an incidence of 1–7% [10].

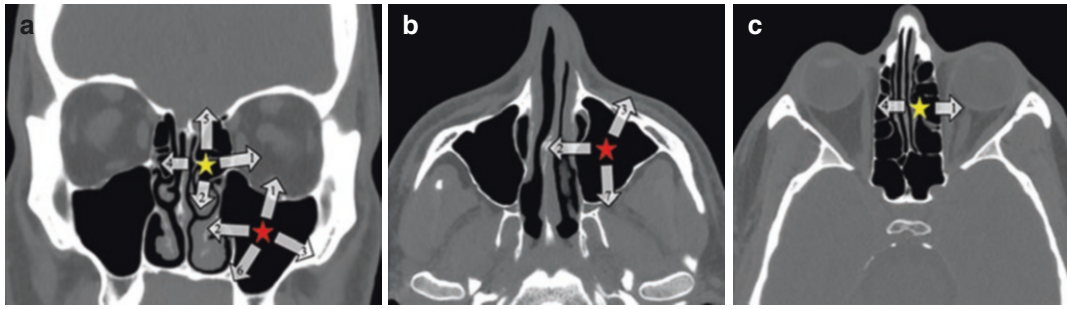

Fig. 32.1 Potential directions of growth of ethmoidal (yellow star) and maxillary (red star) tumours in different CT scan views ((**a**), coronal; (**b**) axial at the level of maxillary sinuses; (**c**) axial at the level of the orbits). Legend: 1 orbital infiltration; 2 nasal cavity extension; 3 anterior/lateral maxillary wall infiltration; 4 contralateral nasal cavity extension; 5 intracranial invasion; 6 extension into the oral cavity; 7 posterior extension into the pterygopalatine or infratemporal fossa

Diagnostic Workup

In cases of suspected sinonasal expansile lesions, the patient must be referred to an otolaryngologist for a complete clinical examination.

Nasal endoscopy, performed with flexible or rigid scopes, is the first diagnostic test of utmost importance since it can detect the lesion, its characteristics (e.g. ulceration, bleeding) and its possible site of origin.

CT Imaging

The second step is computed tomography (CT) imaging, generally done without contrast, to evaluate the sinonasal anatomy and the presence of bony alterations, which can present with different patterns:

- *Bone remodelling*, that is displacement and thinning of bony structures (more frequently observed in benign neoplasms or chronic inflammatory processes)
- *Cortical destruction*, that is interruption in the whole thickness of mineralized bone
- *Intra-diploic growth*, in cases of intra-osseous spread, that is the replacement of spongiosa by solid tissue
- *Permeative invasion*, that is subperiosteal spread with diffuse demineralization (mostly observed in lymphomas and adenoid cystic carcinomas)
- *Sclerosis*, as a result of chronic inflammatory reaction of the spongiosa [11]

The CT scan facilitates the evaluation of the lamina papyracea and skull base, thus providing preliminary details of intraorbital and intracranial extension. Moreover, the enlargement of bony fissures or foramina may be an indicator of perineural spread. Lastly, modern CT scans with three-dimensional reconstruction in axial, coronal and sagittal planes are crucial in surgical planning.

MRI Imaging

The third step consists of magnetic resonance imaging (MRI) scan with contrast (gadolinium), which has the potential to differentiate soft tissue densities and to assess the grade of vascularization. MRI of the head is strongly recommended on occasions where a CT head scan demonstrates unexpected unilateral sinonasal mass in patients with no sinonasal symptoms.

A systematic approach to different MRI sequences is crucial in characterizing the lesion and in evaluating its relationship with adjacent structures. For this purpose, it is useful to compare T2 with plain T1 and contrast-enhanced T1 sequences: The first shows fluid as bright, the second highlights fat as bright, whereas the latter enhances vascularized neoformations, which are

usually hypointense on T2. "Fat-sat" (applicable to both T1 and T2) is another useful sequence that suppresses fat signal, hence helping in delineating the relationship between tumour and fat tissue.

The usefulness of MRI is demonstrated by its ability to assess eventual infiltration of the orbit, anterior cranial fossa and pterygopalatine/infratemporal fossa, which dramatically influences the treatment planning.

Orbital walls appear hypointense on T1 and T2 sequences because of the reduced water content of lamina papyracea and periorbita; thus, neoplastic infiltration is suspected when the hypointense interface is not recognizable.

T2 and contrast-enhanced T1 sequences enable evaluation of different stages of anterior cranial fossa invasion, by looking at its three different layers (cribriform plate, dura and cerebrospinal fluid); indeed, a thickened and enhanced dura suggests skull base invasion.

Posterior extension to the pterygopalatine and infratemporal fossa is demonstrated by maxillary bone erosion, loss of fat signal or altered signal intensity of the pterygoid muscles [12].

However, it is important to appreciate that in almost all cases CT and MRI findings are nonspecific and do not allow to differentiate between different malignant histotypes.

As a general rule, biopsy is best performed after completing imaging studies to minimize the risk of bleeding from vascular tumours (e.g. juvenile angiofibroma, meningoencephalocele). Biopsy is generally performed under local anaesthesia with rigid scopes, but in some cases, general anaesthesia is required.

A pathological second opinion in centres with dedicated expertise is strongly recommended in order to confirm the definitive diagnosis and plan the adequate treatment.

Additional Scanning Protocols

Once a malignant tumour has been confirmed, it is essential to exclude or identify regional and/or distant metastatic disease, according to the policy of the local radiology department. This typically includes ultrasound neck and CT chest and abdomen.

Total body positron emission tomography (PET-CT) scan is preferred in cases of aggressive histotypes (e.g. mucosal melanoma, neuroendocrine carcinoma) or advanced stages.

Staging

Different staging systems have been developed in the past decades to evaluate sinonasal malignancies.

The Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) TNM classification, now in its eighth edition, is the most widely used. In this staging system, the T classification depends on the progressive involvement of adjacent structures; the sinonasal tract is divided into maxillary sinus and nasal cavity/ethmoid sinus. All histotypes are included except for mucosal melanoma, which has its own TNM classification (T3 is the minimum) due to its extremely aggressive behaviour [13].

Different staging systems have been proposed for esthesioneuroblastoma, because of its peculiar biological behaviour: The Kadish classification, which was developed in 1976, is the most commonly used and divides patients into three categories [14]; a fourth new category, for patients with metastases, was introduced by Morita in 1993. In 1992 Dulguerov and Calcaterra developed a new staging system, which was found to be better correlated with survival [15].

The Wang staging system was developed for carcinoma of the nasal vestibule, which is an aggressive cancer with a worse prognosis than other head and neck skin cancers; this staging system is based on the invasion depth and is a better prognostic indicator than the TNM classification [16] (Tables 32.1, 32.2, 32.3, 32.4 and 32.5).

Table 32.1 T staging according to the AJCC eighth edition

		Maxillary sinus	Nasal cavity and ethmoid sinus
T1		Tumour limited to the mucosa (no erosion or destruction of the bone)	Tumour restricted to one subsite[a] of the nasal cavity or ethmoid sinus
T2		Tumour causing bone erosion or destruction (hard palate and/or middle meatus extension is included, whereas extension to posterior maxillary wall and pterygoid plates is excluded)	Tumour involves two subsites in a single site or involves an adjacent sites within the nasoethmoidal complex
T3		Tumour involves any of the following: • Posterior maxillary bony wall • Floor or medial orbital wall • Subcutaneous tissues • Pterygoid fossa • Ethmoid sinuses	Tumour involves any of the following: • Maxillary sinus • Floor or medial orbital wall • Palate • Cribriform plate
T4a		Tumour involves any of the following: • Anterior orbital contents • Skin of the cheek • Pterygoid plates • Sphenoid or frontal sinuses • Cribriform plate • Infratemporal fossa	Tumour involves any of the following: • Anterior orbital contents • Skin of the nose or cheek • Pterygoid plates • Sphenoid or frontal sinuses • Minimal extension to anterior cranial fossa
T4b		Tumour involves any of the following: • Orbital apex • Dura • Brain • Middle cranial fossa • Cranial nerves other than V2 • Nasopharynx or clivus	Tumour involves any of the following: • Orbital apex • Dura • Brain • Middle cranial fossa • Cranial nerves other than V2 • Nasopharynx or clivus

[a] Anatomical site and subsites: nasal cavity (septum, floor, lateral wall, vestibule), maxillary sinus, ethmoid sinus (left, right)

Table 32.2 N staging according to the AJCC eighth edition

Regional lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastases
N1	Metastasis in a *single* ipsilateral lymph node, ≤3 cm in greatest dimension (no extranodal extension)
N2a	Metastasis in a *single* ipsilateral lymph node, between 3 and 6 cm in greatest dimension (no extranodal extension) or <3 cm with extranodal extension
N2b	Metastasis in *multiple* ipsilateral lymph nodes, ≤6 cm in greatest dimension (no extranodal extension)
N2c	Metastasis in *bilateral or contralateral* lymph nodes, ≤6 cm in greatest dimension (no extranodal extension)
N3a	Metastasis in a lymph node >6 cm in greatest dimension (no extranodal extension)
N3b	Metastasis in a single (>3 cm) or multiple lymph nodes with extranodal extension

Table 32.3 T staging of malignant melanoma of upper airways and digestive tract according to AJCC eighth edition

Malignant melanoma of upper airways and digestive tract	
T3	Tumour is limited to the epithelium and/or submucosa
T4a	Tumour involves the bone, cartilage, deep soft tissue or overlying skin
T4b	Tumour involves any of the following: • Brain • Dura • Skull base • Lower cranial nerves (IX, X, XI, XII) • Masticator space • Carotid artery • Prevertebral space • Mediastinal structures

Table 32.4 Kadish-Morita and Dulguerov-Calcaterra staging system for esthesioneuroblastoma

	Kadish-Morita		Dulguerov-Calcaterra
A	Tumour is limited to the nasal cavity	*T1*	Tumour involves the nasal cavity and/or paranasal sinuses (excluding sphenoid), sparing the most superior ethmoidal cells
B	Tumour involves the nasal cavity and paranasal sinuses	*T2*	Tumour involves the nasal cavity and/or paranasal sinuses (including the sphenoid), with extension to or erosion of cribriform plate
C	Tumour extends beyond the nasal cavity and paranasal sinuses	*T3*	Tumour extends into the orbit or protrudes into the anterior cranial fossa, without dura invasion
D	Regional or distant metastases	*T4*	Tumour involves the brain

Table 32.5 Wang T staging system for carcinoma of the nasal vestibule

Wang T staging system	
T1	Tumour confined to the skin
T2	Tumour invades subcutaneous tissue and cartilage
T3	Tumour invades the bone

Histology-Driven Treatments

In this section the most common histotypes and their multimodal treatment protocols are presented.

Squamous Cell Carcinoma (SCC)

SCC is the most common sinonasal malignancy in the United States: It originates in the maxillary sinus in 60% of cases, less frequently in the nasal cavity or ethmoid. Tumours occur in men twice as much as in women in their 50s and 60s.

It can present with different subtypes: keratinizing (KSCC), non-keratinizing (NKSCC) and other rarer variants.

KSCC is the most common (50% of cases) and is characterized by keratinization; indeed epithelial markers (e.g. citokeratins) are expressed. It is identical to KSCC arising in other sites and it can be found in approximately 5–10% of sinonasal inverted papillomas [17].

NKSCC accounts for 20% of sinonasal SCC and is similar to that one arising in the oropharynx. It is characterized by minimal squamous differentiation and does not have tumour grading. The association with high-risk HPV is found in almost 50% of cases and correlates with a trend towards improved survival [18].

The standard treatment is surgical resection followed by adjuvant radiotherapy; irradiation should include the neck in case of advanced stages (T3–T4), given the high risk of nodal metastases (20%). In case of positive margins or evidence of neural/lymphovascular infiltration, adjuvant chemotherapy can be administered.

Patients with high-grade carcinoma in advanced stages (T3–T4) can be treated with induction chemotherapy regimens followed by surgery and postoperative chemoradiation or definitive chemoradiation; tumour response to induction chemotherapy is associated with better survival and prognosis [19] (Fig. 32.2).

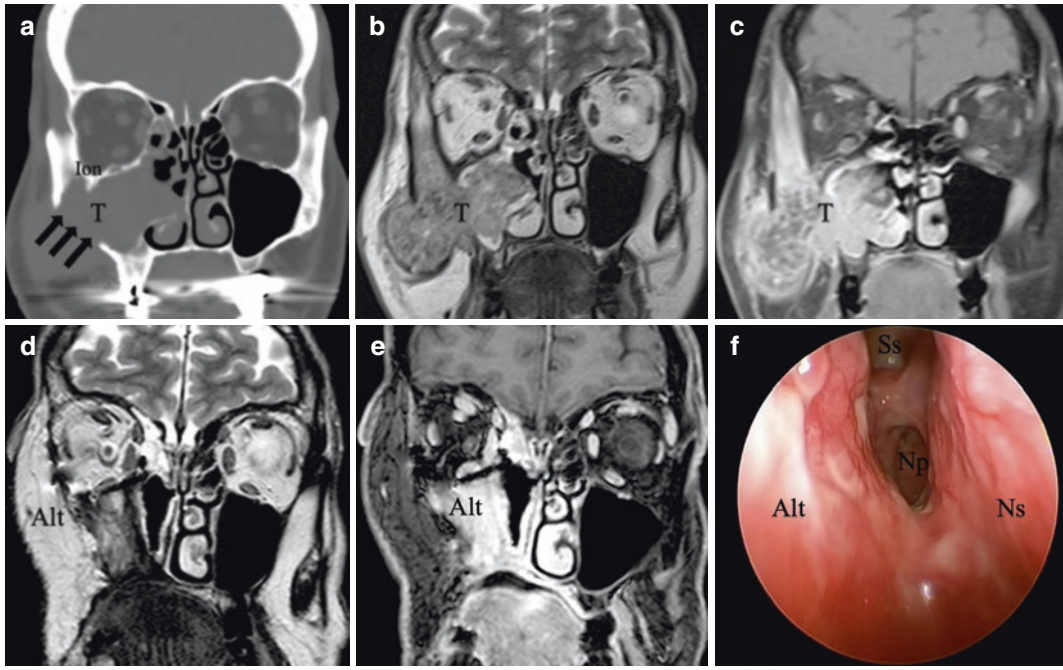

Fig. 32.2 A 54-year-old female affected by right maxillary sinus squamous cell carcinoma G2 extending into the infratemporal fossa, parotid, temporalis muscle and subcutaneous cheek (T4aN0M0). Preoperative CT (**a**) and MRI scans ((**b**) T2W; (**c**) T1W with contrast) in coronal views. The patient underwent craniofacial resection with right selective neck dissection (I–IV), reconstruction with anterolateral thigh free flap and adjuvant radiotherapy (60Gy). MRI scans in coronal views ((**d**) T2W; (**e**) T1W with contrast) and nasal endoscopy (**f**) at 1-year follow-up: the patient is alive without disease. Legend: *Alt* anterolateral thigh free flap, *Ion* infraorbital nerve, *Np* nasopharynx, *Ns* nasal septum, *Ss* sphenoid sinus, *T* tumour, black arrows erosion of the lateral maxillary wall

Adenocarcinoma (ADC)

ADC is the most common sinonasal epithelial malignancy in Europe and it generally originates in the ethmoid (85%), followed by the olfactory cleft (13%).

Intestinal-type adenocarcinoma (ITAC) takes its name from the morphological analogy with intestinal adenocarcinomas and correlates with occupational exposure to leather or wood dust in up to 87% of cases [7]. It affects predominantly men aged between 40 and 70 years.

According to Barnes's classification, different subtypes can be distinguished: papillary (75% of cases), solid, mucinous (e.g. signet-ring cells) and mixed. Solid and mucinous patterns are indicative of poorly differentiated cancers, thus behaving more aggressively [20].

Non-intestinal-type adenocarcinoma (nITAC) represents a diagnosis of exclusion; features of intestinal or salivary gland tumours are absent; positive for markers of seromucinous differentiation (e.g. S100, DOG1) are often demonstrated. As opposed to ITAC, it is not correlated with occupational exposure and patients are generally younger (50s) with a mild female predilection.

Surgical resection is the mainstay of treatment: It is the single effective treatment for low-grade tumours in early stages (T1–T2), but it should be followed by postoperative radiotherapy (PORT) in case of high-grade neoplasms, advanced stages (T3–T4) or infiltrated surgical margins. In case of high-grade lesions with intracranial extension, a prophylactic brain irradiation should also be considered, given the potential risk of leptomeningeal involvement [21] (Fig. 32.3).

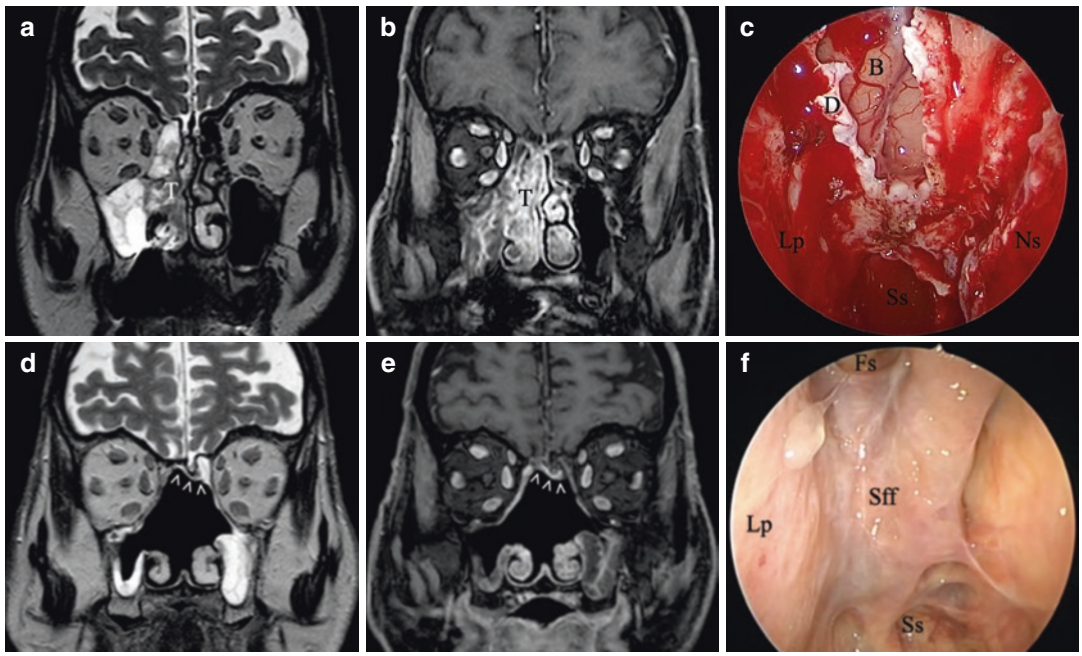

Fig. 32.3 A 78-year-old male, former woodworker, affected by right sinonasal intestinal-type adenocarcinoma G1 (T3N0M0). Preoperative MRI scans in coronal views ((**a**) T2W; (**b**) T1W with contrast). Right endoscopic resection with transnasal craniectomy (ERTC) and skull base reconstruction with fascia lata and septal flip flap was performed ((**c**) right nasal fossa intraoperative view after dura removal), adjuvant radiotherapy followed (66Gy). MRI scans in coronal views ((**d**) T2W; (**e**) T1W with contrast) and nasal endoscopy (**f**) after 5 years demonstrate no evidence of the disease. Legend: *B* brain, *D* dura mater, *Fs* frontal sinus, *Lp* lamina papyracea, *Ns* nasal septum, *Sff* and white arrowheads septal flip flap, *Ss* sphenoid sinus, *T* tumour

The neck is not routinely treated as regional metastases occur in only 7% of patients. Induction chemotherapy has been proposed for advanced-stage (T3–T4) ITAC with functional p53, showing promising results in survival [22].

Adenoid Cystic Carcinoma (ACC)

ACC is a rare salivary gland tumour that involves most frequently the maxillary sinus (60%) and the nasal cavity (30%). It has a slight prevalence in women, with a peak of incidence in the fifth and sixth decades.

Given the strong propensity for perineural and bony spread, intracranial extension (including cavernous sinus) is likely and local recurrence is common (60%). Another important characteristic is distant metastases (lung, bone and brain), often presenting many years after the initial tumour and occurring in approximately 40% of patients [23].

ACC presents in different subtypes: cribriform, tubular and the less differentiated solid. Different grading systems have been proposed to emphasize the importance of histological subtypes; indeed, according to the Perzin/Szanto system, ACC is classified as high grade if the solid component represents more than 30%. In this case the tumour behaves locally more aggressively and tends to develop early distant metastases [24].

ACC is considered a relative radiosensitive tumour; hence the standard treatment is surgical radical resection, whenever feasible, followed by adjuvant radiotherapy to clear positive margins (microscopic or macroscopic) [25].

In cases of locally advanced stages, with involvement of vital structures, function-sparing tumour debulking reduces the target volume, making PORT more selective and efficient.

Heavy particle radiotherapy, with protons or carbon ions, has recently been introduced and demonstrates improved local control, both for postoperative patients and those with unresectable ACC. A significant advantage of this technique is the ability to deliver high tumouricidal doses whilst sparing adjacent normal tissues.

Esthesioneuroblastoma (ENB)

ENB, also named olfactory neuroblastoma, is a malignant neuroectodermal neoplasm that arises from the olfactory neuro-epithelium. It has a slight predominance in male (male-to-female ratio 1.2:1), and although a bimodal distribution in age has been initially reported, it affects patients in the fifth or sixth decade [26].

It is typically located in the superior portion of the nasal vault and involves the cribriform plate. Ectopic location within the paranasal sinuses is extremely rare. It can present with a paraneoplastic syndrome but only in 2% of patients (e.g. syndrome of inappropriate antidiuretic hormone/ADH secretion) [27].

Metastases at presentation are rare; furthermore they develop late in the natural history of the disease, most frequently in cervical lymph nodes. Several staging systems have been proposed, but the Kadish staging system is the most commonly applied.

The Hyams grading system classifies ENB into four grades, from most (grade I) to least differentiated (grade IV), depending on specific histopathological features. Higher grades are associated with more aggressive locoregional disease and worse disease-free survival.

The differential diagnosis is wide, and immunohistochemistry is of utmost importance: neuron-specific enolase, synaptophysin and chromogranin A are typically positive. Review of pathological specimens by expert pathologists is crucial especially when dealing with poorly differentiated ENBs, given that they could easily be confused with other neuroendocrine tumours.

The standard treatment is surgical resection, with removal of the anterior skull base dura and olfactory bulb, followed by adjuvant radiotherapy; irradiation should include the neck in cases of intracranial extension (Kadish C).

The role of chemotherapy is debated; however neoadjuvant regimens (e.g. etoposide/cisplatin) are generally advocated for patients with poorly differentiated ENB in locally advanced stages [28]. Follow-up should be long term, and should metastatic neck disease present at a late stage, neck dissection with possible PORT should be considered (Fig. 32.4).

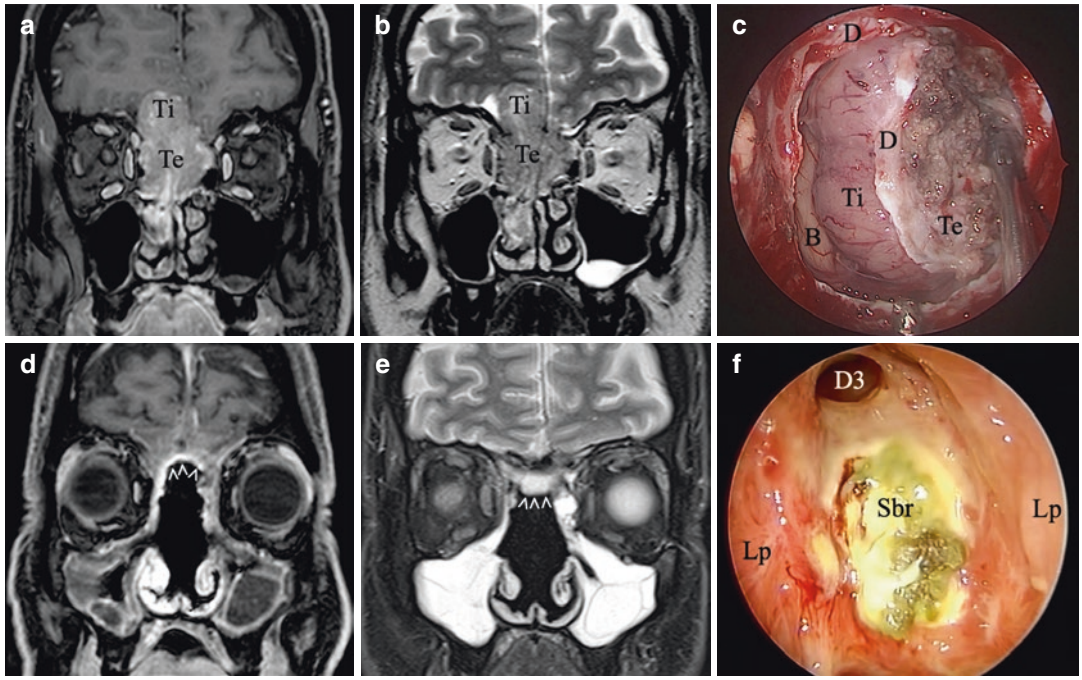

Fig. 32.4 A 58-year-old male affected by right esthesioneuroblastoma Kadish C, Hyams II. The preoperative MRI scans in coronal views ((**a**) T1W with contrast; (**b**) T2W) and intraoperative view (**c**) show the intracranial extension of the disease. The patient underwent bilateral ERTC and skull base reconstruction with fascia lata followed by adjuvant radiotherapy (60/54 Gy on T/N). MRI scans in coronal views ((**d**) T1W with contrast; (**e**) T2W) and nasal endoscopy (**f**) performed at 7-month follow-up demonstrate local control of the disease. Legend: *B* brain, *D* dura mater, *D3* Draf III, *Lp* lamina papyracea, *Sbr and white arrowheads* skull base reconstruction, *Ti* intradural tumour, *Te* extradural tumour

Neuroendocrine Carcinoma (NEC)

Sinonasal tumours with neuroendocrine differentiation is a heterogeneous group of rare neoplasms with neuroectodermal (ENB) or epithelial origin (NEC).

NEC is a high-grade carcinoma with features of neuroendocrine differentiation that accounts for 5% of sinonasal malignancies; it is an aggressive tumour characterized by a dismal prognosis with a high rate of local recurrences and distant metastases (lung, liver and bones). It can be categorized into typical and atypical carcinoids and small cell and large cell NECs.

It has a slight male predominance and a median age at diagnosis of 56 years. The most common site of origin is the ethmoid (64%), followed by the nasal cavity (32%) and the maxillary sinus (14%) [29].

NECs are strongly positive for cytokeratins, epithelial membrane antigen and markers of neuroendocrine differentiation (e.g. synaptophysin); according to a European multicentre study, CK8/18 immunohistochemistry is strongly recommended in order to avoid a misdiagnosis of ENB, due to the negative staining for CKAE1/A3 [28].

Mixed neuroendocrine-nonneuroendocrine neoplasm is a recently described histopathological entity, in which the neuroendocrine component represents at least 30% of the lesion, characterized by an aggressive biological behaviour with frequent recurrences (80%) and poor survival outcomes [30].

The role of neoadjuvant chemotherapy is still debated but promising, due to the frequent distant failures and the chemosensitivity of NEC; the rate of response to induction chemo-

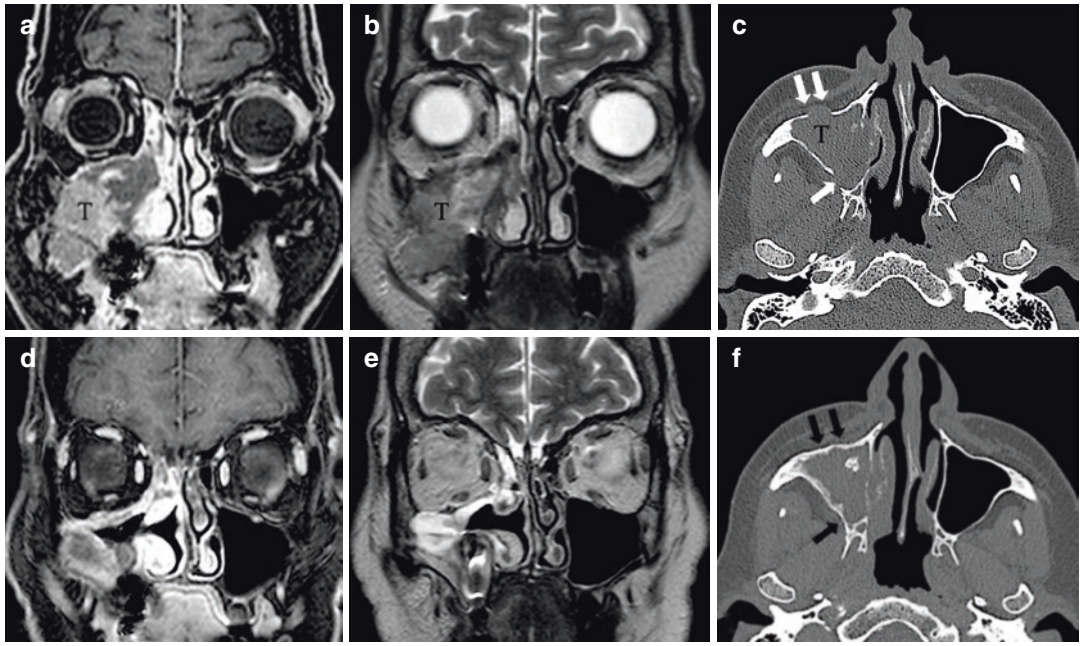

Fig. 32.5 A 52-year-old female affected by right maxillary sinus small cell neuroendocrine carcinoma G3 (T4aN0M0). Pretreatment MRI scans in coronal views ((**a**) T1W with contrast; (**b**) T2W) and (**c**) axial CT scan show focal erosion of the anterior and posterior maxillary walls and extension into the premaxillary soft tissue. Given the good response to induction chemotherapy, the patient underwent exclusive radiochemotherapy. MRI scans in coronal views ((**d**) T1W with contrast; (**e**) T2W) and axial CT scan (**f**) at 8-month follow-up demonstrate local control of disease. Legend: *T* tumour, white arrows focal erosion of the anterior and posterior maxillary walls, black arrows the erosion of the maxillary walls is no more visible

therapy could stratify patients in "responders", eligible for exclusive radiochemotherapy, and "nonresponders", who may benefit from surgery followed by adjuvant radiotherapy or radiochemotherapy [31] (Fig. 32.5).

Sinonasal Undifferentiated Carcinoma (SNUC)

SNUC is a rare, highly aggressive, undifferentiated carcinoma that lacks by definition squamous or glandular differentiation. The average age at diagnosis is 50–60 years, and it shows a male predominance (2–3:1). The most common sites involved are the nasal cavity and ethmoid sinus, and it is usually locally advanced at presentation, frequently showing orbital, skull base and intracranial involvement.

Nodal metastases occur in less than 15% of cases, whereas distant metastases are frequent. The differential diagnosis is broad and includes lymphoma, non-keratinizing SCC, ENB and high-grade NEC; immunohistochemistry demonstrates positivity for cytokeratins and neuron-specific enolase [32].

In 2014 Bishop et al. reported a subset characterized by a lack of SMARCB1 tumour-suppressor gene (also known as INI-1), the presence of rhabdoid features and a more aggressive behaviour with tendency for regional and distant metastases [33].

Gray et al. demonstrated a higher prevalence of HPV in SNUC (64.3%) than previously reported, thus suggesting a role in the carcinogenic process with a trend towards improved survival [34].

SNUC is a chemosensitive tumour, which generally presents in local advanced stages (almost 70% of cases are T4) and may benefit from aggressive multimodality treatment: Induction chemotherapy followed by either

chemoradiation or surgery with postoperative irradiation provides the best survival outcomes.

Different studies have demonstrated the feasibility and effectiveness of induction chemotherapy, which may reduce the incidence of distant metastases; the most frequently employed regimen is cyclophosphamide, doxorubicin and vincristine.

Mucosal Melanoma (MM)

MM is an aggressive malignant neoplasm, accounting for 1% of all melanomas, characterized by a high tendency for recurrence and systemic spread. It does not show gender predominance and the incidence peak is in the seventh decade.

Mucosal and cutaneous melanomas are biologically distinct; indeed, MM is characterized by a complex array of abnormalities with high rates of KIT mutations (20–40%), followed by NRAS (15%) and rare BRAF mutations (0–3%) [35].

In the sinonasal tract, the most common site of origin is the nasal cavity and tumours originating in the paranasal sinuses are associated with worse survival [36].

In 50% of cases, MM is amelanotic, therefore contributing to a diagnostic delay and a broader differential diagnosis (that includes ENB, SNUC and NEC). According to the seventh edition of the AJCC cancer staging, all MMs are considered T3–T4 and associated with extremely poor prognosis (5 years overall survival <30%).

The treatment of choice is surgery and minimally invasive endoscopic approaches should be preferred to external aggressive surgeries, which may be associated with impaired immune balance, hence a higher risk of local recurrence or systemic dissemination [37].

Adjuvant radiotherapy is generally delivered in cases of positive surgical margins, although MM is known to be radioresistant. According to a large multicentre retrospective study, carbon-ion irradiation achieves superior local control and notable survival benefit compared to conventional radiotherapy [38].

Recently, novel targeted therapies such as tyrosine kinase inhibitors (given the high prevalence of KIT gene mutations) and immunotherapy have shown encouraging results; moreover the combination of radiation, in particular carbon-ion radiotherapy, with concurrent immunotherapy might synergistically promote tumour response and prolong survival [39] (Fig. 32.6).

Long-term follow-up and endoscopic review is essential. Interval MRI surveillance scans are recommended to detect hidden recurrence in inaccessible areas such as the infratemporal fossa.

Key Learning Points

- Malignant tumours of the paranasal sinuses are rare and account for less than 5% of head and neck cancers.
- The diagnosis is generally delayed and tumours present in advanced stages because of non-specific clinical features.
- Unilateral signs and symptoms (e.g. nasal obstruction, rhinorrhoea, epistaxis, swelling) unresponsive to medical treatments must raise suspicion; particular attention must be paid in patients with occupational exposure to leather or wood dust.
- A thorough diagnostic workup requires clinical examination with nasal endoscopy, imaging (CT scan, MRI scan with contrast, total body CT scan) and biopsy; because of the wide spectrum of histological entities, a pathological second opinion should be considered to confirm the diagnosis.
- Multidisciplinary management is of utmost importance in the management of sinonasal malignancies.
- A correct histological diagnosis is mandatory in order to plan appropriately among different multimodal treatment protocols.

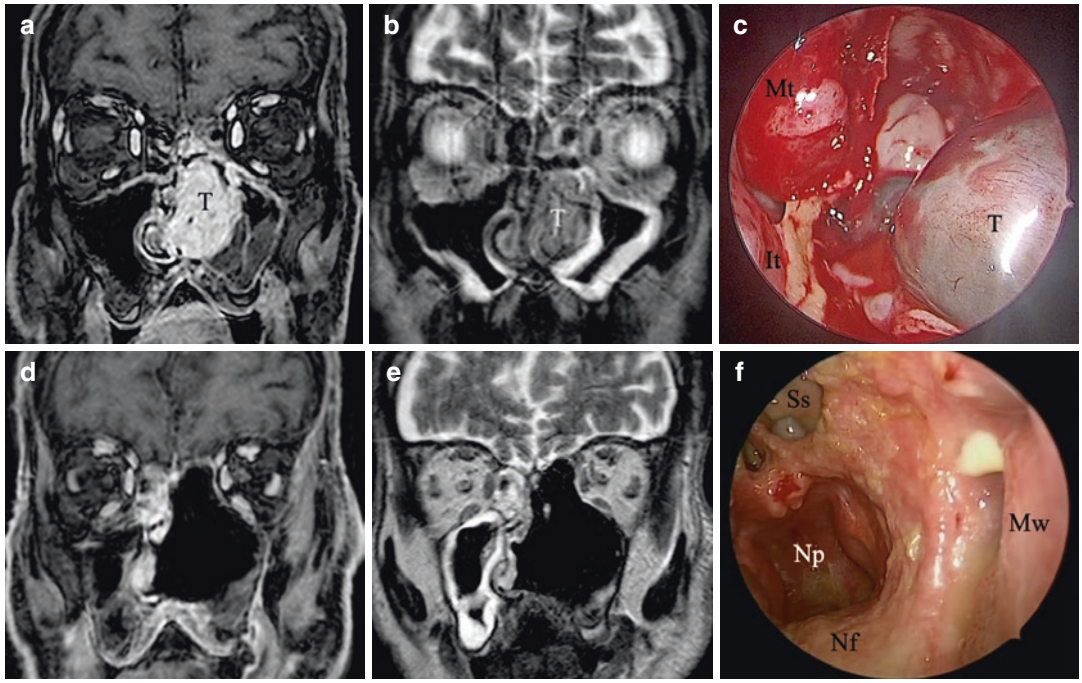

Fig. 32.6 A 71-year-old male affected by left nasal fossa mucosal melanoma T3N0M0. Preoperative MRI scans in coronal views ((**a**) T1W with contrast; (**b**) T2W) show the tumour occluding the left nasal fossa and infiltrating the nasal septum. The patient underwent a left transnasal endoscopic medial maxillectomy type IIIb with removal of the nasal septum and drilling of the hard palate. Intraoperative view (**c**) shows the tumour in the left nasal fossa after removal of the infiltrated nasal septum. Adjuvant carbon-ion radiotherapy was delivered (65.6 Gy). Postoperative MRI scans in coronal views ((**d**) T1W with contrast; (**e**) T2W) and nasal endoscopy (**f**) at 8-month follow-up confirm local control of disease. Legend: *It* inferior turbinate, *Mt* middle turbinate, *Mw* lateral maxillary wall, *Nf* nasal floor, *Np* nasopharynx, *Ss* sphenoid sinus, *T* tumour

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