When is a multidisciplinary surgical approach required in sinonasal tumours with cranial involvement?

Quando è indicato un approccio chirurgico multidisciplinare nei tumori naso-sinusali con estensione cranica?

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SUMMARY

The term "sinonasal tumours" includes a large spectrum of diseases, which are characterized by heterogeneous biological behavior and prognosis, and located in a critical anatomic area. Diagnosis and treatment of sinonasal tumours require the contribution of different disciplines. A narrative review was performed to highlight the role of surgeons in contributing to a multidisciplinary approach to sinonasal tumours. Diagnosis and staging of sinonasal tumours is challenging and requires collaboration between surgeons, radiologists, and pathologists. The identification and management of critical extensions (orbital or intracranial encroachment, vascular abutment or encasement) is fundamental for successful treatment. Most cases of advanced sinonasal tumours can undergo surgical intervention by an adequately trained otorhinolaryngological team. The contribution of neurosurgeons and oculoplastic surgeons is required in selected scenarios. In rare circumstances, multidisciplinary reconstructive strategies can be indicated for complex tissue defects. Furthermore, a multidisciplinary approach is pivotal in the management of perioperative complications. While surgery remains the mainstay of treatment, the role of non-surgical adjuvant or even exclusive treatments is constantly expanding.

KEY WORDS: sinonasal tumours, anterior skull base tumours, cranial involvement, multidisciplinary team, multidisciplinary treatment

RIASSUNTO

I tumouri nasosinusali includono un ampio spettro di neoplasie caratterizzate da un comportamento biologico eterogeneo e dalla localizzazione in un distretto anatomico critico. Diverse discipline mediche sono coinvolte nella diagnosi e nel trattamento di tali tumori. Una revisione narrativa della letteratura è stata condotta per identificare i ruoli delle specialità chirurgiche che appartengono al gruppo multidisciplinare. La diagnosi e la stadiazione dei tumori nasosinusali richiede la collaborazione tra chirurghi, radiologi e patologi. L'identificazione delle estensioni tumorali critiche è fondamentale per un corretto trattamento. L'intervento chirurgico necessario per la maggior parte dei tumori nasosinusali avanzati può essere eseguito da un team otorinolaringoiatrico con adeguato training. Il contributo di neurochirurghi e di specialisti in chirurgia orbitaria è necessario in scenari selezionati. Nei casi di difetti chirurgici complessi possono essere necessarie strategie ricostruttive multidisciplinari. La collaborazione chirurgica multidisciplinare è essenziale per la gestione delle complicanze nel periodo perioperatorio. Nonostante la chirurgia rimanga il trattamento principale, si sta affermando una vasta gamma di trattamenti non-chirurgici, adiuvanti o esclusivi.

PAROLE CHIAVE: *tumori nasosinusali, tumori della base cranica anteriore, coinvolgimento cranico, gruppo multidisciplinare, trattamento multidisciplinare*

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Introduction

Ideally, sinonasal tumours should always be managed through a multidisciplinary team (MDT) approach. In fact, while most surgical procedures for advanced sinonasal cancers are performed by a single-specialty surgical team, the path leading patients to the operating theater requires a long list of surgical specialists and non-surgical physicians, whose contribution is variably needed based on the characteristics of each case. The need for multidisciplinary management owes to the vast spectrum of diseases included in the term "sinonasal tumours", which are located in a watershed area where the combined knowledge of different specialties and subspecialties is frequently a must.

The benefit of using MDT approach has been thoroughly and objectively demonstrated for head and neck cancers [1]. The present article aims to highlight the surgical aspects of a modern MDT approach to advanced sinonasal tumours.

Sinonasal cancer frequently represents a challenge due to a number of critical issues, the most relevant being reliability of diagnosis, extension towards the intracranial spaces, face and orbit, possibility to spare content of the orbital cavity, sensitivity to non-surgical treatments, expected treatment-related morbidity, and prognosis. Therefore, sinonasal cancers are frequently at the top of the list of malignancies requiring thorough multidisciplinary assessment. Similarly, some benign or borderline sinonasal diseases that are usually treated by surgery might benefit from a MDT approach in view of some special characteristics they can display. The rarity of sinonasal tumours alongside with the willingness of patients to refer to centers with adequate experience lead most cases to concentrate into "superspecialized" centers. On one hand, this implies that expertise in management of sinonasal tumours cannot prescind from training in those centers where an adequate volume of cases is managed by an MDT. On the other hand, cases diagnosed in centers with a low volume of sinonasal tumours should be cautiously managed and referral to or consultation with institutions with acknowledged experience should be considered as an act of medical responsibility [2]. This is even more true when considering that for the majority of sinonasal tumours the actual chance to cure the patient relies on primary treatment, whereas recurrence is much more difficult to treat irrespective of MDT experience [3].

The professional figures who should ideally participate in a MDT are summarized in Table I and clustered as "essential" and "required on a case-by-case basis" depending on how often they are consulted according to authors' experience. Though surgeons are frequently the "quarterback" of the MDT approach to sinonasal tumours, different non-surgical physicians alternatively lead case management depending upon the specific phase and circumstances.

Pretreatment diagnosis

Diagnosis of tumours of the sinonasal tract is a considerable challenge to the pathologist. This is mostly due to the rarity, pathological heterogeneity, and possible morphological similarity of different sinonasal tumours.

An emblematic example is represented by "small round blue cell tumours". This term was coined by Bridge et al. in 2010 and refers to tumours displaying a non-specific morphology, which consists of "monotonous population of undifferentiated tumour cells with relatively small-sized nuclei and scant cytoplasm" [4]. This non-specific morphology is potentially underlaid by a number of cancers including adenoid cystic carcinoma (ACC), Ewing-family tumours, human papilloma virus (HPV)-related, ACC-like carcinoma, non-keratinizing squamous cell carcinoma (SCC), lymphoepithelial carcinoma, NUT carcinoma, SMARCB1/INI1-deficient carcinoma, sinonasal undifferentiated carcinoma (SNUC), neuroendocrine carcinomas (NEC), mucosal melanoma (MM), olfactory neuroblastoma (ONB), rhabdomyosarcoma, mesenchymal chondrosarcoma, and other tumours [5]. As a consequence, a rational investigation through immunohistochemistry is essential to unveil molecular hints that ultimately lead to correct diagnosis [5]. As for all pathological conundrums, information coming from clinical history as well as endoscopic and radiologic findings can be of help to anticipate a diagnosis or at least estimate its reliability in the pretreatment setting [6,7].

Another challenge faced by the MDT is that knowledge of sinonasal tumours has been evolving with an accelerating pace [8]. This concept is well exemplified by SNUC histology. Originally described by Frierson et al. in 1986 [9], SNUC soon raised the interest of many researchers and clinicians. Since its description, it has represented a diagnosis of exclusion, thus early acquiring the role of "wastebasket entity" which still characterizes SNUC [10]. However, refinements in molecular diagnostics and biological understanding of sinonasal tumours progressively led some cancers initially labelled under the umbrella of SNUC to be diagnosed based on an immunohistochemical identifier rather than by exclusion. SMARCB1/INI1-deficient carcinoma [11], SMARCA4-deficient carcinoma [12], IDH2-mutant SNUC [13], HPV-related SNUC [14], and NUT carcinoma [15] (formally not considered a SNUC subtype) [16] are the most relevant examples of this phenomenon. While providing new diagnostic tools, this process should also prompt pathologists and their MDTs to be updated on the constant advancements of diagnosis of sinonasal

Table I. Members of the multidisciplinary team to treat advanced sinonasal tumours.

Multidisciplinary team member	Role(s)
Essential members	
Otorhinolaryngologist, head and neck surgeon	Clinical diagnosis and pre-treatment biopsy Surgical excision and skull base reconstruction Pathologic staging* Clinical follow-up
Radiologist, PET-trained physician	Tumour mapping and re-staging Pathologic staging* Radiologic follow-up
Pathologist	Preoperative pathologic diagnosis Postoperative pathologic evaluation of the surgical specimen Pathologic staging*
Medical oncologist	Neoadjuvant chemotherapy Concomitant chemotherapy Palliative chemotherapy Immunotherapy and biotherapy
Radiation oncologist	Definitive radiation therapy Adjuvant radiation therapy Palliative radiation therapy Referral to a particle therapy center
Required on a case-by-case basis	
Neurosurgeon	Management of cases with critical transcranial and/or orbital apex extension Bypass surgery Management of intracranial complications
Plastic surgeon, surgeon with advanced plastic surgery training	Reconstruction of complex defects
Ophthalmologist, oculoplastic surgeon, maxillofacial surgeon	Management of cases with advanced involvement of the orbit and/or lacrimal system
Neuroradiologist, interventional radiologist	Temporary occlusion test Endovascular occlusion/stenting of the internal carotid artery
Anesthesiologist, critical care physician	To anticipate complex cases from an anesthesiologic standpoint To support management of intraoperative and early postoperative complications To minimize early postoperative events potentially favoring failure of the skull base reconstruction (e.g. nausea, vomit, cough)
Dentist/oral health consultant	To address dental/periodontal disease before radiation therapy Dental rehabilitation in patients who undergo midfacial bone reconstruction
Psychiatrist, psychologist, mental health professional	To diagnose and address mental health disorders
Pediatrician, pediatric subspecialist(s)	To anticipate and manage age-related medical/surgical issues in pediatric patients To lead management of complex cases in syndromic patients To propose and manage complementary antiangiogenic and other medical therapies
Geriatrician	To anticipate and manage age-related medical/surgical issues in elderlies
Endocrinologist	To anticipate and manage surgery- and/or disease-related endocrinological disorders
Hematologist	To lead management of lymphoproliferative disorders
Palliative medicine physician, pain management specialist	To lead management of patients for whom palliation is indicated
Thoracic surgeon and other surgeons	To perform metastasectomy in carefully selected patients
Prosthetic anaplastologist	To organize facial/orbital/nasal/palatal prosthetic rehabilitation
Hyperbaric medicine physician	To indicate and organize hyperbaric oxygen therapy in patients with skull base radionecrosis, osteomyelitis, or similar disorders

** Pathologic staging is best performed in consensus between the pathologist, radiologist, and surgeon who performed the resection.*

tumours and equip them with the most modern and promising staining methods.

Despite improvement in the understanding and definition of sinonasal tumours, diagnosis remains a challenge, as witnessed by the considerable rate of misdiagnoses observed even in referral centers. Mehrad et al. analyzed 500 consecutive cases of head and neck tumours and found 20 (4.0%) had major diagnostic discrepancies (with "major" denoting a "significant change in patient management and/or prognosis"), 4 (20.0%) of which were sinonasal tumours [17].

Considering the prevalence of sinonasal tumours in their series, the sinonasal tract was the site with the highest rate of major diagnostic discrepancies (19.0% *vs* 0.0-8.3%). Schreiber et al. reported on a series of 77 nasoethmoidal tumours on which they analyzed diagnostic reliability of pretreatment biopsy [7]. They found that the overall reliability was 83.1%, with pretreatment diagnosis of SCC or miscellaneous tumours (*i.e.* "malignant neoplasm", "mesenchymal neoplasm", "poorly differentiated carcinoma", "undifferentiated carcinoma not otherwise specified", and NEC) and sampling of a small volume of tissue being significantly associated with the highest risk of misdiagnosis. On the other hand, diagnosis of adenocarcinoma, MM, and ONB was associated with high reliability (97-100%), which led the authors to conclude that well-defined clinical scenarios such as, respectively, wood or leather workers, elderly with pigmented sinonasal lesions, and lesions centered in the olfactory cleft with a cystic component on the intracranial aspect could be reasonably sampled in the outpatient clinic under local anesthesia. Other presentations should warrant ample sampling (*i.e.* at least 2 mL), which is best achieved under sedation or even general anesthesia. Similarly, Ganti et al. described 11/52 (21.2%) cases of discrepancy between preoperative and postoperative histopathology over a 4-year time span [18]. In particular, they distinguished 4 (7.7%) cases of shift from benign to borderline/malignant disease, 3 (5.8%) from a malignancy to another cancer with more aggressive behavior, and 4 (7.7%) from malignancy to a benign disease.

These data dispel doubts that pathologists should be an active member of MDTs treating sinonasal tumours. Not only is the pathologist in charge of providing pretreatment diagnosis, but also in sharing its estimated reliability, potential pitfalls, and most probable alternative diagnoses with the MDT. As a final remark, the pathologist is also involved in other essential phases of the diagnostic-therapeutic process, which includes postoperative diagnosis, detection of pathological risk factors, and pathological staging. In this regard, it is the authors' opinion that definition of margin status and pathological staging should be the result of a teamwork from the MDT. In fact, both these processes require in-depth anatomical mapping of tumour extension, which cannot ignore a simultaneous analysis of imaging and consultation with the surgeons who performed surgery.

Mapping of local extension of the tumour through pretreatment imaging

Improvement of cross-sectional imaging, with special reference to magnetic resonance (MRI), has been one of the main evolutionary drivers in the field of sinonasal tumours.

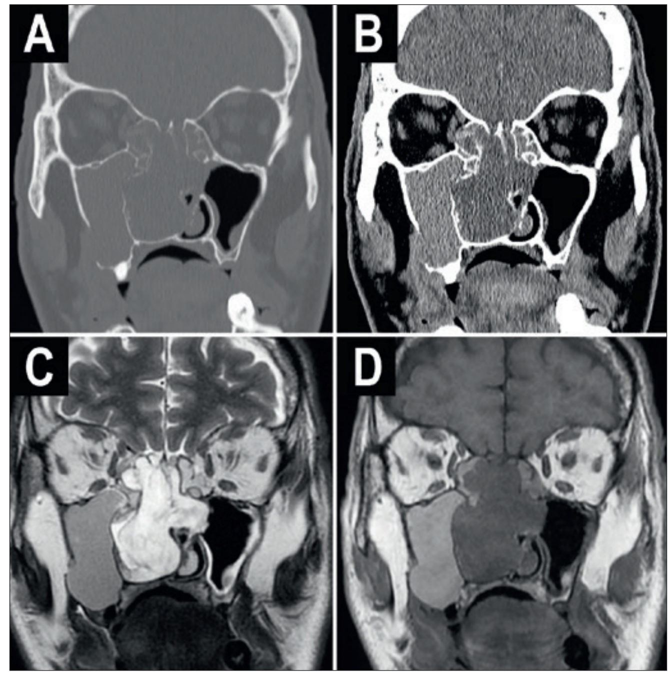

Figure 1. Computed tomography (**A, B**) and magnetic resonance imaging (**C, D**) of a mucinous, signet-ring cell, intestinal-type adenocarcinoma of the right nasoethmoidal complex. Different imaging modalities allow depiction of tumour extension with respect to the most relevant adjacent compartments (i.e. orbital cavity, skull base).

Precise mapping of tumour extension is a pivotal step in treatment planning, particularly in relation to orbit and skull base invasion (Fig. 1). The presence in the MDT of a head and neck radiologist with specific expertise in sinonasal tumours is therefore crucial [19].

Nasal cavity and paranasal sinuses are separated from the orbit and the intracranial space by several bony laminae, which are thought to serve as barrier against tumour spread. Computed tomography (CT) depicts changes and losses of mineralization of bony structures [20,21]. However, resorption of the mineral content of a bony wall does not necessarily imply that the tumour has invaded the adjacent compartment. In fact, the most effective barrier to neoplastic spread beyond sinonasal boundaries is known to be the periosteum [22]. Therefore, knowledge of infiltration and/or transgression of the periosteum represents a critical information for therapeutic planning. In this regard, MRI has an intrinsic advantage over CT. In fact, the cortical bone and periosteum can be adequately demonstrated as a single, homogeneous hypointense layer, irrespective of bone mineralization [23]. Similarly, the dura and bony skull base appear as a single hypointense layer in non-contrast-enhanced sequences. The dura differs from extracranial periosteum because it frequently reacts to an advancing lesion by significantly increasing its thickness and enhancement [24]. Overall, the biological heterogeneity of sinonasal tumours translates into 4 different patterns of bone involvement [25]: 1) bone remodeling, with displacement and thinning of bony walls [26]; 2) cortical destruction, with interruption of the cortical bone layer; 3) permeative invasion, which is replacement of medullary bone in the absence of obvious cortical interruption; 4) medullary sclerosis, with fibrous-like tissue formation in the medullary portion of a bone structure.

Once bony boundaries are transgressed, accurate description of the stage of involvement of adjacent compartments becomes paramount. In fact, infiltration of adjacent compartments such as the orbit, soft tissues of the face, and intracranial space might dictate the need for neoadjuvant treatment, the response to which cannot be adequately evaluated unless the initial extension has been accurately staged.

Maroldi et al. demonstrated that MRI is superior to CT in predicting the absence of orbital invasion (negative predictive value: 100% *vs* 75%, overall accuracy 96% *vs* 81%, respectively) [27]. In a recent study, Ferrari et al. analyzed the diagnostic performance of MRI in detecting the involvement of single orbital structures: the adjusted diagnostic accuracy was satisfactory (≥ 80.0%) for the bony layer, extraconal fat, and muscular layer, but suboptimal (< 80.0%) for the periorbit and intraconal compartment [28]. Overall, MRI was confirmed to provide precious preoperative information on orbit involvement, though with specific shortcomings the MDT should be aware of. Another goal of imaging is to establish the depth of transcranial invasion [29,30]. Different degrees of invasion through the anterior skull base can be identified by analyzing the signal of dura, cerebrospinal fluid (CSF), brain, and tumour, which is best depicted by MRI [25]. Finally, potential contraindications to surgery such as encasement of internal carotid artery and involvement of the cavernous sinus should be evaluated on preoperative imaging.

In order to facilitate comprehensive radiologic evaluation of sinonasal tumours, Maroldi et al. proposed a checklist approach [19]: 1) the first step consists of separating the tumour from the signal of retained mucus or inflamed thickened mucosa; 2) the second step is mapping gross tumour extension: once the epicenter of tumour is located, its 3-dimensional extent should be analyzed systematically including six "vectors of growth" (*i.e.* anterior, posterior, medial, lateral, caudal, cranial); 3) the last step is inference of potential patterns of non-macroscopic spread based on imaging findings (*e.g.* enhancement, signal replacement) and clinical information (*e.g.* histology, primary *versus* recurrent presentation). The same authors suggested that the radiologist joining the MDT should carry "hand luggage" with 4 epistemic compartments [19]: mastering of technical solutions, knowledge of radiologic anatomy, understanding of information with practical implications for other MDT members, and awareness of different biological behaviors displayed by tumours of the sinonasal tract.

Preoperative embolization and preventive measures against major vascular complications

Resection of sinonasal tumours with a critical relationship to major vessels and/or intrinsic hypervascularity (Tab. II) represents a challenge [31]. In fact, uncontrolled bleeding causes poor visualization, increases the risk of complications such as cranial nerve injury, CSF leak, and rupture of major vessels, and limits the ability to completely remove the tumour. Potential additional morbidity includes postoperative anemia and blood transfusion-related issues. Even if immediate corrective protocols are available, death is also a possible consequence of unresolved massive intraoperative blood loss [32]. Consequently, all sinonasal tumours displaying hypervascularity and/or abutting or encasing a major vessel should be discussed with and possibly managed by an MDT including an interventional radiologist.

Angiography and embolization

Blood supply to the tumour can be surmised based on the location and extent of the lesion. This particularly applies

Table II. Most common hypervascularized tumours of the sinonasal tract.

Benign vascular tumours and tumour-like lesions	Juvenile angiofibroma Hemangioma (lobular capillary hemangioma) Angioleiomyoma Sinonasal paraganglioma
Vascular malformations	Venous malformation (cavernous hemangioma)
Borderline/low grade malignant tumour	Glomangiopericytoma Solitary fibrous tumour
Primary malignant vascular tumours	Angiosarcoma
Secondary hypervascularized tumours	Renal cell carcinoma

to juvenile angiofibroma (JA), which predominantly receives vascular supply from the external carotid artery but can also be fed by branches arising from the internal carotid artery (ICA), especially in case of large lesions. Notably, 30% of JAs show a bilateral vascular supply, which increases to almost 70% in advanced cases [33]. Vascular feeders of sinonasal paragangliomas [34], hemangiopericytomas [35], haemangiomas [36], and other hypervascularized lesions [37,38] are less well known given their rarity. Transarterial angiography provides the MDT with a case-specific map of vascular feeders, which enables estimation of intraoperative risks, morbidity of embolization or ligation, and potential residual vascularity following embolization.

Embolization is meant to reduce tumour vascularity through the injection of particles, coils, liquid embolic agents, or other substances. It can be performed through direct puncture of the tumour and/or via an endovascular approach. Traditionally, tumour embolization has been achieved via a transarterial route (most commonly through the femoral artery) with superselective catheterization and embolization of feeding vessels. Superselective catheterization of external carotid branches not only depicts the vascular architecture of the lesion, but also unveils potentially dangerous anastomoses with the cerebral/orbital vasculature which can result in subtotal embolization or even dramatic complications such optic nerve ischemia [39]. Evaluation of the contralateral carotid branches should be done to exclude contribution to tumour blush, particularly when the tumour extends beyond the midline [40]. Direct puncture techniques using liquid embolic agents (*e.g.* Onyx) have also been described. They can be used in conjunction with transarterial embolization or as a sole modality of embolization [41].

Timing is a crucial aspect of embolization. Therefore, coordination of different members of the MDT is essential to guarantee a satisfactory result. Early resection following embolization (*i.e.* within 24 hours) may obscure the benefits of the procedure by not allowing enough time for tumour devascularization to occur; on the other hand, waiting too long following embolization can lead to tumour revascularization or even dramatic consequences such as tumour inflammation, infarction, and/or swelling. For these reasons, surgery should not be delayed beyond 48-72 hours following embolization [33,40,42,43]. However, a complex case of JA treated with staged surgery performed 8 days after trimodal embolization has been reported (Fig. 2) [44].

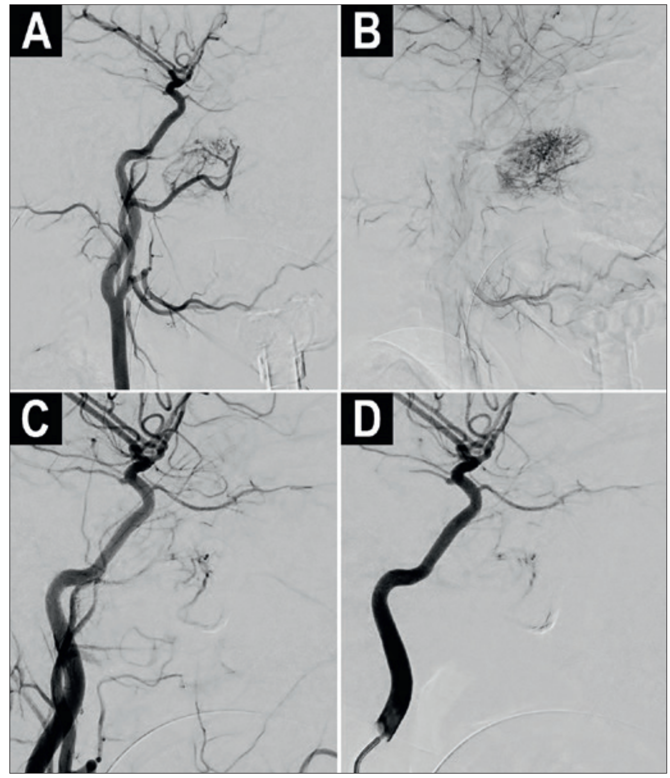

Figure 2. Angiography of a case of right juvenile angiofibroma with feeders coming from both the internal and external carotid artery systems (**A, B**). Following combined transarterial (with polyvinyl alcohol particles) and translesional (with Onyx®) embolization of the lesion and transarterial closure of the ipsilateral maxillary artery, only minimal residual enhancement from internal carotid artery feeders can be observed (**C, D**).

Measures against major vascular complications

While the indications and contraindications to surgery for sinonasal tumours have considerably evolved throughout the last decades, abutment, encasement, and frank invasion of the ICA have been invariably considered as a major criterion of difficult, dangerous, or even impossible resectability. Intraoperative rupture of the ICA has been reported to occur in 28/7160 (0.4%) endoscopic procedures and its consequences ranges from death to non-lethal cerebrovascular events, pseudoaneurysm, carotid-cavernous fistula, and need for vascular occlusion [45,46]. Although one could hypothesize that vessels-encroaching tumours should be referred to radiation oncologists, vascular toxicity actually represents a major concern even in patients undergoing RT that can considerably limit dose delivery in areas neighboring the vessel (Fig. 3). In this scenario, the expertise of a neuroradiologist, interventional radiologist, and neurosurgeon might be game changing in selected cases.

The first step is to adequately analyze the critical relationship to the vessel through CT/MRI angiography [19]. The second is to test the tolerance of a potential ICA occlusion through a temporary occlusion test, which can be achieved via external compression or transarterial balloon occlusion. Tolerance can be evaluated through a combination of several techniques including clinical assessment, cross flow tim-

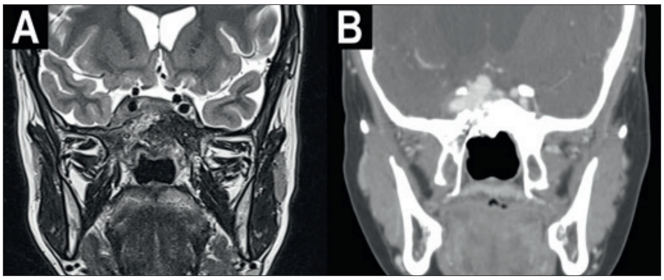

Figure 3. (**A, B**) The panel shows the case of a pseudoaneurysm of the parasellar, paraclinoid, and intracranial tracts of the right internal carotid artery in a patient who was treated through ^{12}C-carbon ion therapy for an unresectable adenoid cystic carcinoma of the right sphenoid sinus.

ing, evoked potentials, and functional imaging. In patients demonstrating adequate cross flow from the contralateral vascular system, the decision on whether or not to perform endovascular ICA occlusion prior to surgery should be based on the estimated risk of intraoperative rupture, which has a known lethality of roughly 7-15% [46,47], and possible need for vessel removal as part of the resection [48]. However, preoperative endovascular ICA occlusion should not be indicated carelessly, as the long-term effects of the procedure are unknown. In patients who would not tolerate ICA occlusion, adequate counselling on potential morbidity and mortality is mandatory and strategies such as endovascular flow diverter protective stenting or extracranial-to-intracranial bypass surgery should be considered when surgery can be staged or delayed while the patient undergoes double antiplatelet therapy (Fig. 4) [49,50].

Intracranial tumour extensions exceeding the rhinologist's expertise

The definition of intracranial involvement is of utmost importance in planning treatment for sinonasal tumours. MRI with contrast enhancement plays a key role in the delineation of the tumour-dura and tumour-brain interface. Specifically, the disappearance of the three "sandwich" layers with different signals at the anterior cranial fossa (ACF) floor (bone-periosteum, dura, and CSF) and/or the evidence of brain edema surrounding the tumour on T2-weighted images are predictors of intracranial and brain invasion, respectively [25].

Historically, the gold standard in the treatment of sinonasal malignancies invading the ACF was anterior craniofacial resection with or without adjuvant RT [51], with bilateral intraorbital and/or optic nerve extension, massive brain infiltration, optic chiasm involvement, distant metastasis, and internal carotid artery encasement being considered as absolute contraindications. By evolving the concepts

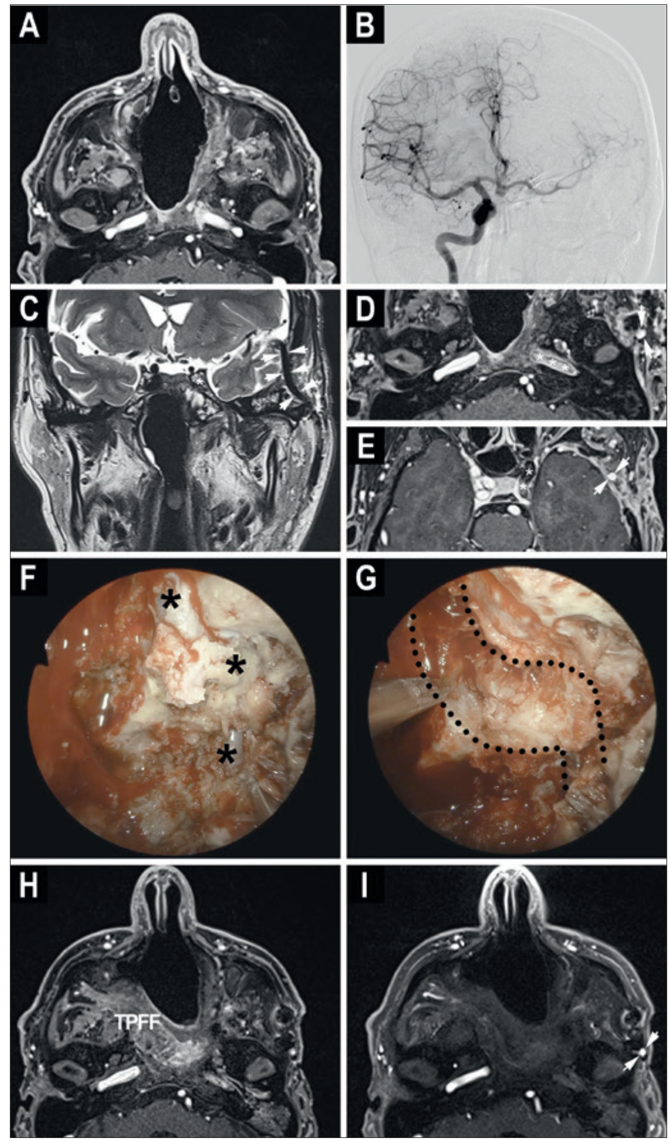

Figure 4. The panel summarizes the complex management of a case of recurrent nasopharyngeal carcinoma. (**A**) An enhancing nodule corresponding to the second local recurrence of nasopharyngeal carcinoma is identified in close relationship with the anterior genu of the left petrous internal carotid artery. (**B**) A temporary balloon occlusion test reveals that the closure of the left internal carotid artery would not be tolerated by the patient. (**C-E**) An extracranial-to-intracranial vascular bypass (white arrows) from the left external carotid artery to the left middle cerebral artery was harvested and the left internal carotid artery was closed transarterially (white asterisks). (**F, G**) A type 3 left nasopharyngeal endoscopic resection was completed and the ipsilateral internal carotid artery (black asterisks) was resected; the carotid canal (black dotted lines) was completely drilled out. (**H, I**) Follow-up imaging showing patency of the vascular bypass and viability of the right temporoparietal fascia flap (TPFF) employed to resurface the surgical cavity.

of subfrontal-subcranial approach firstly developed by Raveh [52,53], in the late '90s endoscopic techniques were introduced in adjunction to open approaches with favorable outcomes [54]. The so-called cranioendoscopic approach

(CEA) combines an endoscopic approach allowing tumour removal from the nasal side with a subfrontal craniotomy that gives wide exposure of the lesion and margin control from above. Main indications for CEA are massive infiltration of the dura, in particular when the dura is involved in proximity to the lamina papyracea or when dural resection would extend far lateral over the orbital roof [55]. Multidisciplinary parallel dissection performed by skilled neurosurgical and otorhinolaryngological teams in CEA, using the microscope and endoscopes respectively, offers accurate control of the resection with clear dural margins. Another scenario that should prompt to consider CEA is the contact between tumour and brain, "even with possible limited infiltration" [54]. Nowadays this can be probably considered a "relative" indication to CEA, or at least a condition mandating an accurate case-by-case selection. During the last two decades, in fact, the growing body of evidence in the field of endoscopic approaches to the nose and paranasal sinuses has paved the way for the first series of pure endoscopic transnasal brain resection in the context of sinonasal malignancies [56]. In cases of limited brain invasion, the proposed technique takes advantage of subpial dissection of the gyrus rectus and/or medial orbital gyrus, with the aim of achieving negative margins of resection. This resection technique requires proper preparation and experience in open and endoscopic approaches to the ACF, including adequate training in dissecting the bony and the dura layers in the context of transnasal craniectomies [57,58]. A series of 19 selected patients with clinically suspected brain infiltration (11 with pathologically-proven brain involvement) including different histologies (> 50% ONB) was recently published by the Brescia and Varese groups [56], showing that 3-year overall, local recurrence-free, and distance recurrence-free survivals were 65.5%, 81.8%, and 68.2%, respectively.

Even in referral centers for endoscopic approaches to the ACF, open approaches to the anterior skull base find their place in case of wide dural involvement, especially with lateral extension or when the tumour abuts the optic chiasm or extends over the orbital roof reaching beyond the mid-pupillary line.

Massive extension of the tumour through the dura and infiltration of falx/superior sagittal sinus and/or brain parenchyma also requires an open approach. In addition, a critical relationship with neurovascular structures as well as infiltration of the anterior wall of the frontal sinus or massive frontal sinus involvement are contraindications for purely endoscopic approaches to the ACF [59]. Furthermore, staged surgery should be considered when the tumour cannot be entirely accessed through a single approach that might require extensive bone removal or be threatened by significant blood loss, as may occur even for benign lesions like JA [60]. Procedure staging would enable complete resection, minimizing the risks related to duration of surgery and surgeons' fatigue [61].

Finally, surgeons must bear in mind that resectability of sinonasal tumours with intracranial extension is influenced not only by the entity of brain and dural invasion itself, but also by the histological diagnosis, with poorly differentiated/aggressive lesions benefitting mostly from multimodal treatment often including neoadjuvant therapy.

Orbital tumour extensions exceeding the rhinologist's expertise

The degree of orbital encroachment is a key element for planning treatment of sinonasal tumours. In the '70s, erosion of the lamina papyracea by sinonasal cancers was considered as an indication to orbital exenteration [51]. Over the last decades, several groups have demonstrated the oncologic safety of orbit-sparing surgery in adequately selected cases [62-65]; however, criteria guiding orbit-sparing surgery still lack univocal consensus [66-69]. Since the first proposal in the '80s of sparing the orbit in tumours eroding the medial orbital bony wall by Perry et al. [63] and Scott McCary et al. [64], the decisional barriers to indicate the need for orbital exenteration has been settled to the involvement of extrinsic muscles, optic nerve, ocular bulb, and/or skin overlying the eyelid, as described by Iannetti et al. in the early 2000s [70]. More recently, endoscopic and endoscopic-assisted orbit-sparing surgery was shown to be useful and oncologically safe [71]. Turri-Zanoni et al. described a multimodal treatment algorithm for sinonasal cancers with orbital invasion based on histology-driven treatment and accurate staging of the degree of orbital invasion through contemporary preoperative imaging (Figs. 5, 6) [72]. Poorly differentiated cancers without orbital apex involvement were submitted to neoadjuvant chemotherapy, which was continued up to a maximum of 5 cycles in good responders. Patients achieving complete response or ≥ 80% reduction of initial tumour volume at the end of neoadjuvant chemotherapy were sent for definitive chemoradiation; patients with less favorable response to neoadjuvant chemotherapy underwent surgical resection followed by adjuvant radiotherapy or chemoradiotherapy. Patients whose general conditions prevented chemotherapy and those affected by well differentiated sinonasal cancers or chemoresistant tumours received primary surgery, which was followed by adjuvant treatment if mandated by risk factors identified at definitive histologic examination. The multimodal treatment algorithm maximized the orbital preservation rate (76.6%) in patients with orbit-encroaching sinonasal cancer. According to a recent

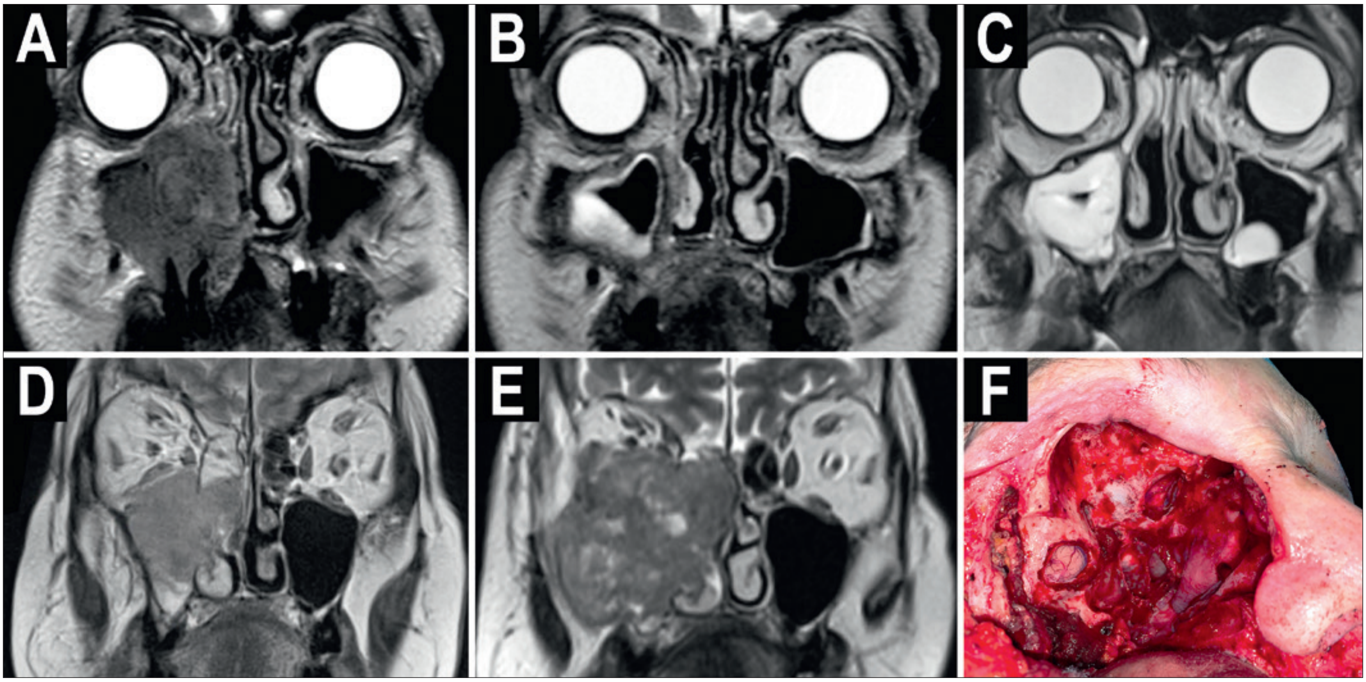

Figure 5. The panel illustrates two cases of moderately differentiated squamous cell carcinoma of the right maxillary sinus (**A, D**), both receiving neoadjuvant chemotherapy with taxane, cisplatin, and 5-fluorouracile as the primary treatment modality. The first tumour (**A**) had a partial response (**B**) and was therefore sent for proton therapy, which resulted in a complete response (**C**). The second tumour (**D**) had progression of disease (**E**) and therefore mandated surgery including total maxillectomy with orbital exenteration, middle and anterior craniectomy with dural resection (**F**), reconstruction of the defect through a multilayer skull base plasty and an anterolateral thigh free flap, followed by adjuvant radiation therapy.

publication, patients receiving orbital ablation for a sinonasal cancer unamenable to orbit-sparing surgery have a high probability of bearing nodal disease (29.8%), poor chances of surviving (5-year overall and disease-specific survival: 27.8%), and high risk of experiencing a local relapse despite aggressive surgery (5-year local recurrence-free survival: 44.6%) [28]. These data should be considered as a “red flag” for the MDT, with an indication to orbital ablation deserving thoughtful evaluation of potential alternatives.

The need to combine orbit sparing with functional preservation and offer the patient an adequately experienced handling of orbital tissues justifies why an oculoplastic surgeon should be part of the MDT. For instance, Shi et al. described the feasibility and oncologic adequacy of a combined external and endoscopic *en bloc* orbit-sparing resection in malignancies arising from the lacrimal drainage system [73]. Recently, Fontes et al. reported on the satisfactory functional outcome of surgical reconstruction of the medial rectus muscle after iatrogenic rupture during endoscopic transnasal sinus surgery [74]. Based on these results and keeping in mind the potential negative effects of adjuvant treatment, one could hypothesize to partially resect and primarily reconstruct a focally-invaded extrinsic ocular muscle. This approach could indeed reduce morbidity of treatment in patients who will have an ominous prognosis irrespective of surgical aggressiveness. However, this additional step forward in surgical orbital preservation would be unfeasible without the contribution of oculoplastic surgeons and/or maxillofacial surgeons trained in oculoplastic surgery.

Another unsolved challenge of sinonasal oncology is represented by sinonasal cancers macroscopically invading the orbital apex. When invasion of the orbital apex is detected at preoperative imaging, 5-year overall survival probability is as low as 15.0% in patients undergoing multimodal treatment including orbital exenteration/clearance [28]. Sugawara et al. reported a 5-year overall survival rate of 86.2% in 15 patients with macroscopic orbital apex involvement treated through an “extended orbital exenteration” [75]. The surgical procedure was performed by a multispecialty team composed of neurosurgeons, head and neck surgeons, and plastic surgeons. In addition to resection of the nasoethmoidal box and anterior skull base, the authors removed the orbital apex as surrounded by its bony walls and sectioned the neurovascular structures in their intracranial tracts through a transcranial approach. The obvious gain in overall survival reported by Sugawara et al. should encourage one to offer multidisciplinary surgery by both head and neck and neu-

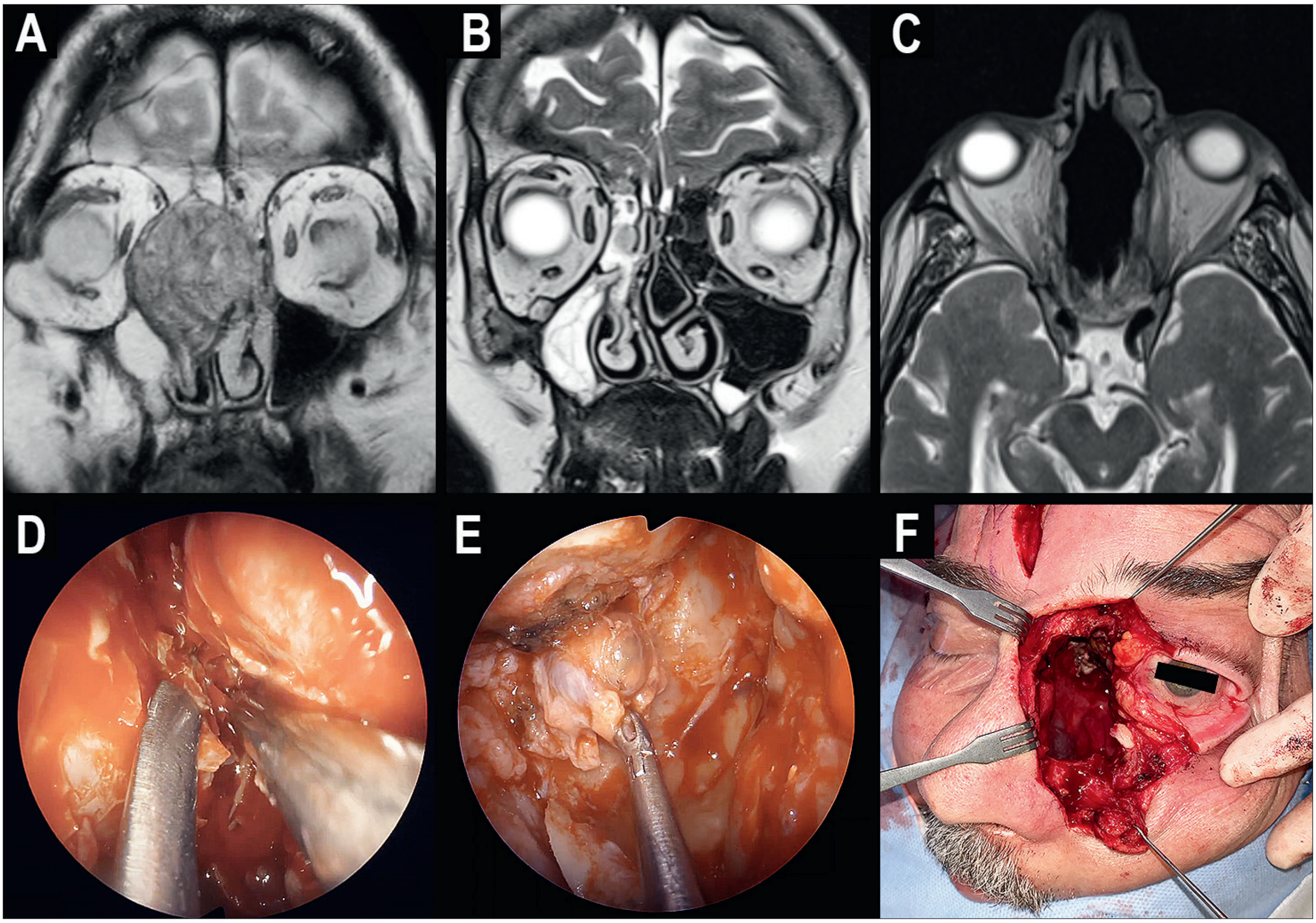

Figure 6. Panel showing three examples of surgical orbital preservation in patients affected by sinonasal cancers. (**A, D**) A right nasoethmoidal intestinal-type adenocarcinoma encroaching the orbit with no interruption of the periorbit at preoperative imaging was resected through an orbit-sparing endoscopic approach. (**B, E**) A recurrent adenoid cystic carcinoma located into the inferior aspect of the right orbital cavity was resected through an orbit-sparing transnasal endoscopic prelacrimal approach. (**C, F**) A unifocal, left preseptal recurrence of intestinal-type adenocarcinoma was resected through an orbit-sparing rhinectomy extended to the medial canthus and lacrimal sac.

rological surgeons to those unfortunate patients requiring orbital ablation for an orbital apex-invading cancer.

Post-ablative defects requiring plastic surgical expertise

The majority of resections for sinonasal tumours with cranial involvement result in skull base defects that can be effectively reconstructed by an otorhinolaryngologist and/or neurosurgeon through multilayer reconstruction possibly including a vascularized flap [76-79]. Regional flaps such as the pericranial or temporoparietal fascia flap can be used upfront or left as backup options when the risk of postoperative CSF leak is deemed high (Fig. 7) [80,81].

In rarer circumstances, the defect can be variably extended to the external nose, orbit, midface, upper face, maxillofacial skeleton, oral cavity, and/or scalp, which mandates the use of more complex reconstructive strategies. Another scenario that requires advanced plastic surgery expertise is when graft-based and vascularized local and regional reconstructive strategies are unavailable or have already failed [82-86]. In both circumstances, reconstruction with revascularized free flaps has been reported as an effective strategy [87]. A variety of free flaps have been used in patients requiring complex skull base reconstruction. According to a recent systematic review, 1628 cases of skull base reconstruction using free flap as the sole strategy or in combination with other techniques have been reported, with the large majority of cases including an anterior skull base defect [88]. Fasciocutaneous flap such as the anterolateral thigh and radial forearm free flaps have been most frequently employed, with bulkier myocutaneous flaps such as the

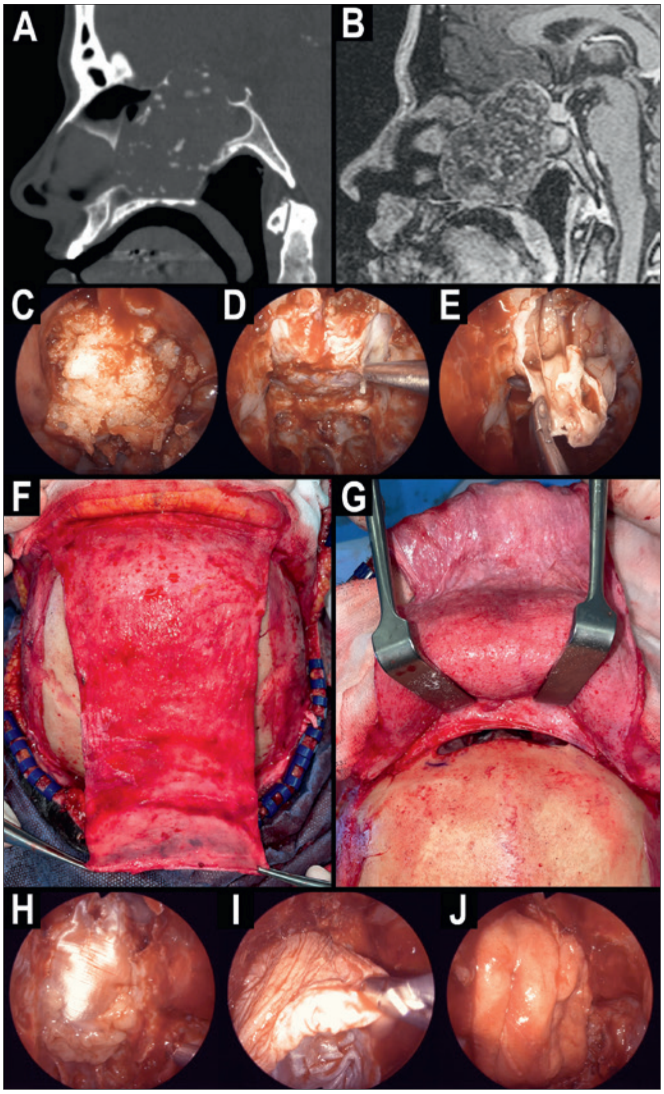

Figure 7. Panel illustrating the surgical management of a chondrosarcoma of the nasal septum encroaching the anterior skull base. (**A, B**) Preoperative imaging of the tumour. (**C-E**) Exemplificative steps of the endoscopic transnasal resection of the chondrosarcoma. (**F, G**) Harvest of the pericranial flap and preparation of the so-called "mailbox" for flap transposition towards the skull base defect. (**H-J**) Three-layer reconstruction of the skull base through grafts of iliotibial tract and subcutaneous fat, which was lined with a pericranial flap.

rectus abdominis and latissimus dorsi flap being indicated for very large defects. Bone-including free flaps have also been reported for reconstruction requiring a rigid vascularized framework, with special reference to those harvested from the subscapular system due to its versatility in terms of bony and soft tissue components [89,90]. Skull base infection and osteoradionecrosis also benefit from transfer of non-infected, non-irradiated, (re-)vascularized tissue following necrosectomy and debridement, which should be delivered in the context of a comprehensive therapy including a combination of tailored antibiotics, pentoxifylline, alpha-tocopherol, and hyperbaric oxygen therapy [91-93].

Of note, it is the authors' opinion that reconstruction of the bony and dural defect in the skull base should adhere to the principles of a multilayer technique to ensure watertight closure before the free flap is in-set. It is indeed surmised that this minimizes the chances of CSF leak, which can subtly occur even though a thick layer of well vascularized tissues covers the defect, but skull base closure is not watertight. Considering this, it seems logical that a plastic surgeon or head and neck surgeon with expertise in plastic surgery be included in MDT for advanced sinonasal tumours. Moreover, adequate briefing and planning of the reconstruction is mandatory, with each surgical specialist being in charge of different phases of reconstruction including multilayer skull base reconstruction, flap harvesting, in-set, and microvascular anastomoses (Fig. 8).

Intraoperative complications requiring multidisciplinary management

Several intraoperative complications can occur during surgery for advanced sinonasal tumours. The present paragraph summarizes the main concepts on two important events of which the MDT should be aware, namely intraoperative ICA rupture and neurogenic cardiovascular alterations.

Injury of the ICA is a rare but potentially catastrophic intraoperative complication of endoscopic skull base surgery. Wang et al. reported that an incidence of 0.016% to 1% was estimated based on large endoscopic transnasal surgery series [94]; AlQahtani et al. reported an in-depth analysis of 28 cases of ICA injury out of 7160 endoscopic procedures, with a resulting frequency of 0.4% [46].

In case of intraoperative ICA rupture, the current opinion is that bleeding should be temporarily controlled by nasal packing possibly anticipated by an attempt at direct endoscopic hemostasis by an adequately trained surgical team [47,95]. This explains why the anesthesiologist should also be considered as part of the MDT. For instance, optimal blood pressure control is warranted in case of ICA injury [96], with arterial hypotension and hypertension being sequentially necessary to facilitate bleeding control and ensure adequate collateral/contralateral flow towards ischemic areas, respectively. Adequate preoperative briefing with the anesthesiologist is therefore suggested in cases with potential ICA injury. Thereafter, the patient should be moved to the angiography room and urgent occlusion test followed by endovascular stenting and/or occlusion should be performed by an interventional radiologist [95,97,98].

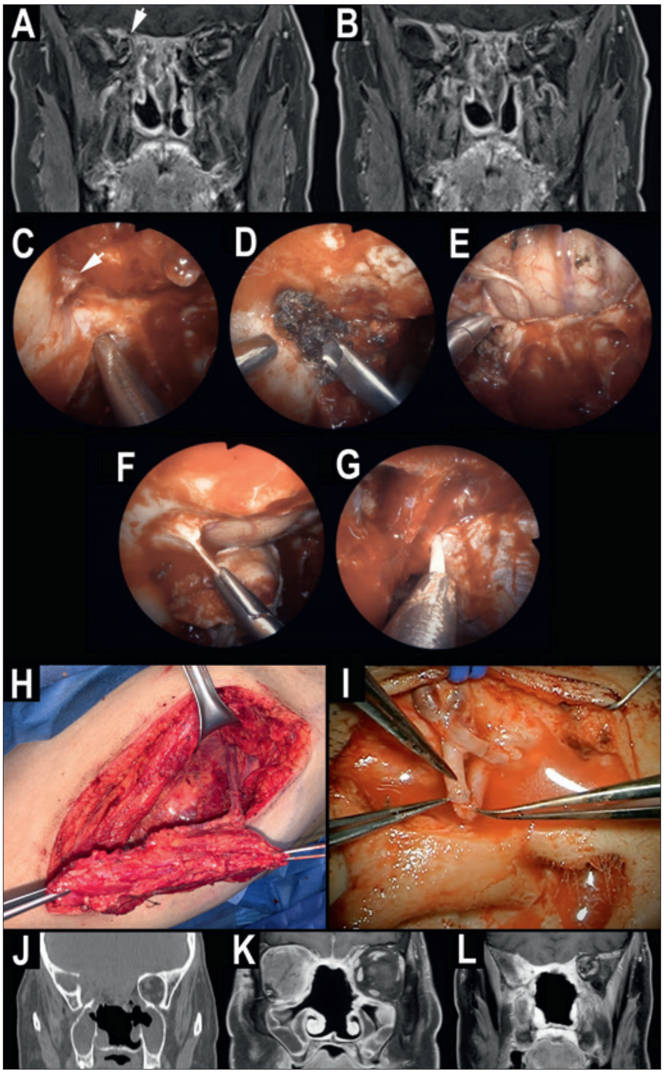

Figure 8. Panel illustrating the complex surgical management of a recurrent nasopharyngeal carcinoma located into the nasoethmoidal box (**A, B**) and extending to the right orbital apex through the posterior ethmoidal canal (white arrow). (**C-G**). Main phases of the first part of the surgical procedure, which includes endoscopic resection with transnasal craniectomy, orbital exenteration, and three-layer reconstruction of the skull base with iliotibial tract and subcutaneous fat. (**H, I**) Harvesting and microvascular anastomosis to the right superficial temporal pedicle of a left muscular anterolateral thigh flap used to fill the orbital cavity and line the posterior portion of the skull base reconstruction. (**J**) Early postoperative computed tomography scan showing the lateral and posterior extent of the bony defect. (**K, L**) Postoperative MRI acquired before re-irradiation with proton therapy; contrast-enhanced images demonstrate pedicle patency and adequate vascularization of the skull base plasty.

As a consequence, the interventional radiology unit should be notified when surgery with non-negligible risk of ICA injury is performed. Rupture of vessels other than the ICA might also need radiologic interventional procedures or even transcranial open surgery when primary hemostasis cannot be achieved. Therefore, if not directly involved in the surgical procedure, a neurosurgeon, preferably trained in bypass surgery, should be alerted when an operation at risk of causing an intraoperative intracranial bleeding is performed.

In case of endoscopic surgery involving any part of the trigeminal nerve, adequate briefing with the anesthesiologist is also mandatory. In fact, trigeminal stimulation might suddenly provoke dysrhythmia, hypotension, or even asystole due to the trigemino-cardiac reflex [99,100]. Management of the trigemino-cardiac reflex is mainly based on preoperative risk evaluation, vigilance during anesthesia, effective communication for a rapid cessation of precipitating stimuli, and prompt correction of cardiovascular changes.

Conclusions

The present narrative review highlighted that most cases of advanced sinonasal tumours can be managed by an adequately trained otorhinolaryngological team. However, since a minor yet non-negligible case rate requires additional expertise, a systematic MDT discussion of sinonasal tumours have, among others, the advantage of selecting patients requiring the intraoperative skills of neurosurgeons, oculoplastic surgeons, and physicians with plastic surgery training. As a final remark, one should consider that non-surgical specialties participating in the MDT approach to sinonasal tumours have been and are noticeably evolving. As a consequence, the paradigms of treatment of sinonasal tumours, with special reference to cancers and selected advanced benign tumours, are considerably changing. This fact mandates approaching advanced sinonasal tumours through a comprehensive MDT approach to provide the patient with the best possible treatment he/she can be offered.

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