

# Sinonasal Malignancies of Anterior Skull Base



## Histology-driven Treatment Strategies

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### KEYWORDS

- Radiotherapy • Chemotherapy • Endoscopic endonasal • Paranasal sinuses
- Skull base cancer • Olfactory neuroblastoma • Adenocarcinoma
- Mucosal melanoma

### KEY POINTS

- Endoscopic endonasal surgery represents an oncologically sound alternative to open surgery in selected patients with sinonasal malignancies with lower morbidity, faster recovery, and better quality-of-life outcomes.
- A correct diagnosis by means of histology, immunohistochemistry, or molecular biology represents the key factor for initiating an appropriate treatment strategy.
- Integration of multimodal treatment strategies, including different regimens of chemotherapy, photon, and heavy-ion radiotherapy, is able to improve survival rates, especially for high-grade and advanced-stage tumors.
- Cooperation in a multidisciplinary oncologic skull base team is mandatory to offer patients the best treatment options, and to minimize complications and failures.

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## INTRODUCTION

Sinonasal tumors are rare diseases, accounting for 3% to 5% of head and neck malignant neoplasms and the 0.2% to 0.8% of all tumors.<sup>1</sup> There are several histologic subtypes with different natural histories. The most frequent tumors of this region have epithelial origin and poor prognosis, such as squamous cell carcinoma, intestinal-type adenocarcinoma (ITAC), undifferentiated carcinoma, and neuroendocrine carcinoma (NEC). Although there are several staging systems, none are ideal or universally used. However, stage at presentation is generally highly predictive of survival and, despite a maximum treatment of the primary tumor, local, regional, or distant recurrences can occur even after many years.<sup>2</sup> From a surgical standpoint, the introduction of craniofacial resection (CFR) in the 1960s represented a significant advance in the care of these patients and has served as the mainstay for their treatment for the past 50 years.<sup>3</sup> However, this approach has been associated with perioperative mortality and major complications in 0% to 13% and 35% to 63% of patients, respectively.<sup>4</sup> The advances in endoscopy have revolutionized the management of sinonasal and skull base lesions. Many complex cancers that traditionally required open approaches are now amenable to purely endoscopic endonasal resection, providing less invasive surgery with lower morbidity but with comparable oncologic outcomes in terms of survival rates.<sup>5</sup> The endoscopic endonasal approach has become accepted with precise indications for the treatment of selected skull base cancers. Therefore, at present, external traditional and endoscopic approaches should not be considered as two competing techniques, but rather as different approaches useful for suitable cases, performed in centers with extensive experience, according to the oncologic principle of radicality. At present, the surgical strategy has to be driven by the cancer histology and its extension rather than the available surgical expertise and equipment, and therefore surgeons have to be equally comfortable in managing patients by open craniofacial as well as endoscopic approaches.<sup>6</sup> So far, no standard and uniform protocols of treatment of such aggressive tumors have been reported, given their rarity, heterogeneity in histology and stages of diseases, and in the absence of prospective studies. Surgery followed by radiotherapy (RT) has been generally adopted as the usual treatment strategy. However, some studies also explored the role and feasibility of induction chemotherapy and the prognostic value of the response to it in several histotypes.<sup>7,8</sup> Recently, heavy-ion therapy using proton or carbon ion beams has been introduced in the treatment of these tumors as exclusive therapy or in the postoperative setting with encouraging outcomes.<sup>9</sup> Proton/carbon ion beam therapy, compared with conventional photon therapy, provides a more accurate and intense dose to the tumor area, with potentially greater control of disease.<sup>10</sup> Moreover, this therapy may produce less toxic side effects in particularly critical areas exposed to late RT toxicities and potentially can help in organ preservation strategies for locally advanced cases, especially to avoid orbital exenteration.<sup>11</sup> In this scenario, even in the absence of prospective data, the integration of multiple modalities of treatment tailored to the histology; molecular profile; and, in selected cases, to the response to induction chemotherapy seems to be the best approach for these rare and aggressive cancers.<sup>12</sup> This article discusses the current evidence for the multimodal management of sinonasal and anterior skull base (ASB) cancers, focusing on the different treatment protocols driven by histologic subtypes. Preoperative work-up, indications and exclusion criteria, surgical techniques, and postoperative management are analyzed. Oncologic outcomes stratified according to histology are presented and future directions for the management of these cancers are discussed.

## DIAGNOSTIC WORK-UP

Diagnosis is often made late because these tumors are asymptomatic or produce nonspecific symptoms in their early stages. Nasal endoscopy under local anesthesia can help to determine the site and extent of the tumor. Computed tomography (CT) and contrast-enhanced MRI can provide information on the exact location and the extent of the disease. In many cases, both imaging modalities are necessary for an accurate treatment plan. After imaging, an endoscopic-assisted biopsy of the sinonasal lesion is mandatory in order to clearly identify the specific histotype of cancer. What seems to be crucial is reaching the correct histologic diagnosis considering that histology and molecular pattern of the tumor can guide the type of treatment to be administered. For this reason, when dealing with rare and particularly aggressive histotypes, a second histopathologic opinion is mandatory for confirming or reaching the correct diagnosis. Before planning the treatment, complete staging of the patient is advisable. To this end, ultrasonography examination of the neck and contrast-enhanced CT scan of the chest and abdomen are performed to rule out regional or systemic dissemination of the disease. In contrast, a total body PET-CT scan is preferred in cases of aggressive histotypes (ie, sarcoma, malignant melanoma, undifferentiated and NEC) and for advanced-stage lesions.

## MULTIDISCIPLINARY TREATMENT PROTOCOLS

The multimodal treatment protocols currently available are tailored for specific histologic subtypes.

### *Squamous Cell Carcinoma*

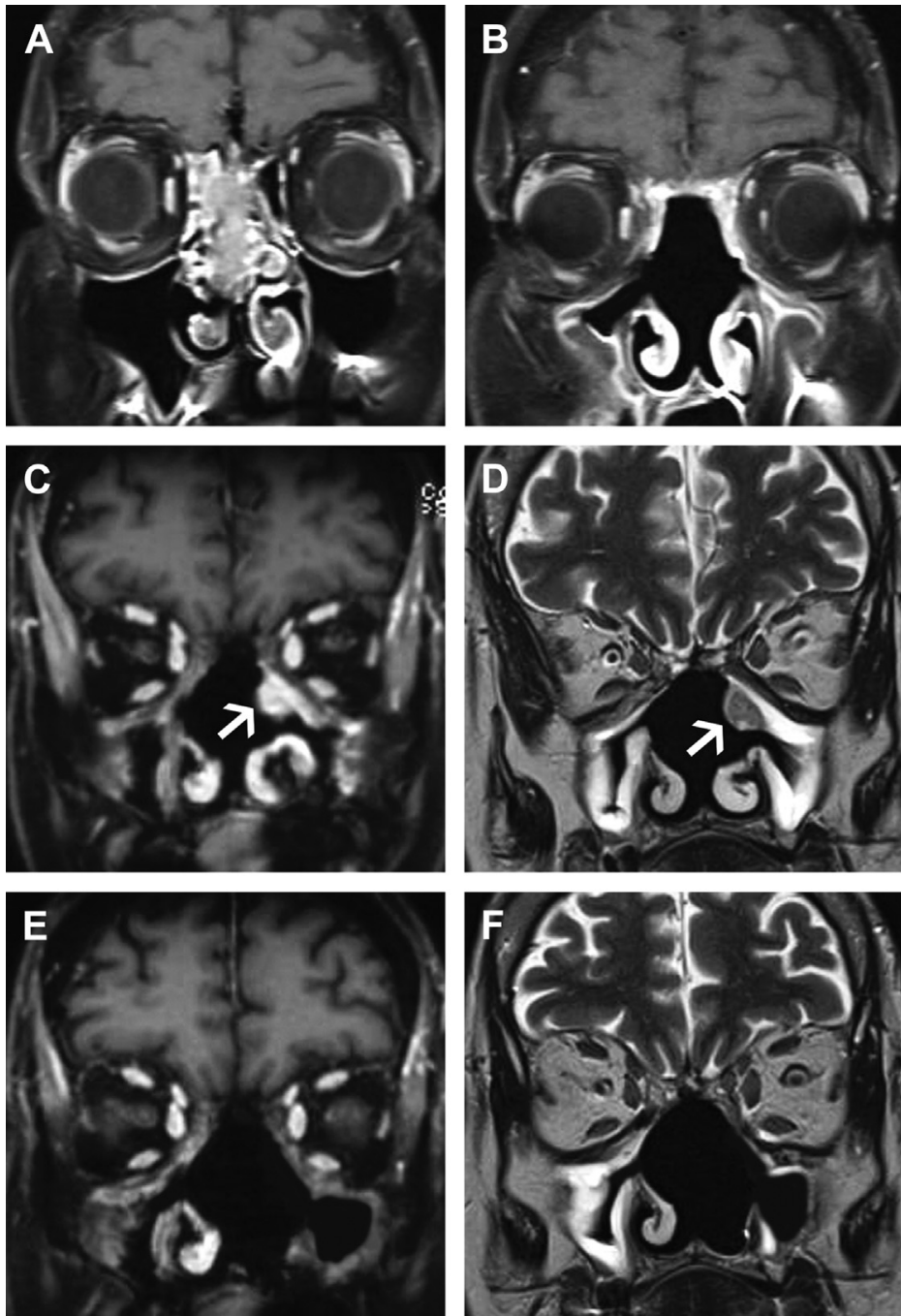
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This is the most common tumor of the sinonasal tract in the United States, originating in approximately 60% of cases from the maxillary sinus. The standard treatment of this tumor is radical surgery followed by adjuvant intensity-modulated radiotherapy (IMRT).<sup>12-14</sup> Elective irradiation of the neck should be considered for locally advanced lesion (T3–T4) because of the frequency of cervical lymph node metastases (23%).<sup>1</sup> Platinum-based adjuvant chemoradiotherapy is generally used only in cases of positive margins after surgery and for pathologic evidence of neural or lymphovascular invasion.<sup>1</sup> When dealing with poorly differentiated squamous cell carcinoma in advanced stages (T3–T4), induction chemotherapy regimens including mainly a combination of a taxane and platinum followed by surgery and adjuvant (chemo)radiation or by definitive (chemo)radiation showed promising results. In the MD Anderson Cancer Center experience with 46 consecutive cases, a partial or complete response to this induction chemotherapy protocol was observed in 67% of patients and it was predictive of treatment outcome and prognosis.<sup>7</sup>

### *Adenocarcinoma*

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This is the most common mucosal epithelial malignancy in Europe, occurring predominantly in the ethmoid sinuses (85%) and olfactory region (13%). Men develop adenocarcinoma 4 times more frequently than women, implying an occupational hazard related to wood and leather dusts exposure.<sup>15</sup> This finding also explains the multifocality of tumors observed in different mucosal area of the nasal cavities, even distant to each other, especially for ITAC. For this reason, a bilateral ethmoid labyrinth resection is always recommended, because the contralateral ethmoid may be exposed to the same carcinogenic risk factors as the neoplastic nasal fossa (**Fig. 1**).<sup>15,16</sup> Surgery is the mainstay for the treatment of such cancers. Endoscopic endonasal surgery is effective as a single treatment modality for early-stage (T1–T2) low-grade lesions,



**Fig. 1.** (A) Preoperative T1-weighted contrast-enhanced coronal magnetic resonance (MR) scan showing right ethmoid ITAC. The patient underwent an endoscopic resection with transnasal craniectomy followed by adjuvant IMRT (70 Gy). The lesion was staged pT3N0M0. Two-year postoperative contrast-enhanced MR scan was free of disease (B). Four-year postoperative contrast-enhanced coronal MR scan T1 (C) and T2 (D) weighted showed a local recurrence of disease (*white arrows*) localized on the left papyrcea (contralateral to the primary tumor). The recurrence was treated surgically through an endoscopic endonasal approach. Six-year postoperative contrast-enhanced coronal MR scan T1 (E) and T2 (F) weighted was clear, without evidence of recurrences.

radically resected with negative margins. In contrast, postoperative IMRT improves survival rates for high-grade sinonasal adenocarcinomas (G3, signet-ring variant, solid type) regardless of the stage of disease at presentation. The role of adjuvant IMRT is also widely accepted for advanced-stage lesions (T3–T4) and in the presence of positive surgical margins.<sup>17</sup> Given the possibility of tumor spread to leptomeninges at

diagnosis or late during the follow-up, a prophylactic brain irradiation could be considered in high-grade lesions with intracranial invasion.<sup>18</sup> Elective treatment of the neck lymph nodes is not routinely performed in sinonasal adenocarcinoma because the risk of regional metastases is low (7%).<sup>1</sup> Moreover, in the presence of advanced-stage ITAC (T3–T4), a chemotherapy regimen based on cisplatin, fluorouracil, and leucovorin followed by surgery and radiation has been proposed for tumors with functional p53 protein, being highly effective with promising results in terms of disease-free survival.<sup>8</sup>

### ***Olfactory Neuroblastoma***

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Olfactory neuroblastoma (ONB) arises from the neural-epithelial olfactory mucosa. The mainstay treatment of ONB generally comprises radical surgical resection.<sup>19</sup> In our experience, surgical excision should include the dura of the ASB together with the ipsilateral olfactory bulb in every case, not only to obtain a free-margins resection of the disease but also for staging purposes.<sup>19</sup> The removal of both olfactory bulbs is performed only for bilaterally extended cancers. Postoperative irradiation has been shown to reduce local recurrence rates and improve survival, so it is recommended in all cases, irrespective of extent of disease at diagnosis.<sup>19–21</sup> Radiation treatment is typically delivered using IMRT, which provides optimal sparing of radiation dose to sensitive normal structures, such as the optic nerve or brain. The recent introduction of intensity-modulated proton beam radiation therapy (IMPBRT) deserves particular mention, showing promising results for the management of ONB both as exclusive primary therapy and in the postoperative setting.<sup>22</sup> Cervical lymph node metastases are infrequent at presentation for patients diagnosed with ONB, with reported rates between 5% and 12%. However, given the high reported rates of late regional failures and limited morbidity-associated IMRT, elective neck radiation may warrant consideration in patients with intracranial disease at presentation (Kadish C).<sup>20,21</sup> Particular attention should be paid to Hyams grading, which accurately characterizes tumor biology and represents an independent predictor of locoregionally recurrence of disease and overall survival (OS).<sup>20</sup> For this reason, it is a valuable asset to consider when contemplating adjuvant or neoadjuvant therapies. In detail, poorly differentiated ONB, namely Hyams grade IV lesions, presenting in locally advanced stages (T3–T4), could benefit from different regimens of induction chemotherapy (etoposide/cisplatin<sup>23</sup> or cyclophosphamide/vincristine<sup>24</sup>) to improve both disease control and survival rates; however, the existing data do not provide any definitive indication in this field.

### ***Neuroendocrine Carcinoma: Small Cell and Large Cell Types***

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Sinonasal NEC is a highly aggressive tumor, usually presenting at advanced stages, developing a broad range of systemic metastases (47.6% of patients) in a short interval of time, without significant possibilities for cure and a dismal prognosis. For such cancer, aggressive multimodal therapy seems to be the most effective approach, although survival remains poor. Recent data reported that neoadjuvant chemotherapy mainly consisting of etoposide and cisplatin followed by surgical resection and adjuvant IMRT or IMPBRT could be effective, improving survival outcomes and reducing recurrence rates, therefore its standard use was recommended for these patients.<sup>25,26</sup> Moreover, the response to such induction chemotherapy can also represent a strong prognostic factor.<sup>26</sup>

### ***Sinonasal Undifferentiated Carcinoma***

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This is a highly aggressive carcinoma of uncertain histogenesis, with or without neuroendocrine differentiation, typically presenting with locally extensive disease and showing a greater tendency to metastasize compared with conventional squamous



cell carcinoma. From a histopathologic viewpoint, sinonasal undifferentiated carcinoma (SNUC) may be difficult to distinguish from high-grade ONB and sinonasal NEC.<sup>27</sup> The nuances of differentiating these neoplasms are not merely academic because there are significant differences in prognosis and treatment strategies. Given the advanced stage of disease at presentation, high incidence of distant failure, and its chemosensitivity, neoadjuvant chemotherapy followed by either chemoradiation or surgery followed by postoperative IMRT shows promise for ideal management of SNUC.<sup>28,29</sup>

### ***Hemangiopericytoma***

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This is a rare tumor of vascular origin with low risk of malignancy and distant metastasis but with a strong tendency to recur locally. The mainstay of treatment is wide surgical excision with clear resection margins as a single treatment modality, because the tumors are fairly radioresistant and chemoresistant.<sup>30</sup>

### ***Adenoid Cystic Carcinoma***

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Sinonasal adenoid cystic carcinoma (ACC) is salivary gland tumor with high propensity for perineural spread (eg, trigeminal branches) and bony invasion, which can lead to significant skull base involvement and intracranial extension, including cavernous sinus and middle cranial fossa. Surgery combined with postoperative radiation provides the best OS in such patients.<sup>31</sup> The goal of surgery is to radically resect the lesion whenever feasible; however, also the debulking of the gross volume of the tumor mass may make sense when dealing with this kind of cancer. The rationale for adjuvant irradiation may be to clear positive margins (microscopic or macroscopic) that are left after surgery. Postoperative radiation may be delivered using conventional photon radiotherapy (eg, IMRT) or taking advantage of recently introduced particle therapy, especially carbon ion therapy, which showed promising rates of local control of the disease not only in the postoperative setting but also for inoperable cases.<sup>32</sup> Pretreatment methionine-PET can be useful for predicting the therapeutic efficacy of heavy-particle therapy for these patients.<sup>33</sup> Globally, although local recurrences develop in a significant percentage of patients (65%), survival from ACC exceeds that of the other sinonasal cancers.<sup>31</sup>

### ***Mesenchymal Tumors: Soft Tissue Sarcomas and Ewing Sarcoma***

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In these patients the first treatment strategy is generally chemotherapy, with or without radiotherapy, leaving the surgical option only for nonresponders or in case of recurrence of disease.<sup>34</sup> Specific treatment strategies can be adopted for Ewing sarcoma, particularly affecting children between 7 and 15 years of age. At present, neoadjuvant chemotherapy followed by radical surgery and adjuvant irradiation (brachytherapy or conventional IMRT) seems to be the best treatment option for this subset of young patients.<sup>35</sup> In this regard, a treatment regimen including vincristine, ifosfamide, doxorubicin, and etoposide followed by complete endoscopic resection and brachytherapy was described with promising results (AMORE framework: Ablative surgery, MOulage brachytherapy and REconstruction).<sup>36</sup>

### ***Hematolymphoid Tumors***

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The role of surgery for such tumors is only to obtain a proper histologic diagnosis in order to guide the appropriate regimen of chemotherapy and/or radiation therapy.<sup>37</sup> For this reason, a minimally invasive endoscopic endonasal approach is paramount in order to minimize the surgical morbidity for the patients. Surgery may also be useful in the posttreatment setting to exclude persistence of disease whenever a radiological suspect needs to be proved.

## ***Mucosal Melanoma***

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Surgery with curative or palliative intent is considered the primary treatment of choice for sinonasal mucosal melanoma (MM).<sup>38,39</sup> Minimally invasive endoscopic approaches are generally associated with better survival rates than those obtained with mutilating external surgeries. In this regard, Lund and colleagues<sup>38</sup> hypothesized that aggressive surgery might cause severe disturbances in immunobalance and, consequently, may promote dramatic recurrence and/or explain cases with rapid systemic dissemination.

The indication for adjuvant IMRT is debated, with several studies reporting that postoperative IMRT improves only local control of disease without affecting survival.<sup>38,39</sup> For this reason, at present, adjuvant IMRT is generally delivered only in the presence of involved surgical margins. Particle therapies such as carbon ion irradiation have emerged in the last few years as effective options, improving survival outcomes of this serious disease. However, future large-scale studies are necessary to validate these preliminary results.<sup>40</sup> In addition, in the presence of metastatic spread of disease, selected cancer-specific molecular abnormalities might lead to the development of tailored targeted therapies; for example, by using inhibitors of KIT and mitogen-activated protein kinase pathways, which are currently under intense investigation.<sup>39</sup>

## **SURGICAL APPROACHES**

### ***Indications and Contraindications***

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From a surgical perspective, the degree of intracranial extension and orbital involvement have been shown to be independent prognostic factors and are also the determinants of whether an entirely endoscopic endonasal approach is possible.<sup>41,42</sup> However, a combination of endoscopic endonasal technique with subfrontal craniotomy is an effective option for extensive tumors with anterior or lateral involvement of the frontal sinus, infiltration of the dura far over the orbital roof, or with extensive infiltration of the brain.<sup>43</sup> For this reason, all patients scheduled for a purely endoscopic endonasal approach must be informed about the possibility of switching to a combined cranoendoscopic resection (CER), even intraoperatively, if deemed necessary. The currently indications and contraindications for these minimally invasive approaches are detailed in **Table 1**. Patients were considered inoperable in the presence of massive infiltration of the orbital apex, cavernous sinus involvement, and internal carotid artery encasement.

### ***Preparation and Patient Positioning***

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The endoscopic transnasal approaches require adequate instrumentation for a correct procedure. The surgical set should include several dissectors of different sizes, and delicate scissors of different angles. Delicate bipolar forceps with straight and angled tips can be very useful. Moreover, an intraoperative magnetic navigation system is strongly advisable. Patients are placed in anti-Trendelenburg position, under general anesthesia. A perioperative prophylactic antibiotic regimen including third-generation cephalosporin is used. Some minutes before surgery, the nasal cavities are packed with cottonoids soaked in 2% oxymetazoline, 1% oxybuprocaine, and adrenaline (1:100,000) solution to reduce bleeding and improve transnasal operative spaces.

### ***Surgical Techniques***

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According to the site of origin, extension, and tumor histology, the endoscopic resection can be performed unilaterally (resection extended anteroposteriorly from the

<b>Table 1</b> <b>Indications and contraindications for the endoscopic endonasal management of sinonasal and ASB malignancies</b>	
<b>Indications</b>	<b>Contraindications</b>
Ethmoid cancer involving lamina papyracea, cribriform plate, or roof of the ethmoid	Infiltration in nasal bones, palate, skin, and subcutaneous tissue
Lesions involving the medial portion of the frontal sinus	Massive involvement of the frontal sinus
Lesions vegetating in the sphenoid or involving maxillary sinus (medial, superior, and posterior walls)	Erosion of lateral, anterior, or inferior bony walls of the maxillary sinus
Involvement of nasolacrimal duct or medial wall of the lacrimal sac	Massive involvement of the lacrimal pathway
Pterygopalatine fossa invasion and limited infratemporal fossa extension	Massive infratemporal fossa extension
Periorbital layer invasion	Orbit content infiltration
Infiltration of ASB dura or olfactory bulbs	Massive infiltration of the dura over the orbital roof or brain parenchyma infiltration

posterior wall of the frontal sinus to the planum sphenoidale and laterolaterally from the nasal septum to the lamina papyracea) or bilaterally (resection extended from one lamina papyracea to the opposite one).<sup>44</sup> The previous focus of oncologic surgery on en-bloc resection to avoid the risk of tumor spilling is now debated, gradually being replaced by the concept of disassembling the lesion, having under view the limits between normal and diseased mucosa. The step-by-step technique of endoscopic endonasal resection (EER) is summarized later.

#### ***Tumor origin identification***

The lesion is gradually debulked starting from the core, in order to identify its site of origin. In this phase, it is crucial to preserve the surrounding anatomic structures, because these are useful landmarks for orientating the subsequent surgical steps.

#### ***Exposure of the surgical field***

Removal of the posterior two-thirds of the nasal septum is performed to gain better exposure of the surgical field and to optimize the endonasal maneuverability of dedicated instruments, using the 2-nostrils 4-hands technique. In this step, a wide sphenoidotomy with removal of intersinus septum and sphenoid rostrum is crucial to expose the posteroinferior margin of the dissection. The frontal sinus is approached by Draf type IIb sinusotomy in the case of monolateral EER, whereas Draf type III median sinusotomy is performed if the EER involves both sides. The frontal sinusotomy represents the anterosuperior margin of the dissection, allowing precise identification of the beginning of the anterior cranial fossa.

#### ***Centripetal removal***

Once the posteroinferior and anterosuperior margins of the resection are exposed, a subperiosteal dissection of the nasoethmoidal-sphenoidal complex is performed unilaterally or bilaterally (according to the extension of disease), to expose the lateral margins.<sup>44</sup> The lamina papyracea is included in the dissection when the tumor is in close proximity to or frankly involved in it. When required by the extension of disease, an endoscopic medial maxillectomy can be performed, to achieve good control of the



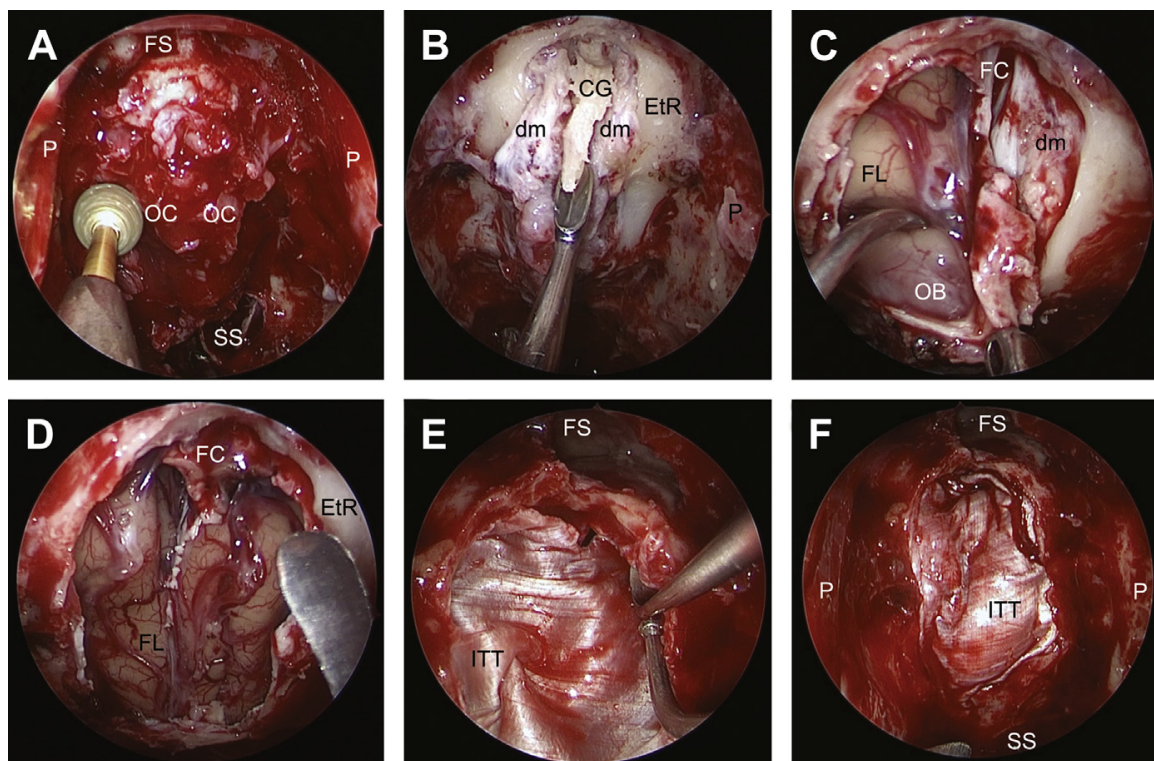
whole maxillary sinus. This surgical phase has to be associated with nasolacrimal duct exposure and resection, just below the lacrimal sac. Superiorly, the dissection is continued in the anteroposterior direction, by resecting the olfactory fibers and the basal lamella of the ethmoidal turbinate, to mobilize the monoblock. The entire nasoethmoidal-sphenoidal complex is then isolated and pushed toward the central part of the nasal fossa (centripetal technique) to extract it transorally or through the nasal vestibule.<sup>44</sup> The surgical margins are checked by frozen section and, if necessary, the dissection is continued until free margins are obtained.

### Skull base removal

According to the extension of the disease, the EER can be extended to include the ASB as well (endoscopic resection with transnasal craniectomy).<sup>45</sup> The ethmoid roof is exposed using a drill with a diamond burr (Fig. 2A). The anterior and posterior ethmoidal arteries are identified, cauterized, and divided. The crista galli is carefully detached from the dura and removed with blunt instruments, preserving the integrity of the dural layer (Fig. 2B).

### Intracranial work

The key point for subsequently performing an optimal skull base reconstruction is to properly dissect the epidural space over the orbital roofs laterally, the planum



**Fig. 2.** Step-by-step endoscopic resection with transnasal craniectomy of a sinonasal malignancy encroaching on the ASB. (A) After removing the ethmoidal box bilaterally, the ethmoid roof is exposed using a drill with a diamond burr; (B) crista galli removal, preserving the integrity of the dural layer; (C) transnasal resection of the dural layer together with the right olfactory bulb affected by the tumor; (D) bilateral resection of the ASB dura from the frontal sinuses back to the sphenoid and from one papyracea to the other; (E) skull base reconstruction using a free graft of iliotibial tract placed intradurally (first layer); (F) the second layer of iliotibial tract was placed in the epidural gap. CG, crista galli; dm, dura mater; EtR, ethmoidal roof; FC, falx cerebri; FL, frontal lobe; FS, frontal sinus; ITT, free graft of autologous iliotibial tract; OB, olfactory bulb; OC, olfactory cleft; P, papyracea; SS, sphenoid sinuses.

sphenoidale posteriorly, and the posterior wall of the frontal sinus anteriorly before starting the resection of the dura. The dura is then incised and circumferentially cut with angled scissors or a dedicated scalpel, far enough away from the suspected area of tumor spread (**Fig. 2C, D**). The falx cerebri is clipped in the anterior portion before its resection, to avoid sagittal sinus bleeding; then its posterior portion at the level of the sphenothmoidal planum is resected. The arachnoid plane over the intracranial portion of the tumor is then dissected and separated from the brain parenchyma. The specimen, including the residual tumor, the ASB, and the overlying dura, together with 1 or both of the olfactory bulbs, is removed transnasally. The dural margins are sent for frozen sections. With small tumors, the dural resection can be performed by leaving the ethmoidal complex attached to the skull base at the level of the olfactory grooves in a monoblock fashion.

### ***Skull Base Reconstruction***

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The resulting skull base defect is reconstructed by the endoscopic endonasal multi-layer technique, performed preferably using autologous materials. In our experience, the fascia lata and/or the iliotibial tract possess the best characteristics in terms of thickness, pliability, and strength.<sup>45</sup> For the first intradural layer of duraplasty, the graft has to be at least 30% larger than the dural defect and split anteriorly on the midline to adjust to the falx cerebri in case of bilateral resection.<sup>45</sup> The second layer, intracranial and extradural, needs to be precisely sized and tacked between the previously undermined dura and the residual ASB bone (**Fig. 2E, F**). Pieces of fatty tissue are placed to eliminate the dead space between the second and third layers and to flatten the residual denuded ASB. The third extracranial layer has to cover all the exposed ASB, but must not overlap the frontal sinusotomies. The borders of the second and third layers are properly fixed with fibrin glue. In the case of a tumor sparing the nasal septum and without multifocal localizations (eg, not ITAC), for the third layer of the skull base reconstruction it is also possible to use a mucoperiosteum/mucoperichondrium pedicled nasoseptal flap (Hadad-Bassagasteguy flap).<sup>46</sup> Its use facilitates rapid healing of the surgical cavity, especially in patients who require adjuvant irradiation. At the end of the procedure, in selected cases, the frontal sinusotomies can be stented with rolled polymeric silicone sheaths to allow subsequent frontal sinus debridement with no risks for the duraplasty. The surgical cavity is packed for about 48 hours.

For lesions filling the frontal sinus or encroaching on the ASB with intradural extension over the orbital roof or with brain parenchyma infiltration, the EER has to be combined with an external approach (CER).<sup>43</sup> The procedure is performed by 2 surgical teams (neurosurgeons and otorhinolaryngologists), working simultaneously through a transnasal and transcranial corridor, respectively. The endonasal approach allows the ethmoidal labyrinth to be mobilized in a monoblock, by removing the nasal septum and rostrum and dissecting the sphenoid posteriorly and the lamina papyracea laterally. The transcranial approach consists of a subfrontal (or frontal) craniotomy, the size and shape of which depends on the surgical requirements. The craniotomy is performed a few millimeters above the orbital upper arches in order to obtain an approach to the frontal skull base as broad and tangential as possible, to reduce as much as possible any excessive retraction of the cerebral parenchyma and thus avoid excessive kinking of the pericranium flap during the ASB reconstruction. A bony flap including the anterior and posterior wall of the frontal sinus is harvested. After detaching the bony flap from the dural layer and clipping the sagittal sinus emissaries to control the bleeding, the exposed dura is incised, the cerebral falx is dissected, and the intracranial portion of the tumor is carefully resected from the brain parenchyma. The intracranial dissected lesion, together with the ethmoidal box, are extracted

transcranially by the two surgical teams cooperating through the different approaches. The dural defect is rebuilt by suturing the dura mater to the temporal fascia or fascia lata. The ASB defect is reconstructed using a galeoperiosteum flap that is folded over and fixed with sutures to the remaining sphenoidal border and to the orbital process of the frontal bone (medial edge). The bony flap is put back into place and fixed with titanium plaques and screws. The galeal skin flap is then relocated and sutured. At the end of the procedure, the endoscopic endonasal approach is useful to verify the watertight closure and to apply connective tissue in overlay fashion (temporal fascia or fascia lata), for reinforcing the ASB reconstruction.

### **Complications**

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In general, the complication rate and overall morbidity of endoscopic procedures compares favorably with those of external procedures such as CFR, even though the extent of surgery is comparable with that of open procedures.<sup>2,5,41,42</sup> The absence of facial incisions and osteotomies, improved visualization of tumor borders, less postoperative pain, shorter hospitalization time, and the reduced intraoperative mortality are the major advantages promoting the EER as a good alternative to traditional external procedures whenever feasible, despite the longer surgical training and extensive experience required.<sup>41</sup> The 2 largest endoscopic series of recent years reported an overall complication rate of 9% to 11% and a mortality of 0% to 1%,<sup>41,42</sup> compared with an overall complication rate of 36.3% and mortality of 4.5% for CFR.<sup>4</sup> As expected, the most frequent major complication in endoscopic series was cerebrospinal fluid (CSF) leak, with a prevalence of 3% to 4.3%.<sup>41,42</sup> A recent analysis performed by the Italian group on a subset of 62 patients who underwent endoscopic removal of tumor with dural resection showed that the occurrence of CSF leak is related to the learning curve of the surgical team and to the refinement of surgical technique.<sup>45</sup> Other possible complications observed were infections (local or systemic), epiphora, mucocele formation, and epistaxis. The overall complication rates increased with T4 lesions and larger tumors and if an endoscopic craniectomy was added.<sup>47</sup>

### **Postoperative Care**

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All patients undergoing skull base reconstruction require a brain CT scan on the first postoperative day to rule out complications and to evaluate the extent of pneumocephalus, and they must observe complete bed rest keeping the head in a 20° upright position until the third postoperative day. Nasal packing is gradually removed under endoscopic vision within 48 hours. Intravenous third-generation cephalosporin therapy is started the day before surgery and continued for at least 5 days. During the early postoperative period, stool softeners are suggested and the patient is recommended to avoid blowing the nose or exerting physical effort for some weeks. Nasal irrigation with saline solution and application of mupirocin ointment twice daily is recommended for at least 2 months.

### **Follow-up**

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All patients are followed according to a protocol that includes monthly endoscopic examinations and MRI every 4 months during the first year; endoscopic examination and MRI every 2 and 6 months, respectively, during the second year; and thereafter both examinations at 6-month intervals until the fifth year. Thereafter, patients are followed with endoscopy and MRI every 12 months until the 10th year. During this period, attention should be given also to potential metastatic dissemination of disease. Our protocol includes a whole-body staging of the disease performed once per year using chest radiograph and neck ultrasonography for low-grade tumors and PET-CT for aggressive

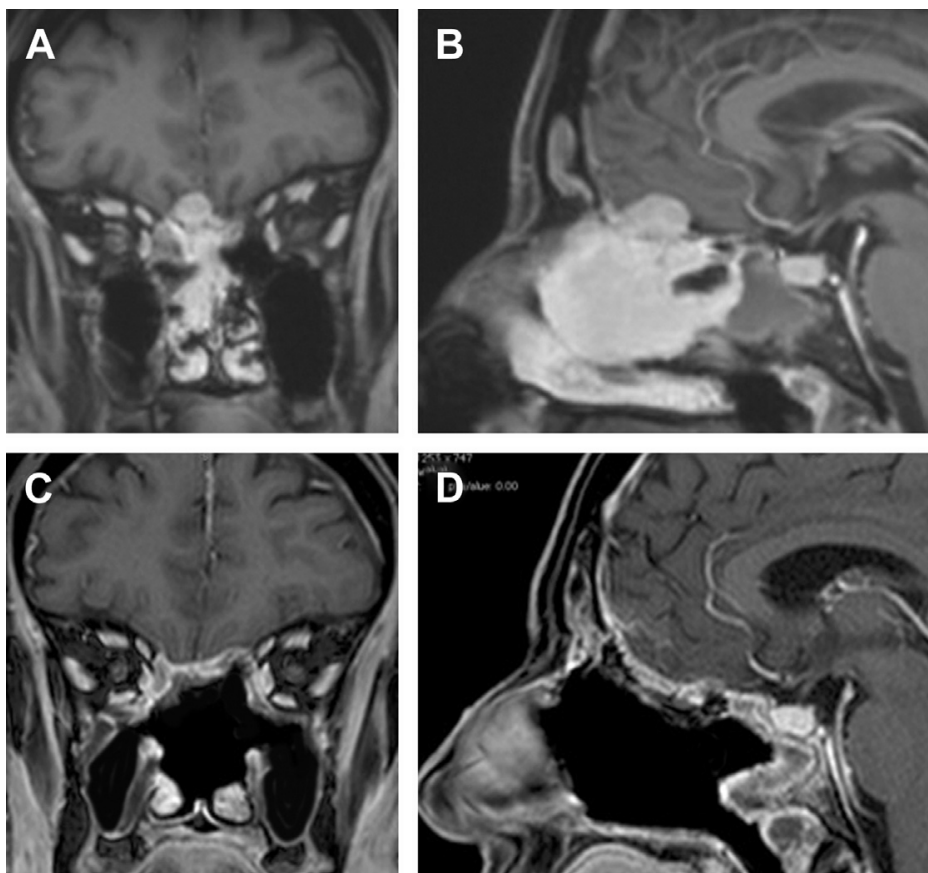
histologies (eg, MM, NEC, SNUC, sarcoma).<sup>2,5</sup> For specific histotypes showing a late recurrence pattern (eg, ONB), a long-term close follow-up for more than 10 years or, whenever possible, extended for an individual's lifetime is recommended.<sup>12</sup>

## OUTCOMES

Because endoscopic techniques have been applied with curative intent, there have been many publications reported in literature, although most of them have been characterized by small numbers, mixed histologies, and short follow-up.<sup>41,42</sup> Data emerging from these studies underline that the endoscopic approach is safe and effective and it can be undertaken in cases of appropriate histology and extent of disease, with the expectation of equivalent results to CFR and in many cases with reduced morbidity and hospital stay. However, at present, it is mandatory to perform analysis of survival outcomes in relation to specific histologies, in order to clarify the role of endoscopic surgery in the multidisciplinary management of such cancers and, possibly, to refine it based on available data.

### *Olfactory Neuroblastoma*

Endoscopic surgery has an accepted role for the resection of this tumor, showing encouraging outcomes that are higher than for other sinonasal cancers (Fig. 3). In a



**Fig. 3.** Preoperative T1-weighted contrast-enhanced MR scan in coronal (A) and sagittal (B) views showing an olfactory neuroblastoma with intracranial extension and right olfactory bulb involvement (Kadish C). The tumor was excised through an endoscopic resection with transnasal craniectomy followed by adjuvant IMRT (68 Gy on the surgical area and 54 Gy on the neck with retropharyngeal nodes). Postoperative MR scan obtained 5 years after surgery (C, D) excluded local recurrence of disease.



meta-analysis of 23 publications comparing endoscopic with open surgery, endoscopic surgery was associated with better survival (10-year OS of 90% compared with 65% for open resection).<sup>48</sup> Hyams grading represents an independent prognostic factor, as shown by the Gustave Roussy experience on 44 cases published in 2013, in which 5-year OS of patients with Hyams grade IV was 14.8% versus 100%, 90.9%, and 86.2% respectively for patients with Hyams grade I, II, and III. The University of Virginia reported 15-year and 20-year disease-free survival (DFS) of 82.6% and 81.2%, respectively,<sup>49</sup> and the MD Anderson Cancer Center found a median time to recurrence of 6.9 years and incidences of overall recurrence and distant metastasis of 46% and 15%, respectively.<sup>20</sup> These data suggest that recurrences may occur late, even beyond 10 years after the initial diagnosis, confirming that lifelong follow-up is required irrespective of the treatment.

### ***Neuroendocrine Carcinoma***

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The limited number of cases published, difficulties of diagnosis, and heterogeneity of treatment approaches has hampered meaningful evaluations.

The largest series (28 patients) was reported by Mitchell and colleagues<sup>25</sup> with 5-year OS, disease-specific survival (DSS), and DFS of 66.9%, 78.5%, and 43.8%, respectively. The incidences of local, regional, and distant failure were 21%, 25%, and 18%, respectively.<sup>25</sup> Other studies reported local recurrence rates of 45% to 50% and distant metastasis rates of 35% to 42%, which shows the aggressive biological behavior of this cancer.<sup>25-27</sup>

### ***Sinonasal Undifferentiated Carcinoma***

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The prognosis of SNUC is generally dismal with patients presenting with locally advanced disease in 67% to 81% of cases and nodal or distant metastasis in 13% to 21% of cases.<sup>50</sup> Al-Mamgani and colleagues<sup>51</sup> published a series of 21 patients divided between chemoradiation therapy, neoadjuvant chemotherapy, or surgery as primary modes of treatment. Predictors of local control on multivariate analysis were T staging and treatment with 3 treatment modalities compared with 2 modalities (**Fig. 4**). This series reported the best survival outcomes published to date (OS of 74%), suggesting that a tailored treatment approach is better than any 1 strategy.<sup>51</sup>

### ***Squamous Cell Carcinoma***

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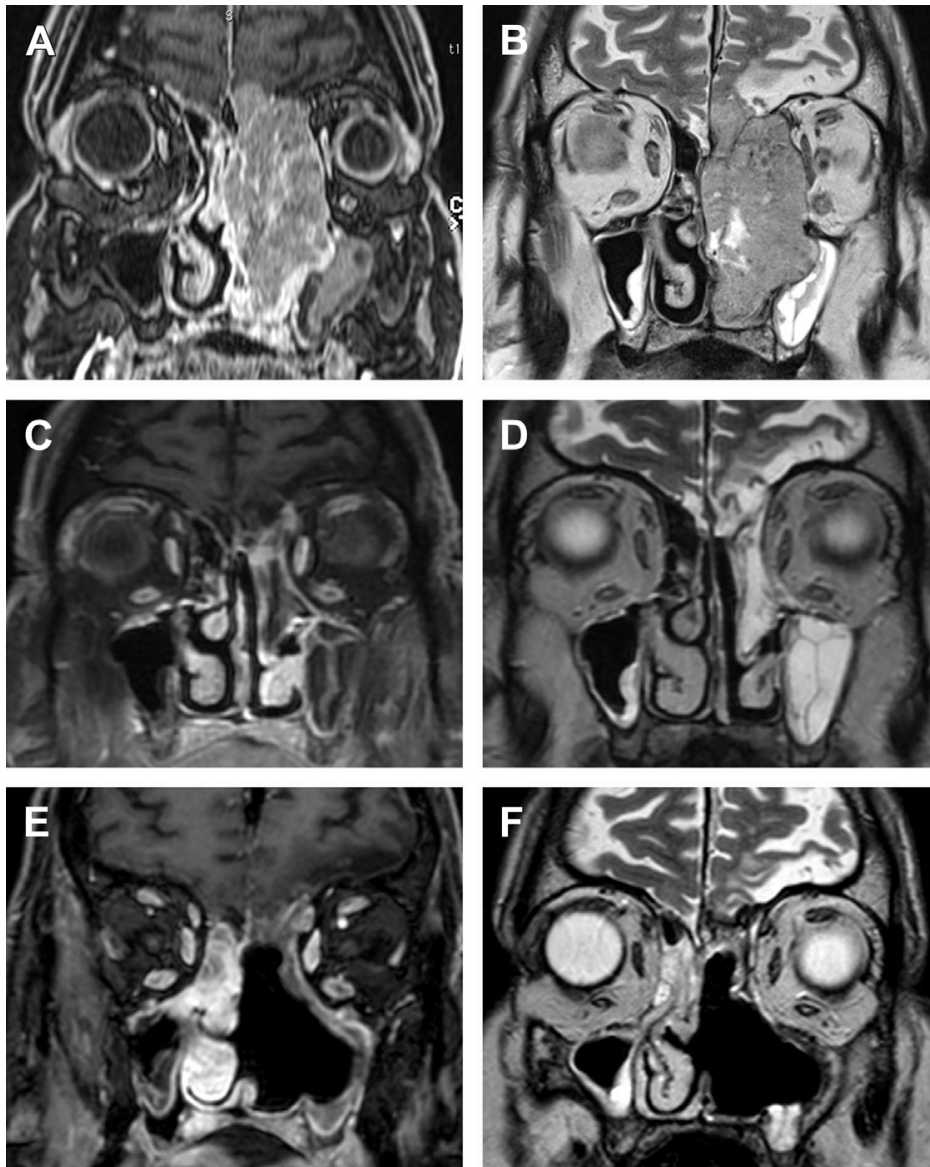
Published studies on endoscopic resection of squamous cell carcinoma consist of small series, the largest of which reported a 5-year DSS rate of 61%.<sup>1,41,42,52</sup> The University of Pittsburgh Medical Center recently presented its experience of 34 patients treated with endoscopic surgery.<sup>13</sup> The cohort consisted mostly (85%) of stage T3 to T4 tumors. Seventy-four percent of patients were treated with the purely endoscopic endonasal approach and 26% were treated with combined transcranial/transfacial and endoscopic endonasal approaches. Twenty-seven patients had definitive resection and 7 had debulking surgery. The definitive resection group had 5-year DFS and OS rates of 62% and 78%, respectively. The positive margin rate was 19% in the definitive resection group. Survival was comparable with that for open surgery.<sup>13</sup>

### ***Adenocarcinoma***

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Preliminary experiences published more than 10 years ago suggested that the endoscopic technique is safe and effective in sinonasal adenocarcinoma resection, obtaining acceptable oncologic outcomes and minimizing morbidity and hospitalization time for the patients.<sup>41,42</sup> Thereafter, Antognoni and colleagues<sup>16</sup> reported a series of





**Fig. 4.** Contrast-enhanced T1-weighted (A) and T2-weighted (B) MR scan showing a sino-nasal undifferentiated carcinoma involving the left ethmoid with intracranial extension, staged cT4bN0M0. The patient was initially treated with chemotherapy (carboplatin and taxol), obtaining a partial response (postchemotherapy MR scan is shown in C, D). The remaining lesion was surgically removed through an endoscopic endonasal approach, followed by adjuvant IMRT (62 Gy). The 2-year posttreatment MR scan (E, F) was clear, without evidence of recurrence.

30 consecutive patients with 5-year OS, DSS, and Recurrence-free survival of 72.7%, 78%, and 69.2%, respectively, outlining the efficacy of a treatment regimen based on endoscopic resection followed by adjuvant irradiation. The largest series reported to date was recently described by Nicolai and colleagues<sup>18</sup> analyzing 169 consecutive patients affected by ITAC and obtaining 5-year OS and event-free survival of 68.9% and 63.6%, respectively. Advanced pT stage, high grade, and positive surgical margins were independently predictive of poor survival. Comparable rates of 5-year OS were also observed by Camp and colleagues<sup>53</sup> (68% from a series of 123 patients) and Vergez and colleagues<sup>54</sup> (62% from a series of 159 patients). These data strongly support a definitive paradigm shift in the management of ITAC toward a schedule including endoscopic surgery with or without adjuvant IMRT in place of external surgical techniques, which have a role only in a minority of patients.

## ***Mucosal Melanoma***

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Sinonasal MM is one of the most aggressive tumors of the head and neck region, with a very high propensity to recur and metastasize, regardless of the radicality of resection and adjuvant treatments administered.<sup>1</sup> In this regard, the seventh edition of the American Joint Commission for Cancer staging system (2010) omitted the T1 and T2 stages for upper aerodigestive tract MM, allowing the staging of lesions only as T3 or T4a-T4b.<sup>55</sup> Such dismal prognosis is supported by Lund and colleagues' <sup>38</sup> analysis of a series of 115 surgically treated patients, with 5-year OS of 28% and DFS of 23.7%. Adjuvant radiotherapy did not improve local control or survival. As expected, cervical metastases conferred a dramatically worse outcome.<sup>38</sup> Other studies found that OS was not superior to 50% at 3 years and between 26.9% and 38.7% at 5 years, confirming the aggressive behavior of the disease.<sup>39,56</sup> Moreover, there was no statistically significant association between T and N stage and the risk of death.<sup>39,56</sup> This observation confirms the high risk of failure for sinonasal MM even in apparently less aggressive lesions.

## **OPEN ISSUES**

The role of endoscopic surgery in the multidisciplinary management of sinonasal malignancies is continually being refined. In this regard, prospective analysis of data focusing on specific histologies will be paramount to understanding the natural history of, and the development of the best treatment options for, each tumor.

Recent advances in irradiation modalities, such as particle therapy with carbon ion or proton beam, need future studies to understand the potential to improve oncologic outcomes. Induction chemotherapy in specific histologies has to be further investigated to select patients who could benefit from this treatment in terms of survival rates, organ preservation, or better definition of the subsequent treatments according to response to the chemotherapy.

The possibilities to stratify tumors based on new molecular biology techniques and the tailoring of the treatment based on behavior of the tumor will further refine decision making in the future. Constant training of the multidisciplinary oncologic skull base team should help to reach these goals, minimizing the rate of complications and failures.

## **SUMMARY**

Endoscopic surgery offers an oncologically sound alternative to open surgery in selected patients with sinonasal malignancies. It offers the advantages of lower morbidity, faster recovery, and better quality-of-life outcomes. Globally, a correct classification by means of histology, immunohistochemistry, or molecular biology represents the key factor for initiating an appropriate treatment strategy. Recent data emphasized the role of appropriate histology-driven and patient-tailored adjuvant or neoadjuvant treatments by expert multidisciplinary teams in the management of sinonasal malignancies, including otolaryngologists, neurosurgeons, ophthalmologists, radiation oncologists, medical oncologists, occupational doctors, and pathologists. Although the optimal strategy is yet to be determined, individualized treatment that takes into account the stage of tumor, patient comorbidities, and histologic characteristics can achieve better survival. Pathology-specific and long-term follow-up survival data are required to further define the role of endoscopic surgery in the setting of multidisciplinary care.

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