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Organo Ufficiale della Società Italiana di Otorinolaringoiatria e Chirurgia Cervico-Facciale

107th Congress of the Italian Society of Otorhinolaryngology Head and Neck Surgery - 2021

Official report

Edited by Gaetano Paludetti

Limits of ENT surgery: when a multidisciplinary approach is required in skull base, orbit, dental pathologies and head-neck tumours involving skin

Patologia di confine otorinolaringoiatrica: approccio chirurgico multidisciplinare alle malattie della base cranica, dell'orbita, dell'apparato dentario e dei tumori testa-collo con infiltrazione della cute

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Limits of ENT surgery: when a multidisciplinary approach is required in skull base, orbit, dental pathologies and head-neck tumours involving skin. Introduction

Patologia di confine otorinolaringoiatrica: approccio chirurgico multidisciplinare alle malattie della base cranica, dell'orbita, dell'apparato dentario e dei tumori testa-collo con infiltrazione della cute. Introduzione

I really thank the Italian Society of Otorhinolaryngology and Head & Neck Surgery for assigning me such a difficult task. Our specialty has experienced a profound change over the last twenty years, by refining the knowledge about the spectrum of ENT diseases and improving our surgical performance with an increasing number of surgical treatment modalities. This new wave of innovation changed our way of working, driving us to exceed our limit and going beyond the line of the standard ENT anatomic fields. In this scenario, great efforts have been made in order to cope with the risks of a new extended surgical approach, requiring an integrated collaboration with other head and neck surgical specialists.

We are witness of an epochal change, consisting of an evolutionary significance, never seen before. I first-hand experienced, during my very long ENT activity, the importance of an increasing multidisciplinary surgical approach to several ENT pathologies. The official report of the Italian Society of Otorhinolaryngology and Head & Neck Surgery for this year, essentially aimed to focus the attention on this topic, by outlining the complementarity between the different surgical specialties that share the head and neck district as the main field of action. The overlapping surgical practice by several surgeon in the same anatomic region may represent a prickly issue; this situation, in fact, if well-handled could guarantee better surgical outcomes, which could significantly improve the quality of life of patients; on the other hand, the relationship with other specialists may not always be simple, and close cooperation and mutual trust are essential to ensure higher levels of care. Moreover, it is important from a medico-legal point of view, in order to reduce the number of troubles, to strictly follow updated guidelines and other specialists' expertise.

Cooperation between the ENT surgeon and other specialists is crucial, since all of the different anatomic areas affected by pathologies have distinctive characteristics and the best results in terms of life expectancy and patients' quality of life can only be achieved through a synergic surgical approach. The cooperation between specialists should always start from the early diagnosis of different pathologies that involve shared field of action and should continue along the all diagnostic work-up, in order to achieve the best therapeutic strategy. This kind of tailored management, takes into account the needs of each

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patient, driving step by step to the correct therapeutic approach by involving several surgeons, each of them with a different expertise but with a complementary action.

Herewith, in our report we focused the attention on the modalities of cooperation between surgeons during the surgical management of complex disease, involving borderline anatomic sites. We underlined how other specialists' expertise allows to manage difficult situations and their potential complications, in the light of a decreasing rate of surgical failures. In particular, the communication between the ENT surgeon and other surgeons (such as ophthalmologist, neurosurgeon, dentist and reconstructive surgeon) is critical and time-sensitive for a successful treatment with high success rate. In this report, we have intentionally excluded the discussion about the lateral skull base, as it was the central topic of the official report of 2019, and about the medical diseases in the ENT domain in which cooperation with other specialists is needed (neurologists, immunologists, etc.).

I am finally profoundly grateful to all the Authors who contributed to this official report. All this work was carried out hoping that it could be subject of debate and an instrument for the enrichment of all the readers.

Gaetano Paludetti

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.

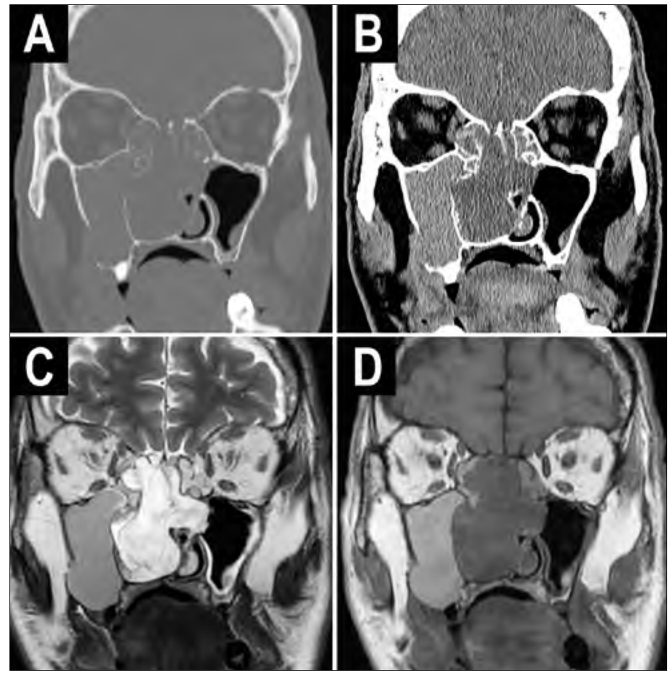

Figure 1. Computed tomography (**A, B**) and magnetic resonance imaging (**C, D**) of a mucinous, signet-ring cell, intestinal-type adenocarcinoma of the right nasoethmoidal complex. Different imaging modalities allow depiction of tumour extension with respect to the most relevant adjacent compartments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

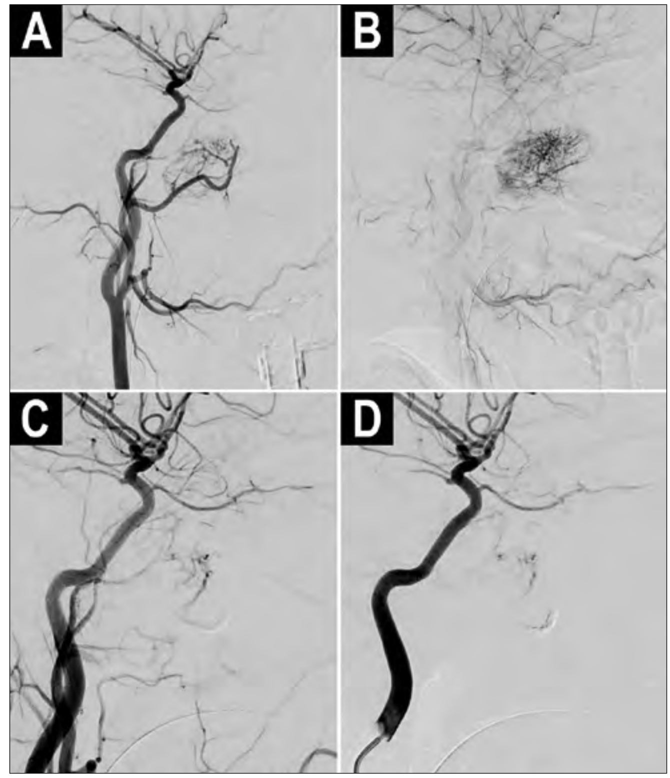

Figure 2. Angiography of a case of right juvenile angiofibroma with feeders coming from both the internal and external carotid artery systems (**A, B**). Following combined transarterial (with polyvinyl alcohol particles) and translesional (with Onyx®) embolization of the lesion and transarterial closure 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-

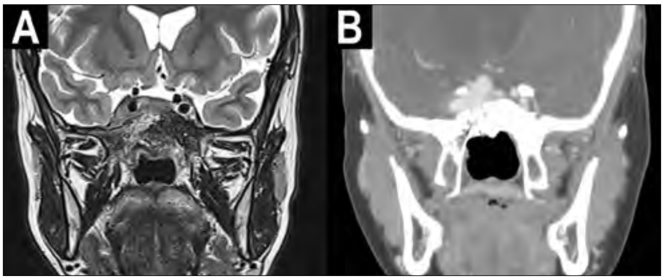

Figure 3. (**A, B**) The panel shows the case of a pseudoaneurysm of the parasellar, paraclinoid, and intracranial tracts of the right internal carotid artery in a patient who was treated through ^{12}C-carbon ion therapy for an unresectable adenoid cystic carcinoma of the right sphenoid sinus.

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

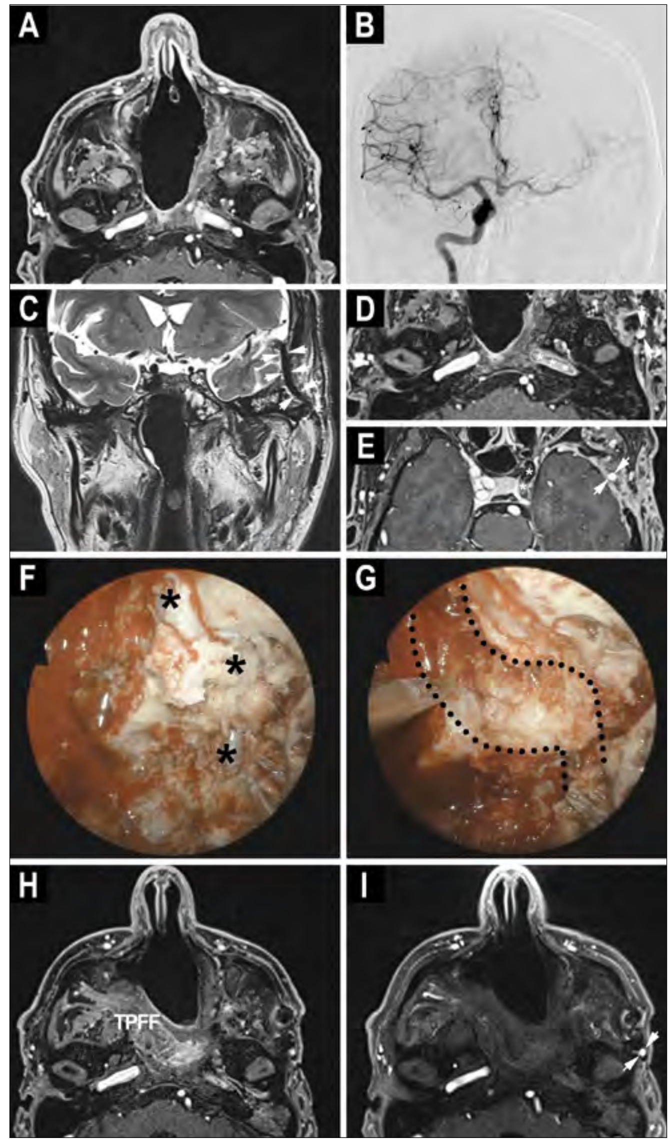

Figure 4. The panel summarizes the complex management of a case of recurrent nasopharyngeal carcinoma. (**A**) An enhancing nodule corresponding to the second local recurrence of nasopharyngeal carcinoma is identified in close relationship with the anterior genu of the left petrous internal carotid artery. (**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

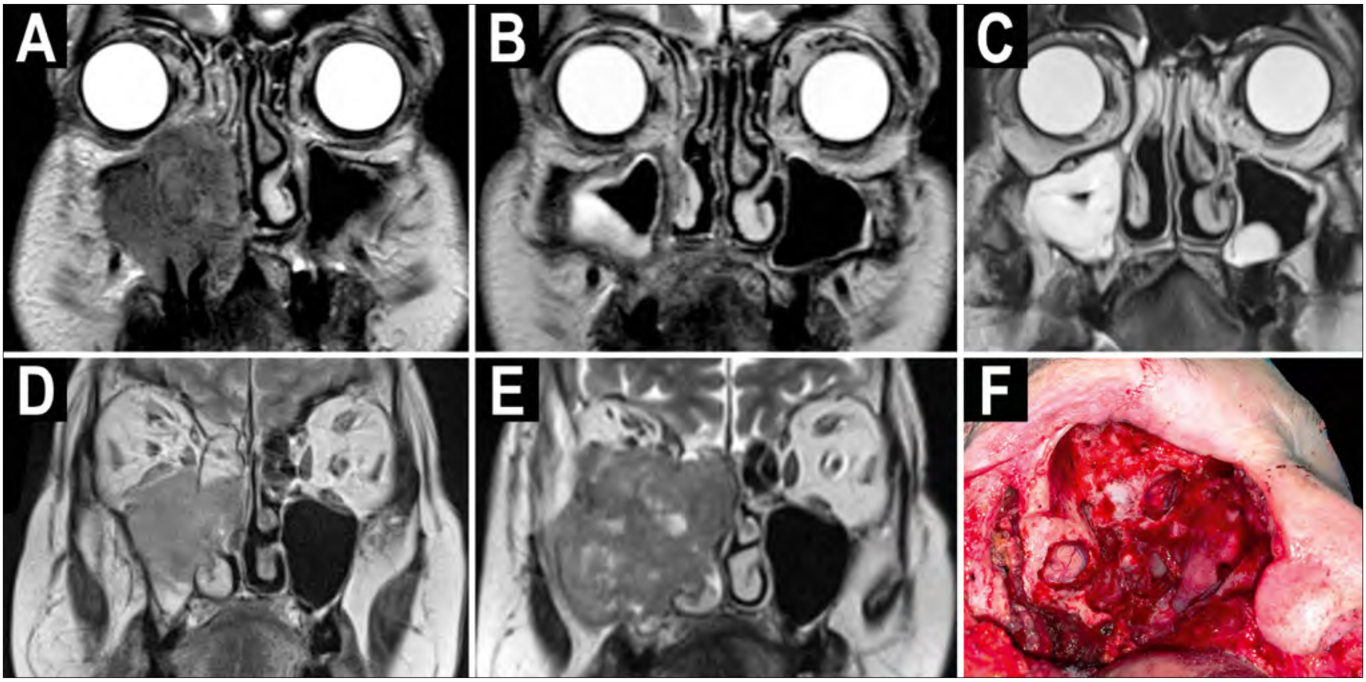

Figure 5. The panel illustrates two cases of moderately differentiated squamous cell carcinoma of the right maxillary sinus (**A, D**), both receiving neoadjuvant chemotherapy with taxane, cisplatin, and 5-fluorouracile as the primary treatment modality. The first tumour (**A**) had a partial response (**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-

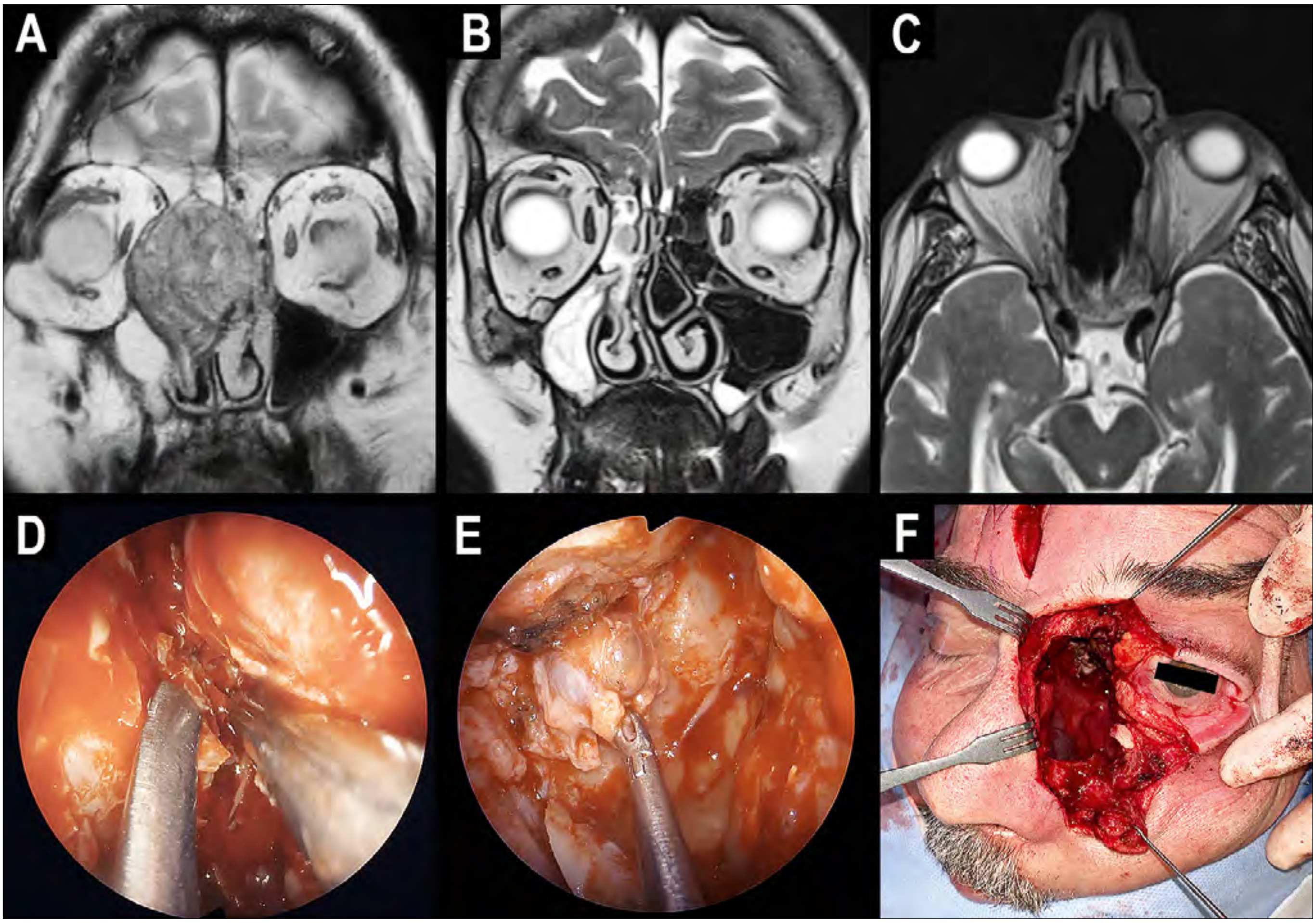

Figure 6. Panel showing three examples of surgical orbital preservation in patients affected by sinonasal cancers. (**A, D**) A right nasoethmoidal intestinal-type adenocarcinoma encroaching the orbit with no interruption of the periorbit at preoperative imaging was resected through an orbit-sparing 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

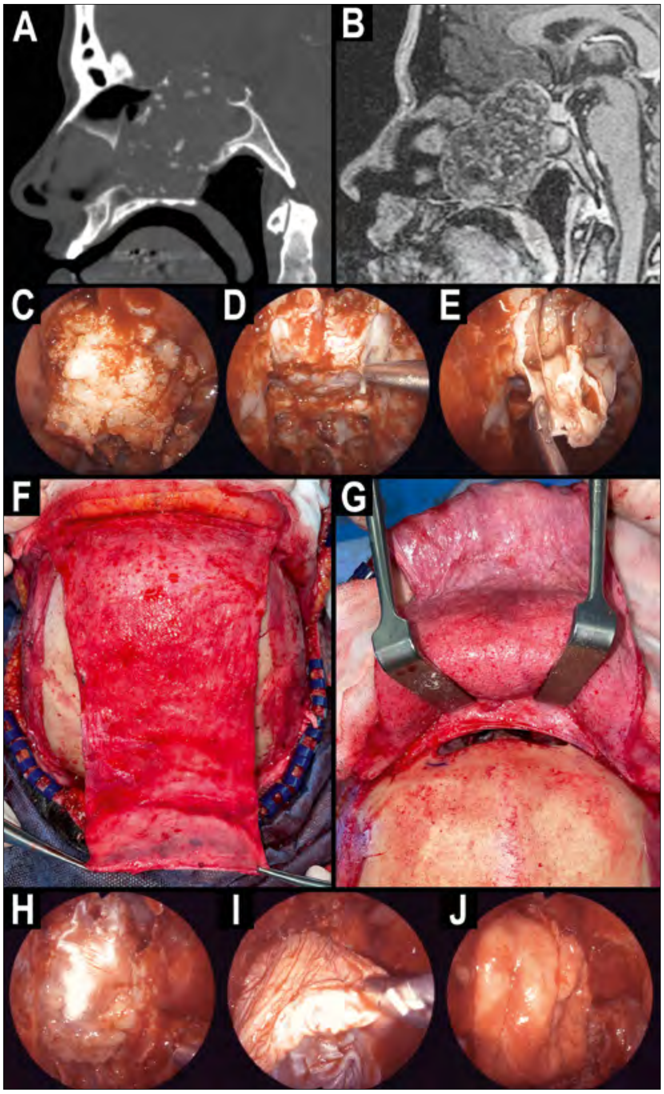

Figure 7. Panel illustrating the surgical management of a chondrosarcoma of the nasal septum encroaching the anterior skull base. (**A, B**) Preoperative imaging of the tumour. (**C-E**) Exemplificative steps of the endoscopic transnasal resection of the chondrosarcoma. (**F, G**) Harvest of the pericranial 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].

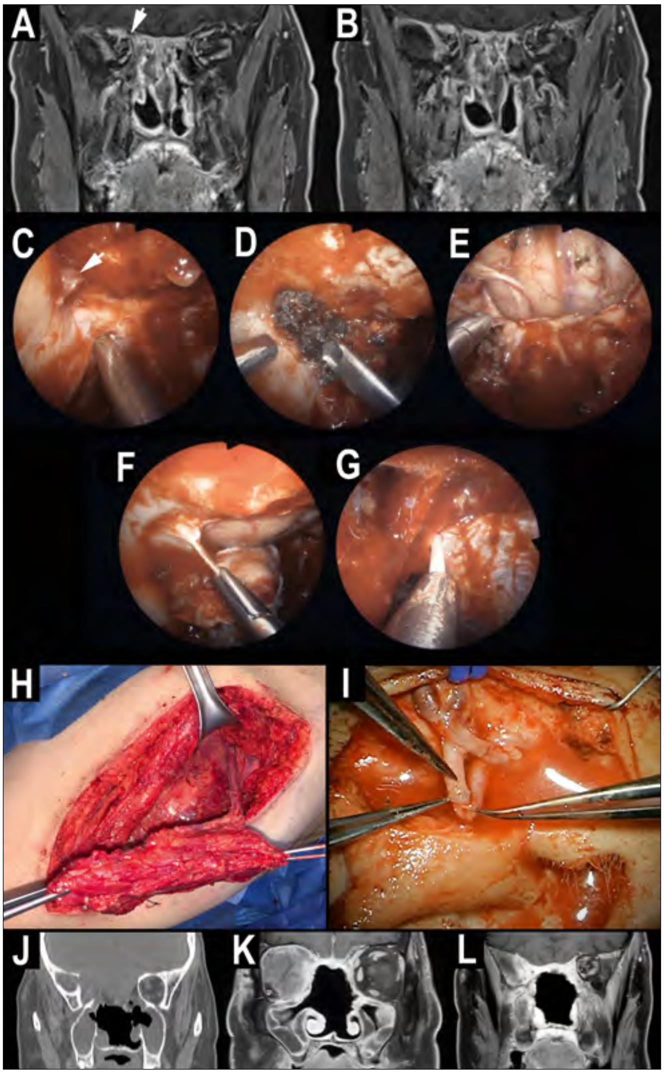

Figure 8. Panel illustrating the complex surgical management of a recurrent nasopharyngeal carcinoma located into the nasoethmoidal box (**A, B**) and extending to the right orbital apex through the posterior ethmoidal canal (white arrow). (**C-G**). Main phases of the first part of the surgical procedure, 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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Management of cerebrospinal fluid leak: the importance of multidisciplinary approach

Trattamento delle fistole rinoliquorali: quando è richiesto un approccio chirurgico multidisciplinare al basicranio?

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SUMMARY

Cerebrospinal fluid (CSF) leak remains a rare condition, characterized by serious complications and potentially fatal. According to different etiologies, CSF leaks may be classified into two main categories: traumatic and spontaneous. Spontaneous fistulas seem to be mainly related to obesity and idiopathic intracranial hypertension. Diagnosis is both clinical and radiological. During the last three decades, surgical treatment has mostly shifted to endonasal endoscopic approach, which widely demonstrated to be more effective than invasive intracranial ones. Post-operative complications, long-term sequelae and hospital stay are strongly reduced thanks to endoscopic approach. The diagnosis and treatment of CSF leaks represent a difficult and challenge task. The main effort seems to be related to the precise localization of the leak. An accurate assessment of both predisposing factors and comorbidities is mandatory in case of spontaneous leaks. However, a clinical multidisciplinary evaluation as well as treatment, is essential to decrease the rate of failure of surgery. The presence of a dedicated instruments, the Skull Base Team, the knowledge of reconstructive materials and techniques represents a decisive result in therapeutical management even if for each patient an effective therapeutic algorithm can be obtained considering the correct leak detection and characteristics. In conclusion the strict teamwork with neurosurgeons, neuroradiologists, ophtalmologists will enable the development also of innovative biomaterials, which could spread and standardize multi-layer techniques, nowadays still related to surgeon preferences.

KEY WORDS: CSF leak, rhinoliquorrea, endoscopic skull base surgery

RIASSUNTO

Le fistole rinoliquorali sono una patologia poco comune ma, a causa delle temibili complicanze, potenzialmente fatale. A seconda dell'eziologia, possono essere classificate in traumatiche e spontanee. La diagnosi è sia clinica che radiologica. Negli ultimi tre decenni, il trattamento chirurgico si è molto evoluto, passando da un approccio invasivo intracranico ad un approccio endoscopico endonasale, il quale si è dimostrato maggiormente efficace a fronte di un minore numero di complicanze post-operatorie a breve e lungo termine e della riduzione dei tempi operatori e di ospedalizzazione. La diagnosi ed il trattamento delle fistole rinoliquorali sono da sempre stati alquanto complessi. Le principali problematiche dipendono dalle difficoltà di localizzazione della sede della fistola e, nel caso delle forme spontanee, anche dal corretto inquadramento di eventuali fattori predisponenti e comorbilità. Al fine di ridurre al minimo i rischi di insuccesso del trattamento chirurgico è necessario un approccio gestionale di tipo multidisciplinare. In conclusione, la possibilità di assumere le decisioni terapeutiche nell'ambito di un équipe multidisciplinare dedicata – Skull Base Team –, che si avvalga della presenza di otorinolaringoiatra e neurochirurgo, così come del neuroradiologo e dell'oculista, è fondamentale per localizzare con precisione la sede e delineare le caratteristiche della fistola in modo da ottenere il successo terapeutico. La stretta collaborazione multidisciplinare potrà inoltre permettere lo sviluppo in futuro di nuovi biomateriali in grado di facilitare e standardizzare le tecniche di riparazione multistrato, oggi in gran parte condizionate dalle preferenze del chirurgo.

PAROLE CHIAVE: *fistole rinoliquorali, rinoliquorrea, chirurgia endoscopica, basicranio*

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Introduction

Cerebrospinal fluid fistula, also called CSF leak, is an uncommon but severe condition with potentially fatal outcome. CSF leaks can be essentially classified according to two criteria: etiology and location.

Considering etiology, O'Connell's historical classification [1], subsequently revisited by Ommaya [2] and then by Har-El [3], considers two large groups:

- ***traumatic***, with generally delayed clinical manifestation, divided into:
  - *iatrogenic,* related to nasal (e.g. functional endoscopic sinus surgery [FESS], endoscopic sinus surgery [ESS]) (Fig.1), or cranial surgery (e.g. craniotomies), which are further divided into accidental and imperfect reconstruction. Patients with extensive pneumatization are most at risk [4].
  - *non iatrogenic,* linked to blunt or penetrating trauma, which do not always result in an obvious liquor loss, but become evident, sometimes several years later, presenting a complicated clinical picture (e.g. meningitis, encephalocele). CSF leaks occur in 3% of closed head injuries, in 9% of open head injuries, and in 10-30% of skull base fractures [5]. The frequency is higher in males between their thirties and fifties and are quite rare in childhood due to elasticity of cranial bones [6]. In 80% of cases, early symptoms occur within the first two days of the event, and in 95% within the first three months of the traumatic event.
- ***non-traumatic***, divided according to CSF pressure into *high-pressure* and *low-pressure*.

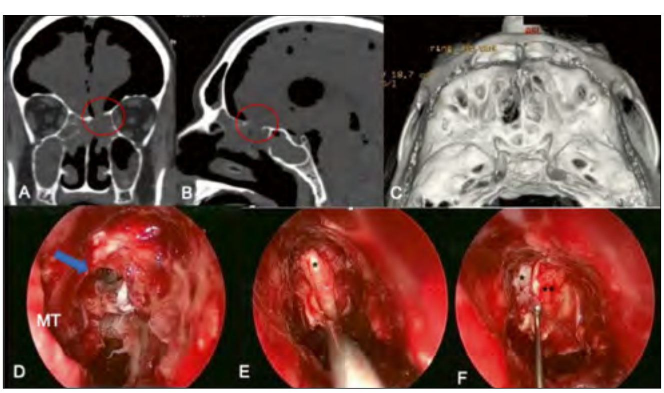

Figure 1. A CT scan in coronal (**A**) sagittal (**B**) and 3D reconstruction (**C**) of posttraumatic (jatrogenic) CSF leak at the level of the left ethmoid sinus occurred during Functional Endoscopic Sinus Surgery (FESS) surgery for nasal polyposis. A massive pneumocephalus occurred due to delayed diagnosis of intraoperative leak. The patient underwent to endoscopic repair of the wide defect (**D** arrow) using fascia lata graft in a multilayer fashion (**E** and **F**): first* underlay layer and second** overlay layer + rotation of middle turbinate (MT).

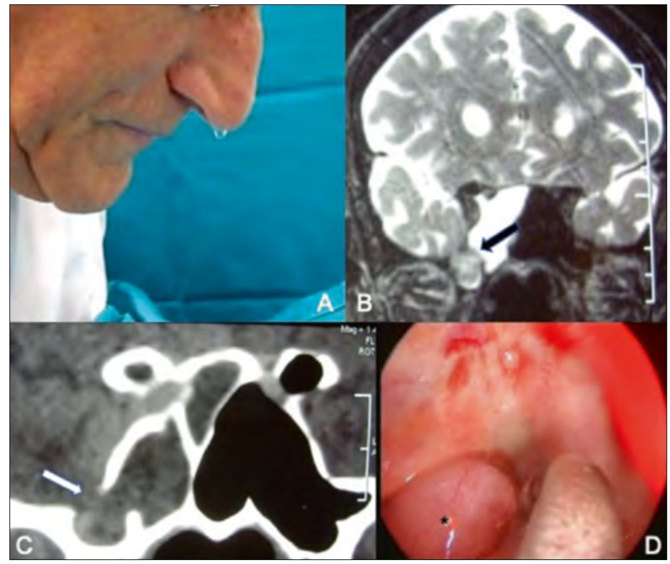

Figure 2. A case of spontaneous right nostril rhinoliquorrea (**A**) in a patient with a meningoencephalocele in the right sphenoid sinus as showed in T2 weighted MRI (**B** arrow) through a bony defect (**C** arrow) in the lateral recess of sphenoid (Sternberg's canal) (**C** arrow) and how it appears (*) with 45° angled endoscopic examination of the sphenoid sinus.

Diagnosis is difficult and depends mostly on disease etiology. Clinical diagnosis of a post-traumatic leak is immediate. Instead, spontaneous leaks are more complex to identify, because they are characterized by intermittent symptoms; therefore, absence of external abnormalities and infrequent symptoms cause often diagnostic delay. Spontaneous leaks comprise all leaks without recognized causal mechanisms and are more often associated with meningeal herniations (Fig. 2), multiple localizations and higher recurrence rates.

The treatment of CSF leaks, posttraumatic as well as spontaneous, was until the recent past nearly exclusively referred to the neurosurgeon. Nowadays, the successful management of CSF leaks has changed almost exclusively into endonasal endoscopic approach, even if a multidisciplinary team and different treatment options, not only limited to surgery, are still necessary. Aim of this review is to provide an update on CSF leak management by discussing when and how a multisciplinary approach could improve outcomes.

Diagnosis

The diagnostical algorithm is still a challenge and is of paramount importance for final therapeutical success. The diagnostic work up includes clinical ENT, neurosurgical and ophtalmological evaluation, in order to assess the potential etiological factors, the site and features of the CSF leak (i.e. flow, predisposing factors, etc.), laboratory findings of the

collected nasal liquid and radiological evaluation. All these specialists contribute to the diagnosis and to the decision making process in the CSF leaks, but more extensively take part to the constitution of the Skull Base Team, that take care also of the problem of reconstruction of defect following surgical treatment of pathologies rising in this region [7].
The clinical evaluation of suspected CSF rhinorrea can be pointed out inviting patient to perform maneuvers that can increase intracranial pressure, to reveal any leak, nasal endoscopy can confirm the presence of bone defect or meningoceles or meningoencephaloceles. The collection of nasal secretions or liquid is used to test beta-2-transferrin and beta trace protein assays, the most sensitive and specific laboratory tests for CSF leak diagnosis, the former more commonly used because of availability [8]. The opthalmogists can diagnose the presence of increased intracranial pressure evaluating the fundus oculi and eventual papilledema or using ultrasound to check optic nerve status [9].
When there is a clinical suspect or clear diagnosis of CSF leak the neuroradiological evaluation is essential, detecting leaks using computed tomography, magnetic resonance imaging, or nuclear imaging [10,11]. The use of High Resolution Computed Tomography (HRTC) scan to assess any bony defect in the skull base, including also the petrous bone, followed by MRI that can show the presence of meningocele, meningoencephaloceles, inflammatory reaction of the nasal or middle ear mucosa, and obviously any meningeal or intracranial involvement (i.e. meningitis or meningoencephalitis, etc.). The MRI is also important in cases of spontaneous CSF leak to suggest long-standing Idiopathic Intracranial Hypertension (IIH), including empty sella, flattening of the posterior globes, optic nerve head protrusion, distention of the optic nerve sheaths, tortuosity of the optic nerve, cerebellar tonsillar herniation, meningoceles, CSF leaks, and transverse venous sinus stenosis [12]. Other radiological examination such as CT cisternography, MR cisternography are still used in IIH diagnosis [13], both are nowadays disused due the introduction of intrathecal use of fluorescein that allows integration of diagnosis and treatment in one procedure reducing the morbidity of such invasive radiological examination. The use of intrathecal fluorescein (ITF) is still not FDA approved and require a specific informed consent even if low-dose ITF is a safe and useful tool during endoscopic endonasal repair of CSF leaks with minimal complications and successful localization of the leak [14].

Treatment

Treatment may include:

- *conservative medical therapy*, which is first choice in patients without immediate need for intervention or patients with spontaneous healing possibilities; however, surgery might be necessary in case conservative medical therapy is ineffective;
- *surgical therapy*, which is indicated in patients without spontaneous healing chances, as for example patients with cerebral herniations, iatrogenic dural leaks, spontaneous leaks – which are highly unlikely resolvable without surgery – or patients with underlying disease, such as tumours, requiring by default surgery including dural resection.

Both approaches have the goal of preventing complications, which are recurrent meningitis, intracranial abscesses, pneumoencephaloceles, and refractory epilepsy. The incidence of meningitis related to a posttraumatic CSF leak, either pre-operatively or during conservative management, ranges from 10% to 37% and is proportional to the duration of this condition [6].
The final decision of both therapeutical options is generally discussed in a multidisciplinary setting (Skull Base Team). Conservative medical therapy includes bed rest with the head raised by 30° for 1-2 weeks. During this period, the patient must avoid activities, which may result in increased intracranial pressure. Some surgeons prescribe patients medications such as antiemetics, stool softeners and antitussives [15]. Corticosteroids or diuretics can be additionally administered to reduce intracranial pressure, although their effectiveness is still debated in literature [16].
Lumbar drain might be recommended in an effort to minimize increased intracranial pressure, but drains are related to significant risks if used excessively, including drastic liquor pressure collaps and tension pneumocephalus [17].
Prophylactic antibiotics are often administered to decrease the risk of meningitis or local infection during conservative management of CSF leaks. However, this strategy carries the risk to create resistant bacteria; as a result, routine use of prophylactic antibiotics has been questioned [10-12]. Nevertheless, prophylactic antibiotics are indispensable for high-risk patients like those with medical history of upper airways infection or meningitis [15].
Conservative treatment should be continued for at least two weeks; if conservative treatment fails, surgical therapy becomes imperative [20,21].
The risk of meningitis in cases of patients treated with conservative approach varies between 10 and 37% [20,21], therefore, recent literature suggests performing surgery as early as possible (Fig. 5). The time interval between onset of the pathology and diagnosis with subsequent hospitalization is extremely variable with a duration of symptoms ranging from only few hours to two years before consulting a physician at the hospital. That delay is related to complexity of this pathology and lack of a multidisciplinary approach (i.e.

collegial integration and sharing of the clinico-radiological informations).

The surgical strategy strongly depends on leak size, but also on the type, which can be classified in three categories:

- *traumatic, non-iatrogenic skull base defect:* in this leak type, the following risk factors should be considered: location, size, bone dislocations, and meningocele (Fig. 4), meningoencephalocele or cerebral hematoma. When the fracture is linear, less than 1 cm and not associated with intracranial complications, frontal sinus posterior wall or ethmoidal roof fractures, a wait-and-watch approach can be considered, because spontaneous healing due to fibrosis might be possible. Spontaneous healing occurs in 70-80% of patients within one week and in 20-30% of patients within few months, those leaks rarely recur. In all other patients, surgical strategy should be performed;
- *traumatic, iatrogenic leaks:* early surgical repair, if possible intraoperative, should be performed, because spontaneous healing is improbable, and the risk of recurrence is quite high. Moreover, infectious risk is directly proportional to the time in which the subarachnoid space and nasal cavities are interconnected. Indeed, it is necessary to operate as soon as possible in case of CSF rhinorrea after surgery to avoid meningitis or meningoencephalocele (Fig. 1);
- *non-traumatic leaks (recurrent or intermittent rhinoliquorrea and/or meningoencephalitis):* non-traumatic leaks can be divided depending on the intracranial pressure, into **high-pressure leaks**, which are linked to neoplasms, hydrocephalus, idiopathic intracranial hypertension (IIH), empty sella syndrome (Fig. 5), and **low-pressure leaks**, related to congenital anomalies. Surgery should be considered in all patients. If the patient experiences a single, spontaneously resolvable episode of rhinoliquorrea, leak identification can be difficult. The risk of complications is rare and an absolute indication for surgery does not exist.

Surgical approaches for CSF leaks

Surgical therapy involves two different approaches, which are intracranial and extracranial (endoscopic) surgery. The choice between these two surgical approaches is conditioned by:

- size and location of the leak;
- recurrences;
- meningocele or meningoencephalocele;
- patient's general condition;
- surgeon's preference.

Open intracranial approach

The repair of CSF leaks has rapidly evolved over the past 30 years. Open intracranial surgery, a typical neurosurgical approach, has historically been used for CSF leak repair, but in the recent two decades, the technique was largely replaced by endonasal endoscopic approaches, given to their high success, lower morbidity and complication rates, less invasiveness and shorter hospitalization time [20,22].

The type of intervention depends on the location and extension of the leak. Frontal craniotomy is performed in case of anterior leaks. Temporal or posterior craniotomy is indicated in case of middle or posterior cranial fossa leaks.

The visualization of dural lesions and the adjacent cerebral cortex are advantages of this approach, especially in case of increased intracranial pressure. Open intracranial surgery has a success rate ranging from 50 to 75%. Limited visualization of the leak at the sphenoidal level can cause hematoma, edema, convulsive seizures or permanent anosmia by damaging the nervous tissue, leading to increased morbidity and prolonged hospitalization. Complications are significantly higher in patients treated with an open intracranial approach compared with an endonasal endoscopic approach: meningitis, 3.9% versus 1.1%, respectively; abscesses, 6.8% versus 0.7%, respectively; and sepsis, 3.8% versus 0%, respectively [22].

Contraindications for an open intracranial approach are presence of intracranial hematomas, ethmoidal fractures extended to the orbit or frontal sinus posterior wall fractures. Instead, leak size and shape do not represent an absolute contraindication for open intracranial approach.

Extracranial approach

Extra-cranial non-endoscopic-endonasal surgery consisting in a bicoronal or eyebrow incision to create anterior osteoplastic flaps is nowadays rarely performed. Although the approach has a high success rates (86-100%), other concomitant abnormalities are not resectable and the approach causes visible scars compared with endoscopic approaches. Several techniques – external ethmoidectomy, trans-orbital ethmoidectomy (Lynch technique), trans-ethmoidal sphenoidotomy, trans-tectal sphenoidotomy and trans-antral – can be performed during extra-cranial non-endoscopic-endonasal surgery to implant autologous and/or heterologous materials.

Endonasal endoscopic treatment

In the last three decades, a complete revolution of surgical approach towards the endoscopic surgery occurred [23], which in the primary cases has almost completely replaced the open intracranial intervention [24,25], nowadays almost entirely reserved to complex cases. In 1981, Wigand et al. [23] described first an endoscopic approach to repair CSF leaks. Since then, several case series and reports described various endoscopic methods and materials for leak repair, with success rates varying between 60% and 100%, averaging around 90% [25] and nowadays the endonasal endoscopic approach is considered a gold standard [26,27]. The endoscopic approach allows a wider view of the operating field, resulting in more precise and advanced interventions, which lead to a higher initial CSF leak repair success rate, and reduced complications and hospitalization time [22].

Furthermore, new endoscopic technologies led to further diagnostic characterization as well as treatment improvements [28,29]. For example, ENTs, supported by neurosurgeons, perform nowadays endonasal endoscopy and have a predominant role to manage extensive intradural neoplasms where reconstruction of wide and complex CSF leaks is necessary. In particular, those leaks of the posterior cranial fossa require specific competences and simultaneous use of more tools during a four-handed endonasal endoscopic approach at the dural and intradural section of the skull.

The endonasal endoscopic approach can be described as follows:

- first, both imaging and endoscopic exploration should be employed to localize the exact site of the leak. Intrathecal fluorescein can be used to aid an exact diagnosis and localization of CSF leaks [30,31]. It is necessary to observe carefully the spread of fluorescein at the terminal middle turbinate. If fluorescein spreads medial, at the level of the spheno-ethmoidal recess, the leak is probably at the sphenoidal level, posterior ethmoidal or close to the lamina cribrosa; instead, fluorescein in the middle meatus indicates that the leak is located at the level of the anterior ethmoid or frontal sinus;
- secondly, CSF leaks mucoperiostal edges should be accurately detached for at least 1 cm to regularize residual bone margins. It is crucial not to remove any residual lamellae to facilitate healing and closing of the CSF leak. The endoscopic procedure is based on a "four-hand" technique to act with multiple surgical instruments in both nostrils under endoscopic vision. Depending on leak location, size and type, surgeons choose one out of five possible access ways/techniques:
  - *direct paraseptal to the olfactory fissure* - This technique is used in case the leak is localized at the level of the anterior third of the olfactory fissure and if the possible herniated mass has lateralized the lateral lamella of the middle turbinate. The approach avoids major damage to the ethmoidal structures. Initially, electrocoagulation of herniated sac pedicles is performed, which might require the additionally removal of the entire lesion in case of larger hernias. The second step involves intracranial skeletonization of the dural edge with subsequent mucosa removal of the surrounding defect area at the level of the olfactory fissure, corresponding portions of the nasal septum and lateral wall, to prepare the transplant area;
  - *direct paraseptal with sphenoidotomy* - This access way allows reaching the sphenoidal sinus' posterior wall, when the leak is located at the sellar floor or sinus roof; however, the sphenoid sinus is usually obliterated during intervention. The procedure involves the endoscopic identification and enlargement of the sphenoid sinus ostium to remove the intersphenoid septum and to create a single cavity. In the event that the natural ostium is unrecognizable, the sphenoid rostrum is opened in medial position to prevent internal carotid or iatrogenic optic nerve damage to gain access. The rostrum and posterior nasal septum end is additionally removed allowing the use of both nasal passages for a four-hand approach. Advantages is that the clivus region can be reached and a nasoseptal mucosa flap can be used;
  - *trans-ethmoidal with conservation of the basal lamina of the ethmoidal cornets* - This approach is preferable when the defect is located at the ethmoidal level, particularly if laterally to the lamina of the cornets. The ethmoidal roof must be fully exposed to identify the precise lesion site. The technique involves the removal of the ethmoid labyrinth with exposure of the skull base and paranasal sinuses. The use of intrathecal fluorescein and endoscopic blue and yellow light filters allows identifying further leak locations, which might have remained unobserved during the diagnostic phase;
  - *trans-ethmoidal with removal of the basal lamina of the ethmoidal cornets* - This approach is used in case the defect is located at the level of the middle and/or posterior third of the olfactory fissure, or at the level of the ethmoidal roof with medial involvement of the olfactory fissure. In case of smaller lesions, not entirely involving the olfactory fissure leaving the olfactory mucosa and olfactory filaments substantially intact, the middle turbinate and the entire basal lamina of the ethmoid cornets are obliterated to obtain a regular plane. On this regular plane a septal or turbinal mucoperiostial graft is implanted, which can only be achieved with overlay positioning. If the defect is localized at the ethmoidal roof level, the bone defect should be regularized by dissecting the epidural space even if this means enlarging the defect. After this step, the leak is closed with multilayer technique;
  - *transethmoidal-pterigoido-sphenoidal* - This technique is performed to treat lateral wall sphenoid sinus leaks and other leaks requiring ethmoido-sphe-

noidotomy and a large middle meatal anthrostomy [32]. The posterior fontanelle area is during the technique obliterated to expose the posterior wall of the maxillary sinus and the pterygoid base. The septal and nasal branches of the sphenopalatine artery are subsequently causticized. After, the anterior wall of the sphenoid sinus and the pterygoid base are milled to dominate the lateral wall of the sphenoid sinus and to access the lesion in order to perform the dural repair at the level of the middle cranial fossa.

Repair materials for CSF leaks

Studies comparing different graft types are still lacking in literature; in consequence, standardized criteria to choose adequate repair material are absent. The choice of CSF repair material depends much on location, size, bone dehiscence, surgeon's preference as well as availability and quality of the materials [16,33].

The primary goal of a reconstruction is to separate intracranial and extracranial spaces to prevent complications such as pneumocephalus, leak and infection. Secondary aim is to promote rapid scarring, to protect neural and vascular tissues and to minimize morbidity.

Grafts should be at least 30% larger than the bone defect, because of post-operative retraction, and should perfectly fit in the implant site, to avoid tension [35].

Generally, graft types can be distinguished in autologous and heterologous.

Heterologous grafts (e.g. synthetics) have a greater rejection risk, which can cause infections. The effectiveness of the CSF leak repair, with different kind of heterologous materials, is related revascularization, which varies widely. Poor or insufficient revascularization of flaps depends on adjacent tissue transfer, and atrophic or previously irradiated nasal mucous membranes, which increases the risk of CSF leak recurrence.

Different heterologous grafts can be considered:

- *absorbable collagen sponges (e.g. DuraGen®Secure, Dural Regeneration Matrix)* - This type of graft is used to close smaller CSF leaks, after tumour removal such as pituitary adenoma, chordoma and Rathke cysts, using a trans-sphenoid endonasal access. Absorbable collagen sponge grafts have three major advantages: First, onlay positioning of the sponge on the dura mater allows a fast fibrinic adhesion of the collagen to the dura to promote, from the first day on, fibroblast penetration into the collagen matrix and proliferation. Second, the collagen sponge, created using a bovine flexor tendon, is inert and well tolerated, which means that it does not cause chronic inflammation nor rejection. Third, this technique does not require autologous grafts or fibrin glue;
- *hydroxyapatite cement (HAC)* - Less utilized.

Autologous grafts can be divided into nasal and extra-nasal. To repair CSF leaks abdominal fat, muscles, deep temporal, fascia lata (Fig. 1), and pericranial flap, or middle turbinate mucoperiostal and septal mucopericondral flaps (Fig. 5) can be used. Septum mucopericondrals flaps are most commonly used for leaks smaller than 20 mm, because of their availability on the surgical site; they are easy to prepare and adapt to bony surfaces; their capillarity and the reduced postoperative traction minimize potential CSF leak recurrence. Additionally, muscle, temporal and abdominal fat grafts can be considered CSF leak larger than 20 mm, which can be subsequently covered by septal mucosa flaps. A composed tissue graft might be considered, if associated with cartilage or bones. In 2003, Schick et al. [34] demonstrated that compound tissue grafts are most suitable for dura mater graft surgery, as they facilitate cell migration (fibroblasts and epithelial cells) to the center of the dural perforation. This is contrary to synthetic materials or cartilage, which limit or even inhibit this process. But the real revolution is in the use of pedicled vascularized different mucoperiosteal and mucopericondrals flaps that strongly improved the success rate of reconstruction of skull base defect.

Autologous grafts can be placed with different techniques:

- *underlay technique* - During underlay technique, the dura mater is separated from the skull base dehiscence edges to obtain an adequate support plan. This support plan has the aim to stabilize the autologous graft, which must be prepared or shaped accordingly to fit between the bone and dura mater on all dehiscence sides;
- *overlay technique* - The overlay technique foresees to remove the mucosa and in a second step, the autologous graft is placed above the dural lesion and the exposed bone margins. Mucopericondral and mucoperiostial flaps are most frequently used, which are placed with the connective side towards the defect;
- *obliterative technique* - This technique is mainly used in case of a poorly pneumatized sphenoid (Fig. 3) and frontal sinus. In a first step, complete removal of sinus mucosa should be achieved to avoid mucoceles; secondly, sinus cavities should be filled with autologous abdominal fat used preferably in a monobloc; after, the anterior sinus wall should be coated with a free autologous graft of mucopericondrium or muco-periosteum [35].

The choice between these techniques depends on different variables. Regarding the leak diameter, usually the bigger the diameter, the easier and safer an underlay graft can

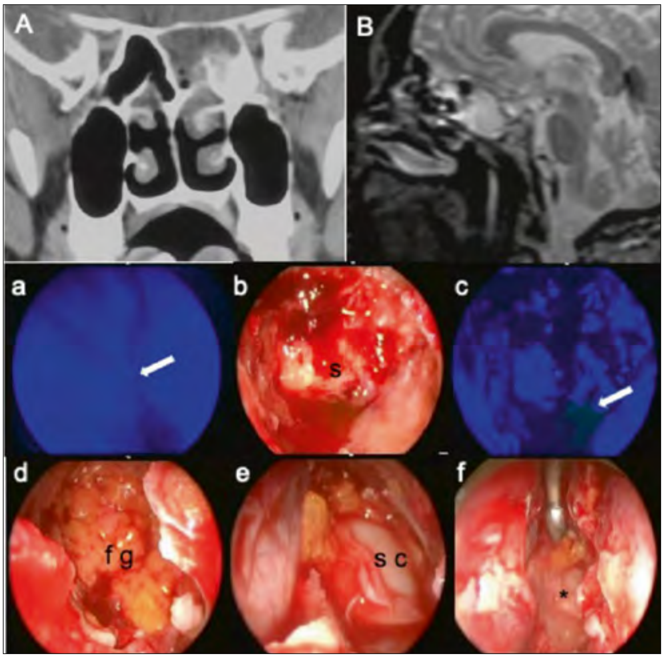

Figure 3. Coronal CT scan (**A**) and sagittal (**B**) T2 weighted MRI showed the presence of sphenoiditis and erosion of the clivus in a 54-year-old male patient with rinoliquorrea 2 years after chemoradiotherapy for a nasopharyngeal cancer. The precise site of leakage was uncertain at the imaging so we used intrathecal fluorescein for a precise localization. The endoscopic pictures shows fluorescein coming out from the sphenoid ostium (**a**) and after sphenodotomy the trasudation of the liquor (**b, c**) throught the clivus and below the sella (S). An obliterative technique (**d**) was preferred using an autologous fat graft (fg), a cartilage graft of the nasal septum (**e**) in a gasket seal way on the sphenoidotomy, and fibrin glue (*).

be implanted. Concerning leak location, in case the leak is placed at level of lamina cribrosa, dura is very difficult to detach from the intracranial bone at the level of olfactory fissure, because of tenacious adhesion between dura and olfactory holes. Therefore, overlay technique should be performed. Furthermore, the space to move surgical instruments should be considered; overlay technique is more preferable in smaller spaces.

Regarding large ventral skull leaks (over 2 cm), comprising bone and dura, but even smaller leaks associated with high intracranial pressure, multilayer technique is recommended. This multilayer technique should consist of an intradural collagen graft between dura and brain, a second onlay graft in contact with the dura and bone and as a third layer a vascularized or mucosa flap [36,37]. In a further step, some defects might be supplemented with adipose tissue. Numerous variations of these techniques are successfully used today [38,39].

Generally, rigid reconstruction with bone or allograft material is less recommended because this type of graft is related to a higher migration and infection risk.

Reconstructions based on the location of the leak

Snyderman et al. [17] tried to standardize various reconstructions types based on the leak location. Particularly, authors described intervention types more suitable for anterior, middle and posterior cranial fossa reconstruction.

Anterior cranial fossa: lesions in the anterior cranial fossa, necessitating surgery, are typically caused by sinonasal tumours and less commonly by cranio-facial traumas. If they originated from large sized anterior cranial base defect, they usually extend frontal from one orbit to the other and sagittal from the planum sphenoidale to the posterior wall of the frontal sinus. Generally, a three-layer reconstruction is performed. Circumferential dissection of the epidural plane facilitates to implant the graft in the epidural space. The three layers are represented by a first internally placed layer that prevents liquor flow, without totally sealing off the leak. This layer can be autologous or heterologous, and has to be shaped that it exceeds for 1 cm the dural edges. It is positioned between the cerebral and dural surface with incisions on the grafts edges to allow anterior adaptation to both sides of the cerebral falx.

As a second or middle graft layer, non-porous materials need to be used. The autologous fascia lata graft is generally preferred among the various options of several autologous materials, such as cadaveric tissues, as it is easy to implant and obtain, and well tolerated, because it heals fast. An adequate size needs always to be considered, as the graft must generously overlap the edges of the leak. Importantly, complete demucosization should be achieved to avoid mucoceles and to allow adherence.

Finally, for the third layer a nasoseptal flap is usually used, which can be raised from the antero-superior portion of the nasal septum, and might be additionally enlarged to the lateral wall rather than to the floor of the sphenoid sinus. If additional material is required to reach the required length, the clival recess can be obliterated with fat grafting. However, it is not necessary to cover entirely the fascia lata with the nasoseptal flap, because vascularization of the central part of the fascia lata graft initiates early. If for surgical or oncological reasons a nasoseptal flap cannot be used, an extracranial flap of pericranium can be alternatively raised by a bicoronal incision and implanted through a bone window measuring 1.5 x 2.5 cm at the root of the nose from one orbit to the other. The flap pedicles can be attached unilaterally or bilaterally to the supraorbital arteries. If unilaterally attached, an obstruction of the frontal sinuses is less likely, because the rotation arch is greater; instead, if bilaterally attached the blood support will be more robust, but the rotation arch is inferior and increased compression on the vascular pedicles from the bone window can cause postoperative edema. Endoscopic graft positioning allows keeping the proximal frontal sinus in contact with the posterior bone table; laterally the flap can be pushed between orbital content and orbital roof or can be used to reconstruct the periorbita, if previously resected to verify tumour margins. Both types of flaps should be stabilized with nasal packing to keep them in place for 5-7 days [17].

Posterior cranial fossa: the typical defect requiring reconstruction – often associated with the treatment of tumours such as nasopharyngeal cancer, chordomas and chondrosarcomas – extends from the dorsum sella floor above the inferior foramen magnum in the sagittal plane and is limited by the carotids. Clival defects are located in an area with intense liquor flow and therefore most difficult to reconstruct. Reconstruction with vascularized flaps is essential, especially in case of irradiated tissue and exposed carotid arteries [40]. Clival bone coverage helps to prevent from osteoradionecrosis and consequent osteomyelitis.

Instead, at the posterior cranial fossa level, a multilayer reconstruction is mandatory with inlay and onlay grafts similar to previous used materials, which cover the entire defect with a vascularized flap. Unlike the anterior skull base, the clival defect should be filled with body fat above the lata fascia onlay graft to allow easier positioning of the vascularized flap and contact with the underlying surface, which reduces the risk of pontine herniation of the paraclival carotids. Nasoseptal flaps extending at the floor and lower meatus of the nasal fossa, are widely used to reconstruct the posterior cranial fossa and to obtain a greater mucous surface; they can be horizontally oriented when transferred. If unavailable, temporoparietal, pericranial fascia or lateral nasal wall flaps can be used. However, the lateral nasal wall is more difficult to prepare and has a limited rotation arc [17].

Middle cranial fossa: defects are located in the Meckel's cave and limited by the inferior and medial internal carotid arteries, the upper orbital fissure and the orbit above. They are less common, smaller and necessitate generally a two-layer reconstruction; an inlay and a vascularized layer might be sufficient even though a classic three-layer approach can be performed using nasoseptal flaps, which require generally a transpterigoid approach from the affected side [17].

Stabilization of the graft with "fixers"

Once reconstruction is completed, grafts should be stabilized. A fixer called fibrin glue is mainly used for autologous free grafts such as mucosa, fat, muscle and mucoperiostal flaps. Another type of "fixer" are nasal swabs. Merocel and surgicel are most widely used and in alternatives avitene, gelfoam and lyfoam can be utilized.

Drainage types after reconstruction

Lumbar or spino-peritoneal drainage can be placed during the intervention, which can remain in place for about three days. The advantage of spino-peritoneal drainage is that during this period, liquor pressure can be directly measured to monitor and regulate the eventual recurrence of liquorrea. Additionally, fluorescein can be intrathecally injected [31]. Once the intervention is completed, presence of fluorescein in liquor allows a quick and immediate intraoperative control if the CSF leak repair was successfull. The place of the pre-existing leak is displayed with a blue light filter: a negative finding confirms leak closure. Operation's success can also be verified through Valsalva maneuver, realized with anesthesiologists help.

Instead, placement of a permanent drainage (ventricle-peritoneal or spino-peritoneal) is reserved to selected cases and should be discussed in a multidisciplinary team.

Intraoperative navigation systems for skull base reconstructions and CSF leak

Real-time intraoperative navigation systems are a new technology, which process pre-operatively acquired CT and MR images (Fig. 4), to establish the position of surgeon's instruments on a monitor during the surgery [28]. This system allows visualization of deeper portions of the skull to avoid lesions of vascular and nervous structures. Additionally, surgical navigation systems can be useful to diagnose neoplastic forms, allowing targeted biopsies. Through imaging fusion tools, it is possible to map any areas removed to verify radicality of surgical treatment. On the monitor, various

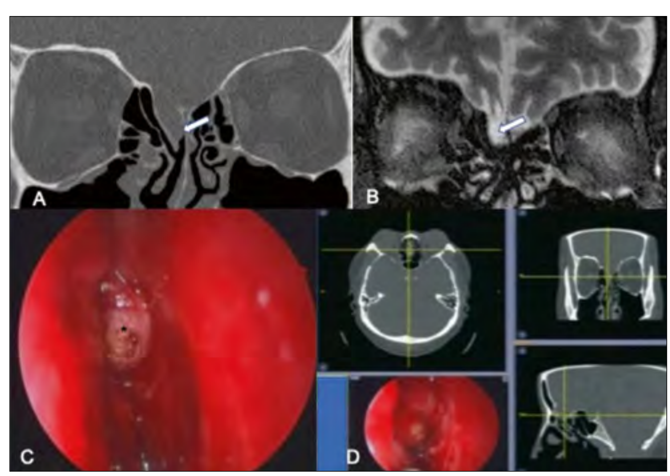

Figure 4 Coronal CT scan (**A**) and T2 weighted MRI of a case of spontaneous CSF leak due to meningocele of the right olfactory groove. The endoscopic view (**C**) after precise localization using Navigation System (**D**) yellow cross-air in the 3 planes and endoscopic view of the tip of the instrument.

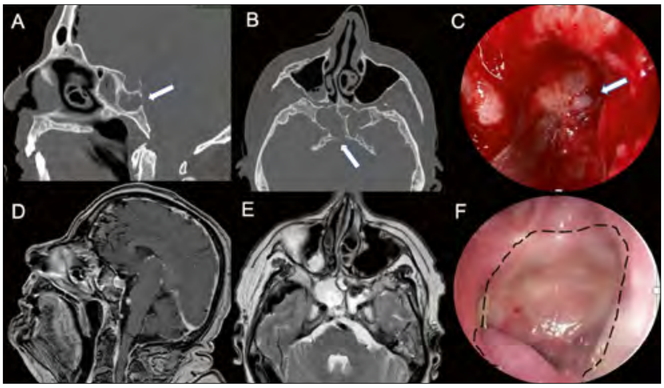

Figure 5. CT scan in sagittal (**A**) and axial view (**B**) in a case of meningoencefalitis (showed in the Sagittal post Contrast Enhancement MRI (**D**) and T2 weighted MRI (**E**) The bony erosion on the clivus as it appear endoscopically (arrow) The lesion was treated with multilayer technique and finally nasoseptal flap was used (dotted line in **F**) as it appear 2 months after surgery.

CT and MR images are simultaneously reported and the location of surgical instruments and video endoscopes are indicated in real-time.

This imaging technique is especially helpful if the surgeon faces the following several difficulties during surgery: anatomical variants, excessive bleeding reducing visibility; absence of reference points due to previous surgeries or invasive diseases, and loss of depth perception related to endoscopy. Mainly two categories of navigation systems exist: those using electromagnetic signals and those using optical signals. Recently, hybrid systems have been developed, which allow using both technologies, depending on the intervention type. New technologies are in constant evolution and can be used for an increasing number of nasosinusal diseases like neoplastic pathologies, severe polyposis, invasive mycotic sinusitis, traumas, orbital decompression, drainage of orbital abscesses, closure of rhinoliquoral fistulas**,** trans-sphenoidal access to pituitary, coanal atresia, and skull base mucocele (cordomas, chondrosarcoma). Further technological progress concerns the add-on of new generation surgical instruments like 3D, 4K endoscopic systems in addition to the neuronavigation [4,42,43].

Post-operative management

Time of hospitalization and post-operative therapeutic measures vary according to patients' general condition and leak features. Life parameters and diuresis should be constantly monitored. The most important element is bed rest. As previously described, patients must remain in supine position for 48 hours, with the head 30° inclined. The nasal package is usually removed during the fifth post-operative day. It is necessary to perform daily nasal hygiene with physiological solution. Antibiotics should be taken for at least ten days after surgery to prevent form infections. Patients are usually discharged between the fifth and seventh post-operative day, with the indication to avoid physical stress, sneezing or other activities causing increasing of intracranial pressure for about 30 days. Air travel is not recommended. At discharge, a first follow-up visit after 10-15 days from surgery is scheduled in which nasal debridements and residues of the reabsorbable material are removed. Fibrin and the intranasal clots should be aspirated to examine clearly patency of the senotomies, graft tightness and vitality. A normal or uneventful post-operative course foresees follow-up visits every three months for one year with MRI scheduled at least every 6 months. After that semi-annual checks including MRI visits are planned for two years. Finally, annual checks including MRI for two more years should be performed.

Discussion

CSF leaks are historically difficult to diagnose and treat because of their wide variability [14]. Recent years' technical innovations, increasingly combined by multidisciplinary collaborations, have changed the diagnostic and therapeutic paradigm, which is mostly related to a better comprehension of CSF leaks anatomical and physiological aspects [19,41].

The main objective of the diagnostics has been to improve the anatomical localization of the leak. It is essential to assess precisely leak dimensions and localization to create adequate therapeutic planning. Nowadays, the combination of multiple CT and RMN fusion imaging strategies allow obtaining a 91% accurate identification pre-operatively. The interaction and role of expert neuroradiologist is of paramount importance. Moreover the development of new and detailed RMN sequences has helped to outline complex CSF leaks. In addition, the possibility to obtain a more sophisticated image navigation systems allows comparing various types of defects and helps to understand differences between CSF leaks and their presentation.

Several critical issues require close collaboration of neurosurgeons and all other professional figures involved in the Skull Base Team, who contribute to manage this complex pathology from an anatomic-functional point of view.

Collaboration with neurosurgeon starts during non-invasive preoperative functional diagnostic and allows clarifying the diagnostic field and gives the possibility to acquire preoperative information on liquor dynamics, intracranial pressure development and differentiation between high and low flow leaks to create a targeted surgical setting. Whenever possible a dedicated radiologist assesses, in collaboration with ENT and neurosurgeon, MRI and CT scans to identify likely idiopathic intracranial hypertension. Posterior Sclera flattening, widening of optic nerve subarachnoid space widening, optic nerve head protrusion, arachnoid pits (bony scalloping) skull base foramina enlargement, bilateral transverse sinus stenosis, total/partial empty sella are amongst the most common signs of this hypertension type [4].

Body mass index (BMI), especially in female gender, has a linear relationship with intracranial hypertension, which is closely related to leak's complexity [42]. This population need a strict diagnostic follow-up and a preventive treatment of intracranial hypertension in order to prevent leak's onset. In this population, even after repair intervention, permanence of underlying risk factors involves a chronic increase of intracranial pressure itself with a remodeling and a thinning of basicranium at the level of the thinnest bone limiting. That process favors meninges' bulging through orifices [36-38]. Careful monitoring methods allow early recognition of complications and make it possible to make a second surgical exploration. This kind of multidisciplinary collaboration, could finally allow to deeper and better understand etiology of pathologies still poorly clarified (as in the case of spontaneous CSF leaks).

In recent years, technological advances overcome many of the obstacles associated with endonasal cranial base surgery. The most recent visualization technologies (e.g. 3D and 4K cameras), angled instruments [49] and their different applications aided also by navigation systems contributed to the fact that the endoscopic endonasal approach become the best surgical approach to treat CSF leaks by offering the best surgical outcomes.

This approach allows achieving success rates of almost 95%, and reduces significantly patient morbidity if performed by highly skilled surgeons [22]. Although ENT surgeons are directly involved in the surgical procedure, neurosurgeons are necessarily involved to manage and choose complex dural and intracranial reconstruction and to treat eventual complications. Therefore, surgeons need intensive training to acquire surgical skills and experience [50,51]. To date, no adequate risk stratification to outline reconstructive algorithms still exist. The development of a treatment algorithm based on leaks localization (regardless from causes), dimension and presentation methods is therefore most desirable.

Moreover the predictive criteria to support decision-making on lumbar drain in patients with spontaneous leaks and intracranial hypertension are still absent. It remains unclear how different factors like time of placement (before during or after surgery), intensity of adjustment (more or less than 10 cc/h), and time of removal (correlated to infection risk) influence outcomes [17,44]. Neurosurgeons' experience is essential to answer these unsolved questions and to decide on lumbar drain placement during the multidisciplinary assessment in preoperative setting. Increased risks for infections and pneumocephalus causing higher morbidity, mortality, longer hospitalization and cost are well known and need to be considered. Until now the placement of lumbar drain can be generally considered in cases of spontaneous CSF leak due to intracranial hypertension, in case of large dural defects, and high flow fistulas in the anterior and posterior cranial fossa and it is generally not indicated in the reconstruction of sellar or suprasellar defects. Lumbar drain can reduce fistula recurrence from 41% to 5% after transsphenoidal surgery [52,53].

Conclusions

CSF leaks remain a challenging issue requiring new and innovative techniques for early diagnosis and treatment. Dynamic multidisciplinary teams, who apply various imaging techniques represented by newer diagnostic and endoscopic technologies to diagnose, treat and rigorously follow up patients, are the future for CSF leak management. Additionally, neurosurgeon's experience will contribute significantly to develop new biomaterials with increased durability, which may replace autologous grafts in the future. New biomaterials might facilitate multilayer repairs and standardize heterogeneity of repair methods, which is related to variability of materials used today and still conditioned largely only by surgeon's preferences.

Conclusively, the correct diagnosis and best treatment can only be determined in a dedicated Skull Base Team composed by neurosurgeons, otolaryngologists, neuroradiologists, ophthalmologists, endocrinologists, in order to completely evaluate a patient with CSF leak from the first visit, during treatment and follow-up.

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Sellar and parasellar lesions: multidisciplinary management

Lesioni della regione sellare e parasellare: gestione multidisciplinare

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SUMMARY

Introduction. The endoscopic endonasal transsphenoidal approach to the sella and parasellar regions is now increasingly used for removal of a variety of lesions localized in the ventral skull base. The advantage of the endoscope is enhanced visualization and improved panoramic view that can result in more complete removal of the tumor. An extensive knowledge of the anatomy is mandatory to approach this region.

Materials and methods. From February 2009 to March 2020, the endoscopic endonasal approach was used in 153 patients with sellar and parasellar lesions, at our Institution: 136 pituitary adenomas, 7 craniopharyngiomas, 3 Rathke's cysts, a tuberculum sellae meningioma, an aneurysm of the internal carotid artery (ICA), a clivus chordoma, a papillary glioneuronal tumor, an histiocytosis, a pituitary metastasis from breast cancer and a chondrosarcoma.

Results. The most common surgical complications were cerebral spinal fluid leak (9), bleeding (2), pituitary abscess (2). Among endocrinological complications, the most important were diabete insipidus (23) and panhypopituitarism (3). Two patients complicated with meningitis. There were no visual worsening and no operative mortality. We had persistence of disease in 20 cases. Twelve patients underwent surgical revision for recurrence of the disease.

Conclusions. Pre-operative planning and collaboration with several specialists are necessary in order to offer the patient the best treatment, minimizing complications.

KEY WORDS: skull base, sellar and parasellar region, pituitary adenoma, endoscopic endonasal approach

RIASSUNTO

Introduzione. *L'approccio endoscopico endonasale trans-naso-sfenoidale alla sella e alla regione parasellare è a oggi l'approccio più utilizzato per lesioni localizzate nella parte ventrale della base cranica. Il vantaggio di questa tecnica consiste in una miglior visualizzazione panoramica del sito chirurgico che consente una rimozione quanto più completa del tumore. Un'approfondita conoscenza dell'anatomia è d'obbligo per iniziare ad approcciare questa regione.*

Materiali e metodi. *Da febbraio 2009 a marzo 2020, abbiamo trattato nel nostro Istituto 153 pazienti con lesioni sellari e parassellari mediante approccio endoscopico endonasale; di questi 136 erano adenomi dell'ipofisi, 7 craniofaringiomi, 3 cisti di Rathke, un meningioma del tubercolo sellae, un aneurisma dell'arteria carotide interna, un cordoma del clivus, un tumore glioneuronale papillare, un'istiocitosi, una metastasi pituitaria da cancro al seno e un condrosarcoma.*

Risultati. *Le complicanze chirurgiche più comuni sono state la rinoliquorrea (9), il sanguinamento (2), l'ascesso pituitarico (2). Tra le complicanze endocrinologiche, le più importanti sono state il diabete insipido (23) e il panipopituitarismo (3). Due pazienti si sono complicati con meningite. Non ci sono stati deficit visivi né mortalità intraoperatoria. Abbiamo avuto persistenza di malattia in 20 casi. Dodici pazienti sono stati sottoposti a reintervento per recidiva.*

Conclusioni. *Un'adeguata pianificazione preoperatoria e la collaborazione tra diversi specialisti sono necessarie per offrire al paziente il miglior trattamento possibile, riducendo al minimo le complicanze.*

PAROLE CHIAVE: *base cranica, regione sellare e parasellare, adenoma ipofisario, approccio endoscopico endonasale*

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Introduction

The sphenoid bone sits at the center of the skull base, representing the fulcrum of this region and the border point between the anterior and middle cranial fossa. The sella turcica is a bone depression included between the anterior and posterior clinoid processes of the sphenoid bone. It represents the central portion of the middle cranial fossa and contains the pituitary gland. Laterally to the sella turcica, along the fusion line between the body of the sphenoid and greater wings, there is the carotid sulcus for the passage of the parasellar portion of the internal carotid artery (ICA).

The pituitary gland is composed of two parts: the adenohypophysis (anterior lobe), which represents about 70% of the volume of the entire gland and the neurohypophysis (posterior lobe).

A semitransparent, thin but tight capsule surrounds the gland's surface. The pituitary gland is completely surrounded by dura mater: its anterior, inferior and posterior walls are surrounded by a double layer and by sellar bone; on the contrary, the upper and lateral walls are covered only by dura mater and both offer less resistance to tumour growth [1].

The upper wall which forms an inextensible diaphragm, is thick at the periphery, thin at the centre, where it is depressed and perforated by the hypothalamus-pituitary stalk. Anteriorly the two layers of dura mater continue with the dura mater covering the sphenoidal planum and the anterior cranial fossa, posteriorly they continue with the dura of dorsum sellae and clivus. Laterally, the two layers separate: the outer periosteal layer continues laterally to form the sphenoidal or anterior wall of the cavernous sinus, while the inner meningeal layer remains attached to the gland and runs backwards towards the posterior clinoid process and the dorsum sellae to form the medial wall of the cavernous sinus. Consequently, both walls (anterior and medial) of the cavernous sinuses are made up of a single layer of dura mater [2]. The arachnoid is located just above the diaphragm and, therefore, there is usually no liquor inside the sella.

The parasellar region includes all the structures surrounding the sella turcica [3]: the suprasellar region at the top, the two cavernous sinuses laterally, and the clival region at the bottom. It represents a crossroads region where a high number of neoplastic, inflammatory, infectious and vascular diseases can develop [4].

The suprasellar region extends above the sellar diaphragm to the floor of the third ventricle and contains the optic chiasm, optic nerves, the pituitary stalk and the Willis' circle. It is close to the third ventricle, the hypothalamus, the tuber cinereum and the mammillary bodies. The most common lesions of this region are:

- suprasellar extension of pituitary adenomas;
- craniopharyngiomas;
- hypothalamic or optic chiasm gliomas;
- hamartomas;
- germinomas;
- dermoid and epidermoid tumors.

The cavernous sinuses, two venous structures that delimit the pituitary fossa laterally, are in relationship with the following cranial nerves: oculomotor (III), trochlear (IV), first and second branches of the trigeminal nerve (V1 and V2), and abducent (VI). All the nerves are contained in the lateral wall of the cavernous sinus, except the abducent nerve which is located laterally to the carotid artery and medially to V1. Within the cavernous sinus there is also the cavernous carotid artery (with three segments and two genua) and its branches. The lesions that most affect the cavernous sinuses are:

- lateral extension of pituitary adenomas;
- meningiomas;
- schwannomas;
- aneurysms of the ICA.

Clivus is a bony portion behind the dorsum sellae that slopes obliquely backward to the magnum foramen getting in touch with the ventral face of the brain stem. The clival region extends inferiorly to the dorsum sellae and includes the sphenoid sinus, the nasopharynx and the clivus. The most common lesions of this region are:

- chordomas;
- chondrosarcoma;
- meningiomas;
- nasopharyngeal carcinomas;
- tumors of the sphenoid sinus;
- mucoceles;
- juvenile angiofibromas.

Histology of sellar and parasellar lesions is heterogeneous but the main role is played by the pituitary adenomas; however, in 9% of cases we find different histologies with peculiar biological features that is essential to know for adequate surgical treatment (Tab. I). The biological variety does not reflect the clinic, since symptoms of sellar and parasellar neoplasms depend on the sub-site of origin: in this particular district, knowledge of the anatomy is essential not only for surgical purposes, but also to define the clinical picture.

The radiological study plays a key-role in the diagnostic framework of these pathologies. The Magnetic Resonance Imaging (MRI) with gadolinium and the Computer Tomography (CT) scan are complementary: the first provides information about the nature of the lesion and the involvement of vital structures; the second defines in detail the bone involvement and allows to identify the possible presence of intralesional calcifications.

Table I. Main lesions of sellar and parasellar region.

Pathology	Symptoms	Radiological features	Differential diagnosis	Treatment	Multidisciplinary approach
Pituitary adenoma	Endocrine dysfunction; visual impairment; obstruction of the liquor drainage; rhinoliquorrea	Brain MRI: lower density than healthy glandular parenchyma in T1 sequences; heterogeneous increased signal with hyper-intense areas in T2 sequences	Pituitary abscess; pituitary carcinoma; pituitary metastasis; craniopharyngioma; hypothalamic glioma; parasellar meningioma	Surgical treatment with trans-sphenoidal approach	Mandatory
Meningioma	Visual impairment; endocrine dysfunction; cranial nerves deficits; obstruction of the liquor drainage	Brain MRI: same density as the cerebral parenchyma in both T1 and T2 sequences, with marked contrast-enhancement	Pituitary adenoma; paraganglioma	Surgery in symptomatic or growing mass. Adjuvant radiotherapy in macroscopic residual	Strongly recommended
Craniopharyngioma	Hydrocephalus and endocranial hypertension (especially in children); visual impairment; endocrine dysfunction	- Brain MRI: lower density than cerebral parenchyma with hyper-intense cystic areas in T2 sequences. - Brain CT-scan: calcific components in adamanthomatous forms	Optic glioma; Rathke's cyst; pituitary adenoma	Exclusive surgical resection (complete/ subtotal) or subtotal resection associated with radiotherapy	Mandatory
Glioma	Visual impairment; hydrocephalus and endocranial hypertension	Brain MRI: lower density than cerebral parenchyma with hyper-intense cystic areas in T2 sequences	Craniopharyngioma	Surgery followed by adjuvant radiotherapy in aggressive forms	Strongly recommended
Chordoma	Diplopia due to abducent nerve impairment; facial nerve paralysis; vertigo and tinnitus; trigeminal paresthesia	- Brain CT-scan: hyperintense lesion surrounded by reabsorbed bone; - Brain MRI: hypointense in T1 sequences, hyperintense in T2 sequences	Fibrous dysplasia; Paget's disease; pituitary adenoma; clival meningioma; paraganglioma; chondrosarcoma	The radical surgical treatment is considered the main prognostic factor in literature	Strongly recommended
Hemangiopericytoma	Endocrine dysfunction; hydrocephalus	- Brain CT-scan: expansive mass associated with bone thinning; - Brain MRI: iso / hypointense signal in T2 sequences, intermediate in T1 sequences and avid contrast enhancement	Hemangiomas; vascular leiomyomas; sarcomas	Surgery followed by adjuvant radiotherapy in case of incomplete removal or recurrence	Strongly recommended

CT: Computed Tomography; MRI: Magnetic Resonance Imaging.

Materials and methods

Since February 2009, a collaboration between our Otorhinolaryngology, Neurosurgery Academy and Endocrinology Units has been started for the management of sellar and parasellar pathologies. From this date to March 2020, a total of 153 patients underwent endoscopic trans-sphenoidal surgery. 136 patients (89%) were affected by pituitary adenomas, the remaining 17 patients was affected by the following: 7 craniopharyngiomas, 3 Rathke's cysts, a tuberculum sellae meningioma, an aneurysm of the ICA, a clivus chordoma, a papillary glioneuronal tumour, an histiocytosis, a pituitary metastasis from breast cancer and a chondrosarcoma.

Multidisciplinary management is necessary for the correct approach to the patient and pathology. The specialists involved are Endocrinologist, who often refers the patient for surgical evaluation and requires complete serum pituitary hormone panels both pre and postoperatively, Neuroradiologist for imaging evaluation of the lesion and anatomy, Neurosurgeon for four-hands technique which we always perform, and the Ophthalmologist in case of visual impairment at diagnosis.

A multidisciplinary skull base conference meets twice a month to discuss the cases. Then, all patients undergo an endoscopic endonasal approach, which provides the most direct access to the ventral skull base while obviating the need for retraction and manipulation of critical neurovascular structures.

The trans-sphenoidal approach performed by an expert surgeon is nowaday a safe procedure, with a remission rate from 42% to 95%, depending on the case studies (with most between 70-85%) [5]. This surgical technique can be divided into three phases: nasal, sphenoidal and sellar.

Nasal phase: two endoscopic approaches can be used to reach the sellar region.

The paraseptal trans-sphenoidal approach tangent to the nasal septum removing the upper turbinate body (or supreme, when present) represents the preferred choice. If the anatomy avoids an easy approach to the sphenoid sinus, for example in case of nasal septum deviations, the posterior third of the nasal septum can be removed to obtain a wider route, to use the four-hand technique.

The trans-ethmoid-sphenoidal approach is useful when more space is necessary or in the laterally extended transpterygoidal approaches.

Once the sphenoid ostium or anterior sinus wall has been identified, the surgical procedure is the same for both approaches.

Sphenoid phase: the anterior wall of the sphenoid sinus is opened using a Kerrison's rongeur to expose the anterior margin of the intersphenoidal septum. The mucosa is preserved to save the nasal branch of the sphenopalatine artery. The sphenoidal septum and rostrum must be gently removed because they can be connected with ICA. The anatomical landmarks of the lateral wall of the sphenoid sinus are now visible (Fig. 1). The bony irregular edges are then carefully drilled out to obtain a wide access to the sellar floor. When tumours develop into cavernous sinus, more bone must be removed in the lateral direction towards the anterior face of the parasellar carotid artery; when tumours reach the suprasellar region, sellar floor removal is required.

Sellar phase: once the dura mater is exposed, a cross incision is made to avoid damage to the carotid artery and the anterior arachnoid cistern. From now on the four-hands technique with the Neurosurgeon is applied to remove the tumor. The lesion is detached using ring-shaped curettes: in case of pituitary adenoma, it can be identified as a greyish region in contrast with the pink colour of the gland and for its soft consistency (Fig. 2). The adenomatous tissue is carefully separated from the glandular tissue using a microdissector and removed en bloc. The advantage of a dissection along the pituitary pseudo-capsule in order to completely remove the lesion and reduce tumour residue has been demonstrated [6-10]. Once the lesion is totally excised, the inspection of the sellar cavity with angled optics and hydrodissection is mandatory, paying attention to the suprasellar and cavernous sinus areas.

A variety of thoroughly evaluated techniques exist to close the skull base defects, depending on the location and the size of the defect. We always prefer autologous grafts (bone of the middle turbinate, mucoperiosteum, septal cartilage and mucopericondrium) or other autologous materials (such as fascia lata or rarely fat), that allow highly compatible repair of the dura and can be readily harvested compared to heterologous grafts. The area of the defect must be prepared: the mucoperiostium surrounding the defect

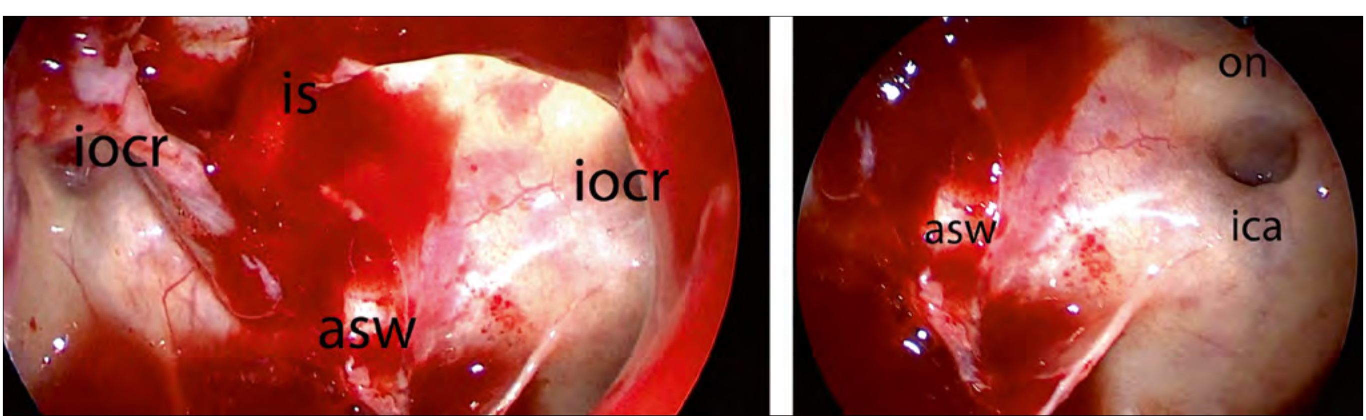

Figure 1. Sphenoidal sinuses after drilled out the intersphenoidal septum – asw: anterior sellar wall; ica: internal carotid artery; on: optic nerve; iocr: interoptic-carotid recess.

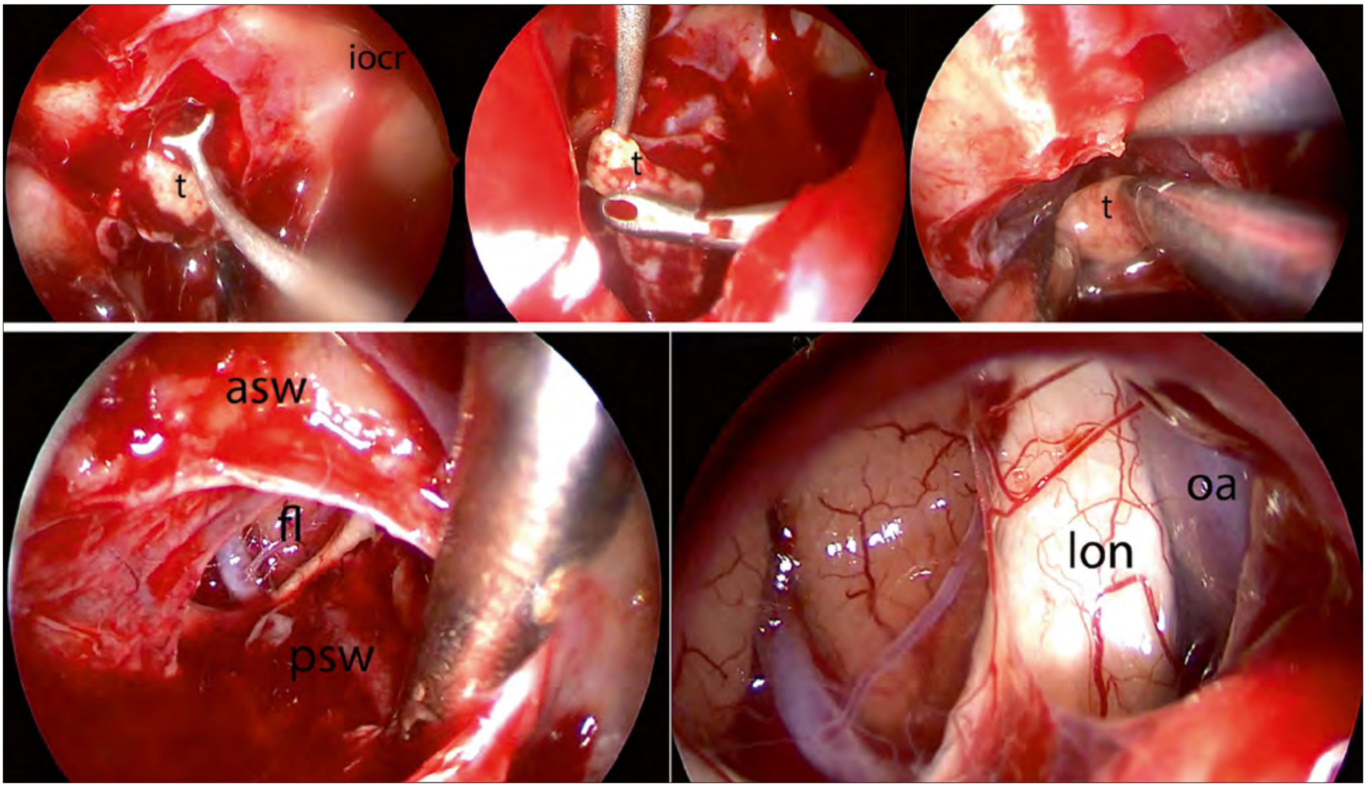

Figure 2. Removal of the tumour (t) with four hands technique and vision at the end of the procedure with a 0° and 45° telescopes – asw: anterior sellar wall; psw: posterior sellar wall; fl: frontal lobe; lon :left optic nerve; oa: ophtalmic artery.

is detached with straight and angled dissectors in order to expose the bone and locate the dural defect (Fig. 3). When no cerebrospinal fluid (CSF) leak or dripping is confirmed by the Valsalva maneuver, we use autologous endonasal tissues positioned undelay (intracranially extradurally). When moderate or massive CSF leak is present, a multilayer technique is preferred using fascia lata positioned underlay and septal cartilage or bone from the middle turbinate positioned immediately above the first layer. A further layer of fascia lata is positioned overlay (extracranially extradurally), covered by mucoperiosteum or mucopericondrium. Considering that fascia lata physiologically shrinks, grafts larger than 30% of the dura defect must be removed. In case of massive CFS leak or high flow defect, the Hadad flap vascularized on the nasal branch of the sphenopalatine artery can be prepared.

Once repaired the defect, the surgical field is gently filled with absorbable sponge material that maintains the correct positioning of the grafts.

This study was conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Results

Of the 153 patients operated, 56 were males and 97 females. The mean age at the time of diagnosis was 49 ± 13 years. In 35 cases the lesion was a recurrence of previous surgery performed elsewhere.

Of the 136 patients affected by pituitary adenomas, 43 were microadenomas and 93 macroadenomas, divided as follows: 50 non-secreting tumours, 43 ACTH-secreting adenomas, 27 GH-secreting adenomas, 6 PRL-secreting adenomas, 4 TSH-secreting adenomas, 1 FSH-secreting adenomas and 5 mixed lesions (3 GH-PRL, 1 TSH-GH and 1 TSH-FSH).

Considering all the patients, endocrinological disorders such as acromegaly, Cushing's disease, panhypopituitarism, hyper- or hypothyroidism, insipidus diabetes, decreased libido, amenorrhea and galactorrhea were the most frequent symptoms. In 9 cases the tumour was incidentally found during a brain imaging performed for other reasons. Sexteen patients also referred visual impairment such as homonymous or bitemporal hemianopsia or decrease in visual acuity (usually unilateral): in 12 cases the post-surgical visual recovery was complete while in 2 cases it was partial; in 2 patients there was no improvement.

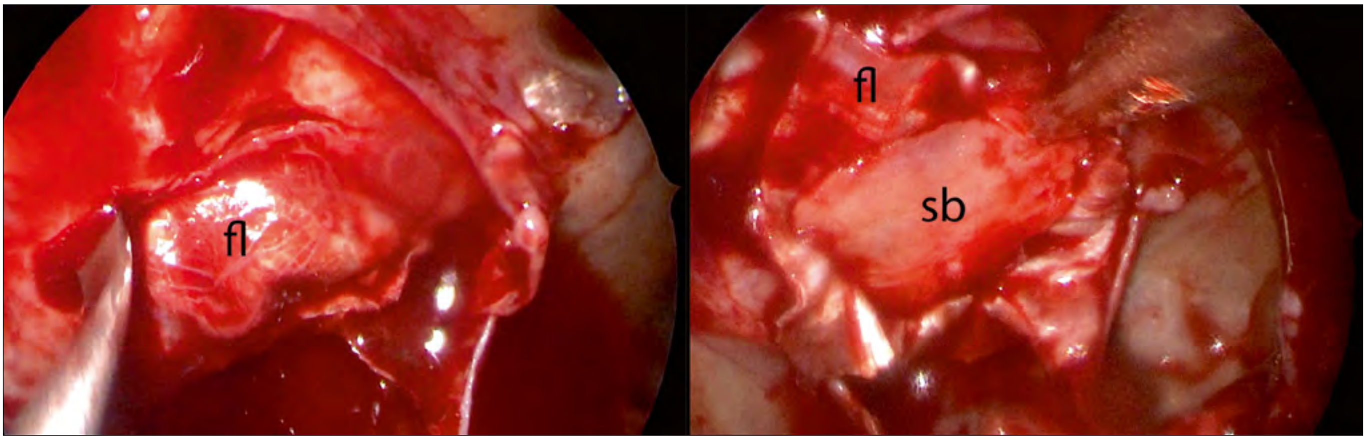

Figure 3. Reconstruction of the anterior wall of the sella with a multilayers technique – fl: fascia lata; sb: septal bone.

Based on the extension and histologic type of the tumor, we decided to perform a paraseptal approach tangential to the nasal septum for purely sellar lesions (136 cases), or a transethmoidal approach for lesions extending laterally into the cavernous sinus (8 cases). Extended endoscopic transsphenoidal approach was preferred for suprasellar and clival lesions (9 cases).
Endoscopic endonasal examination was performed on the 15th and 30th postoperative day, then every month during the first six months and every three months during the first year; every six months for the second year and annually thereafter. In our case series, the postoperative follow up period ranged from 9 to 132 months.
Follow-up includes endocrinological evaluation with complete hormonal assessment at 30 days, within three months and then at 6-months intervals, to assess any persistence or recurrence of disease.
Neuro-ophthalmologic evaluation was required three months after surgery only for those who had visual impairment preoperatively, or at any time for patients who reported alterations of new onset.
The most common surgical complications were:

- epistaxis, which required transfusion in one case and caustication of the sphenopalatine artery in another case;
- cerebrospinal fluid leaks (9 cases) with surgical revision of the dural plasty repaired with a multilayer technique using autologous fascia lata, cartilage or bone (from turbinates or septum) and mucoperiosteum from the inferior turbinate. Hadad flap was used in 3 cases, when a high flow leak was present;
- pituitary abscess (2 cases), the fist successfully treated with surgical drainage, the second quickly complicated in a brain abscess leading to coma and subsequent patient's death.

Among the endocrinological complications, we had diabete insipidus in 23 patients (most of which transient) and panhypopituitarism in 3 patients. Two patients complicated with meningitis.
Brain MRI performed 4 months after surgery showed persistence of disease in 20 patients, 4 of which were ACTH-secreting adenomas: in most cases it was intentionally left during surgery, in order to avoid damage to neuro-vascular structures close to the tumour. Twelve patients underwent surgical revision for recurrence of the disease.

Discussion

The skull base represents the boundary between the intracranial and facial region and is crossed by important neurovascular structures that enter and leave the brain through bone foramina. For this reason, this anatomical area is one of the most complex to treat surgically. The pituitary gland, enclosed in the sella turcica, is located at the center of the skull base: the extension of any pathology at this level can lead to endocrinological dysfunctions of hyper or hypo-secretion. Lateral to the gland there are the cavernous sinuses, which contain the III, IV and VI cranial nerves and the first and second branches of the trigeminal nerve. Therefore, the involvement of a cavernous sinus will be reflected in the alteration of ocular motility and consequent diplopia. The VI cranial nerve is the most frequently involved, due to its completely intracavernous course. The involvement of intracavernous ICA rarely causes clinical manifestations. Sometimes, pupillary defects can occur, due to irritation or deficit of the pericarotid sympathetic plexus. The suprasellar region houses many important structures, first of all the optic nerves, tracts and chiasm: a neoplasm at this level can appear with visual impairment; moreover, the hypothalamus, which can lead to various diseases: endocrinological dysfunctions such as hypopituitarism due to

hypo-secretion of the release factors or diabetes insipidus for the interruption of the hypothalamic-pituitary stalk, furthermore, alterations of thermoregulation and metabolism. It is also essential to remember the close relationship of the suprasellar region with the third ventricle: an expanding lesion at this level can obstruct the liquor's circulation increasing the intracranial pressure [11]. Finally, large tumours can grow in the clival region, involving the apex and the endocranial surface of the petrosal bone with trigeminal nerve compression at the Cavum Meckel, facial and vestibulocochlear nerves deficit, compression of the jugular vein's bulb or mixed nerves at the level of posterior foramen lacerum, even symptoms of nasal obstruction in case of massive growth towards the nasopharynx.
Below, are briefly analysed the main lesions that can affect this complex anatomical district.

Benign tumours

Pituitary adenomas: they are the most frequent neoplasm of the sellar region, with possible parasellar extension. Signs and symptoms can be determined by tumour hormonal hyper-secretion, reduced hormonal secretion (due to the compression on healthy glandular tissue), compression of the surrounding structures from an extrasellar adenoma.
The expansion can occur in all directions: caudally, the lesion can cause thinning of the sellar floor and occupy the sphenoid sinus and the nasal cavities, with nasal obstruction, epistaxis and/or rhinoliquorrea.
Cranial growth can cause symptoms of optic-chiasmatic compression (bitemporal or homonymous hemianopsia), hypothalamic compression (hypersomnia, alterations of hydro-electrolytic balance and metabolism), or obstruction of the liquor drainage (hydrocephalus, intracranial hypertension) (Figs. 4-6). The Hardy's classification describes four levels of suprasellar extension depending on the relationship between the neoplasm and the optic chiasm [12].
The lateral development of the adenoma can cause compression of the cavernous sinus or epilepsy if the temporal lobe is achieved. The classification system used to define the involvement of the cavernous sinus is the Knosp's classification [13], which recognises four levels of lateral extension according to the relationships between the tumour and the ICA at MRI coronal sections.
In some cases, acute pituitary apoplexy can occur, with sudden blindness and acute hypopituitarism [14].
Preoperative brain MRI is essential for diagnostic workup. In T1 sequences, the density of the adenoma is lower than healthy glandular parenchyma, while it has an increased signal in the T2 sequences. Macroadenomas often show a heterogeneous signal, particularly in T2 sequences, with hyper-intense areas corresponding to cystic, necrotic or haemorrhagic areas [14]. CT scan offers complementary information to MRI, since it provides a better definition of the bone landmarks for the surgical approach. In case of suprasellar lesion close to the optic chiasm, a pre-operatory visual examination with Hess screen is necessary. Moreover, young patients with family history of pituitary adenomas or other endocrinological pathologies (primary hyperparathyroidism, neuroendocrine neoplasms) should undergo genetic investigations for mutations of the AIP, MEN1 and MEN4 genes research.
In the differential diagnosis of a non-typical sellar mass, pituitary abscesses, pituitary carcinomas, pituitary metastases from primitive other tumors (especially breast and lung), craniopharyngiomas, hypothalamic gliomas, parasellar meningiomas must be considered. In most cases, differential diagnosis is based on clinical and radiological features [15].

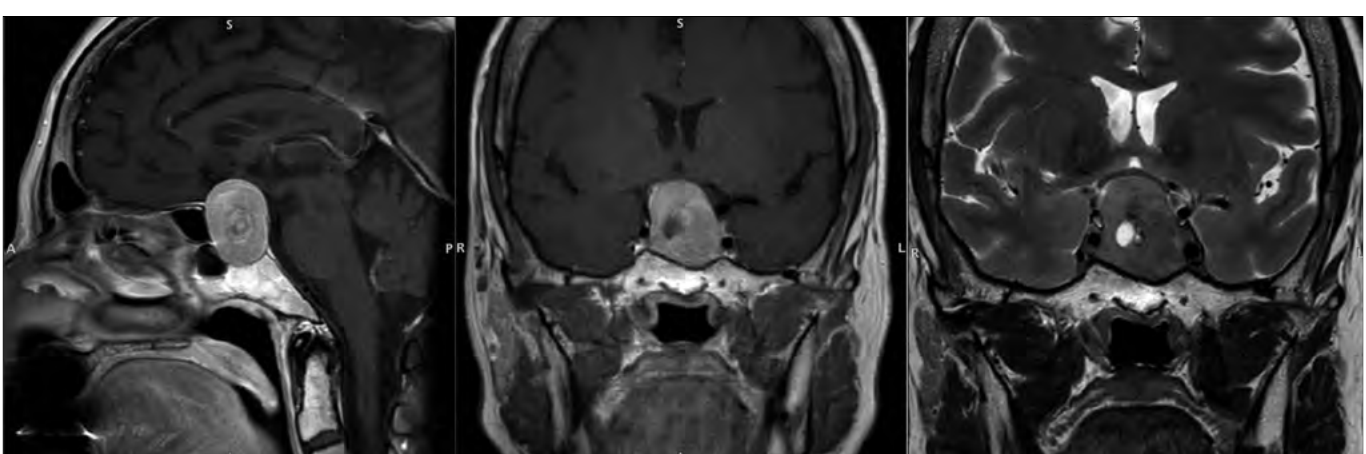

Figure 4. Sagittal and coronal MRI T1 with gadolinium and coronal T2 views showing a macroadenoma stretching upward the optic chiasm.

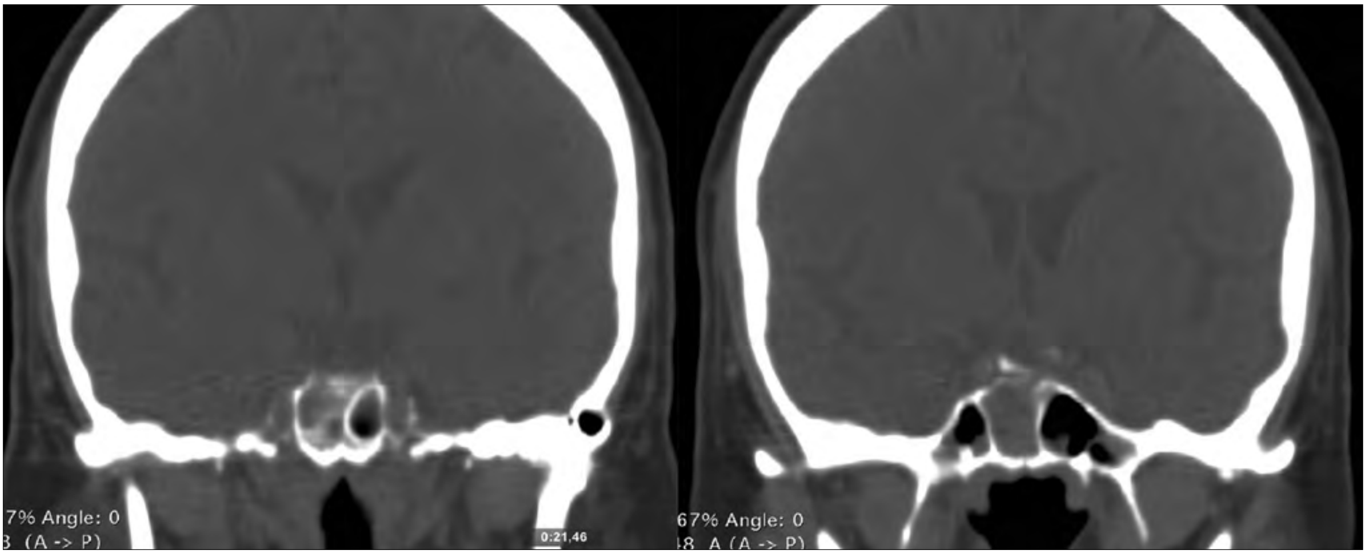

Figure 5. Brain CT-scan 6 hours after surgery showing complete removal of the tumour.

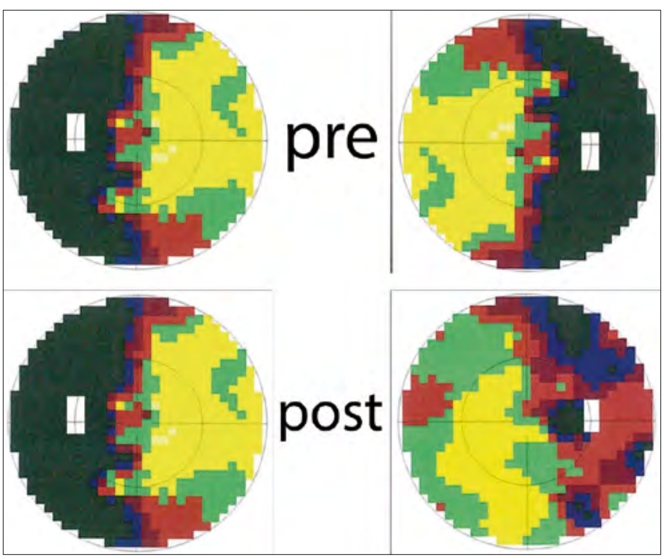

Figure 6. Visual field pre surgery and ten days after surgery.

Meningiomas: they originate from arachnoid cells located in the Pacchioni's bodies. They represent 13-25% of all primary intracranial tumours [16], the second most common neoplasm of the parasellar region, after pituitary adenomas, with an incidence peak between the sixth and the seventh decade of life. Meningioma in children is mainly linked to genetic diseases, especially neurofibromatosis type 2 [17]. The World Health Organization distinguishes 3 categories of meningiomas [18]:

- Grade I: benign meningiomas (92% of cases);
- Grade II: atypical meningiomas (5-7% of cases);
- Grade III: anaplastic meningiomas (1-2% of cases).

To define a meningioma as atypical, a high mitotic index or cellular atypical features such as an increased nucleus/cytoplasm ratio or high cellularity must be found. Anaplastic meningiomas have a clearly malignant appearance and behavior.

In sellar and parasellar region, these lesions can originate from the sellar diaphragm, the sellar tuberculum, the anterior clinoid process and the medial portion of the small wings [19]. Symptoms are related to compression of the surrounding structures, such as visual impairment, hormonal or cranial nerve deficits. The gold standard for the radiological study is MRI: the meningioma shows the same density as the cerebral tissue both in T1 and T2 sequences, with an intense contrast-enhancement. Surgery is the therapy of choice in symptomatic or growing lesions. Adjuvant radiotherapy can be used in selected cases of macroscopic residual after surgical resection.

Craniopharyngiomas: they are slow-growing epithelial tumours from ectopic embryonic cells of the pituitary recess. Despite benign histology, these lesions have an aggressive behaviour since they localize and grow close to critical neuro-vascular structures. The incidence is bimodal with a peak between 5 and 14 years and between 50 and 74 years [20]. Most craniopharyngiomas develop in suprasellar region, with possible extension in all directions, rarely totally intrasellar. In children, craniopharyngiomas represent 1-4% of all brain tumours and the prevalent histology is adamanthomatous, typically associated with cystic and calcific components at CT-scan imaging. The cystic growth inside the third ventricle causes the occlusion of the Monro's foramen and consequent hydrocephalus with signs of endocranial hypertension, that is the more frequent presentation of craniopharyngiomas in pediatric patients. Craniopharyngiomas represent 1.2-4% of all adult intracranial tumours and the most common histology is papillary, characterized by squamous cells nests surrounded by stromal tissue [21]. In adult patients, the typical symptoms are visual impairment and endocrine dysfunction. The main problem of treatment is the need for radical excision avoiding damage to the surrounding structures. The therapeutic options are exclusive surgical resection (complete or subtotal) or subtotal resection associated with radiotherapy.

According to a review conducted by Clark et al. [22], in pediatric patients the recurrence of craniopharyngiomas amount to 35% after a gross total resection, while in case of subtotal resection it is 65%, and becomes 50% if surgery is combined with adjuvant radiotherapy; furthermore, the two options are not significantly different in terms of 5-year disease-free survival. Five-year overall survival is estimated to be 83-96%, but in the review they did not consider the long-term morbidity and quality of life after the treatment. Surgery is considered the gold standard for recurrence, with more surgical risks and greater morbidity due to anatomical alterations caused by previous treatments. Postoperative radiotherapy is the choice for residual disease.

Rathke cleft cyst: it is a congenital lesion from the embryonic Rathke's cleft. Although these lesions are mainly asymptomatic, they can suddenly grow due to intralesional bleeding or infection causing endocrine dysfunctions. Therapy is surgical excision.

Schwannomas: they are rare parasellar tumours, usually from the first and second branches of the trigeminal nerve in the Cavum Meckel, rarely from the nerves of oculomotion. They are characterized by slow growth with surrounding bone thinning. Surgical therapy is preferred for progressive forms.

Malignant tumours

Gliomas: they are slow-growing tumours arising from the hypothalamus, the optic chiasm or the optic tract. The most common histology is low-grade pilocytic astrocytoma, considered a benign tumour and related to neurofibromatosis type 1 in one third of cases. The median survival is 7 years [23] and only in advanced stages they present classic signs of hypothalamic or optical pathways impairment. There is also a small share of high-grade gliomas (multiform astrocytomas and parasellar glioblastomas) with a shorter median survival (11.2 months). Therapy is surgery followed by adjuvant radiotherapy for aggressive forms.

Chordomas: they are slow-growing lesions from residues of the notochord. They have low tendency to distant metastases, but a local aggressive behaviour. Three histopathological variants are recognized: the classic form, characterized by nests of eosinophilic cells in a basophilic/myxoid background; the chondroid form, with chondroid differentiation of the matrix; and the dedifferentiated form, which has a malignant fusiform cells component with sarcomatous features. These tumours are mainly localized in the clivus.

Symptoms can occur late, in most cases with headache or cranial nerves defects: the most affected is the abducent nerve with diplopia, but paralysis of the facial nerve, vertigo, tinnitus and paresthesia can also occur due to the close relation with the posterior cranial fossa. Clival chordomas may also present with a spontaneous CSF leak. On CT-scan the lesion appears hyperintense expansive, destructive and lytic, with irregular areas of calcification within the tumour. MRI better defines the relationships with surrounding structures. In T1 sequences, the lesion appears hypointense with hyperintense components corresponding to bleeding areas; while in T2 sequences the lesion is hyperintense. Usually the tumour presents an avid contrast enhancement unless the necrotic component is predominant.

The differential diagnosis must consider all the benign and malignant bone neoplasms, such as fibrous dysplasia or Paget's disease, or pituitary adenomas with caudal extension, clival meningiomas, paragangliomas or chondrosarcomas. Because of the high rate of recurrence, surgery must be as radical as possible, followed by adjuvant radiation therapy (conventional or adrotherapy, preferably) [24]. In the literature, complete resection is considered one of the main prognostic factors.

Chondrosarcomas: they originate from residual embryonic mesenchymal tissue of the cranial cartilage at the level of the petro-occipital and spheno-petrosal sutures. Often mistaken for chordomas, they have a more aggressive behavior and a faster growth: this paradoxically involves an earlier diagnosis and a better prognosis than chordomas [25]. Differentiating between chordomas and chondrosarcomas is imperative as they have different behaviors and treatment response: chordomas tend to be median lesions with an epicenter at the clivus and spheno-occipital synchondrosis, whereas chondrosarcomas often have an epicenter at the petroclival synchondrosis.

Germ cells tumours: the most representative histology is the germinoma, a midline tumour typical of the pineal area, which can affect the suprasellar region in 20% of cases [4]. The remaining histologies are extremely rare at this level and include embryonic cell carcinomas, choriocarcinomas and teratomas. Chemo-radiotherapy represents the treatment of choice, surgery is often necessary to obtain a definitive diagnosis.

Hemangiopericytomas: they are highly vascularized and locally invasive lesions. In the parasellar region they are mostly located above the sellar diaphragm. They originate from the pericytes, mesenchymal cells surrounding the endothelium of capillaries and blood vessels. Their behaviour is borderline, classified as low-grade sarcomas. The prevalence is slightly higher in women with a peak of incidence in the sixth-seventh decade of life. At the CT-scan the lesion appears as an expansive mass associated with bone thinning, the MRI confirms the solid nature of the lesion with iso/hypointense signal in T2 sequences, intermediate in T1 sequences and avid contrast enhancement [26]. Macroscopically, hemangiopericytoma appears as non capsulated but well-defined subepithelial lesion, with a typical perivascular growth. Differential diagnosis includes vascular lesions, such as hemangiomas or vascular leiomyomas, and mesenchymal masses, such as sarcomas or solitary fibrous tumours. Only histology can confirm the diagnosis and drive the treatment. Nowadays, there is no well-coded classification system for these lesions; some authors have proposed the Kadish classification, even if the correlation between stage and prognosis has not been demonstrated. The treatment of choice is surgical, while post-operative radiotherapy is indicated in case of incomplete removal or recurrence. The prognosis is excellent with a 5-year disease-free survival more than 90% in total resection [27]. Local recurrence, however, is reported in the literature up to 40% of cases and even 5 years or more after surgery [28]. Some histopathological features such as size > 5 cm, bone invasion, nuclear polymorphism, increased mitotic activity, proliferation index > 10% are typical of the more aggressive forms [29].

Langherans' cells histiocytosis: it is a rare systemic disease characterized by the proliferation of dendritic cells of the epithelial immune system. It should be reminded for the peculiar tendency of this tumour to involve the hypothalamus and the posterior pituitary lobe, causing diabetes insipidus as single manifestation. Therapy is exclusively medical.

Lymphomas: large B-cell lymphomas located in the cavernous sinus and in close relation with the pituitary gland are described in the literature. Surgery has only diagnostic purpose.

Metastases: in most cases metastases in the pituitary gland derive from breast in women and lung in men, while metastases in the parasellar region are very rare (less than 1% of patients undergoing transnasal surgery).

Treatment

Since the 18th century, surgeons from different disciplines experimented with various approaches to the base of the skull. Francesco Durante, general surgeon from Sicily, in 1883 was the first who successfully removed an anterior cranial fossa meningioma with a transoral-transpalatine approach. In 1907, Schloffer treated a pituitary tumour through an open transnasal-transphenoidal approach, with consequent significant aesthetic and functional problems. Three years later Hirsch, an otolaryngologist, described for the first time the trans-septal endonasal approach to reach the contents of the sella turcica [30]. Some years later, Cushing modified this access using a sublabial incision, later shifted into a transcranial way due to the high risk of rhinoliquorrea, the difficult control of bleeding and post-operative cerebral edema. The evolution of the trans-sphenoidal approach to the sellar and parasellar region was induced by three factors: first and most important, the persistent efforts of the pioneers of surgery often against the colleagues' scepticism; second, the advancement of technology; and third, its application to routine surgery. This was the case of endoscopic technique and its introduction into skull base surgery. Jho and Carrau reported the first surgical series of 50 patients affected by sellar lesion operated between September 1993 and June 1996 with an endoscopic approach [31]. The use of an endoscopic technique (pure or assisted with neuronavigator) to access the sellar and parasellar region is probably the most important achievement in contemporary skull base surgery.

The main advantages of the endoscopic technique are a minimally invasive access without aesthetic defects, an excellent view of the operating field and the management of lateral, superior or inferior lesions ensuring a more radical treatment with reduced post-operative complications [32].

The involvement of the cavernous sinus is considered one of the most negative prognostic factors in the surgical treatment of pituitary lesions. Two different trans-sphenoidal corridors can be used to achieve the intracavernous portion of the ICA: the medial side is better reached inserting the endoscope through the contralateral nasal fossa; on the contrary, lesions in the lateral side of the cavernous sinus can be approached through a trans-ethmoidal trans-pterygoidal access.

Significant lateral extension, encasement of neurovascular structures, and brain invasion in malignant lesions are considered some of the contraindications for an endoscopic approach. In some cases, a combined approach (transcranial and endoscopic) is required.

The complication rate of trans-sphenoidal surgery depends on different factors, such as location, extension, biological behaviour of the tumour and the expertise of the surgical team. In addition, it is well known that the complication rate in revision surgery is significantly higher than in first surgery. Endocrinological and ophthalmic complications can also occur.

CSF leak is the most common surgical complication in pituitary surgery and extended approaches, as confirmed in our series. When the leak is recognized during surgery, the reconstruction of the defect using autologous or heterologous grafts is mandatory [33]. Sometimes, the defect can remain unknown until complications appear (including meningitis and intracranial abscesses), requiring a revision surgery to repair

the defect. High-flow leaks can involve in cerebral parenchymal herniation through the skull base defect, stretching the intradural or subarachnoid vessels, until break them causing an epidural, subdural or parenchymal hematoma. Symptoms vary according to the hematoma extension and location, as well as the treatment that can be conservative or surgical. The development of a subdural hematoma represents a rare but potentially fatal event, often the clinical picture is uncertain, in some cases it remains asymptomatic.
Another possible complication is bleeding, generally from the posterior septal branches of the sphenopalatine artery, more frequent in macroadenomas and during extended approaches. Arterial bleeding stops spontaneously in most cases or can be controlled by coagulation with bipolar cautery. Venous bleeding mainly originates from the cavernous sinus and can be easily solved. Profuse bleeding requires immediate suspension of the surgery.
The internal carotid artery damage represents the worst surgical complication and can lead to permanent disabilities or even death. An accurate preoperative radiological study is mandatory to prevent this complication. The neuronavigator and the micro-doppler also provide important support. The accidental damage of ICA during the trans-sphenoidal approach for pituitary adenomas is reported 0,2-1,4% in literature [34,35]. In 2016, AlQahtani et al. [36] have distinguished the risk factors for ICA damage in: anatomical factors (thinning or thickening of the ICA bone canal in the lateral wall of the sphenoid sinus, the distance between the two intracavernous tracts, possible presence of aneurysms, pseudoaneurysms or arterio-venous malformations, dislocation of the ICA), factors related to the pathology (tumours in close contact or invading the artery, previous treatments), surgeon-depending factors (the surgeon's experience). Emergency treatment in case of vascular damage consists of blood transfusion and plasma expanders infusion in order to avoid hypovolemic shock, the use of hemostatic materials or vascular clips and, once the bleeding has been controlled, the endovascular treatment.
Meningitis is the most frequent intracranial complication after trans-sphenoidal surgery, especially in patients with cerebrospinal fluid leak. Typical symptoms are fever, headache, photophobia and coma in some cases. The diagnosis is performed by the analysis of the CSF; a brain CT scan is also useful to identify a possible leak. Hospitalization and broad-spectrum antibiotic therapy based on the antibiogram is necessary to avoid major complications.
The worst ophthalmic complication is irreversible blindness due to damage to one or both optic nerves. The damage can be direct or indirect, the latter usually due to intraorbital bleeding. The direct injury to the optic nerve, fortunately rare (1-2% of the patients undergoing trans-nasophenoidal surgery), is generally determined by a trauma at the level of the lateral wall of the sphenoidal sinus. Other dangerous regions are the posterior ethmoid in case of Onodi's cell, and the optical chiasm in approaches extended to the suprasellar region. Even the abducent nerve can be damaged along its course in the cavernous sinus, since it is the only structure located inside the sinus.
At routine 24-hour post-operative brain CT-scan a modest pneumocephalus is frequently observed, but in most cases, it is reabsorbed spontaneously within a few days. A dangerous condition occurs when a defect of the dura mater acts as a valve: the air accumulates inside the brain every time the pressure of the upper airway increases. The progressive increase of intracranic pressure can damage the motor cortex or cause the development of subdural hematoma, up to cardiac arrest due to compression of the brain stem.
In experienced hands, endoscopic endonasal removal of sellar and parasellar lesions has become increasingly safe and effective. However, serious complications can occur. Inspection of preoperative MRI and CT scan may predict surgical challenges as anatomical variations (conchal sphenoid sinus, vascular anomalies or narrow surgical corridor because of reduced distance between the parasellar carotid arteries), or tumour feature (invasion of the cavernous sinus, vertical extension). Last but not least, an accurate understanding of the anatomy and a multidisciplinary planning are essential to deal with this type of surgery.

Conclusions

Sellar and parasellar lesions represent a challenge because of their variable features and because of the importance of understanding the anatomy of this region, that is essential for providing improved resections with decreased morbidity. The evolution of the trans-sphenoidal approach has resulted from technological developments, increasing anatomical understanding and collaboration between Otolaryngologist and Neurosurgeon. Especially in this approach, a treatment planning involving several specialists (Otolaryngologist, Neurosurgeon, Neuroradiologist, Endocrinologist, Ophtalmologist) is mandatory in order to minimize complications, offering the patient the best treatment and a high quality of life.

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Clivus pathologies from diagnosis to surgical multidisciplinary treatment. Review of the literature

Patologie del clivus dalla diagnosi al trattamento chirurgico multidisciplinare. Revisione della letteratura

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SUMMARY

The Clivus is a bone that lies in a central position of the skull base, and it is a crucial point that splits and connects different anatomical compartments at the same time. There is significant variability of diseases involving the clivus, from neoplasms to non-neoplastic, inflammatory or traumatic lesions. Each of these is rare in frequency, and this heterogeneity contributes to yield the management even more challenging. Clival pathologies can be asymptomatic or have manifestations ranging from aspecific headache to cranial nerves palsies, till life-threatening complications as cerebrospinal fluid rhinorrhoea, meningitis or brain abscess. There isn't an univocal endorsement among experts with regard to the best approaches to manage the clivus. The paths described are many, the main division is between the transclival and transcranial lateral approaches. We performed a review of the literature, thus highlighting how authors seem to suggest that the surgical approach shouldn't be chosen aprioristically, but based on a patient centred analysis, considering the combination of multiple surgical corridors. From diagnosis to surgery and medical therapy, clival pathologies require a team of multidisciplinary experts to ensure the best standard of treatment and higher survival rate.

KEY WORDS: clivus, clival pathology, transclival approach, transcranial approach, skull base surgery

RIASSUNTO

Il Clivus è localizzato in sede centrale nella base cranica, rappresentando uno snodo cruciale, che separa e collega diversi comparti anatomici. Le patologie che coinvolgono il clivus sono eterogenee: da neoplasie a lesioni non neoplastiche, infiammatorie o traumatiche. Tutte queste sono rare per insorgenza e ciò contribuisce a renderne impegnativo il trattamento. Le patologie clivali possono mantenersi asintomatiche oppure manifestarsi con sintomi che vanno dalla cefalea, alla paralisi di nervi cranici, fino a complicanze potenzialmente letali come, rinoliquorrea, meningite e ascessi cerebrali. Gli esperti non sono sempre concordi riguardo al tipo di approccio chirurgico con cui trattare il clivus. Le vie descritte sono molteplici, principalmente distinte tra approcci transclivali e approcci transcranici laterali. A oggi, dopo una revisione della letteratura, si conclude che la programmazione chirurgica non deve essere scelta a priori, ma con un accurato studio del singolo caso clinico, valutando la combinazione di più corridoi chirurgici, se necessario. Dalla diagnosi alla chirurgia, alla terapia medica, la gestione delle patologie clivali richiede un team multidisciplinare di esperti, tale da garantire la migliore qualità nel trattamento e il più alto tasso di sopravvivenza.

PAROLE CHIAVE: *clivus, patologia clivale, approccio transclivale, approccio transcranico, chirurgia del basicranio*

Introduction

In the early 1990s, Samii and Knosp defined the clivus "no man's land" due to the difficulty of accessing it [1]. Today we can say that the clivus would be

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Conflict of interest
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better called "res in commune multorum", because we are well aware that, due to the variety and the rarity of clival pathologies, the key to a better outcome for the patient is to bring together the expertise of different specialists. Each clinical case should be evaluated by the otorhinolaryngologist together with a multidisciplinary team. In this review we will focus on clival pathologies that require a surgical treatment, which always foresees the collaboration between otorhinolaryngologist and neurosurgeon.
The Clivus is indeed a crucial point that splits and connects different anatomical compartments at the same time. It is a bone that lies in a central position of the skull base, being a boundary between endocranial structures and maxillofacial and neck regions. One of the first scientists that undertook studies involving the clivus was the German Johann Friedrich Blumenbach (1752-1840) that gave name to the bone, therefore called Clivus Blumenbachii. Other neuroanatomists that have to be mentioned are Wenzel Leopold Gruber (1814-1890) who observed the Grubers's ligament, Primo Dorello (1872-1963) for the so-called Dorello's canal and Johann Friedrich Meckel, the first that described the condylus tertius in 1815.

Embryology and anatomy

The clivus originates from the neurocranium and particularly from the chondrocranium [2], which is formed initially by several separate cartilages (i.e. ossification centers) that will fuse and ossify to form the skull base, after cranial nerves and blood vessels have developed [3]. The basisphenoid and basiocciput, formed from the four primary occipital sclerotomes or "vertebrae" (O1-O4) [2], are separated before fusion by the sphenoccipital synchondrosis. Complete ossification of the synchondrosis takes place at the age of 13 to 18 years in males and 12 to 16 years in females [4].
The clivus (Blumenbachii) is the central element of the skull base and is about 4 to 5.5 cm long and about 3 cm wide at its midpoint. The midsagittal section of the clivus clearly presents a wedge-shaped appearance with a thin posterior and thick anterior part. Inside a spongy structure identifies the content of bone marrow. The osseous slope of the clivus slants upward and forward from the anterior aspect of the foramen magnum to the dorsum sellae and the posterior clinoid processes. The sphenoid sinus pneumatization may extend to the clivus with a posterior recess, and rarely this involves the whole clivus. From a caudal view, the anterior margin of the clivus is bordered by the vomer with its alae. Lateral to the clivus is the petro-occipital fissure housing the inferior petro-occipital vein, connecting the cavernous sinus to the internal jugular vein. Cranially, the inferior petrous sinus rests on the petrooccipital fissure and creates the sulcus sinus petrosi inferioris. The lateral borders of the clivus are related to cranial nerves V through XII, the internal jugular veins, and the inferior petrosal sinuses and the foramen lacerum in the anterior part [4]. The posterior endocranial surface is smooth and composed of cortical bone. It is covered with dura mater, which is perforated by the abducens nerves, coming from its cisternal portion, in the central part of the clivus [2]. The medulla oblongata and pons lie adjacent to the posterior surface of the clivus, but are separated by the prepontine and perimedullary cisterns [4]. Several ligaments cross the gap between the petrous apex and the lateral margin of the dorsum sellae, among these the petrosphenoidal or Gruber's ligament is important for the course of the abducens nerve that passes through the foramen sphenopetrosum (fibrosum or osseum) and is fixed with its dural sheath at the superior margin of the petrous pyramid. This narrow passage for the abducens nerve is known as Dorello's canal, though it is actual knowledge that it is not a real canal [5]. The tectorial membrane and superior longitudinal band of the cruciate ligament both attach to the posteroinferior surface of the clivus. The fibrous raphe of the pharynx (superior pharyngeal constrictor muscle), longus capitus, rectus capitus anterior, and the anterior atlantooccipital membrane are found in connection to the inferior exocranial surface of the clivus. The outer surface of the clivus is covered in thick fibrous tissue which is a continuation of the fibrocartilago basalis of the foramen lacerum.
The arterial supply of the clivus is primarily derived from two vessels: a branch off the internal carotid artery, the meningohypophyseal trunk, and a branch of the ascending pharyngeal artery, the posterior meningeal artery. Dorsal to the clivus, the basilar artery and basilar venous plexus are found and can create faint grooves on the bone [4].

Pathologies

There is great variability of diseases involving the clivus, of different nature, and each rare in frequency. This heterogeneity contributes to yield the management even more challenging (Tab. I). Clival pathologies can be asymptomatic or have manifestations ranging from aspecific headache to cranial nerves palsies, visual problems, endocrinopathy (if the sella is involved), till life-threatening complications as cerebrospinal fluid (CSF) rhinorrhoea and episodes of meningitis or brain abscess.

Neoplastic pathologies

Among clival tumors, the most frequent are chordomas. Chordoma is a rare cancer that accounts for 1-4% of all bone malignancies. The incidence is of 0·08 per 100.000,

Table I. Multidisciplinary management for clival pathologies.

Pathology	Surgery	Multidisciplinarity between surgeons	Other specialists involved
Fibrous dysplasia	Biopsy + / decompression	ENT surgeon +/- neurosurgeon	/
Neurenteric cyst	Removal	ENT surgeon +/- neurosurgeon	/
Ecchordosis physaliphora	Removal + skull base plasty	ENT surgeon + neurosurgeon	/
Epidermoid	Removal	ENT surgeon + neurosurgeon	/
Cholesterol granuloma	Marsupialization	ENT surgeon +/- neurosurgeon	/
Sphenoid mucocele	Marsupialization	ENT surgeon +/- neurosurgeon	/
Chordoma	Removal with ETCA / MTCA / combined	ENT surgeon + neurosurgeon	Radiotherapist +/- oncologist
Chondrosarcoma	Removal with ETCA / MTCA / combined	ENT surgeon + neurosurgeon	Radiotherapist
Meningioma	Removal with ETCA / MTCA / combined	ENT surgeon + neurosurgeon	Radiotherapist +/- oncologist
Metastasis	Biopsy	ENT surgeon + neurosurgeon	Radiotherapist +/- oncologist
Tumors of adjacent compartments	Biopsy / rescue surgery	ENT surgeon + neurosurgeon	Radiotherapist +/- oncologist
Plasmocytoma	Biopsy / rescue surgery	ENT surgeon +/- neurosurgeon	Radiotherapist +/- hematologist
Osteomyelitis and Osteoradionecrosis	Debridement	ENT surgeon + neurosurgeon	Infectious disease specialist
CSF leak and meningocele	Skull base plastic	ENT surgeon +/- neurosurgeon	/
Traumatic lesion	Decompression + / skull base plastic	ENT surgeon + neurosurgeon +/- maxillofacial surgeon	/
Craniovertebral junction disease	Anterior odontoidectomy + decompression	ENT surgeon + neurosurgeon	/

ENT: ear nose throat; ETCA: endoscopic transnasal transclival approaches; MTCA: microsurgical transcranial approaches; CSF: Cerebrospinal fluid.

with predominance in men and peak incidence between 50-60 years of age; chordomas rarely affect children and adolescents (< 5% of all chordoma cases) [6]. These tumors are thought to arise from the transformed remnants of the notochord. Actual data suggest they are almost equally distributed among the three sites of the skull base, mobile spine, and sacrum [7]. Although slow-growing and histologically low grade, chordomas are locally invasive and have a high recurrence rate, making their clinical progression similar to malignant tumors [8]. They are not typically metastatic on presentation, but the often late-stage diagnosis of the disease makes distant metastasis more likely. In 5% of chordomas there are metastasis to the lungs, bone, skin, and brain at the time of initial presentation. Because of the notochordal origin of these tumors, chordomas are midline entities; thus, in contrast to chondrosarcomas, they tend to grow from the midline, expanding posteriorly and laterally. At CT, clival chordoma appears as a midline soft-tissue lesion with bone destruction. The margin between the tumor and normal bone is usually non-sclerotic and sharp. Radiodensities are frequently present and are thought to represent remaining fragments of the destroyed clivus rather than new matrix formation. At MRI, they are usually hypo- to isointense on T1-weighted imaging, with cystic components that may contain protein or haemorrhage, giving them a bright signal. On T2-weighted images, they are characteristically of high signal. However, poorly differentiated chordomas have low T2 signal intensity. The enhancement pattern is variable: heterogeneous enhancement is more common than a homogeneous pattern [8].

The second tumor that may involve the clivus is chondrosarcoma, that account for 6% of skull-base tumors. Chondrosarcomas develop from primitive mesenchymal cells in synchondroses of the skull base with a high predilection for the petroclival synchondrosis. Therefore they are paramedian lesions that often expand not only into the clivus and sphenoid sinus but also into the middle and posterior cranial fossae, as well as the upper cervical area. The mean age of presentation of chondrosarcoma is 40 years [8]. With their usually slow growth rate, they are capable of reaching sizable dimensions, promoting bone erosion and significant displacement of neurovascular structures before causing symptomatology. Despite this local aggressiveness, these lesions often spare the dura, compressing and displacing rather than transgressing it [9]. Bone destruction and calcification occur in about 50% of chondrosarcomas and low-grade tumors tend to have more extensive calcification. These tumors are generally low-to-intermediate signal on T1-weighted images and high signal on fluid-attenuated inversion recovery (FLAIR), and T2-weighted images. Stippled foci of calcification, a hallmark of this tumor, may be demonstrated as heterogeneous areas of low signal within the tumor.

Meningiomas are another type of tumor that also affects the clival region. They represent the most frequent primary central nervous system tumors and they are considered benign lesions with favorable survival rates; however, on occasion, they may have a high-grade subtype, associated with a poor prognosis and higher risk for metastasis. Petroclival meningiomas are defined as being located medial to the exit of the trigeminal nerve. Some clival meningiomas are entirely dural and subdural, but others may have a tendency to involve the extradural and osseous compartments [10]. A non-contrast CT scan shows that these lesions have either a high- or low-attenuation signal compared with the surrounding brain. Hyperostosis, increased vascular markings and calcification are characteristic findings of meningiomas on CT; however, malignant meningiomas can be more destructive of bony structures and more invasive of soft tissue [11].

In the chapter of clival malignancies, it is important to mention also metastatic tumors. In patients with known cancer, the probability of a mass lesion in the clivus being a metastasis is high. The most common primary sites are prostate, kidney, liver (HCC), thyroid, gastrointestinal tract (adenocarcinoma), breast, lung, melanoma and lymphoma [12,13]. Metastasis may be low signal on T2 and this potentially differentiates them from chordomas and chondrosarcomas [14].

Furthermore, plasmacytoma is exceptionally reported in the clivus [15]. These lesions tend to enhance homogeneously on imaging; on T1-weighted MRI they are isointense or hypointense, but hyperintense on T2. Plasmacytoma can show cavernous sinus invasion, carotid encasement, sphenoid sinus invasion and suprasellar extension [16].

Finally the clivus is prone to be involved in a variety of tumors of nearby structures: the dorsal extension of an invasive pituitary adenoma, trigeminal schwannomas may extend to the clivus leading to scalloping of its laterodorsal surface, even tumors arising from the jugular foramen or cerebellopontine cistern rarely extend as far as the clivus. Nasopharyngeal carcinomas (NPC) from their origin site can directly invade the adjacent basisphenoid and basiocciput.

Non-neoplastic pathologies

Most of the non-neoplastic occupying-space lesions develop with a clival bone resorption. One is the neurenteric cyst, a congenital lesion that may occur along the neural tube, which is formed by a failure of separation between endoderm and ectoderm in utero. The lesion is hyperintense (relative to grey matter) on T1-weighted and iso-intense to hypo-intense on T2-weighted MRI [10]. Another one is the cholesterol granuloma, rarely reported in literature involving the clivus [17] (Fig. 1).

Histologically, it is characterized by chronic inflammation, fibrous tissue reaction, cholesterol crystals and foreign

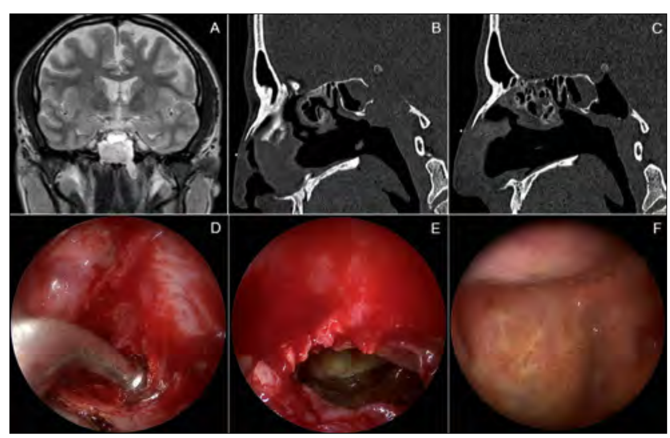

Figure 1. Images of a 46 years-old man who developed headache and photophobia due to a cholesterol granuloma. MRI revealed a sphenoid-clival growing lesion, with regular margins and 45 mm of diameter. The mass was hyperintense on T1 (**A**), iso-hyperintense on T2 and determined an elevation of the pituitary gland, with no signs of infiltrations of surrounding structures. A basal CT confirmed the presence of osteolysis of the posterior sphenoidal wall replaced by a mass of 29 x 30 mm (**B**). Swelling of the nasopharyngeal roof was seen, through nasal endoscopy. An endoscopic transsphenoidal approach was made to reach the posterior sphenoidal wall where the cystic lesion was drained (**D, E**), with no sign of CSF leak. Postoperative endoscopic view with sella and ICAs visible through the thin clival bone left (**F**). A CT control 24 hours later showed no postoperative complications (**C**).

body giant cells [18]. The pathogenesis is controversial and can be potentially explained by either the obstruction-vacuum theory or ex-posed marrow hypothesis [19]. On CT it appears as a smoothly marginated expansile lesion isodense with the brain tissue and non-enhancing. On MRI, distinction from petrous bone cholesteatoma is usually possible as cholesterol granulomas show a typical hyperintense signal on T1 [20]. Also, sphenoid mucocele can result in bony resorption and sometimes erosion of the clivus. Mucoceles demonstrate variable densities at CT and signal intensities at MRI depending on their protein content and presence of associated infection. Rim enhancement may be seen as a hallmark of encapsulation [8].

On the contrary fibrous dysplasia rise from the clivus where the mature bone becomes replaced with a weaker substitute of woven bone and fibrous tissue. This is a benign skeletal anomaly that affects one or multiple bones, with a greater tendency to affect long bones, ribs, and craniofacial bones. The lesions at CT images show a ground-glass appearance, while at T1-weighted MRI show low signal intensity, and T2-weighted MRI signal intensity varies from high to intermediate or low based on cellularity, collagen, bone, and cystic content of the lesion [21].

Another clival congenital lesion is ecchordosis physaliphora. It consists of nodules of gelatinous tissue and it is considered to be an ectopic notochord remnant along the craniospinal axis, at the level of the clivus and sacrum [22]. Radiological typical findings are hypointensity in T1-weighted and hyperintensity in T2-weighted MRI, and, most crucially, ecchordosis physaliphora shows no contrast enhancement after the administration of gadolinium [23].

Epidermoids of the central nervous system consist of epidermal and connective tissue, usually in the form of a sac, characterized by slow growth. They tend to expand and spread along normal cleavage planes and thus they usually occupy more than one intracranial compartment. They have irregular "scalloped" margins and also tend to envelop vital neurovascular structures. Epidermoids may be mistaken for arachnoid cysts. Both lesions are non-enhancing and are hypointense on T1-weighted and hyperintense on T2-weighted images, but, unlike arachnoid cysts, epidermoids have a slightly hyperintense segment when compared to CSF [20].

The principal inflammatory pathology that may involve the clivus is skull base osteomyelitis. Most of the times it follows external ear infection in diabetic, old or otherwise immunocompromised patients, mostly males and has Pseudomonas aeruginosa as the usual pathogen. Patients usually present with ear pain and otorrhea. Skull base osteomyelitis is potentially life-threatening. Imaging is of paramount importance in establishing the diagnosis and CT findings are cortical bone erosion and adjacent soft tissue swelling. The MRI findings are replacement of clival fatty bone marrow by exudate and effacement of soft tissues, resulting in a marked drop of T1-weighted signal in pre-contrast images. The soft tissues and bones involved are greatly enhanced with contrast medium [10].

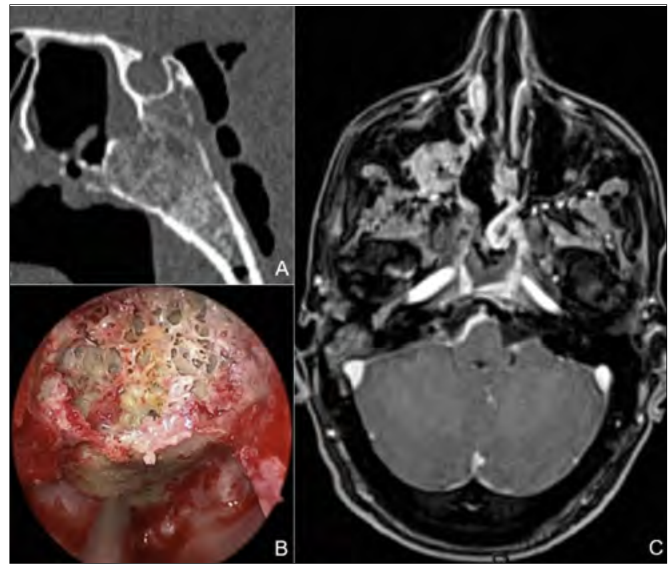

Figure 2. Images of a 36 years-old man who developed general disorientation, progressive tendency to drowsiness, cephalea, fever and aqueous rhinorrhea [26]. Four years before he was treated for undifferentiated NPC with a left-side modified radical neck dissection and elective chemo-radiotherapy, then a second line stereotactic radiotherapy (Cyberknife) for local relapse. At the time of admission CT scan revealed the presence of massive tension pneumocephalus with an erosion of infero-posterior parts of sphenoidal sinus and possible radionecrosis of the clivus (**A**). Nasal endoscopy revealed the presence of necrotic bone in the paramedian portion of the nasopharynx and active CSF rhinorrhea. The patient underwent endoscopic endonasal debridement of necrotic bone (**B**) and repair of the clival fistula with a pedunculated nasoseptal (Hadad) flap. Control CT and MRI cerebral scans showed progressive resorption of the pneumocephalus with the nasoseptal flap covering the bony defect (**C**).

Osteoradionecrosis, a possibly lethal complication of radiation therapy (RT) [24], can develop in the skull base (Fig. 2). In addition to neoplastic cells, RT damages healthy cells of the vascular endothelium, this creates the pathogenetic triad of hypoxia, hypocellularity, and hypovascularity. Type II diabetes mellitus, smoke and vascular diseases are considered possible risk factors. Among head and neck malignancies, RT for nasopharyngeal carcinoma is the main responsible for osteoradionecrosis [25,26].

It is important to mention spontaneous clival CSF leaks [27] (Fig. 3). The diagnosis is made through beta-2-transferrin testing, CT scan and MRI. As reported by Van Zele et al., transclival meningoceles and spontaneous CSF leaks located at the clivus are extremely rare entities [28,29].

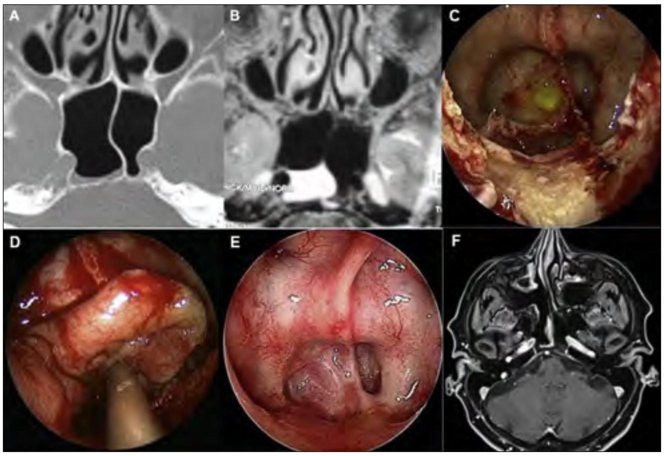

Figure 3. Computed tomography (**A**) and T2-weighted MRI (**B**) in a patient with a right clival spontaneous cerebrospinal fluid leak. Intraoperative endoscopic view showing a paraseptal approach: the sphenoidotomy is enlarged to gain adequate access to the sinus, and the intersinusal septum is drilled out. The cerebrospinal fluid leak with small meningocele can be clearly identified in the posterior wall of the sphenoid. The green colouration is due to the intraoperative use of fluorescein (**C**). Intraoperative view of the nasoseptal flap placed overlay within the posterior wall of the sphenoid sinus, covering the clival area (**D**). Endoscopic endonasal view 24 months after surgery (**E**) and postoperative axial T1-weighted MRI scan with gadolinium showing a nasoseptal flap covering the clival area on the right sphenoid sinus (**F**).

Fractures of the clivus are not uncommon and have been reported in 0.2% of patients with head injuries and in 2% of patients with skull fractures [10]. They can be classified as three types: sagittal (intersecting the dorsum sellae), transverse (intersecting both petrous ridges) and oblique (intersecting one petrous ridge). Oblique fractures are the most common, while patients with a transverse fracture have the highest risk of death [30].

Surgical approaches

The chapter of surgical approaches to the clivus and the craniovertebral junction (CVJ) is still a field of study and open debate: the major certainty is that there isn't a common and univocal endorsement among expert with regard to the best approaches to manage the clivus yet. The paths described to reach clival pathologies are many; the main division is between the endoscopic transnasal transclival approaches (ETCAs) and microsurgical transcranial approaches (MTCAs). Below the table with all the current approaches to the clivus (Tab. II).

Surgery of the lateral skull base has developed in the last 50 years, starting from the traditional transcranial microsurgery. At the same time, different anterior extracranial and transclival approaches have been described and applied, characterized by "waves" with a progressive rise and fall of new procedures [31]. These were initially described with enthusiasm, they might have become widely used, but then fell into disuse after reports of complications, like transcervical and transoral approaches.

Endoscopic transnasal skull base surgery started in the last 25 years, also addressing clival pathologies, with increasing relevance. Since then, the endoscopic transnasal transclival approach has been widely accepted for extradural pathologies, mainly clival chordomas, but its use remains highly debated for intradural lesions due to the issue of dural and skull base reconstruction and the high rate of postoperative CSF leak (Fig. 4).

According to Bossi Todeschini et al. the advantages that make the endoscopic transclival approach a promising technique to treat midline posterior fossa pathologies consist in avoiding cerebral retraction, near-field magnification, better surgical field illumination, minimal manipulation of neurovascular structures, and direct access to the tumor as well as early access to its vascular supply and the possibility of removing the involved bone and/or dura [32].

Belotti et al. published an interesting historical overview about transclival approaches for intradural pathologies, the results showed an initial preponderance of vascular pathologies, mainly posterior circulation aneurysms and some cavernous malformations of the brainstem. Intradural

Table II. Surgical approaches to the clivus.

Endoscopic transnasal transclival approaches (ETCAs)
Transnasal ETCA
ETCA with intradural hypophysiopexy (pituitary transposition)
ETCA with far-medial extension (ETCA-FM)
Aterolateral Microsurgical Transcranial Approaches (MTCAs)
Supraorbital approach (SO)
Mini-pterional approach (MPT)
Pterional approach (PT)
Pterional transzygomatic approach (PTTZ)
Fronto-temporal-orbito-zygomatic approach (FTOZ)
Lateral Microsurgical Transcranial Approaches (MTCAs)
Subtemporal approach (ST)
Subtemporal transzygomatic approach (STTZ)
Posterolateral Microsurgical Transcranial Approaches (MTCAs)
Retrolabyrinthine approach (RL)
Translabyrinthine approach (TL)
Transcochlear approaches (TC)
Retrosigmoid approach
Infratemporal approaches (type A, B, C, D)
Petro-occipital transigmoid approach (POTS)
Far-lateral approach
Extreme-lateral approach

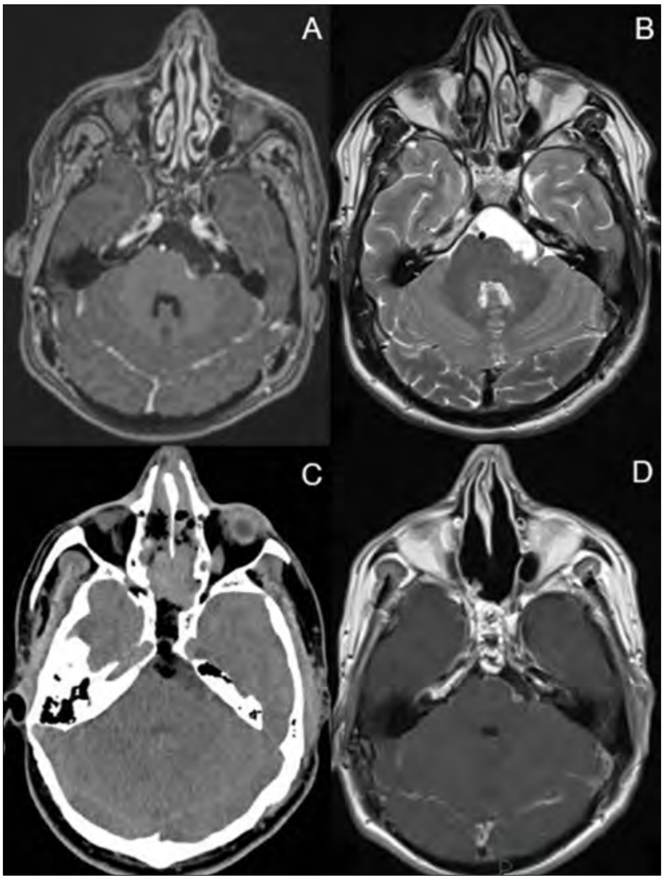

Figure 4. Images of a 35-year-old man admitted with left trigeminal (V1-V2) palsy, dizziness, left ear hearing loss. MRI revealed a large cystic lesion of the left cerebellopontine cistern with posterior displacement of the fifth left cranial nerve and a possible small post-contrast impregnation of a portion of the medial wall (**A, B**). Head CT scan showed the surgical result (**C**) after an endoscopic transsphenoidal/transclival approach performed with the complete macroscopical removal of the lesion, that presented as a large cyst with a thin layer of white capsule containing soft white tissue. A dural plastic with autologous fat, an intradural layer of fascia lata and a septal flap followed, as shown in postoperative MRI (**D**). The results of the histological tests reported aspects indicative of a primary squamous cell carcinoma [42] (this article is distributed under the terms of the Creative Commons AttributionNon CommercialShare Alike 4.0 License).

pathologies, including meningiomas, schwannomas, epidermoid cysts and neurenteric cysts were reported sporadically in the 1990s and showed a significant increase since 2005, parallel with the evolution of transnasal endoscopy. The main boost to the widespread use of endoscopic transclival approaches was most probably the introduction of this technique for the treatment of clival chordomas [31]. This rise has gone together with the refinement of skull base reconstruction techniques and materials from autologous flaps, fat, fascia, cartilage and bone, to synthetic materials as fibrin glue, lyodura, collagen matrix, oxidized cellulose and gelatin sponge.

There is an increasing number of published works that give growing importance to the anterior transclival approaches in terms of comparable gross total resection (GTR) rates compared to the transcranial approaches [33]. As regards possible complications, CSF leak rate was higher in midline approaches, in contrast to postoperative cranial nerve palsy, which was higher in lateral approaches.

There are still some limitations to exclusive transclival approaches, according to other experts opinion, like the management of lesions that further extend laterally to the cranial nerves plane, and midline tumors having a very limited inter-carotid distance with a high risk of ICA rupture and inadequate lesion exposition. According to La Corte et al. such cases should benefit from a combined (one or multi-staged) approach or a lateral TCA to avoid tumor removal between cranial nerves and therefore reduce the risk of postoperative deficits, and to avoid working through a narrow corridor between the ICAs at different segments [34].

Staged surgery is a viable option when using combined approaches, such as extensive extradural surgery followed by the removal of the intradural tumor, with a view to prevent the risk of CSF leak.

An interesting preclinical anatomical study was made by Agosti et al. in order to establish possible advantages of endoscopic approaches in relation to the exposure of lateral structures [35]. ETCAs objectively provide an advantage in terms of clival exposure, when compared with MTCAs. A statistically significant gain of exposure of the lateral anatomical structures and jugular tubercles was offered by ETCAs with far-medial extension (ETCA-FM), that include the exposure of the neurovascular pterygoid structures, Eustachian tube transposition, drilling of the anteromedial portion of the ipsilateral occipital condyle and the medial portion of the jugular tuberculum, identifying the lower cranial nerves [36].

Minghao et al. believe that ETCA-FM approach provides the greatest surgical exposure at the lower clivus, but provides limited lateral exposure and surgical freedom. The Extreme-Lateral approach provides the greatest surgical exposure at the lower clivus among the craniotomy approaches but carries a greater risk of damage to neurovascular structures and increased operative time [37].

Despite these data, it is important to note that, as preclinical studies, these works did not consider the possible increase in working volume and anatomical distortion caused by a space-occupying lesion nor the position of relevant vascular and neural structures in relation to the mass. For such reasons, no surgical approach can be recommended over another based on a preclinical study alone [35].

Recent studies of cadaveric dissection are testing new combined and hybrid approaches, that are more in the field of neurosurgery, like a hybrid anterolateral transcondylar approach to evaluate the use of endoscope-assisted micro neurosurgery through an anterolateral approach [38]. This approach provides lateral access to the cervical spine and craniovertebral joint (CVJ) from C6 to the foramen magnum with early control of the extradural vertebral artery and the major venous structures. The greatest advantage showed by this study is the extension of the surgical corridor to the middle and upper clivus up to the sphenoid sinus. Combining classical microsurgical techniques with the keyhole endoscope-assisted concept a complete resection is achieved, using a single operative corridor rather than combining endoscopic endonasal and anterolateral approaches. Reviewing literature and published experiences, the conclusion is that many variables must be considered when surgery is planned [39]: which is the part of the clivus involved (superior, middle or inferior part), which is the pathology with regard to the histology, the lateral extension and the structures involved; the anatomy of the patient; previous treatments and need for further therapies; comorbidities.

The surgical approach, therefore, shouldn't be chosen aprioristically but based on a patient-centred analysis. Moreover, the combination of multiple surgical corridors, one complementary to another, allows the surgeon to work around the relevant anatomy and to avoid dissection passing the plane of cranial nerves. With this principle, the optimization of the resection and the decrease of morbidity is achieved, also when facing big tumors involving the CVJ [40,41].

Conclusions

From diagnosis to surgery and medical treatment, clival pathologies require the multidisciplinary management of ENT surgeon and neurosurgeon, whose partnership is fundamental, but also neuroradiologist and, when needed, anatomopathologist, radioterapist, oncologist and infectious diseases specialist. Sharing of expertise is the advisable way to ensure the best standard of treatment and higher survival rate to aggressive and recurrent diseases with potential lethal course and complications.

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Multidisciplinary approach to the craniovertebral junction. Historical insights, current and future perspectives in the neurosurgical and otorhinolaryngological alliance

Approccio multidisciplinare alla giunzione cranio vertebrale. Cenni storici, attuali orientamenti e prospettive future nell'alleanza tra neurochirurgia ed otorinolaringoiatria

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SUMMARY

Historically considered as a nobody's land, craniovertebral junction (CVJ) surgery or specialty recently gained high consideration as symbol of challenging surgery as well as selective top level qualifying surgery. The alliance between Neurosurgeons and Otorhinolaringologists has become stronger in the time. CVJ has unique anatomical bone and neurovascular structures architecture. It not only separates from the subaxial cervical spine but it also provides a special cranial flexion, extension, and axial rotation pattern. Stability is provided by a complex combination of osseous and ligamentous supports which allows a large degree of motion. The perfect knowledge of CVJ anatomy and physiology allows to better understand surgical procedures of the occiput, atlas and axis and the specific diseases that affect the region. Although many years passed since the beginning of this pioneering surgery, managing lesions situated in the anterior aspect of the CVJ still remains a challenging neurosurgical problem. Many studies are available in the literature so far aiming to examine the microsurgical anatomy of both the anterior and posterior extradural and intradural aspects of the CVJ as well as the differences in all the possible surgical exposures obtained by 360° approach philosophy. Herein we provide a short but quite complete at glance tour across the personal experience and publications and the more recent literature available in order to highlight where this alliance between Neurosurgeon and Otorhinolaringologist is mandatory, strongly advisable or unnecessary.

KEY WORDS: instrumentation and fusion, endoscopy, transnasal approach, transoral approach, extreme lateral approach, far lateral approach, submandibular retropharyngeal approach, craniovertebral junction

RIASSUNTO

Storicamente considerata "terra di nessuno", la regione della giunzione cranio-vertebrale, così come la chirurgia di questa sede, hanno guadagnato altissima considerazione negli anni recenti per la complessità anatomica, funzionale e tecnica. La gestione multidisciplinare e l'alleanza tra neurochirurghi e otorinolaringoiatri anche in questo ambito è diventata sempre più forte negli anni. La giunzione cranio-vertebrale ha una architettura anatomica ossea, neurovascolare e muscolare unica e complessa in quanto non solo separa e congiunge il cranio con il rachide cervicale, ma presenta pattern speciali di flessione, estensione e rotazione assiale. La stabilità è garantita da una complessa combinazione di supporti ossei e ligamentosi, che consentono ampi gradi di motilità. La conoscenza dell'anatomia e della fisiologia della giunzione cranio-vertebrale consente di comprendere meglio le procedure chirurgiche e le patologie specifiche che interessano questa regione anatomica. Sebbene siano passati anni dell'inizio della chirurgia pioneristica di questa regione, le lesioni situate nella porzione anteriore della giunzione cranio-vertebrale riman-

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gono ancora una stimolante sfida per il neurochirurgo. Molti studi sono presenti in letteratura con l'intento di esaminare l'anatomia microchirurgica delle porzioni anteriori, posteriori, extra e intradurali della giunzione cranio-vertebrale, così come le differenze e tutte le possibili vie di approccio a 360° per esporre al meglio e trattare patologie di questa regione. In questa revisione verrà effettuata una disamina sullo stato dell'arte in tale chirurgia, partendo dall'esperienza personale, dalle pubblicazioni e dalla letteratura più recente, al fine di sottolineare quando la collaborazione multidisciplinare sia fondamentale, altamente consigliata o non strettamente necessaria nella gestione delle patologie della regione cranio-vertebrale.

PAROLE CHIAVE: *fusione e procedure strumentate, endoscopia, approccio endoscopic transanasali, approcci transorali, approcci laterali al basicranio, approccio sottomandibolare retrofaringeo, giunzione cranio-vertebrale*

Introduction

Despite the continuous evolution and refinements of operating techniques, the disposability of dedicated surgical instruments along with the growing awareness and experience of the dedicated surgeons, treatment of craniovertebral junction (CVJ) pathologies still is a complex challenge. The tricky combination of bony, muscular and neurovascular vital structures crowded in a deep and narrow space makes surgical approaches to the CVJ hard and risky. Depending on the location of the lesion, surgical approaches have traditionally been directed toward ventral, dorsal and lateral aspect of the cervico-medullary junction. The anterior aspect of CVJ can be approached by the transoral approach (TOA), simple or extended, the endoscopic endonasal approach (EEA), introduced by Kassam [1], and the submandibular approach (SMA), i.e. retropharyngeal approach, which is indicated only in selected cases.

Posterior suboccipital approach (SOA) intra-extradural approaches along with instrumentation procedures has been traditionally considered for inferior craniectomy with or without C1-C2 laminectomy for CVJ lesions. Through the same route it is possible to perform C0-C1-C2 instrumentation procedures with titanium cables, wires, screws and rods in order to fix and stabilize the CVJ.

Intradural lesions located at the ventrolateral aspect of CVJ can be approached by means of a postero-lateral or far lateral approach (FLA), an extension of the suboccipital approach with removal of a variable amount of occipital bone. Extradural lesions of the same region may require an antero-lateral or extreme lateral approach (ELA), which allows a better control of the entire length of the vertebral artery (VA), the jugular foramen, the lowest cranial nerves, and the jugular-sigmoid complex. Finally, the posterior midline approach is the most popular in the neurosurgical culture both for extra and intradural surgical control of the CVJ and mainly for instrumentation and fusion techniques.

Moving from a comparative analysis of the CVJ approaches, and in the wake of our surgical experience [2-7] consisting of more than 40 anterior surgical procedures including TOA and EEA, more than ten comprising ELA, FLA, SMA and more than hundred posterior instrumentation and fusion procedures, we herein outline the experience matured in our department including an equipped Cranio-Vertebral Junction Laboratory for anatomical dissection [8-10], a II Degree Master Course on Surgical Approaches on CVJ and a University Research Center on CVJ, all mastered and directed by the Senior Authors (MV and GP) along with the Junior Authors (MR and FS) and referring to the Surgical Department / Pole of Medical Interest of our Catholic University of Rome Medical School.

In this review we will try to identify and objectivate the coworking potential of Neurosurgeons and Othorhinolaringologists in the common CVJ surgery field of interest.

Where alliance between neurosurgeons and otorhinolaringologists is mandatory?

Submandibular anterior Approach (SMA)

Terms like anterolateral [11], submandibular [12], anterior high cervical [13], and retropharyngeal pre-vascular [14] have been used to describe a surgical approach between carotid sheath laterally and pharyngeal constrictor muscles medially to high cervical spine. Cloward [15] and Robinson and Smith [16] are generally acknowledged as establishing the anterior approach to the cervical spine for the management of disk herniation. McAfee et al. [14] described the retropharyngeal pre-vascular approach using the same fascial plane described by Southwick and Robinson [17]. Submandibular retropharyngeal approach provides a direct, perpendicular trajectory to the C2-3 interspace through a "natural" corridor above the superior laryngeal nerve (SLN) and below the hypoglossal nerve. The approach requires a very little retraction and, comparing to other approaches (especially ELA) is associated with a lower risk of hypoglossal, glossopharyngeal and superior laryngeal nerves injury. These risks can be further limited using an endoscope-assisted retropharyngeal approach, mainly indicated for lesions involving the clivus. Nevertheless, care must be taken when using the approach in the setting of prior neck dissection. On the other hand, this route can be burdened by some complications as respiratory dysfunctions; pharyngeal fistula; transient hoarseness and dysphagia; dural leakage; hypoglossal and facial nerves paresis and salivary fistula.

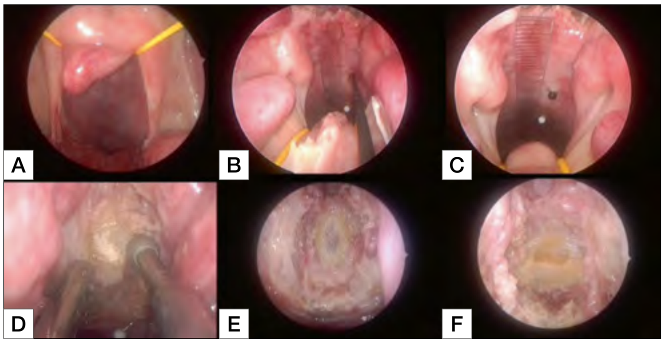

Figure 1. Anatomical studies comparing the exposure of transoral (**A**) and endoscopic transnasal approach (**B, C**) followed by exposure of the anterior arch of C1 (**D**), odontoid (**E**) and its removal (**F**) through a combined transoral transnasal approach.

This surgical field appear more consistent with the oncologic Otorhinolaringological background up to the anterior profile of C1 and C2.

Where alliance between neurosurgeons and otorhinolaringologists is strongly advisable?

TOA and EEA

TOA still represents the "gold standard" for the surgical treatment of several conditions resulting in anterior CVJ compression and myelopathy [18]. Refinements of the approach have been introduced during the late 1970s by Menezes who outlined several issues that now represent pivotal steps of the approach [19]. Nevertheless, some concerns, such as the need of temporary tracheostomy and postoperative nasogastric tube [20], soft palate morbility, overall led in 2005 to the introduction by Kassam et al. [1] of the EEA (Fig. 1).

EEA

Although this approach, conceived in order to overcome these surgical complications, rapidly gained wide attention, a clear predominance over the TOA in the treatment of CVJ pathologies, is still matter of discussion. In recent years, several papers have reported anatomical studies and surgical experiences in EEA to target different areas of the midline skull base, including the CVJ [20-28]. Starting from these preliminary experiences, further anatomical studies defined the theoretical (radiological) and practical (surgical) craniocaudal limits of the endonasal route (Fig. 2) [29-31]. Our group, on the basis of the clinical experience gained after 30 anterior procedures, both transoral and transnasal, did the same for the transoral approach [32,33] and compared the reliability of the radiological and surgical lines of the two different approaches. Very recently, a cadaveric study tried to define,

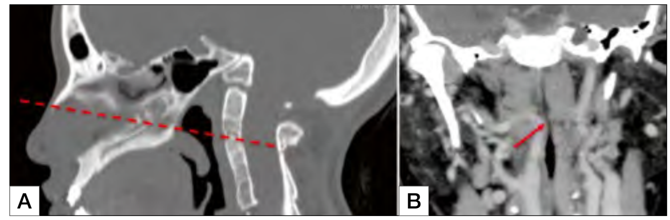

Figure 2. Importance of accurate preoperative radiological evaluation in order to choose the best corridor of approach. (**A**) CT scan of children with impression basilaris in which we preferred a transnasal corridor. (**B**) Angio CT showing an internal carotid kinking in the pharyngeal wall that exclude the anterior route to the CVJ.

with the aid of Neuronavigation (Fig. 3), the upper and lower limits of the endoscopic transoral approach [34].
This approach appears more consistent with the global rhinological endoscopic experience of the Othorhinolaringologist up to C1-C2.

TOA is a ventrally directed approach from the inferior third of clivus to C2-C3 interspace. It allows the shortest, wider and most direct access to the CVJ, among the other approaches to the CVJ [35]. Extensions of the approach, sometimes necessary to expose more rostrally located pathologies, carry the risk of numerous permanent comorbidities expecially on the soft palate and the need for temporary tracheostomy and nasogastric feeding tube [20]. The need to overcome the impact and significance of these comorbidities has led to the development of potentially less invasive techniques, such as the EEA. As widely demonstrated by numerous comparative anatomic and clinical studies, the

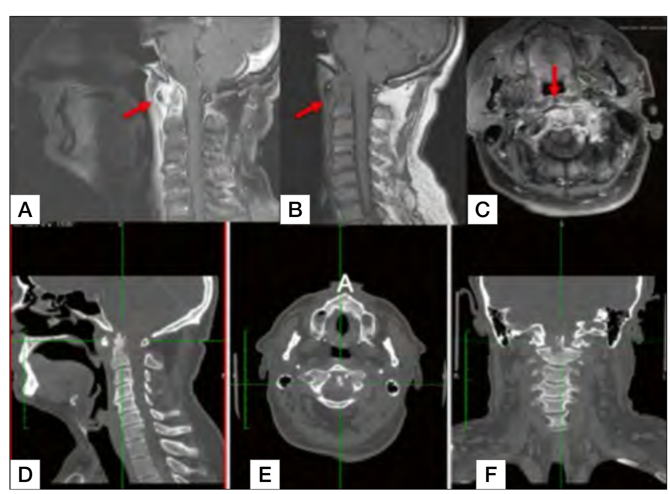

Figure 3. Use of navigation system to perform a biopsy of a lesion (arrow) of the odontoid on sagittal and axial MRI (**A, B, C**). Intraoperative view with CT scan (**D, E, F**) The cross-air revealed a correct target reached through a minimally invasive EEA. The biopsy revealed a localization of myeloma.

endoscope provides also an improved rostral exposure, brighter illumination and closer visualization of the surgical target [35] and can be also used during a TOA, as a valid complement tool in a combined procedure. Nevertheless, a recent systematic review and meta-analysis [37], while demonstrating a statistically significant increased risk of postoperative tracheostomy after TOA comparing with EEA, showed a slight, although not statistically significant, tendency toward a morbidity/mortality prevalence of EEA on TOA (Fig. 4).

In order to clearly define the limits of the TOA, our research group devised a radiologic "theoretical" line, the Palatine Inferior dental Arch line (PIA), as a reliable predictor of the maximal superior extension of the transoral approach and then compared the reliability of the radiological and surgical lines of the two different approaches [33]. Very recently, a cadaveric study tried to define, with the aid of Neuronavigation, the upper and lower limits of the endoscopic TOA [34]. Starting from our previous experimental volumetric studies [32,33] and other recent contributions, we tried to experimentally exploit the accuracy provided by Neuronavigation, to further compare operative sagittal and axial extensions of the transnasal and transoral corridors. Our observations were consistent with a relevant advantage of TOA over EEA in all the specimens. According to other clinical and experimental studies reported in literature, we found several advantages of TOA over EEA: wide working area in terms of both craniocaudal and lateral extension, a more familial anatomy for neurosurgeons, a safer top-down drilling of the clivus and odontoid with a better

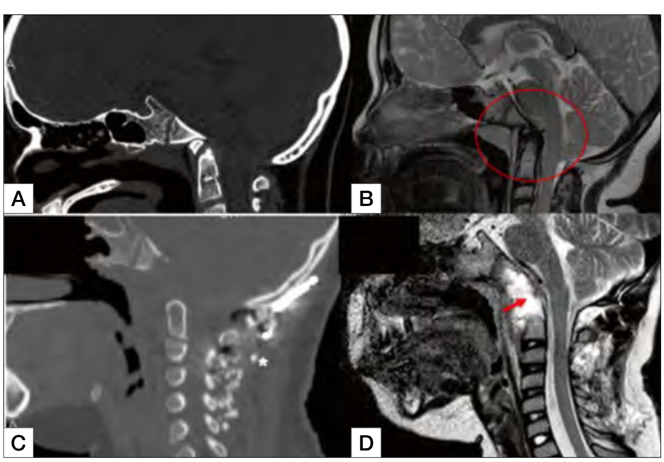

Figure 4. Axial CT scan (**A**) and T2 weighted MRI (**B**) of platybasia and impressio basilaris with bulbo-medullar compression (rounded area) treated through a pure transnasal endoscopic approach. In the inferior line post-operative CT scan (**C**) and MRI (**D**) showing a decompression of the bulbopontine (arrow) angle and the posterior stabilization (*) the absence of tracheostomy can be also observed.

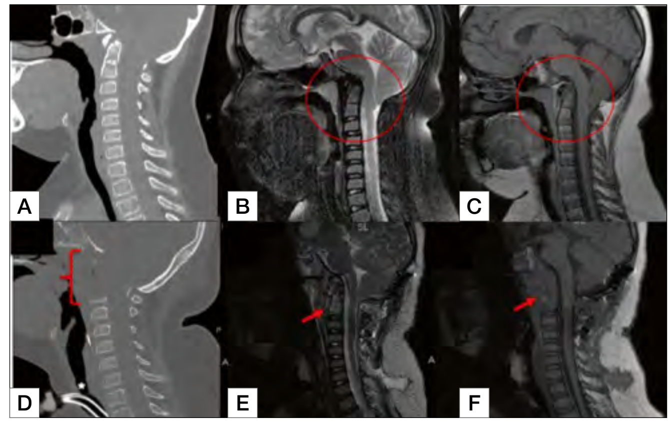

Figure 5. CT scan (**A**) and T2 (**B**) and T1(**C**) weighted MRI of a case of impressio basilaris and platybasia + bulbo-medullar compression (rounded area) This lesion was treated with transoral approach that allowed a wide exposure and resection from clivus to C1({) and decompression (arrow) as showed in postoperative CT (**D**) and T2 (**E**) and T1(**F**) MRI, in which you can observe the presence of tracheostomy (*).

detachment of the ligaments (Fig. 5). On the other hand, excluding some well-known disadvantages and predictable complications appreciable only in clinical setting, such as working in a contaminated field, CSF leak management, the airway swelling, the upper airway obstruction and the velopharyngeal insufficiency, our study confirms the relevance of fixed obstacles to the required retraction as the tongue and the teeth.

The management of TOA requires the role of the Otorhinolaryngologist for performing tracheostomy, cooperate in the surgical exposure and final reconstruction of the pharyngeal opening.

ELA

Starting from the 1970s, many surgeons developed and introduced new skull base approaches to the lesions of the anterolateral CVJ introducing several variations and modifications. Hammon in 1972 and thereafter Heros in 1986 described a true lateral suboccipital approach for vertebral and vertebrobasilar aneurysms [38,39]. Heros described the combination of a lateral suboccipital craniotomy, C1 laminectomy and drilling of the occipital condyle (OC). George described a VA medial mobilization from C2 to its dural entrance point, with ligation of the sigmoid sinus and without condyle drilling. Spetzler, Bertalanffy, and Seeger mobilized the VA from C1 to dural entrance point, by drilling C1 facet, posterior C1 arch and posterior lateral third of the OC [39-43]. In recent years, extensive use of tools like neuroendoscope and neuronavigation, greatly implemented safety and efficacy of this and other skull base approaches, as demonstrated by several cadaveric studies [44-46]. ELA is a direct lateral approach to the deep anterior portion of the SCM, behind the internal jugular vein and anterior to the VA. It is generally considered a more aggressive extension of far lateral approach. This term comes from 1990 when Sen and Sekhar described an alternative way to deal with meningiomas and schwannomas located anteriorly at the CVJ [47]. The rationale behind this procedure is to allow gross total resection of lesions with significant lateral extensions that would be otherwise inaccessible via anterior or classic FLA. ELA involves a greater extent of bony removal, skeletization of the jugular bulb along with the sigmoid sinus (in the transjugular variant), and more often VA transposition. These technical nuances overall widen the surgical corridor, but inherently are associated with a higher rate of morbidity and mortality [48,49].

ELA provides good access to the bone and extradural anterior and lateral space. It can be easily extended caudally to the cervical spine and it offers simultaneous control of the VA, cervical segment of the ICA, the lower cranial nerves, and the sigmoid-jugular complex [50].

In ELA, muscles are detached from their insertion on the transverse process of atlas. Great attention should be paid to avoid damage of VA, internal jugular vein, and spinal nerves, which are under these muscles. The key point for dissection and control of the VA is to preserve the periosteal sheath surrounding it. Our study further confirms that ELA allows exposure of the whole odontoid process, the inferior clivus, and the medial surface of the contralateral atlanto-occipital joint.

In this surgery the more confident knowledge of Otorhinolaryngologists of the superficial and middle and deep plane layers of the neck make this alliance absolutely advisable.

Where alliance between neurosurgeons and otorhinolaringologists is unnecessary?

Transcervical Anterior Approach (TCA)

Wolinsky described an endoscopic transcervical approach in order to perform odontoidectomy without traversing the oral cavity [51]. A recent cadaveric study exploited the feasibility of an endoscope-assisted retropharyngeal approach to the CVJ and clivus following submandibular gland resection [52].

The knowledge of the Neurosurgeons of this region gained by cervical spine surgery along with the skill obtained in spine traumatology aimed to screwing the odontoid fractures with biplanar fluoroscopy, make him confident and no surgical alliance seems to be required for this infrequent surgery.

FLA nowadays represents a mainstay for the surgical treatment of intradural pathologies at the ventral CVJ. Since the first description of Heros and George [53], extensive discussion and modifications of this approach have been reported in the literature. Several cadaver studies have demonstrated the use and benefits of the endoscope in the FLA. A study [54] has divided the surgical corridors for inserting the endoscope into upper, middle and lower. The cranial nerves VII and VIII, IX and X, and XII are respectively roof and floor of the three corridors and provide access and observation of the aspects of brainstem and posterior circulation by means of 0° lens (upper and middle corridor) and 30° lens (inferior corridor). Another cadaver study compared 3D endoscopic and microscopic vision in FLA after partial condilectomy and resection of jugular tubercle. The study concluded that the 3D endoscopic probe is too large and the surgical maneuverability is significantly hampered. Several authors have stated similar benefits of endoscope use in clinical series. These studies report a significant benefit in the endoscope's ability to identify any tumor adherent to brainstem or clivus amenable to resection [55].

For this approach the Neurosurgeon appears to be quite confident, since it can be considered an extension of the classic well known PIFP but in park bench position.

SOA Occipitocervical fusion (OCF) as well as C1-C2 is indicated for instability at the CVJ. Numerous surgical techniques, which evolved over 90 years, as well as unique anatomic and kinematic relationships of this region present a challenge to the neurosurgeon. The current standard involves internal rigid fixation by polyaxial screws in cervical spine, contoured rods and, eventually, occipital plate. Such approach precludes the need of postoperative external stabilization, lesser number of involved spinal segments, and provides 95-100% fusion rates. New surgical techniques such as occipital condyle screw or transarticular occipito-condylar screws address limitations of occipital fixation such as variable lateral occipital bone thickness and dural sinus anatomy. As the C0-C1-C2 complex is the most mobile portion of the cervical spine (40% of flexion-extension, 60% of rotation and 10% of lateral bending) stabilization leads to substantial reduction of neck movements. Preoperative assessment of vertebral artery anatomical variations and feasibility of screw insertion as well as visualization with intraoperative fluoroscopy are necessary. Placement of structural and supplemental bone graft around the decorticated bony elements is an essential step of every OCF procedure as the ultimate goal of stabilization with implants is to provide immobilization until bony fusion can develop.

This historical neurosurgical approach makes the Neurosurgeon absolutely confident, since it is required for conventional posterior cranial lesions approaches.

Future perspectives

In recent years, the surgical armamentarium has been enriched with *high-definition 4 K endoscope* [56] *as well as exoscope* [57] *systems*, which potentially provide a wide viewing angle as well as high-resolution image quality available with an endoscope with an optic resolution power equal or superior to the conventional Operating Microscope (OM) [57].
In particular, the exoscope is a new surgical tool recently conceived in order to overcome some limitations of OM and endoscope. Limitations of the first are mainly ergonomics: the size and weight, the ocular-dependent visualization, the continuous need of refocus because of the short field depth at high magnification and of continuously readjusting the OM and the body position in order to preserve a perfect stereoscopic picture. Limitations of the endoscope include a short focal distance and a limited field of view that requires an endoscope placement in the surgical field with the shaft reducing the available working space. Overall, these limitations are even more evident in complex and narrow anatomical corridors as those of the CVJ. Besides to the classic neuronavigation with preoperative neuroradiological assessment it's worth mentioning also *OArm neuronavigation and intraoperatory System.* Intraoperative imaging represents another important upgrade in neurosurgery.
For spinal surgery in particular, the introduction of the OArm system has made it possible to implement the safety of instrumentation procedures on the one hand, allowing much more accurate intraoperative neuronavigation than traditional techniques; secondly the setting with intraoperative imaging allows a real-time verification of the effectiveness of the procedure, such as in cases of medullary decompression or the correct positioning of arthrodesis systems [58].
OArm acquisition, comparing to fluoroscopy, not only should have the obvious advantage of a better definition with a resulting easier screws insertion, but, for sure, it permits an intraoperative direct and indirect assessment of bony and legamentous CVJ anterior decompression. In two of five cases, after OArm acquisition the cranio-caudal decompression was augmented because it proved to be suboptimal in an absolutely reliable and anatomically detailed way. Otherwise in our previous experience concerning fluoroscopic monitoring of TOA, the use of Iopamire, as contrast filler of the surgical cavity, allowed in a quite fair way to, indirectly, evaluate possible residual compression at the CVJ. Otherwise, it does not provide a real time visualization.
Finally, the possibility to convert the intraoperative neuronavigated 3D modality into 2 D real time OArm monitoring is very unconfortable due to the poor volume space available for the surgeon (also in the presence of EX) and the need of complex, time consuming and uneffective surgical manouvres required.
The spreading diffusion of such technologies seems to belong to the personal and institutional skill of both Neurosurgeons and Otorhinolaryngologists, always more devoted to share common objectives, operative tools for a common clinical and experimental final strategy.

Conclusions

The present paper confirms the irreplaceable role of interdisciplinary coworking in order to improve the difficult knowledge of the CVJ. Anatomical dissections in the training of surgeons, especially when approaching an anatomical region among the most complex such as the CVJ, is possible only with sharing experience and traditions and it is of paramount importance when dealing with this region. Accurate and multidisciplinary preoperative evaluation of the best corridor of approach, taking care also of all the possible intra, perioperative and postoperative problems are nowadays the mainstays for the best treatment of the patients affected of pathologies of CVJ.

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When multidisciplinary surgical trans-orbital approaches should be considered to reach the skull base

Ruolo degli approcci chirurgici multidisciplinari trans-orbitari nella gestione della patologia del basicranio

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SUMMARY

The transorbital approaches are a group of surgical procedures performed passing through the orbital spaces and aimed to reach deeper areas. This kind of surgery has been proved to be safe and effective in the management of selected lesions of the anterior, middle and infratemporal fossa. The aim of the present study is to perform a review of the literature, in order to draw the reader's attention on the main features of this kind of surgery, focusing on the anatomical background and the surgical setting; we will also summary the current indications and contraindications to this approach and find out the related complications and the possible alternatives. Even if we consider the transorbital approach as a promising route to the skull base, we underline that there is no better approach over another and the choice must always consider several elements. Furthermore, as for every skull base procedure, a multidisciplinary management is strongly advisable.

KEY WORDS: skull base, surgical procedures, orbit, endoscopy

RIASSUNTO

Sotto il termine "chirurgia trans-orbitaria" viene attualmente indicato un gruppo di procedure chirurgiche volte a raggiungere la base cranica, sfruttando la finestra orbitaria. Questo tipo di chirurgia si è dimostrata sicura ed efficace per la gestione di patologie selezionate della fossa cranica anteriore, della media e della fossa infratemporale. L'obiettivo di questo lavoro è quello di effettuare una revisione della letteratura, con lo scopo di veicolare l'attenzione del lettore su quelle che sono le principali caratteristiche di questo tipo di chirurgia, concentrandosi in particolare sul necessario background anatomico e sul setting operatorio richiesto; riassumeremo le attuali indicazioni e controindicazioni ed evidenzieremo le possibili complicanze associate a tale chirurgia e le eventuali alternative da intraprendere. Pur reputando che questa chirurgia sia molto promettente nella gestione di alcune patologie del basicranio, vogliamo tuttavia sottolineare come non esista mai un approccio chirurgico migliore di un altro in termini assoluti, e che la scelta finale debba essere sempre il frutto di considerazioni che valutano molteplici elementi. In ultimo, si vuole sottolineare che, come in altre procedure sul basicranio, i migliori risultati si ottengono con una gestione multidisciplinare.

PAROLE CHIAVE: *base cranica, procedure chirurgiche, orbita, endoscopia*

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Introduction

Generally speaking, with the term "transorbital approaches" we consider a group of surgical procedures performed passing through the orbital spaces aimed to reach deeper areas. As a matter of fact, transorbital endoscopic-assisted surgery is one of the most recent, fascinating and promising areas in skull base surgery. Its development should be considered as a natural step of the progression of the minimally invasive surgical approaches to the skull base. Transnasal endoscopic-assisted approaches, although incredibly evolved, have their own limits. Probably the two most important are: 1) the frequent need of angled endoscope and cross-planar technique and instruments to visualize and manage the surgical target; 2) the nasal corridor to the skull base becomes progressively constricted as the target is reached, especially in its lateral aspect. Furthermore, transnasal endoscopic approaches necessitate placement of the endoscope and instruments in a similar vector with minimal offset angle [1]. Based on these grounds, it came naturally to think of the orbit not only as a possible site of pathology but also as a corridor to deeper areas. Thanks to the innovative work of Kris Moe, this idea turned into reality [2]. This kind of surgery, named TONES (Trans-Orbital Neuro-Endoscopic Surgery) has been proved to be safe, and from the very initial experience several groups around the world have started to add their own data to this topic. Among the main advantages of TONES we include a shorter period of hospitalization, rapid recovery, very good cosmetic outcomes and reduced, if not absent, morbidity related to brain retraction [2]. More interestingly, this kind of approach has been successfully combined with other surgical procedures in order to offer multiple entry windows, overcoming the own limits of each of them, giving rise to a "multiportal" procedure. The golden rule of "not being dogmatic" is leading worldwide surgeons to introduce variations to the actually known solutions, always with the intent to improve results and minimize complications and sequelae. The aim of this manuscript is to perform a review of the literature, in order to investigate how this new transorbital approach could improve the skull base surgery. We will, therefore, highlight the characteristics that may be useful to clinician in the choice of the best approach for the patient, in a personalized view of the surgical practice. In this respect, although several incisions and approaches have been described and proposed [1,3], in this chapter we will focus mainly on the superior eyelid endoscopic-assisted approach exploring the following items:

- anatomical background and surgical considerations;
- surgical instrumentation and setting (multidisciplinary management);
- current indications and contraindications;
- possible alternatives;
- complications;
- case examples.

Other transorbital approaches will not be discussed in this paper and we advice to refer to dedicated literature.

Anatomical background and surgical considerations

The superior eyelid, viewed from an anterior to posterior direction, is formed by two lamellae: an anterior lamella, consisting of skin and the orbicularis oculi muscle, a posterior lamella, consisting of Muller's palpebral muscle and levator aponeurosis. The orbital septum, in the upper part of the eyelid, is located between these two lamellae. The orbital septum is in continuity with the periorbita and the periosteum of the external cranial surface and it is a membranous sheet. The superior septum originates from the orbital rim at the arcus marginalis. Supero-medially, it is pierced by vessels and nerves. It is located medially behind the medial palpebral ligament and laterally it is located anteriorly to the lateral palpebral ligament. It attaches itself to Muller's muscle and the superior tarsus inferiorly, ending in the pre-tarsal skin. The upper eyelid is supported by the upper tarsal plate, which forms with its lateral and medial canthal tendons the tarso-ligamentous sling. The levator palpebrae and its aponeurosis form the superior eyelid retractor system, which passes inferiorly from the Whitnall's ligament to reach the tarsal plate and the pretarsal palpebral skin. Anatomically speaking Whitnall's ligament is a condensation of fascial covers around the levator palpebrae superioris muscle. As for the aponeurosis of the levator, its lateral horn is inserted on the Whitnall tubercle, while the medial horn is inserted on the posterior lacrimal crest. Muller's sympathetic muscle should be considered as an accessory tendon of the levator palpebrae, in the context of the upper eyelid. Along the anterior surface of the upper tarsus runs the marginal arterial arcade, mainly from the medial palpebral and lacrimal arteries. This means that the blood supply for the superior eyelid comes mainly from the ophthalmic artery. Lesser contribution comes from the infraorbital, temporal, transverse facial and angular arteries.

At the level of the superolateral aspect of the orbital rim, the upper lobe of the lacrimal gland can be appreciated just behind the orbital septum. It lies above the lateral extension of the levator palpebrae fascial system. The lacrimal gland is divided into two portions: an orbital (or upper) portion that is lodged in the lacrimal fossa (frontal bone) and a palpebral portion that extends through the lateral horn of the levator aponeurosis into the supero-lateral fornix (it can be seen shining through the conjunctival layer). The upper and lower lateral tarsal tendons form the lateral canthal tendon. It inserts into the periorbita overlying the Whitnall's lateral tubercle. In the medial canthal tendon we can identify two heads, superficial and deep. The superficial head attaches anteriorly to the lacrimal fossa and the frontal process of the maxillary bone and it's thicker. The deep head attaches to the posterior lacrimal crest and it's thinner. The posterior limb of the medial canthal tendon gives the medial component of the orbital septum.

From an anatomo-surgical point of view, once the orbital rim is reached and skeletonized as needed, we then proceed with a careful sub-periosteal dissection until the lateral aspects of the superior (SOF) and inferior orbital fissures (IOF) are identified and adequately exposed. We strongly advice to perform a careful dissection, sparing the integrity of the periorbita (in order to avoid fat prolapse into the surgical field). During this dissection several bridging vessels can be identified; they must be coagulated and cut to avoid annoying bleeding during the procedure. In 50-60% of subjects the cranio-orbital foramen (Hyrthl's foramen) can be found; it is close to the superior orbital fissure and transmits usually the recurrent meningeal artery (also named meningolacrimal branch). As anatomical variation, this vessel can pass through the SOF. In transorbital "corridor" surgery, like the one discussed in this paper, when the periorbita is exposed it should be spared in order to create the "pocket room" for the instrumentations. As possible targets, in such an approach, we can identify the anterior and middle cranial fossa and even the infratemporal fossa (Fig. 1). Regardless the target, the first surgical step is to expose completely the inner surface of the temporalis muscle. By doing this, the room for work is enlarged and an increased surgical freedom for the intruments is gained. When dealing with a "middle cranial fossa approach" the orbital part of the greater wing of the sphenoid has to be completely removed to reach the dura mater of the anterior part of the temporal lobe. According to the target of surgery, the approach can be partially extended to the lesser wing of the sphenoid and toward the anterior clinoid process. If necessary, the frontal bone can be partially resected, and if an intradural work has been planned, the spheno-parietal sinus is advisable to be identified and managed. In case of intracranial approaches, the dura is opened and the anterior part of the temporal lobe of the brain is reached, as well as the lateral wall of the cavernous sinus. In more extended approach, once the lesser wing of the sphenoid and partially the frontal bone have been removed, the most medial part of the sylvian fissure and its content can be visualized.

If the meningo-orbital band is split, an interdural way to the lateral wall of the cavernous sinus and Meckel's cave is reached. This is not a proper intradural approach because it spares the integrity of the dura propria and avoids to expose the brain parenchima; anyway it allows a direct and efficent way to reach the Meckel's cave and the anterior petrosal area.

If the lesion is located below the middle cranial fossa or in the upper infratemporal fossa area, an inferior extension of the "middle cranial fossa approach" can be performed removing the floor of the MCF thus exposing the upper aspect of the infra-temporal fossa content.

In an "anterior cranial fossa approach", the orbital part of the frontal bone is removed, along with a part of the lesser sphenoid wing, to perform a craniectomy. The greater wing of the sphenoid is normally only partially resected. Then the dura is exposed and opened if the procedure requires it. Intracranial work follows as necessary.

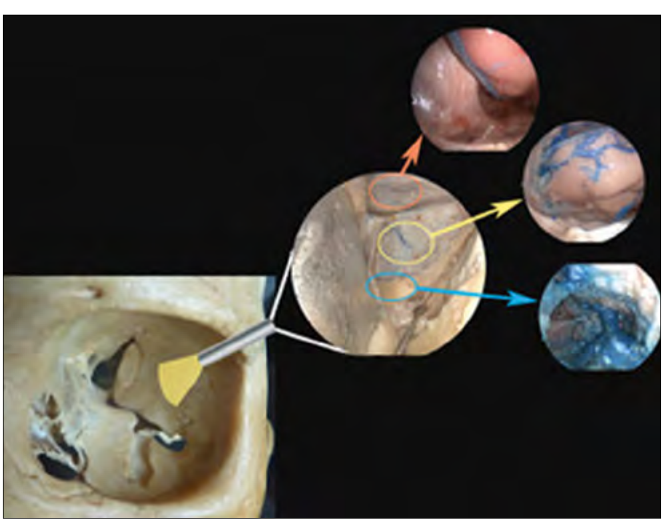

Figure 1. Multipanel figure showing the transorbital endoscopic-assisted approach to the skull base. The orange circle shows the position of the anterior cranial fossa (ACF); the orange narrow its content, the frontal lobe. The yellow circle shows the position of the middle cranial fossa (MCF); the yellow narrow the temporal lobe, which is behind the dura of the MCF. The light blue circle shows the position of the infratemporal fossa (ITF); the light blue narrows the content of the upper part of the ITF.

Surgical instrumentations and setting

Patient position is the same as for any standard endoscopic-assisted skull-base procedure. For extradural approaches we generally do not fix the head of the patient, while the head is normally fixed if intracranial dissection is anticipated. Anyway, the head position may be changed during surgery, thus allowing different angles of attack to the surgical target. It is strongly advisable that the operating room be set to allow a double screen vision and neuronavigation. We would like to emphatize the concept that this kind of surgery can be performed endoscopically and/or microscopically, or better yet in a combined blended solution.

In our experience, we never fix the endoscope in a holder, but it could be probably useful in some instances, as demonstrated by other groups. These procedures are usually performed via a 3-4 hands technique (Fig. 2). In transpalpebral procedures, the role of a third surgeon helping in creating adequate space for working is of paramount importance. In

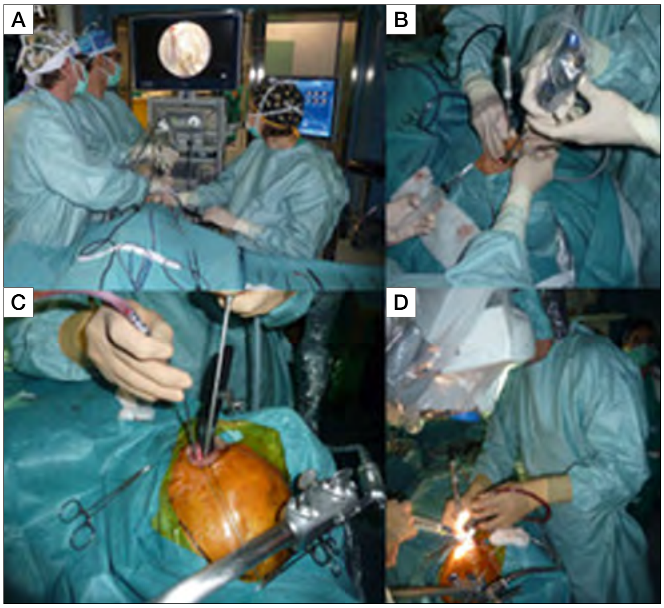

Figure 2. External intraoperative views of the surgical area in endoscopic-assisted superior eyelid approaches. In **A** and **B** the surgical team is composed of 3 surgeons: the second surgeon holds the endoscope, the first surgeon is free to use both hands; the third surgeon create a wide surgical window. In **D** a combined endoscopic and microscopic-assisted procedure.

combined multiportal approaches, a good versatility of the surgical team is required. In this respect we would like to strongly underline the extreme importance of a multidisciplinary evaluation and management. The close collaboration with the neurosurgeon, opthalmoplastic surgeon, but also maxillofacial and interventional radiologist and radiotherapist is the key for the success. In other words we want to stress the concept that this kind of surgery should not be considered a "one-man show" but rather the field where different competences share their own experience and skill in a dynamic and harmonic fashion.

Regarding instrumentations, we can advice the use of typical neuroendoscopic instrumentation. A high-speed drill or eventually piezo-electric tool can be used for bony work. Also ultrasonic bone aspirators have been used for this purpose and showed their potential in selected cases.

Current indications and contraindications

Endoscopic transorbital approaches, although at their dawn, showed to be feasible and safe as a *minimally invasive and minimally disruptive surgery* [4], able to provide direct access to deeper lateral areas of the facial skeleton and skull base. Transorbital procedures may be performed in case of disease involving the orbit itself or structures adjacent to the orbit, such as the paranasal sinuses, the infratemporal fossa, and the anterior and middle cranial base.

The choice of a transorbital endoscopic approach over transnasal or open transcranial pathways implies different considerations:

- the surgical team's preference and expertise;
- a good interdisciplinary cooperation among otolaryngologist, orbital surgeon and neurosurgeon;
- the biological behaviour of the lesion and the possibility to gain direct access to it with adequate surgical freedom;
- the chance to completely control the surgical field and any possible intraoperative complications [5].

Among the current indications of a superior eyelid approach we can describe selected:

- spheno-orbital meningiomas;
- Meckel's cave schwannoma;
- laterally-located anterior cranial fossa meningioma;
- lesions within the lateral recess of the frontal sinus;
- laterally-located epidural abscesses;
- vascular and lymphatic malformations;
- skull base defects (mainly located in the lateral recess of the sphenoid sinus);
- other lesions of the Meckel's cave of the anterior petrous apex region;
- huge mucoceles of the orbit and cranial cavity (in combination with transnasal approach).

The transorbital endoscopic surgery, by means the superior, lateral and supero-lateral approaches (mainly performed via a superior eyelid approach), may be used in case of diseases involving the anterior cranial fossa, providing good access and visualization. Furthermore, the opening of the orbital roof in the floor of the frontal sinus allows reaching lateral lesions of the frontal sinus, difficult to access with transnasal surgery such as inverted papilloma and mucoceles [6]. At the same time, this kind of surgery allows working angles more favorable to expose the anterior skull base, preserving the paranasal system and physiology when possible. Literature on the topic mainly describes case reports and small case series, and one of the largest experiences of pure TONES is described by Ramakrishna and Moe in 2016, with 45 TONES procedures directed to the skull base [4].

Among clinical indications to perform transorbital surgery for ACF, Authors report CSF leaks; repairs of cranial base fractures; selected tumours and optic nerve decompressions; meningoencephaloceles; inflammatory conditions and sinogenic infectious complications involving the anterior cranial fossa [2,4,7]. In all such cases the transorbital endoscopic surgery represented a viable technique for lesions difficult-to-reach with other pathways or an additional tool to gain the greater access to such challenging diseases [8]. One of the current main fields of interest using TONES is related to the management of disease within the middle cranial fossa. Skull base lesions of this area are traditionally challenging to be approached, because of the anatomical complexity of this region and the presence of noble neurovascular structures, such as the Internal Carotid Artery (ICA), several cranial nerves, and venous plexus [9,10]. All classic transcranial approaches used to manage lesions of the MCF have their main limits in requiring an extensive bone removal, the disruption and possible post-operative atrophy of the temporalis muscle and a moderate-to-severe brain retraction [10]. In this scenario, a purely endoscopic approach such as the transorbital superior-eyelid route, may allow to expose the lateral middle cranial fossa by extradural removal of the greater and lesser sphenoid wings, followed by the dissection of the so called meningo-orbital band, with minimal disruption of normal tissue [11,12]. In endoscopic-assisted surgery to Meckel's cave and petrous apex, among the advantages of the transorbital approach over the endonasal patways, Lee reports the shorter access route and the possibility to perform an "interdural" dissection within the lateral wall of the cavernous sinus with a easier manipulation of tumors at their lateral and posterior borders, sparing the vidian nerve [13]. Literature on the topic is in steady growth with several anatomical comparative studies performed to value the feasibility of the transorbital approaches over endonasal and open patways [14,15]. Among published clinical series, the superior eyelid approaches to the middle skull base have been successfully used to manage spheno-orbital meningiomas (even if the en-plaque types remain a challenge) [16] and neoplastic diseases such as trigeminal schwannomas [17] and metastatic lesions [10]. Anyway, different Authors remark the limits of such approach, underlying the possibility that the unfamiliarity with the orbital anatomy may lead to orbital and globe injuries [13,18]. So, it must be stressed that a dogmatic approach to such complex lesions is not appropriate and the surgical expertise and confidence with the transorbital route should be properly considered before choosing the surgical access. Last but not least, the age of the patient, the possible comorbidities and the biological behaviour of the lesion must be carefully evaluated [5,13,18].

The infratemporal fossa is another possible target area reachable through a superior eyelid approach, since it lies inferiorly to the middle cranial fossa floor. Its management may require the use of complex approaches, even if decisive steps forward have been made with the advent of the endonasal endoscopic tecniques [19]. In this respect, the orbit may represent a new potential option to reach the upper aspects of the infratemporal fossa, through both a superior or, probably better, an inferior orbital access (using the inferior orbital fissure as a natural corridor) [20]. It must be underlined that most of these cases, anyway, needs to be managed via a combined multiportal procedure.

Thus said, assuming that a single surgical approach might not be able to complete manage deep, multicompartimental and difficult-to-access skull base lesions, a multiportal approach, providing simultaneous entry windows, should be seriously considered [21]. In such cases, the superior eyelid approach may be associated with other transorbital, transnasal or even transcranial accesses, ensuring a better visualization and manipulation of the lesion from synchronous different perspectives, as well as a reduced risk of collateral damage [18]. If a single approach, in fact, may be insufficient to address lesions that cross neurovascular structures or are deeply located, the use of multiple accesses may allow an augmented visualization, avoiding potentially devastating complications [21].

Technically speaking, the multiportal approach has its strength in the capability to perform a 360° approach, for instance to the optic canal and the cavernous sinus, as well as the infratemporal fossa and selected complex cases involving the anterior and middle cranial fossa [22]. And more than in a single window approach, the multiportal surgery provides a multihands technique, similarly to the open approaches, taking advantages of the role of the second and third surgeons to gain an adequate exposure and visualization [18].

Among surgical target, Meckel's cave and cavernous sinus pathologies seem to benefit from this kind of solution, as an alternative technique that may reduce the high morbidity traditionally associated with the other surgical accesses.

Different Authors report case report and series with the multiportal approach, represented by a combination of transorbital and transnasal routes applied in clinical settings [21-24]. In all cases this combination appeared safe, effective and able to take advantages of each single approach.

As a general rule regarding possible contraindications, we do feel that, whenever major vessels are totally encased by the lesion (regardless the lesion), traditional transcranial routes should be considered as first option. In such cases performing different "alternative" approaches, like multiportal endoscopic-assisted ones, should be well evaluated and balanced. Obviously, a case-by-case evaluation is mandatory by an experienced and wise multidisciplinary team.

Possible alternatives

In Table I, we schematically report the main advantages and limitations of the transorbital endoscopic approach compared to the classical open surgical approaches.

Table I. Advantages and limitations of the superior eyelid endoscopic-assisted approach compared to the more traditional open ones.

	Advantages	Limitations
Superior eyelid endoscopic-assisted approach	Short distance to the target No nerve or major vessels crossing Good control of the anterior pole of the temporal lobe and of the medial aspect of the Sylvian fissure Good access to lateral wall of the CS and Meckel's cave (and petrous apex) No need for brain retraction	Difficult control of the lateral aspect of the temporal fossa Major vessels encasement or highly vascularized lesions Lesions extending too posteriorly or inferiorly
Supraorbital approach	Small incision Good control of anterior and suprasellar/parasellar regions (superior aspect)	No control of ITF No control of anterior temporal lobe region and of infero-lateral aspect of CS (inferior parasellar region)
Fronto-temporal approach	Good exposure of anterior and middle cranial base	Need for bony work with large skin flap Very difficult control of ITF Necessity for management of the anterior part of the temporal lobe to get the lateral wall of CS
Pterional approach	Good exposure of anterior and middle cranial base Good exposure of sylvian fissure	Need for bony work and large skin flap Difficult control of PPS and ITF Need for the management of anterior part of the temporal lobe to get the lateral wall of CS
Subtemporal approach	Good exposure of lateral aspect of parasellar, anterior pole of the temporal lobe and anterolateral posterior cranial fossa	Need for bony work with large skin flap Very difficult control of PPS and ITF No control of anterior cranial base Need for management of anterior pole of temporal lobe to obtain space for access to lateral aspect of parasellar region Need for major retraction to obtain suprasellar access
FTOZ (& variations) approach	Wide exposure of anterior and middle cranial base Good exposure of supralateral aspect of the orbit Access extending to interpeduncolar and prepontine cisterns	Difficult control of PPS and ITF Need for extensive bony work and large skin flap

CS: Cavernous Sinus; ITF: Infratemporal Fossa; PPS: Parapharyngeal Space; FTOZ: Fronto-Temporal Orbito-Zygomatich approach.

Complications

Surgical complications can be mainly divided in two groups: complications related to the surgical approach and complications related to the target regions. Obviously, the latter are independent to the chosen approach and may occur during any approaches. Another issue is the case of complications related to the approach itself. More in details, the palpebral phase can be associated to the damage to the levator palpebrae muscle, thus leading to post-operative ptosis. To avoid such complication, the use of loupes or any other magnification system can be of great help. Post-operative lid swelling may be significant. Chemosis can be present and significant. Severe injuries of the extraocular muscles, mainly the lateral rectus muscle, although really rare can be associated with post-operative diplopia. This occurs especially during drilling of the bone. A piece of silastic sheet could be useful in order to protect orbital tissues. In case of extended superior approach, a possible damage to supraorbital and supratrhroclear bundles can lead to forehead numbness. Corneal abrasion and damage is a possible risk and can be prevented with adequate tricks. Post-operative bleeding and an eventually associated compartimental syndrome (with sight-threathning condition) are rare but possible in transorbital "corridor" surgery, requiring promt management and decompression. All these aspects should be discussed extensively with the patients, and all the possible alternatives taken into considerations.

Clinical examples

In Figure 4 we show a right spheno-orbital meningioma treated with a multiportal transnasal-transorbital endoscopic-assisted approach.

Conclusions

In conclusion, the superior eyelid endoscopic-assisted approach may be considered as a safe and promising approach to selected disease of the infratemporal, anterior and middle cranial fossa. And the multiportal approach, moreover, may overcome the limits of a single procedure, offering a multiperspective view of the spaces and the possibility to

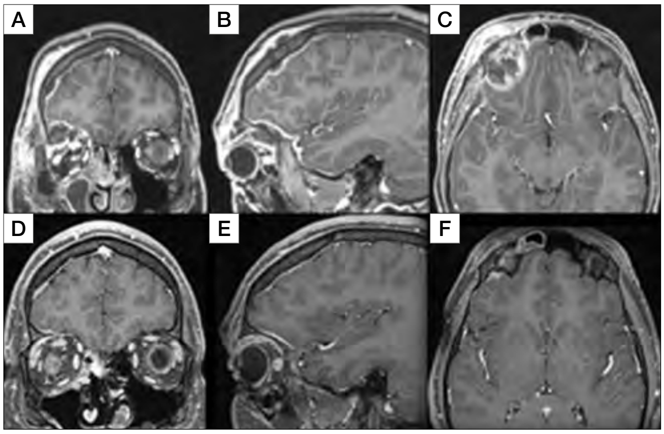

Figure 3. MRI-based evaluation of a right orbital and epidural abscess. In **A**, **B** and **C** the pre-operative findings. In **D**, **E** and **F** the post-operative imaging after a superior eyelid approach to orbit and anterior cranial base.

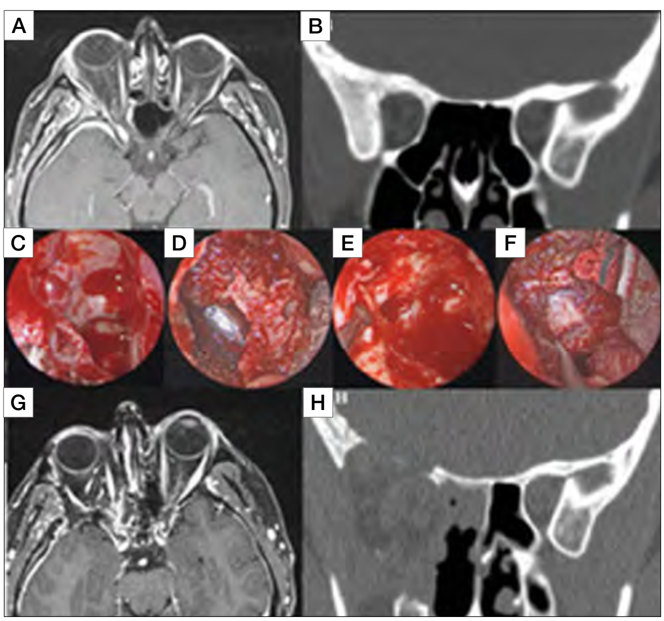

Figure 4. Multipanel figure showing the radiological pre- and post-operative imaging (**A-B**; **G-H**) and the intra-operative endoscopic view (**C-F**) of a right spheno-orbital meningioma treated with a multiportal transnasal-transorbital endoscopic-assisted approach.

perform a 360° approach to complex skull base lesions. When approaching this kind of patient a multidisciplinary evaluation and management is strongly advisable, since the merger of the different skills fits much better with the need of the patient.

Anyway, in our opinion, there is no better approach over another and the choice must always consider several elements such as the surgeon's confidence and preference, the location of the disease, the purpose of surgery.

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When is a multidisciplinary approach required in management of intracranial complications of sinonasal inflammatory disorders?

Quando è richiesto un approccio multidisciplinare nella gestione delle complicanze intracraniche delle patologie infiammatorie nasosinusali?

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SUMMARY

Intracranial complications of sinonasal inflammatory disorders are relatively unusual but can cause significant morbidity and mortality. They often occur in patients with comorbid disorders and immunocompromised but also people without risk factors can be affected. Intracranial complications of acute rhinosinusitis are rare, probably due to oral antibiotics availability, but are less predictable as they often occur in immunocompetent patients without comorbidity. Their management requires a multidisciplinary approach to plan and customize the therapeutic treatment. Intracranial complications of chronic rhinosinusitis are more predictable as they occur often in immunocompromised patient with particularly risk factors. For this reason, a multidisciplinary approach it's important for treatment and mostly for prevention. The aim of this paper is to present an overview of different multidisciplinary management of intracranial complications of sinonasal inflammatory disorders according to their etiology and severity.

KEY WORDS: intracranial complications, rhinosinusitis, multidisciplinary management, nasal endoscopy

RIASSUNTO

Le complicanze intracraniche delle patologie infiammatorie nasosinusali sono relativamente rare, ma presentano un'elevata mortalità e morbidità. Si verificano in soggetti immunodepressi o con diverse comorbidità, ma anche in soggetti immunocompetenti senza particolari fattori di rischio. Le complicanze intracraniche derivanti da rinosinusite acuta sono rare, verosimilmente per la disponibilità di antibiotici per via orale, ma sono le più imprevedibili, poiché spesso si verificano in soggetti immunocompetenti e senza particolari comorbidità. Richiedono una gestione multidisciplinare che coinvolge diversi specialisti per pianificare l'iter terapeutico che deve essere personalizzato in base alla gravità e all'estensione della patologia. Le complicanze intracraniche derivanti da rinosinusiti croniche sono più prevedibili e si verificano in pazienti con particolari fattori di rischio. Per tale motivo è importante per gli altri specialisti riconoscere i primi sintomi per coinvolgere prontamente lo specialista ORL che ha un ruolo importante per la diagnosi e il trattamento chirurgico. Lo scopo di questo lavoro è quello di fornire una panoramica sulla diversa gestione multidisciplinare delle complicanze intracraniche delle patologie flogistiche nasosinusali in base all'eziologia e alla loro gravità.

PAROLE CHIAVE: *complicanze intracraniche, rinosinusite, gestione multidisciplinare, endoscopia nasale*

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Introduction

Sino-nasal inflammatory disorders can potentially spread to any surrounding structures, including orbital and intracranial cavity [1]. Orbital complications are more common but intracranial complications of sino-nasal inflammatory disorders (ICSID) are the most serious and life-threatening.

ICSID are relatively unusual due to the wide availability and use nowadays of antibiotics. However these complication may still occur in the clinical practice and represent a severe condition that can cause significant morbidity and mortality if not promptly recognized [2-4].

ICSID include epidural abscess, subdural abscess, intracerebral abscess, meningitis, and cavernous or superior sagittal sinus thrombosis [5].

In case of intracranial involvement it is vital to achieve an urgent diagnosis in order to start as soon as possible a proper treatment. The management of these cases requires a multidisciplinary approaches in every single phase [6]. Otolaryngologist, radiologist and neuroradiologist, infectious disease specialist, hematologist, neurologist, neurosurgeon, maxillo-facial surgeon/odontologist: all these figures and others can be involved from the diagnosis to the treatment.

Otolaryngologist and neurologist are involved in the clinical diagnosis of ICSID; radiologist and neuroradiologist help to define and locate the primary site of infection and the type of complications; otolaryngologist, neurosurgeon and maxillo-facial surgeon are involved in the surgical management of the patient while infectious disease specialist, neurologist, hematologist and clinicians are involved in the medical management of the infection and patient comorbidities.

There is no universally accepted treatment paradigm for ICSID and that's why the best treatment is probably achieved via an inter-disciplinary perspective [1]. Generally speaking, complications of chronic rhinosinusitis (CRS) are relatively common but ICSID are typically a complication of acute bacterial rhinosinusitis (ABRS) rather than CRS and usually involve indirect spread through hematogenous routes rather than direct spread intracranially through bony defects [7].

Intracranial complications of ABRS

Intracranial complications include Pott's puffy tumor, subdural empyema, epidural abscess, brain abscess, cerebritis, meningitis and cavernous venous thrombosis. They are rare, probably because of the worldwide availability of oral antibiotics, and are estimated at 3 cases per million of population [8]. Nevertheless, complications continue to occur, particularly in children or those individuals who are relatively immunocompromised [7] but can also be seen in adults without comorbidity.

Etiologic mechanisms

Direct and indirect spread are the two major etiologic mechanism described in literature [1,5,9]. Direct spread is less common, it occurs through either a bony defect or infection of bone lying between the sinuses and the intracranial space. The mechanism of indirect spread is thrombophlebitis of the valveless diploic veins that drain the paranasal sinuses. Infection then can spread intracranially either by propagation of the thrombus or by the release of septic emboli [10]. The indirect spread has been most frequently reported in immunocompetent, young male patients. This predisposition is probably related to their highly vascularized diploic venous system that allows indirect intracranial extension through propagation of septic thrombophlebitis [11]. Complications are most often secondary to frontal sinusitis [7], but they can also occur in odontogenic sinusitis [12]. Intracranial complications are relatively rare in pediatric populations and mostly affect older children, probably because the frontal sinuses are the last paranasal sinuses to develop. They are generally detectable after five years of age and are poorly developed until the age of 10 [13]. Usually, polymicrobial infections caused frequently by Streptococcus, Staphylococcus, anaerobic gram-positive cocci, and anaerobic gram-negative bacilli, are responsible for these complications [9,14].

Complications and symptoms

Out of the many intracranial complications of ABRS, subdural empyema is the most common one. It occurs as an extension of acute or subacute frontal sinusitis and mostly affects healthy adults. If a rapid progression of this infection occurs, it can lead to increased intracranial pressure and subsequent neurologic deficits or death. Epidural abscess is the most common intracranial complication of sinusitis in children, symptoms are similar to those of subdural empyema but less severe [3]. Epidural and subdural empyema can spread to the brain parenchyma and cause cerebritis and development of brain abscess. Cavernous venous thrombosis is known as the V stage of Chandler classification as a result of orbital cellulitis, but it can also be a complication of sphenoid, ethmoid, frontal or odontogenic sinusitis as a result of indirect spread mechanism and can lead to the other intracranial complications [15].

Symptoms frequently observed are fever, headache and mental status changes and are related to increased intracranial pressure, meningeal irritation, and cerebritis [15]. Headache is the most common sign of cerebritis, whereas fever and altered mental status are less common. Further neurologic deficits may be identified in accordance with the affected brain area. Finally, many patients can develop seizure activity as a result of increasing intracranial pressure.

Multidisciplinary management

Prompt recognition of intracranial complications of ABRS and multidisciplinary management are extremely important. Imaging is mandatory if central nervous system complications are suspected (CT and contrast enhancement MRI).

Diagnosis and treatment require collaborations between otolaryngologists, infectious disease specialists and neurosurgeons; when there is an odontogenic sinusitis it also include maxillo-facial surgeons/odontologist.

Rapid empiric antibiotic therapy and seizure prophylaxis is indicated:

- penicillins are used to target non-beta lactamase-producing, gram-positive aerobes and anaerobes;
- carbapenems are used for beta-lactamase producing organisms;
- third generation cephalosporins are commonly administered for aerobic gram-negative organisms;
- metronidazole and chloramphenicol, which both penetrate intracranially, provided coverage against anaerobes [16];
- vancomycin is useful in cases of methicillin-resistant Staphylococcus aureus.

In literature the role of neurosurgical treatment with drainage is clear [11,16], both in pediatric and adult patients, and is required early to decrease mortality rate and to reduce persistent neurologic deficit especially in larger intracranial abscesses (> 1 cm). Smaller intracranial abscesses (< 1 cm) can be treated with initial medical management with intravenous antibiotics and serial radiologic evaluation to assess for improvement or progression of disease [11]. They can be followed by radiological evaluations after the onset of empiric antibiotic therapy and can be treated with neurosurgical drainage if there is not a clinical and radiological improvement (Clinical case reported in Figure 1: Male 16-year-old, frontal sinusitis treated at home with antibiotic per OS. Two days after, due to persistent symptoms, was required a MRI that showed a huge abscess in the right frontal lobe. A craniotomic drainage of the abscess was carried out via craniotomic route. A long-time antibiotic therapy was performed with complete symptoms resolution and without neurological sequelae. Endoscopic sinus surgery not performed).

If intracranial complications are caused by odontogenic sinusitis the abscessed teeth should be rapidly extracted and the paranasal sinus drained [12].

The role of Endoscopic sinus surgery (ESS) in intracranial complications of ABRS in controversial. Some authors suggest ESS as an initial management in order to reduce the number of neurosurgical procedures and in some cases to avoid neurosurgical drainage [17-19]. Other studies don't recommend

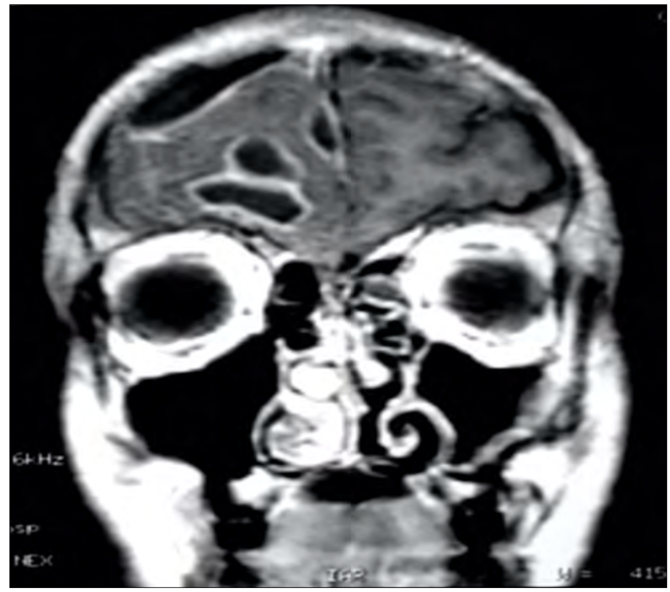

Figure 1. MRI showing a huge abscess in the right frontal lobe.

ESS as the first treatment as it may not prevent neurosurgical drainage and as the most accepted treatment of ABRS is antibiotic therapy with nasal decongestants. Moreover, as most cases of intracranial complications result from indirect spread, can happen that surgical drainage of the sinuses does not seem to have a significant immediate result. On the contrary, ESS is suggested in case of direct spread of the infection from the sinuses to the intracranial space through a bone defect, especially if the defect is near the intracranial abscess [11,20] (Clinical case reported in Figure 2: Male 3-year-old. Frontal-ethmoidal-maxillary right sinusitis with subdural empyema of right frontal lobe. Treated with antibiotic therapy and combined surgery with craniotomy and ESS; complete clinical and radiological resolution). Finally, ESS can also be postponed if, despite medical therapy, there are still clinical and radiological signs of sinusitis and it is useful to avoid recurrence and mucocele (Clinical case of Figure 3: Male 55-year-old, no comorbidity, hospitalized for fever, headache, rapid deterioration of mental status, coma. At CT acute frontal, ethmoid, maxillary sinus sinusitis and ventricular empyema. MRI found out brain abscess with edema. Treated with ventricular drainage, antibiotic therapy, seizure prophylaxis, followed with several radiological evaluations, ESS performed 25 days after symptoms onset to prevent disease recurrence; Clinical case of Figure 4: Male 17-year-old, Frontal sinusitis with pneumocephalus and meningitis. Disappearance of meningitis after medical treatment, at radiological follow-up persistent frontal dysventilation without cerebrospinal fluid leak and pneumocephalus. In a second time performed right frontal sinusotomy with Draf IIa procedure: resection of the floor of the frontal sinus from

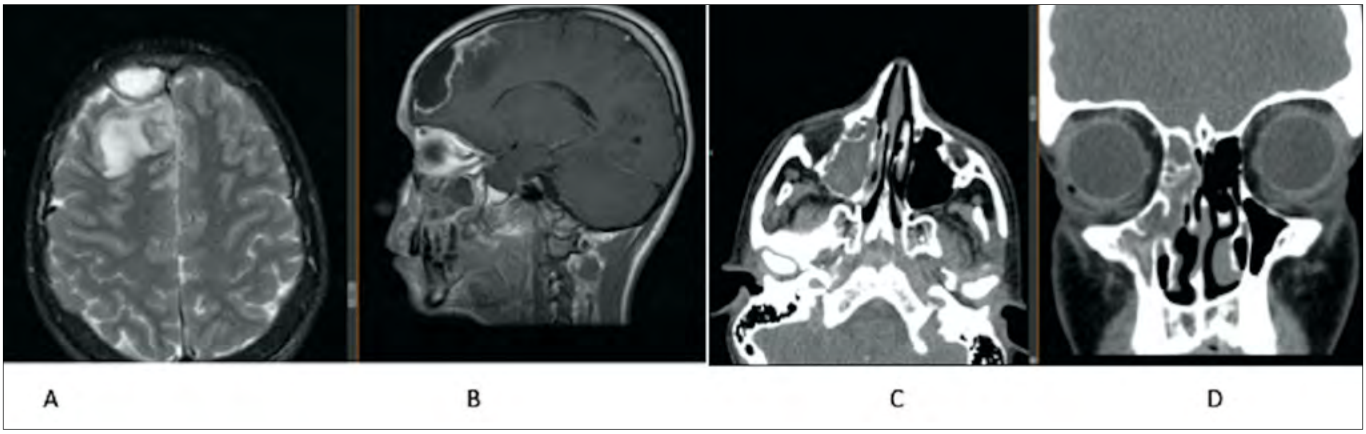

Figure 2. (**A-B**) MRI showing subdural empyema of right frontal lobe; (**C-D**) CT showing frontal-ethmoidal-maxillary right sinusitis.

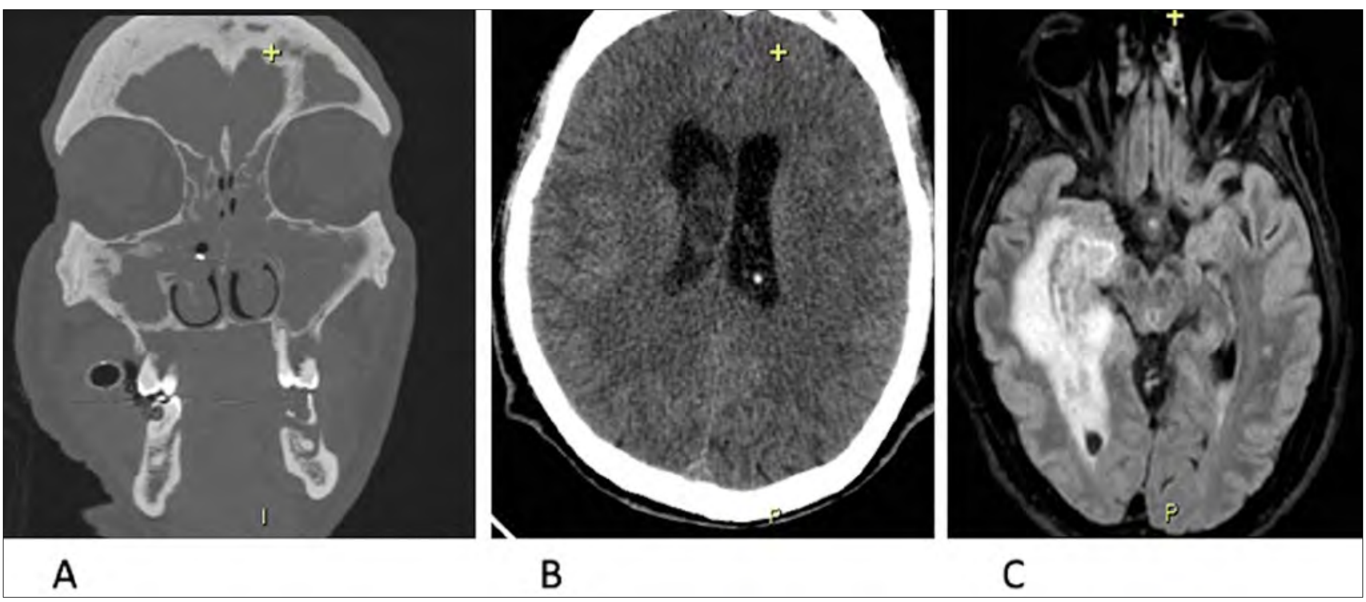

Figure 3. (**A-B**) CT with acute sinusitis (frontal, ethmoid, maxillary sinus; no sphenoid sinus involvement) and ventricular empyema; (**C**) MRI with brain abscess and edema.

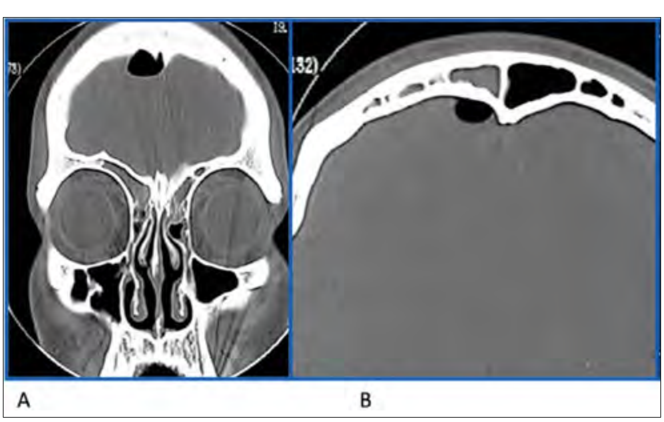

Figure 4. (**A-B**) CT with pneumocephalus and frontal sinusitis.

the nasal septum medially to the lamina papyracea laterally). In Figure 5 we propose a practical algorithm of management of Intracranial complications of ABRS.

Intracranial complications of CRS

Mucoceles and fungal rhinosinusitis are responsible for intracranial complications of CRS.

Mucoceles

Sinus Mucoceles are expansile, mucoid-filled, cyst-like lesions that grow over time, they can completely opacify the affected sinus and can deform surrounding structures [7].

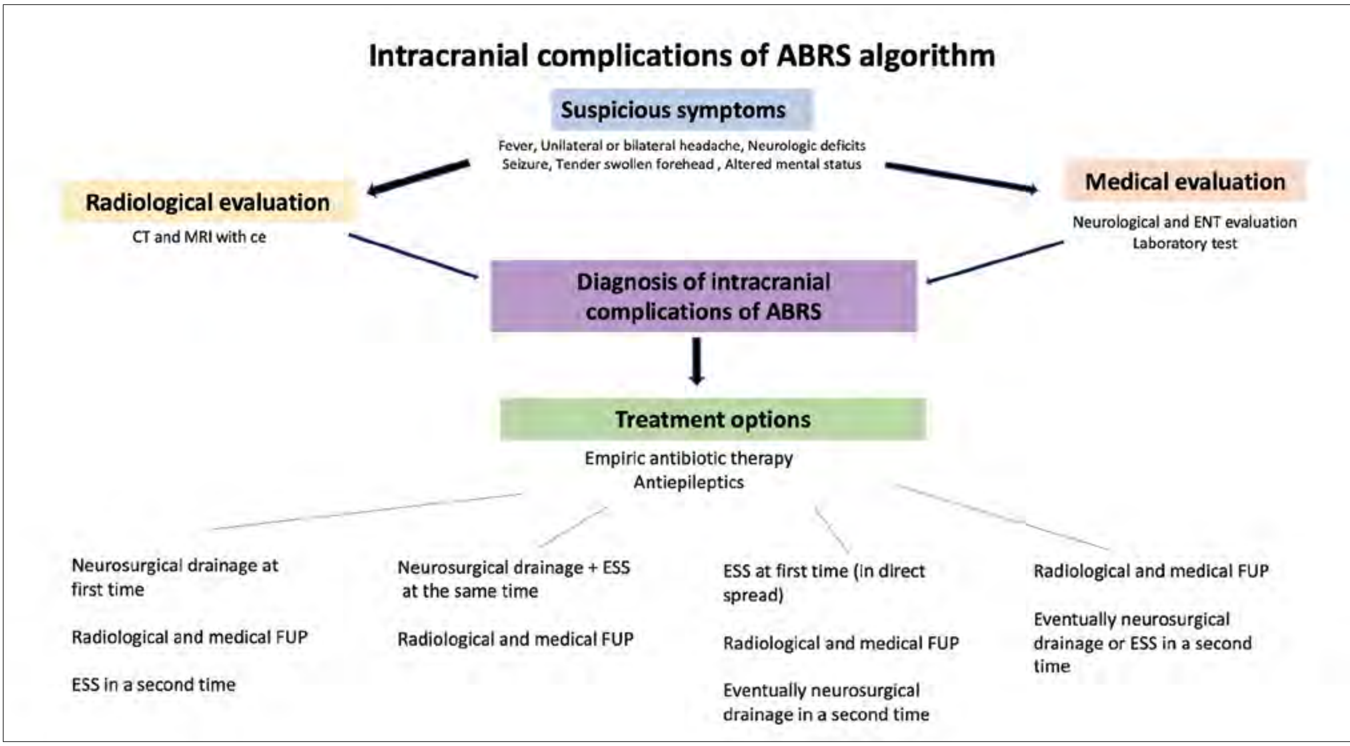

Figure 5. Management of intracranial complications of ABRS algorithm.

They most frequently originate from the frontal and ethmoid sinuses and tend to be unilateral but can be bilateral too [8].

Etiologic mechanism

Mucoceles are caused by trapped mucosal elements in the frontal or ethmoid sinuses after obstruction of the normal pathways of aeration [21]. The obliteration of sinus ostium can be congenital or acquired, it can be caused by allergic rhinitis, post-traumatic event, post-inflammation, post-surgery and infective [22]. Whether there is an infectious etiology or if they become secondarily infected, they are termed mucopyoceles. They grow slowly and their pressure induce necrosis and release of natural osteolytic factors that lead to the destruction of surrounding bony structures [23]. Usually they are diagnosed later in their development, only after orbital or cranial invasion has occurred.

Complications and symptoms

Given the proximity of mucoceles to the brain and to the orbit, significant morbidity and potential mortality may result if these are allowed to grow.

In case of an intracranial extension, they can cause facial pain, headaches, bony erosion of the skull base, leaks of cerebrospinal fluid, brain herniation and infections as meningitis [24,25]. Radiological evaluation with CT and contrast enhancement MRI is mandatory for diagnosis and it is important to plan the surgical treatment.

Treatment

Mucoceles and its complications are treated surgically. Until the 1980s, the only treatment of mucoceles was surgery using an external route, with large incision and osteoplasty, but this technique didn't restore the normal physiological aeration. In recent years there has been an improvement in the management of mucoceles with the use of nasal endoscopy which nowadays can be considered the first option treatment for this pathology. The endoscopic technique is less invasive than the external approach and is successful as it allows the restoration of sinus drainage. It decreases intra and postoperative morbidity, reducing the operative time, allows a larger view of the lesion and surrounding anatomical structures, reduces chances of recurrence but the success rate is strictly linked to the experience of the surgeon. Another approach found in literature is the combined technique (external approach and endoscopy), which can be used in selected and more complicated cases [26], depending on the extension of mucoceles and of its intracranial complications. In case of infections (mucopyoceles and meningitis) it is also necessary to administrate antibiotic therapy (in Figure 6 we propose a practical algorithm of management of intracranial complications of mucoceles).

Intracranial complications of fungal rhinosinusitis (FRS)
Between sinonasal fungal infections the ones that can cause intracranial complications are the allergic fungal rhinosinusitis (AFRS) which are included in the non-invasive variant, and the invasive fungal rhinosinusitis (IFRS).
AFRS occurs in immunocompetent atopic patients with hypersensitivity to fungal allergens and rarely can cause intracranial involvement. AFRS and bone erosion may be more prevalent in younger male patients, and in individuals of African American descent [27,28].
The IFRS can be classified in 3 forms with different clinical and pathologic characteristic depending on the progression of the disease and the immune status of the host [29]. They are categorized into acute invasive form with a course of disease of 4 weeks or less, chronic invasive form and the granulomatous form with a development of more than 12 weeks. These infections occur primarily in immunocompromised patients, with hematologic malignancy, bone marrow transplantation, poorly controlled diabetes, acquired immunodeficiency syndrome, immunosuppressive medications and chemotherapy [30]. Diabetes (50%) and hematologic malignancy (40%) account for 90% of the immunosuppression reported in over 800 invasive rhinosinusitis patients [31]. It is also proved that the extent and duration of immunodeficiency is proportional to the risk of developing IFRS [32].
Although less common, there are also case reports describing these infections in people with normal immune function [33].

Etiologic mechanism
In the AFRS the allergic mucin and polyps form a partially calcified mass obstructing sinus drainage and tend to involve multiple sinuses [34]. As fungal mucin increases, the involved paranasal sinuses begin to resemble a mucocele and bony remodeling, and decalcification may occur with subsequent nasal, intraorbital, or intracranial involvement mimicking malignancy. Causative agents include dematiaceous (Bipolaris, Curvularia, and Alternaria) and hyaline molds (Aspergillus and Fusarium) [35].
In the IFRS species most commonly identified are Aspergillus (flavus, fumigatus, terreus, niger) and fungi of the order Mucorales (Zygomycetes) [36]. Fungal infection begins as mucosal inflammation around the middle turbinate and rapidly spreads to the sinuses. Through direct extension or

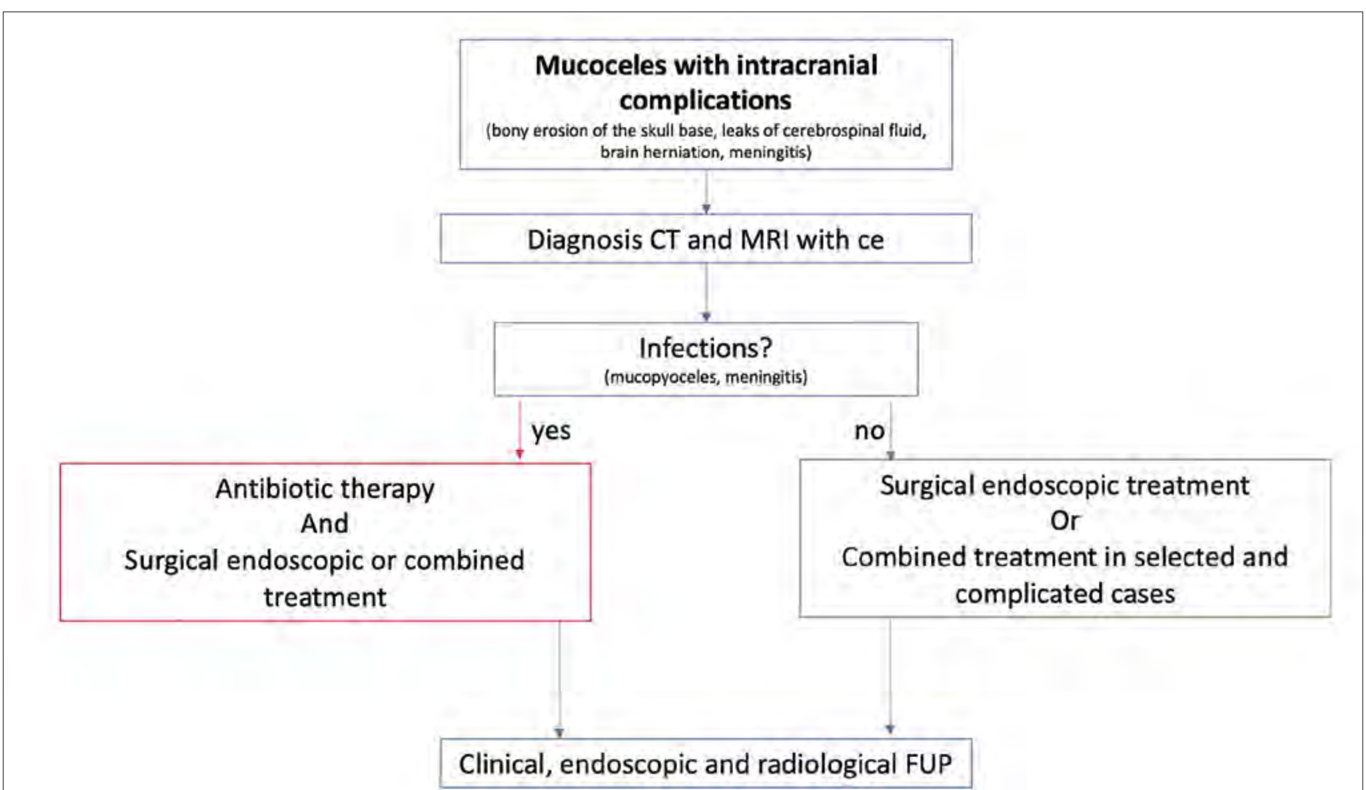

Figure 6. Management of intracranial complications of mucoceles algorithm. ce = contrast enhancement.

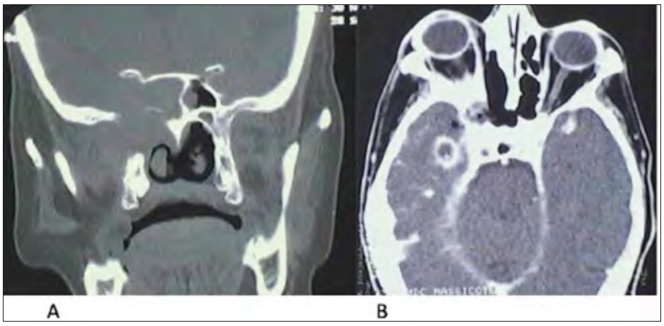

Figure 7. (**A**) CT with pathological tissue in the nasopharynx with invasion of skull base; (**B**) CT with contrast enhancement revealed a right brain abscess.

through vascular spread due to their angio-invasive nature it often extends to skull base and brain causing intracranial complications [37]. Hyphal growth into the vessel lumen causes endothelial dysfunction and thrombosis [35].

Complications and symptoms

Sinus pain, nasal discharge, low-grade fever, and epistaxis are the most observed symptoms. When orbital symptoms, neurologic deficits and altered mental status occur, they suggest an intracranial involvement (Clinical case of Figure 7: Female 75-year-old with poorly controlled diabetes and blindness of the right eye. She came to hospital with right facial nerve paralysis, impaired right ocular motility and glycemia 900 mg/dl. CT and MRI with contrast enhancement revealed pathological tissue in the nasopharynx with invasion of skull base and also right brain abscess. Nasal endoscopy with biopsy revealed a fungal infection. Treated with endoscopic surgical debridement, amphotericin through endovenous administration and restoring normal glucose level with complete resolution of the infectious process).

Intracranial complications include cavernous sinus thrombosis, parenchymal cerebritis or abscess, meningitis, osteomyelitis, mycotic aneurysm, stroke, and hematogenous dissemination [35].

Multidisciplinary management

Diagnosis is made with clinical, radiologic, serologic, and endoscopic data and it should be proven by histologic and microbiological examination.

Nasal endoscopy has shown a good reliability and is very important for an early diagnosis in IFRS [38]. The endoscopic signs of IFRS are commonly located near the middle turbinate, the ethmoid or the septum and include mucosal ischemia, plain necrotic areas with a blackish or grayish color, crusting and absence of bleeding upon scraping. CT is important to show bony changes while contrast enhancement MRI evaluates soft tissue extension and allows a differentiation from neoplastic entities (extremely useful in AFRS). Due to their morbidity and mortality these infections and complications must be urgently recognized to avoid treatment delay.

Diagnosis and treatment require collaborations between otolaryngologists, infectious disease specialists and neurosurgeons; when patients are immunocompromised for hematologic malignancy and bone marrow transplantation it is particularly important that the hematologists promptly recognize risk factor and nasal symptoms (Clinical case of Figure 8: Male, 52-year-old, immunosuppressive therapy for liver transplant. He was hospitalized for mucormycosis with invasion of pterygopalatin fossa, huge frontal abscess and orbital cellulitis. Treated with endovenous antimycotic therapy, endoscopic surgery with aggressive surgical debridement of paranasal sinus and pterygopalatin fossa bilaterally with improvement of symptoms. He died 2 months later for liver failure).

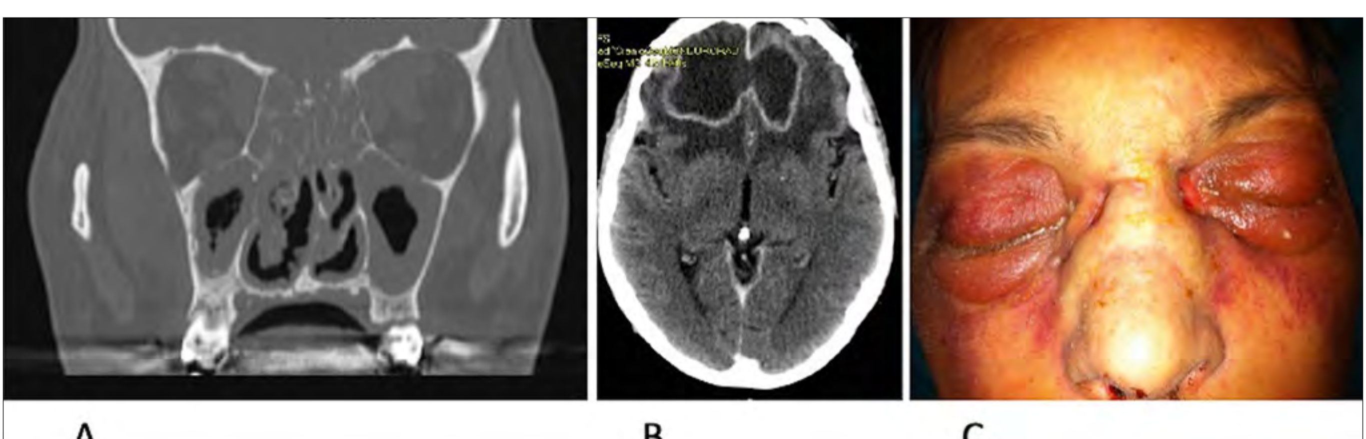

Figure 8. (**A**) CT with mucormycosis of frontal, ethmoidal and maxillary sinuses; (**B**) CT with huge frontal abscess; (**C**) orbital cellulitis.

Table I. Treatment and risk factors of intracranial complication of fungal rhinosinusitis.

	Allergic fungal rhinosinusitis	Invasive rhinosinusitis (acute chronic, granuloumatous)
Risk factors	History of atopy, allergic rhinitis, asthma	Hematologic malignancy, bone marrow transplantation, poorly controlled diabetes, acquired immunodeficiency syndrome, immunosuppressive medications chemotherapy
Surgical treatment	Opening of sinus ostia, polyp and mucin removal	Aggressive debridement
Medical treatment	Oral steroids, topical steroids, antihistamines, leukotriene antagonists	Systemic antifungal treatment

In the AFRS it is important to perform a surgical treatment, to open sinus ostia and remove polyp and mucin, combined with an anti-inflammatory treatment, which include steroids through oral and topic administration, antihistamines and eventually leukotriene antagonists [35].

Regular follow up is mandatory to check assessment of nasal mucosa and for recurrent endoscopic debridement. Postoperative oral steroid therapy is useful to improve symptoms and prevent early recurrences (Tab. I). Extensive AFRS with intracranial complications are still relatively rare [34].

The gold standard of IFRS treatment is surgical debridement and systemic empiric antifungal therapy until the causative fungal species is identified [31,36,38]; the most used are amphotericine and voriconazole [26]. The angioinvasion, thrombosis and resulting tissue necrosis make it difficult for chemotherapeutic agents to penetrate the ischemic tissues, that's why surgical debridement of infected and necrotic tissue is considered an essential component of an optimal management [39] (Tab. I).

These infections represent a life threatening-disease and despite the immediate surgical and antifungal therapy the average mortality remains high when intracranial complications occur. Mortality appears to be related to the extent of disease, with the intracranial extension showing the worse prognosis [31]. Intracranial extension has been shown to be the cause of death in 80% of cases and the infections is considered almost always fatal in presence of intracranial involvement [40].

Conclusions

Whether intracranial complications arise from ABRS or from CRS, they can be life threatening and can significantly impact patient quality of life. Patients with compromised immune system or with multiple risk factors have worse prognosis than immunocompetent patient. Clinicians must be aware of these complications for their potential significant morbidity and mortality, they must promptly recognize symptoms and risk factors to avoid treatment delay.

Intracranial complications of ABRS are not predictable as often occur in patients without risk factors or compromised immune system. Each case must be carefully evaluated, the therapeutic approach must be customized, and a multidisciplinary approach is mandatory as there is not a gold standard treatment.

Mucoceles and AFRS rarely cause intracranial complications and often they are approached with a surgical endoscopic treatment followed by antibiotic therapy in case of infection.

Intracranial complications of IFRS have the worse prognosis as they frequently occur in immunocompromised patients with hematologic malignancies or with several comorbidities. A multidisciplinary approach is important for the treatment and mostly for prevention. The recognition of first symptoms in patient with risk factors is fundamental to avoid treatment delay and to improve the outcomes.

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Critical review of multidisciplinary approaches for managing sinonasal tumors with orbital involvement

Approcci multidisciplinari per la gestione dei tumori nasosinusali con invasione orbitaria: revisione critica della letteratura

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SUMMARY

Orbital invasion is frequently observed in tumors involving the maxillary, ethmoid and frontal sinuses given the proximity of the orbit to the sinonasal tract and ventral skull base. The main objective of the present review is to determine the existing evidences on the frequency, treatment, and outcomes of orbital invasion in benign and malignant sinonasal tumors**.** A systematic review of the literature published from 1995 to 2020 was performed and data sources included PubMed, Cochrane library, NCBI Bookshelf, National Guideline Clearinghouse. Orbital invasion was reported in 2-4% of inverted papillomas, 12-15% of fibro-osseous lesions, 27-32% of juvenile angiofibromas, 35-45% of low-grade malignancies, and 50-80% of high-grade cancers. Surgical resection with negative margins represents the cornerstone of management for benign and low-grade malignant tumors. Histology-specific induction chemotherapy can be used for high-grade sinonasal cancers in order to downstage the tumor and increase the possibility of orbital preservation. When a significant response to induction chemotherapy is observed, exclusive chemoradiation should be offered to improve overall survival rates. Appropriate reconstruction of any surgical defects is essential in order to minimize complications and optimize functional and aesthetic outcomes. Orbital apex invasion represents a negative prognostic factor. In conclusion, a multidisciplinary teamwork is mandatory to maximize local control, minimize morbidity and improve orbital preservation rates.

KEY WORDS: anterior skull base, endoscopic endonasal surgery, induction chemotherapy, orbital exenteration; sinonasal tumors

RIASSUNTO

La vicinanza anatomica dell'orbita con il compartimento nasosinusale e la base cranica giustifica il fatto che un'invasione orbitaria possa essere frequentemente osservata nei tumori che originano dall'etmoide, dal seno mascellare e dal seno frontale. L'obiettivo principale di questa review è quello di analizzare le evidenze scientifiche a oggi disponibili in letteratura circa la frequenza, le strategie di trattamento e i risultati ottenuti nella gestione dei tumori nasosinusali benigni e maligni con invasione orbitaria. È stata condotta una revisione sistematica della letteratura scientifica pubblicata dal 1995 al 2020. Un'invasione dell'orbita è stata osservata nel 2-4% dei papillomi invertiti, nel 12-15% delle lesioni fibro-ossee, nel 27-32% degli angiofibromi giovanili, nel 35-45% dei tumori maligni ben differenziati, e nel 50-80% delle neoplasie maligne scarsamente differenziate. L'asportazione chirurgica radicale con margini di resezione negativi rappresenta il caposaldo per il trattamento delle neoplasie benigne e maligne a basso grado. Schemi di chemioterapia di induzione specifici per ogni sottotipo istologico rappresentano invece il trattamento di scelta per i tumori maligni scarsamente differenziati, nel tentativo di ridurre il volume di malattia e aumentare le possibilità di preservazione del contenuto orbitario. Nei casi in cui si osservi una risposta significativa alla chemioterapia di induzione, un trattamento radio-chemioterapico esclusivo con intento radicale è in grado di migliorare i risultati di sopravvivenza oncologica, lasciando alla chirurgia solo un ruolo di salvataggio in caso di

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persistenza o recidiva di malattia. In caso di preservazione dell'orbita, appropriate strategie di ricostruzione devono essere pianificate durante l'intervento chirurgico al fine di minimizzare possibili complicanze post-operatorie e per ottimizzare i risultati estetici e funzionali a lungo termine. L'infiltrazione dell'apice orbitario rappresenta il fattore prognostico negativo principale nel trattamento di queste neoplasie. Un lavoro di squadra all'interno di un gruppo multidisciplinare è indispensabile per ottimizzare il controllo locale di malattia, ridurre la morbilità per il paziente e aumentare le possibilità di preservazione dell'orbita.

PAROLE CHIAVE: *base cranica anteriore, chirurgia endoscopica endonasale, chemioterapia di induzione, exenteration orbitae, tumori nasosinusali*

Introduction

The proximity of the orbit to the sinonasal tract and ventral skull base facilitates tumoral infiltration of the orbital content via preformed pathways (e.g. inferior and superior orbital fissure, anterior and posterior ethmoidal foramina, nasolacrimal duct), neurovascular structures (e.g. infraorbital and supratrochlear nerves; ethmoidal arteries), or by direct extension through the bone (e.g. lamina papyracea, orbital floor and roof, nasal bones). The periorbit is a highly resistant barrier against invasion but, once the tumor has passed through it, no further barriers are able to prevent orbital content infiltration. Orbital involvement poses unique challenges in the management of sinonasal benign and malignant tumors since the eye represents a borderline anatomical region, between the intracranial and extracranial compartment, containing many neurovascular structures, with also relevant functional and aesthetic implications.

Traditionally, the standard treatment for sinonasal tumors in close proximity to the orbit was radical excision with orbital exenteration [1]. Over the past 20 years, the increased attention to patient's quality of life along with the development of endoscopic surgery and advances in multimodal treatment strategies have led to significant progresses in the management of sinonasal tumors with orbital invasion. As a result, in recent years, treatment protocols including orbital preservation have been increasingly adopted [2,3].

However, there are still several open issues. The definition of "orbital invasion" represents a source of confusion since a universally accepted stratification of the degrees of orbital invasion is lacking. Moreover, data emerging from the case-series available in literature are difficult to compare and sometimes conflicting in terms of surgical and non-surgical treatments adopted, indications for orbital preservation, needs for orbital reconstruction and recurrence rates.

In the present review, we analyze the multidisciplinary approaches currently available for managing benign and malignant sinonasal tumors invading the orbit, in an effort to critically appraise their survival, functional and aesthetic outcomes. The systematic review of the literature was conducted in accordance with current guidelines. Data sources including PubMed, Cochrane library, NCBI Bookshelf, National Guideline Clearinghouse were searched using keywords as follows: "sinonasal neoplasm"; "orbit"; "orbital involvement"; "sinonasal benign tumors"; "sinonasal malignant tumors"; "orbital management". Our research was focused on the time period ranging from January 1995 to June 2020, in order to avoid discrepancy and to promote data consistency. Among the 137 selected articles, only the studies that met the following criteria were included: 1) English language articles; 2) adequate number of patients for significant statistical analysis; 3) appropriate survival analysis to compare data; 4) accurate description of orbital invasion and concerning survival data. Following these inclusion criteria, 21 articles were selected to be reviewed.

Diagnosis

Symptoms can result from orbital compression, nasolacrimal duct obstruction, and real infiltration of the orbital content. Therefore, diplopia, epiphora, chemosis, visual changes, and proptosis may be observed in approximately 50% of the cases [4]. However, the absence of these findings does not rule out the occurrence of tumoral invasion of the orbit. Computerized tomography (CT) of the paranasal sinuses is paramount for identification of orbital bone erosion or reabsorption, and enlargement of fissures and foramina. Moreover, bony lesions such as fibro-osseous tumors can be easily detected using the CT scan. Magnetic resonance imaging (MRI) is superior for analyzing orbital soft tissues, and distinguishing inflammatory secretions (e.g. in the lacrimal sac) from tumor. In addition, by comparing T1-weighted contrast enhanced and T2-weighted sequences, periorbital and extraocular muscles invasion can be distinguished from other changes such as peritumoral edema. The MRI protocol may be further refined by adding dynamic contrast-enhanced (DCE) and diffusion-weighted sequences (DWI) in order to better analyze the interface between orbit and tumor in difficult cases of recurrences after previous surgery and/or radiotherapy [5]. In the suspect of a vascular tumor (e.g. juvenile angiofibroma), an angio-MRI and/or an angiography should be also performed in order to study the distribution of the arterial feeders to the tumor and, possibly, embolize them. With the exception of fibro-osseous lesions and of vascular tumors, where the diagnosis is exclusively based on radiology, all other cases of sinonasal tumors need an endoscopic endonasal evaluation with multiple biopsies to define the tumoral histology and plan the most appropriate range of multimodal treatment. In case of malignancy, neck ultrasound and total body contrast-enhanced CT scan or positron emission tomography (PET) scan are obtained to rule out regional or systemic spread, respectively.

Benign tumors

Benign tumors of the paranasal sinuses are a heterogeneous group of diseases, that reflects the wide spectrum of different tissues present in the sinonasal cavities from which they could originate. Rare pathologies per se, they might involve the orbit in a small percentage of cases, ranging from 2 to 15%; therefore, few data are available in literature (Tab. I). These tumors are generally slow growing lesions that compress without infiltrating the surrounding anatomical structures, invading the orbital compartment by means of bone reabsorption or via preformed skull fissures or foramina. In the majority of cases, the integrity of the periorbital layer is maintained, while the displacement of the orbital content can cause proptosis, diplopia due to extrinsic muscles abnormal mobility, decreased visual acuity until blindness secondary to optic nerve compression, ocular pain and epiphora [6].

The standard treatment of benign tumors is surgical resection, using endoscopic endonasal techniques, transfacial/transcranial resection, transorbital surgery or combined approaches, which could overcome the limits of a single surgical technique in the management of lesions affecting such a complex anatomical compartment. Orbital exenteration is rarely required for benign tumors and orbital preservation is generally obtained. Globally, when selecting the surgical approach, it is necessary to carefully balance the complete excision with the associated surgical morbidity, taking also into account that some selected residual benign tumors, usually tend to remain stable over time.

Fibro-osseous lesions (FOLs)

Benign sinonasal fibro-osseous tumors involving the orbit commonly arise from the frontal and ethmoidal bones, with osteomas representing the most frequent subtypes [6]. While osteomas generally originate or involve the orbital bony walls, without invasion of the orbital contents, other FOLs such as fibrous dysplasia and ossifying fibroma may present higher rates of intraorbital invasion and related clinic [7]. A common feature in this group of lesions is the slow rate of growth, which often makes patients asymptomatic for a long period of time; for this reason, the "wait and scan" policy could be a valid option while the choice of surgical resection should be based on the site of the tumor, its growth pattern as well as on the clinical presentation [8-10]. The endoscopic endonasal technique has been proposed by many authors as a minimally invasive and effective surgical approach to treat these tumors, by using the drill cavitation technique. In this regard, the intraorbital component of the lesion can be used as a corridor to pass through

Table I. Literature review of the main case-series describing treatment outcomes of sinonasal benign tumors with orbital involvement.

Author, year	N. of cases	Histology	Endoscopic or external surgical approach & other treatments	Mean follow-up (months)	Recurrences & persistences/treated cases	Orbital preservation rate
Wang, 2014 [9]	14	Ossifying fibroma	10, EEA (71%) 4, TTA (29%)	25	6/14 (43%)	14/14 (100%)
Ye, 2017 [11]	12	Ossifying fibroma	12, EEA (100%)	43.1	2/12 (17%)	12/12 (100%)
Turri-Zanoni, 2012 [12]	6	Osteoma	4, EEA (66%) 1, EEA+TTA (17%) 1, TTA (17%)	72.6	-	6/6 (100%)
Bertin, 2020 [48]	12	Fibrous dysplasia	6, TTA (50%) 3, Bifosfonate (25%) 3, Wait&scan (25%)	20.8	12/12 (100%)	12/12 (100%)
Ricalde, 2001 [10]	6	Fibrous dysplasia	6, TTA (100%)	NA	NA	6/6 (100%)
Elmer, 1995 [15]	10	Inverted papilloma	2, TTA (20%) 8, Orbital exenteration	51.6	8/10 (80%)	2/10 (20%)
Saldana, 2013 [18]	6	Inverted papilloma	6, TTA (100%) +(3, RT)	22.8	-	5/6 (84%)
Xu, 2012 [23]	18	Juvenile angiofibroma	10, EEA + TTA 8, TTA +(4, RT)	NA	6/18 (34%)	18/18 (100%)

EEA: endoscopic endonasal approach; TTA: transfacial/transcranial approach; RT: adjuvant radiotherapy; NA: not available data.

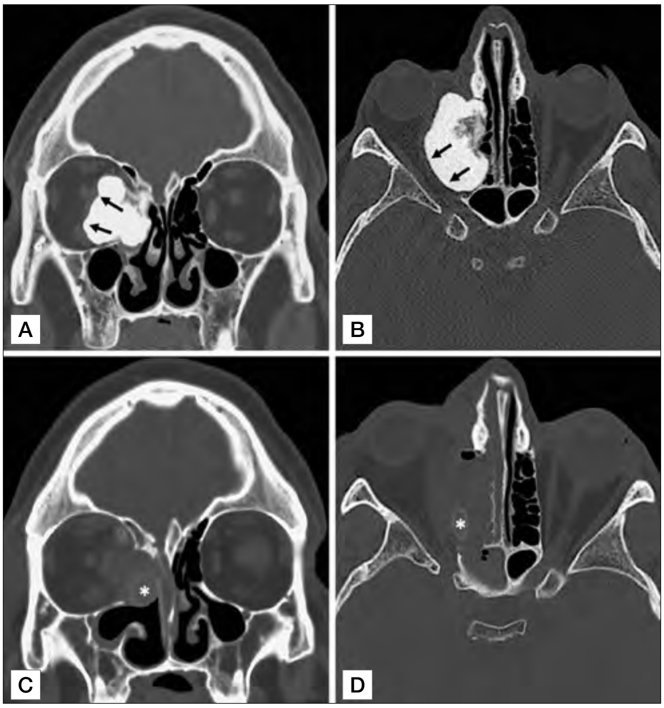


Figure 1. Coronal (**A**) and axial (**B**) CT scan of a 32 year-old male affected by ivory osteoma with right intraorbital extension. White arrows in **A** and **B** highlight the displacement of the extrinsic ocular muscles. The patient was submitted to endoscopic endonasal resection of the lesion using the cavitation technique. The early post-operative CT scan performed 24 hours after surgery (panels **C** and **D**) ruled out any intraorbital complication. White asterisks in **C** and **D** indicate silicon roll sheets placed to maintain the orbital content within the orbital cavity and therefore prevent postoperative sequelae.

without needing to expose all the external boundaries of the lesion (Fig. 1), which could be selectively separated from the orbital periosteum and carefully collapsed and removed [11,12]. Nevertheless, additional external approaches may be required when the tumor extends anteriorly to the nasolacrimal duct or in cases of fronto-orbital tumors not easily manageable with an exclusive endoscopic treatment, as described by Georgalas et al. [8]. In order to achieve complete resection, different approaches through different orbital structures (eyelid, eyebrow, conjunctiva) were successfully employed with minimal residual morbidity and aesthetic defects. In cases with massive involvement of the anterior and/or posterior wall of the frontal sinus, an osteoplastic flap or Riedel-Mosher approach is necessary to reach a complete and safe surgical excision. This is the reason why a teamwork including maxillofacial surgeons, neurosurgeons and ophthalmologists is generally required. Generally, no reconstruction of the orbital walls is performed, except in case of massive removal of the bony orbital floor (more than 50%) [8]. A limited intranasal herniation of the orbital content may occur but the preservation of the periorbital layer prevents diplopia, enophthalmos, or facial deformity; however, in case of major removal of the periorbit or in extensive intraorbital dissection, the placement of a silastic sheet as a protection while pushing the orbital content into the orbital cavity may be sufficient to avoid postsurgical orbital complications and the need for secondary revision surgeries [13]. In some cases of fibrous dysplasia, the lesion may involve the optic canal and orbital apex with optic nerve compression, resulting in progressive loss of visual acuity, color vision and peripheral and central field defects. Although elective surgery is not indicated for asymptomatic cases of optic nerve encasement, due to the potential risk of impaired optic nerve function, an immediate referral for surgical optic nerve decompression should be recommended if there is evidence of visual loss and periodic follow-up is essential to monitor any recurrences [10,14]. It appears clear that such critical patients should be managed in a multidisciplinary way, by means of periodical radiological, ophthalmological and surgical evaluations to define the best treatment strategy.

Inverted papilloma (IP)

Sinonasal IP may invade the orbit in 2-4% of cases, involving frequently also the nasolacrimal system. However, especially in huge tumors spreading into the orbit, it's difficult to define whether the IP has been originated from the lacrimal structures or from the paranasal sinuses, since the nasolacrimal duct also represents one of the most common route of diffusion of sinonasal tumors to the orbit [15,16]. In the largest case-series of IPs invading the orbit currently available in literature, 10 cases were described and foci of malignant transformation were found in all cases, respectively six squamous cell carcinomas and four transitional cell carcinomas [15]. The high rate of malignant transformation observed in IP involving the orbit was confirmed also by other authors reporting smaller case-series [17-19]. Having in mind these critical issues, when dealing with a histologically-proven IP that shows an intraorbital extension at the preoperative MRI, one should keep in mind the possibility that this lesion might harbor foci of malignant transformation. Although in literature the mean recurrence rate is around 5-10% for sinonasal IPs [18], when the tumor invades the orbit the reported incidence of recurrence is considerably higher, ranging from 20 to 80% [18,19]. This finding can be explained by the more frequent occurrence of malignant transformation compared to other IPs. In this regard, Johnson et al. [17] reported four cases of IP with orbital invasion, of whom three experienced recurrences after the initial surgery in a period ranging from 4 months to 6 years; similarly, Elner et al. [15] described a recurrence rate of 80% in a series of 10 cases. Considering such significant rates of recurrences, a multidisciplinary approach is recommended when dealing with sinonasal IPs invading the orbit. The radiologist should be consulted in order to exactly define the grade of orbital involvement and signs of clear infiltration; the pathologist plays a crucial role in analyzing the surgical specimen to find out possible signs of malignant transformation; medical and radiation oncologists should be also included in the design of treatment's strategy whenever cancerization is detected. Few data are available in the current literature about the proper surgical management of these tumors but, taking into account their aggressive behavior, there is a general consensus that aggressive surgical resection is recommended in order to obtain complete removal of the lesion. Radical surgical treatment, even including orbital exenteration, may be required (Fig. 2) [15,18]. No evidences are currently available regarding indications for adjuvant treatments in such cases; however, some authors suggested the importance of adjuvant radiotherapy in case of orbital involvement by an IP harboring signs of malignant transformation in order to improve long-term local control of disease [20,21].

Juvenile angiofibroma (JA)

This vascular tumor is supposed to originate from vascular embryonic remnants in the cancellous bone around the vidian canal and basisphenoid, typically showing an expansive and destructive pattern of growth with spread to adjacent anatomical compartments throughout foramina and fissures. Tumoral extension to the orbit, across the inferior orbital fissure, turns out to be a common finding in advanced staged lesions, ranging from 27 to 32% of cases [22]. Ophthalmological disorders and visual defects are caused by direct compression of the eye, optic nerve and chiasm, with proptosis reported as the most frequent symptom [23]. Considering that JA is a vascular lesion and its surgical removal carries a high risk of profuse bleeding, preoperative embolization is advised in advanced-stage cases, paying special attention to the feeding vessels coming from the internal carotid artery (ICA) which can be more frequently involved when the JA extends to the orbital compartment. Xu et al. [23], in a series of 18 patients affected by JA involving the orbit and optic nerve, described the occurrence of blood supply to the tumor from small arterial vessels branching from the ophthalmic artery, which should be properly recognized by the interventional radiologist and not embolized, in order to avoid vision loss due to central retinal artery occlusion [24]. Different treatment strategies have been proposed in the last decades, such as radiotherapy, chemotherapy and hormone therapy, with little or no success. Surgical excision is considered as the best treatment option, aiming complete tumor excision to avoid persistent disease and therefore

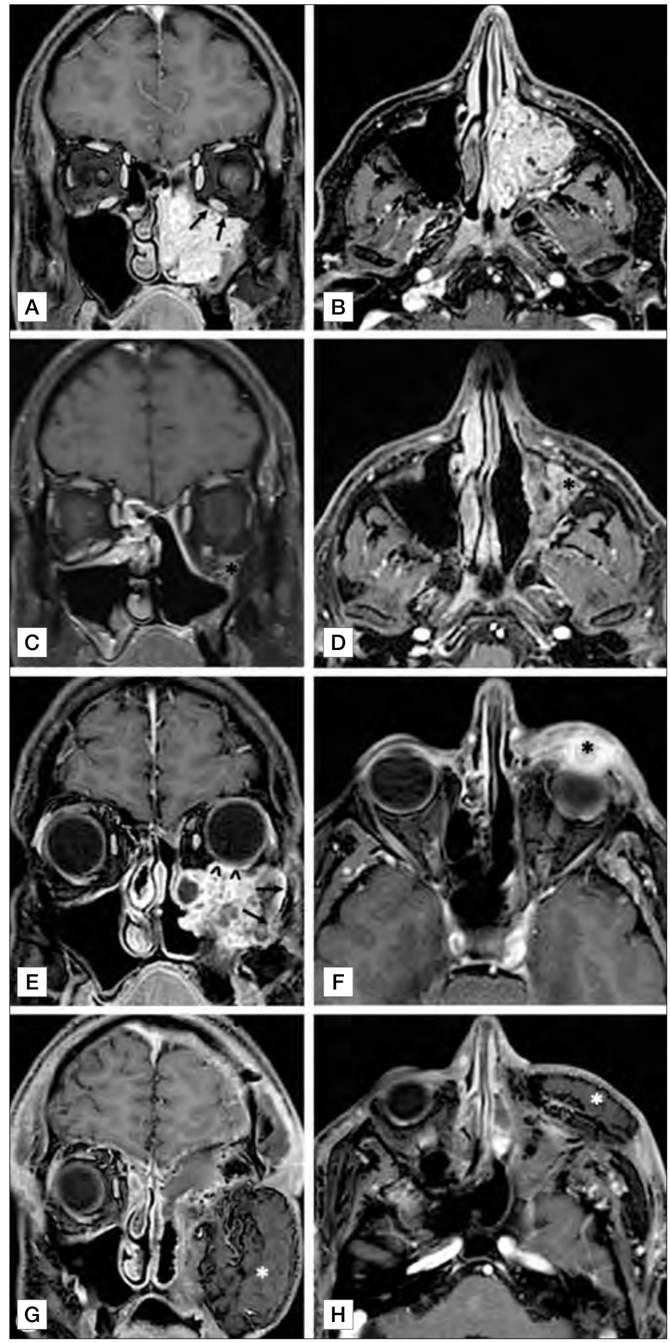


Figure 2. Contrast-enhanced MRI in coronal (**A**) and axial views (**B**) of a 46 year-old man affected by left ethmoid-maxillary inverted papilloma eroding the floor of the left orbit (black arrow in **A**), who underwent endoscopic endonasal resection with left medial maxillectomy type III. Postoperative MRI (**C** and **D**) excluded residual disease with hyperintense signal (black asterisk) at the left orbital floor, interpreted as post-surgical scar tissue requiring close radiological follow up. MRI performed 3 months after the surgery (**E** and **F**) demonstrated an extensive recurrence of disease involving the orbital floor (black arrowheads in **E**), anterior orbital content (black asterisk in **F**), hard palate and lateral bony wall of the left maxilla (black arrows in **E**), thus the patient was submitted to transfacial radical maxillectomy associated with orbital exenteration and reconstruction with an anterolateral thigh (ALT) flap. Final histology revealed an invasive SSC arising on IP. The MRI performed 3 years after the surgery (**G** and **H**) excluded local recurrences of disease (white asterisks indicate ALT flap).

minimize recurrence rates. Nowadays, the increase of endoscopic surgical skills together with advances in surgical instrumentation, imaging and intraoperative surgical navigation systems allows a minimally invasive endoscopic endonasal resection even in advanced staged lesions, like those with orbital involvement. Compared to traditional transfacial approaches, the endoscopic endonasal surgery improves surgical results, with limited blood loss, reduced postoperative sequelae and minimized recurrence rates [25-28].
In the surgical management of JA involving the orbit and orbital apex, particular care must be taken to avoid injury of the optic nerve, III, V2, and V1 cranial nerves. Similarly, adequate endoscopic surgical skills are required in order to manage intraoperative bleeding, especially for tumor feeders originating from the ophthalmic artery, which should be coagulated without damaging any intraorbital neurovascular structures.
Another crucial aspect is the management of a recurrent or persistent intraorbital JA, since tumoral regrowth in such areas has not been described frequently in literature and small remnants might undergo an involution over time. Therefore, in case of a partial resection with a stable asymptomatic intraorbital JA persistence (e.g. inferior orbital fissure), there is not a strict indication for an immediate revision surgery unless there is measurable tumor growth or new symptoms [26].
In the light of all these aspects, JAs should be treated in tertiary-care referral centers, specialized in skull base surgery, by a multidisciplinary team including ENT surgeon, neurosurgeons, ophthalmologist, neuroradiologists and interventional radiologists, in order to achieve best results in terms of complete resection and low morbidity for the patient.

Malignant tumors

Malignant sinonasal tumors are extremely rare, accounting about 3% of all head and neck tumors and less than 1% of all malignant neoplasms. They include a variety of different histotypes with different behaviors, survival outcomes and treatment protocols [29-31]. The most frequentely encountered are squamous cell carcinoma, intestinal type adenocarcinoma (ITAC), esthesioneuroblatoma (ENB) and sinonasal undifferentiated carcinoma (SNUC) [32].
Sinonasal tumors are frequently diagnosed in advanced stages due to their delayed symptoms that easily mimick inflammatory diseases. The incidence of orbital invasion by sinonasal malignancies depends on the site of origin, histology, and aggressiveness of the specific tumor and it is reported between 62 and 82% of all ethmoidal tumors, 55% of maxillary neoplasms, and 46% of nasal cavity tumors [33].
Tumors may invade the orbit through preformed pathways (nasolacrimal duct, orbital fissures, optic canal, ethmoidal foramina), neurovascular structures (infra- e supraorbital nerves) or by direct invasion transgressing surrounding bones (e.g. erosion of the lamina papyracea in most cases) [3,6]. This condition inevitably impacts on survival rate, functional outcomes and therapeutic strategies. It has been widely accepted that the grade of orbital infiltration strongly impacts on prognosis, with worst survival rates in case of extensive orbital involvement [3,34]. Different case series in literature reported 5-year disease free survival of 69% for tumors abutting the lamina papyracea, 51% for tumors invading the periorbital layer, 34% for tumors involving the orbital content and, lastly, down to nearly 0% in case of orbital apex involvement [3].

Grade of orbital invasion

Orbital invasion must be preoperatively graded, by means of an accurate radiological imaging, as minimal (erosion of lamina papyracea, loss of the fat plane between tumor and extraconal muscles, periorbital irregularities) or massive, often accompanied by clinical signs of orbital involvement (proptosis, visual loss, restriction of ocular motility) [35]. The recent 8th edition of the AJCC (American Joint Committee on Cancer) cancer staging system considers orbit involvement as a significant factor upgrading tumor classification: tumor is staged as T3 when invasion is limited to orbital bony wall, as T4a in case of invasion of the anterior orbital contents, and as T4b when the orbital apex is involved. The lack of an officially recognized classification defining the depth of orbital involvement by the tumor poses some challenges. Firstly, comparison of results from different studies can be challenging [29]. Secondly, the lack of a clear definition as to what constitutes orbital invasion has been a source of confusion, and an accurate distinction should be made between bony erosion, orbital soft tissues involvement and apex infiltration. Thirdly, considering that surgical resection has always been considered as the cornerstone in the management of sinonasal tumors invading the orbit, a recognized classification is needed in order to correctly define indications whether to preserve or exenterate the orbit. In fact, orbital exenteration appears to be an invasive procedure conditioning a significant functional defect, esthetic deformity and, consequently, emotional impact [29]. Over the years, different classifications have been proposed, aimed to stratify patients according to tumor aggressiveness and to guide adequate treatment planning (Tab. II) [3,33,36,37]. Current indications for orbital exenteration are: gross orbital contents invasion; extensive infiltration of the extraconal fat, extraocular muscles; intraconal and retrobulbar fat invasion; eye bulb and optic nerve involvement; bulbar conjunctiva or sclera, eyelid, and/or proximal lacrimal path-

Table II. Grading systems of orbital invasion and relative treatments.

Author, year of publication		Grading of orbital invasion	Treatment
McCary et al., 1996 [35]	A	Tumor adjacent the orbit without infiltration of the orbital wall	RT/CT + surgery
	B	Tumor eroding the orbital wall without ocular bulb displacement	
	C	Tumor eroding, infiltrating and displacing the orbital wall without periorbital invasion	
	D	Tumor invading the orbit with periorbital invasion	RT/CT + surgery with resection of involved periorbita (exenteration if extensive involvement)
Iannetti et al., 2005 [36]	1	Erosion or destruction of medial orbital wall	Resection of medial orbital wall
	2	Extraconal invasion of periorbital fat	
	3	Invasion of medial rectal muscle, optic nerve, ocular bulb or skin overlying the eyelid	Orbital exenteration
Neel et al., 2016 [32]	1	Tumor adjacent to orbital wall, which may be thinned, bowed or eroded without periorbital invasion	Drilling and resection of involved bone
	2	Tumor eroding the orbital wall, with resectable periorbital involvement	Resection of periorbita and underlying extraconal orbital fat
	3	Tumor with extraocular muscle, intraconal fat, globe or orbital apex invasion	Orbital clearance
	4	Tumor invading the nasolacrimal system, eyelids duct and/or sac	Orbital exenteration
	5	Tumor with cavernous sinus, optic canal or massive intracranial invasion	Unresectable, pallation
Turri-Zanoni et al., 2018 [3]	1	Erosion or destruction of lamina papyracea	Endoscopic endonasal surgery
	2	Invasion of the periorbital layer and/or focal invasion of the extraconic periorbital fat	
	3	Invasion of the anterior 2/3 of the orbit	Orbital exenteration
	4	Involvement of the orbital apex	Unresectable, palliation

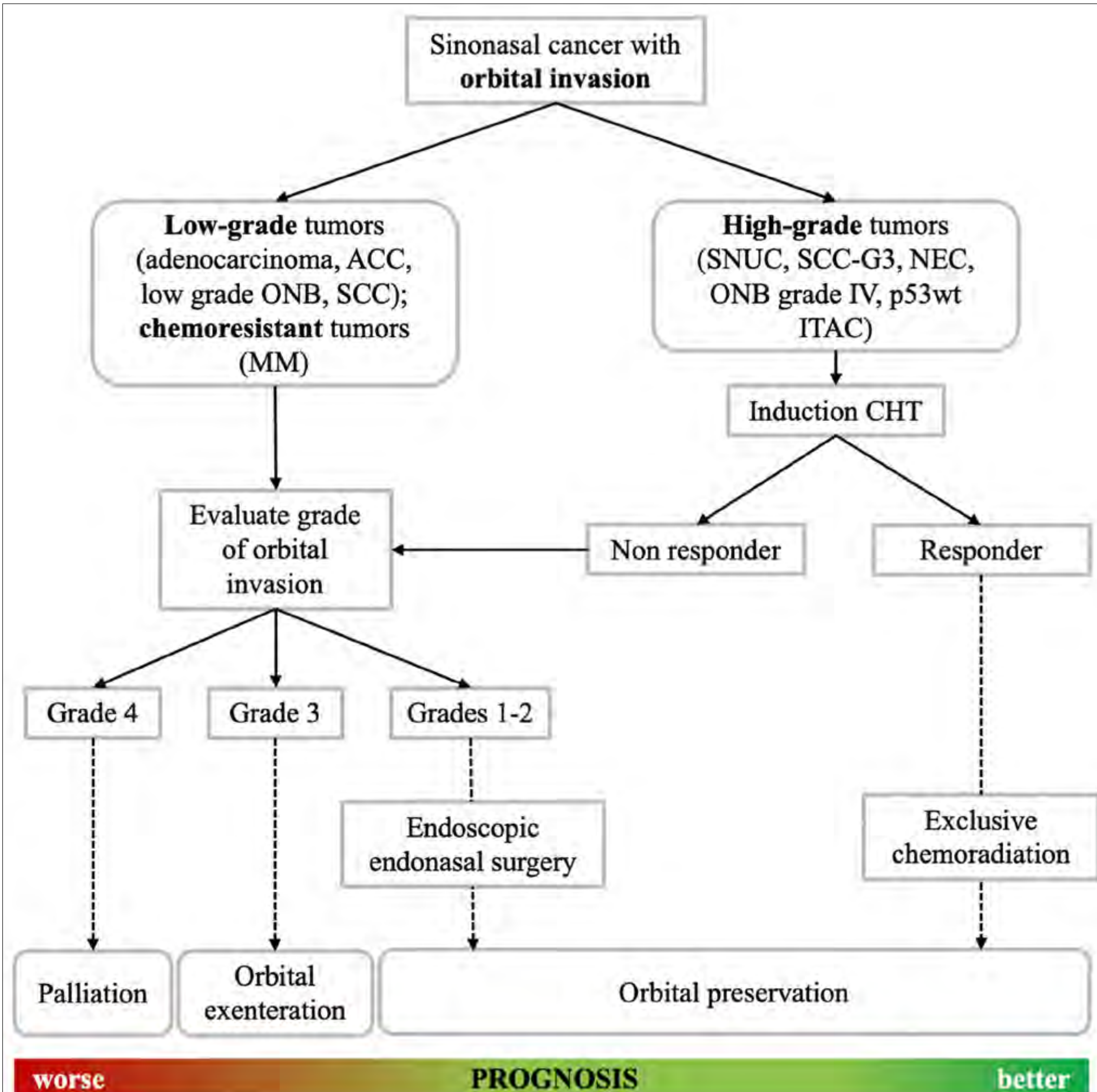
RT: radiotherapy; CT: chemotherapy.

ways infiltration. Although orbital apex involvement has been considered in the last decades as an indication to orbital exenteration [6,30,33], recent scientific reports found that, in such cases, prognosis remains poor regardless the extent of surgery and, in general, any kind of multimodal treatment adopted [3]. Thus, current trends tend to exclude orbital exenteration when orbital apex is massively involved by the cancer.

Management of sinonasal tumors invading the orbit

The gold standard treatment of sinonasal malignancies invading the orbit still remains controversial, and it has been widely debated in recent literature. The main reasons are the small amount of available data and the lack of a standardized universally-accepted classification of orbital invasion, as previously mentioned [29]. Traditionally, the standard treatment of sinonasal tumors invading the orbit was radical excision with orbital exenteration [1]. In recent years, increased attention to patient's quality of life, the refinement of minimally invasive endoscopic techniques and the development of multimodal treatment protocols have led to significant progress in managing such patients, with an ever-growing trend to orbital preservation. Currently, available treatments include surgical removal (via pure endoscopic surgery or open endoscopic-assisted surgery), chemotherapy in an induction or adjuvant setting, and adjuvant radiotherapy. All these therapeutic options must be previously discussed during a multidisciplinary tumor board [3,33].

Based on these assumptions, a histology-driven treatment algorithm has been proposed (Fig. 3) in order to offer tailored therapies to high-grade tumors (poorly differentiated squamous cell carcinoma, neuroendocrine carcinoma, esthesioneuroblastoma Hyams grade IV, sinonasal undifferentiated carcinoma, ITAC p53 wild type) and other specific treatments to well differentiated malignancies (adenocarcinoma, adenoid cystic carcinoma, low-grade esthesioneuroblastoma and squamous cell carcinoma) and to chemoresistant tumors (mucosal melanoma) [3]. High-grade tumors might be submitted to induction chemotherapy [30], up to a maximum of five cycles, conducted with different protocols



ACC: adenoid cystic carcinoma; ONB: olfactory neuroblastoma; SCC: squamous cell carcinoma; SNUC: sinonasal undifferentiated carcinoma; NEC: neuroendocrine carcinoma; p53wt ITAC, p53 wild type intestinal type adenocarcinoma

Figure 3. Flowchart describing the multimodal management of sinonasal cancers with orbital invasion.

based on the specific histotype (TPF, PE/AI regimen, PFL regimen) [3]; the response rate to induction chemotherapy is radiologically evaluated by seriated contrast-enhanced MRI and can be used to segregate "good responders" from "non-responders". Patients achieving complete or good response (> 80% reduction of initial tumor volume) can be treated with exclusive orbital-sparing chemoradiation with curative intent (Fig. 4). Conversely, patients achieving partial response (tumor reduction inferior to 80%), non-responder patients (reduction inferior to 30%), and pa-

Figure 4. Contrast-enhanced MRI in coronal views (panels **A** and **B**) of a 30 year-old female affected by poorly-differentiated small cells neuroendocrine carcinoma, with intracranial involvement (black asterisk) and bilateral orbital invasion (black arrows). The patient received induction chemotherapy (cisplatin/etoposide scheme, 5 cycles) with complete response. The patient was therefore submitted to exclusive chemoradiation with curative intent. The contrast-enhanced MRI performed 2 years after treatment excluded recurrences of disease (**C** and **D**).

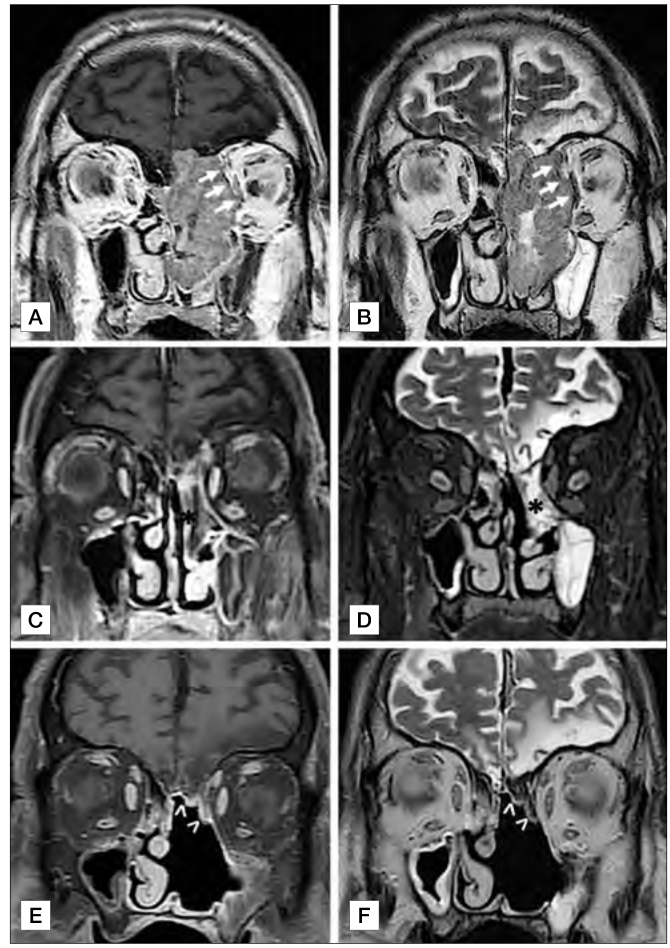
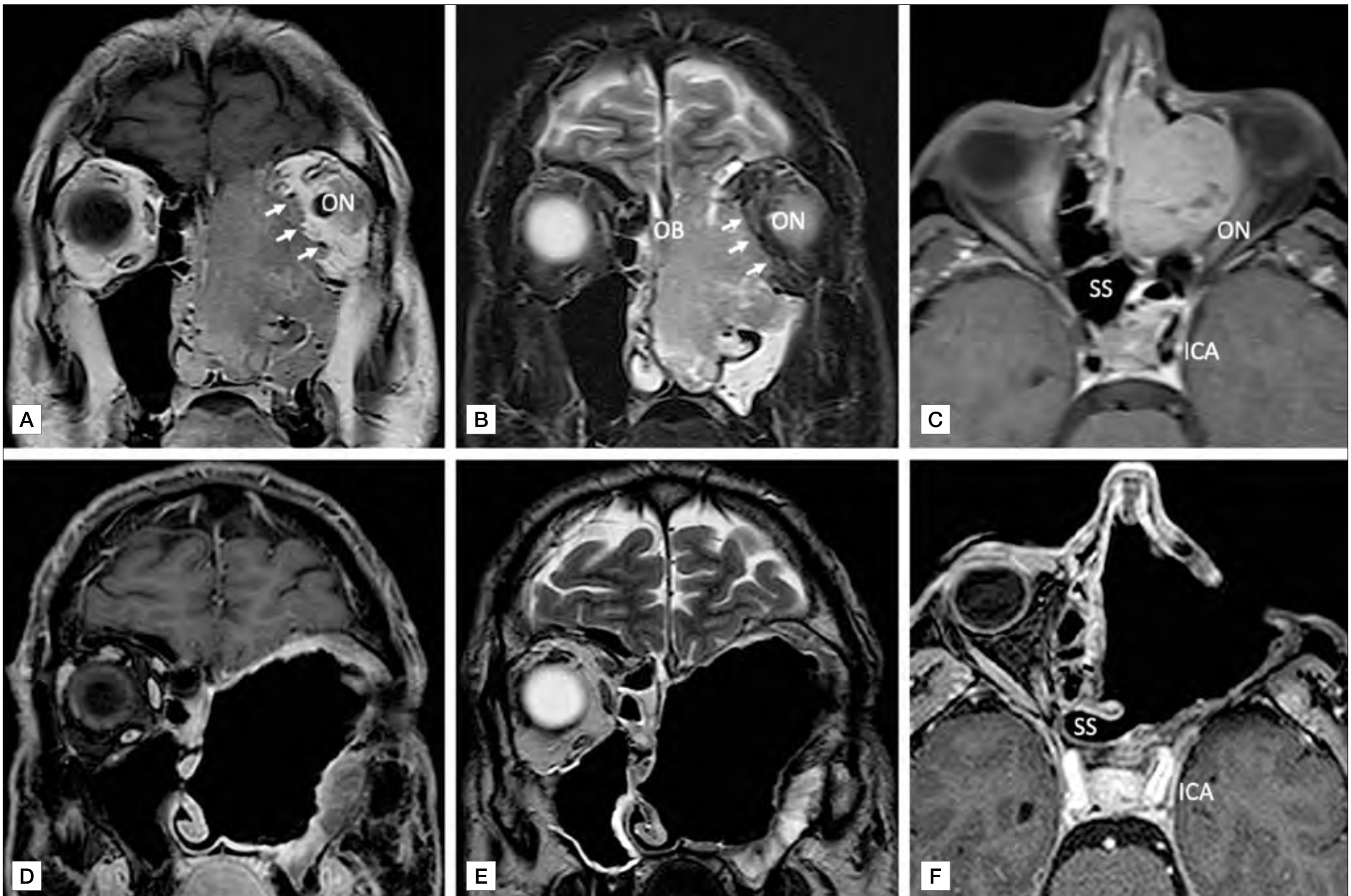


Figure 5. Contrast-enhanced MRI in coronal views (**A** and **B**) of a 69 year-old man affected by locally advanced sinonasal undifferentiated carcinoma involving the left orbit (white arrows). The patient underwent induction chemotherapy (TPF scheme, 5 cycles) obtaining partial response (black asterisks in panels **C** and **D** indicate the persistence of disease). A left unilateral endoscopic resection with transnasal craniectomy and skull base reconstruction (white arrowheads) was performed to remove the residual disease. Finally, the patient received adjuvant irradiation using intensity-modulated radiotherapy (62 Gy). The contrast-enhanced MRI performed 5 years after treatment showed no evidence of disease (**E** and **F**).

tients with disease progression might be directed to surgical resection, followed by adjuvant radiotherapy or chemoradiation (Fig. 5). On the other hand, patients affected by low-grade tumors, chemoresistant tumors, and high-grade tumors non-susceptible to systemic chemotherapy due to age and/or severe comorbidities, can be submitted to upfront surgery. When a surgical resection is planned, an endoscopic endonasal approach must be preferred when feasible, eventually combined with a traditional transfacial or craniofacial surgery in case of massive intracranial or facial skeleton involvement, always respecting the oncological principle of complete excision. The surgical management and the decision whether to preserve or exenterate the orbit, must be carefully discussed and planned according to the extent of orbital invasion. In case of limited orbital involvement (tumor abutting the orbital bones, erosion of lamina papyracea, orbital periosteum, minimal extraconal fat infiltration), an orbital-sparing endoscopic surgery might be adopted and intraoperative frozen sections examination should be used to assess the free-margins resection. Conversely, orbital exenteration should be planned in case of extensive invasion of the extraconal fat, extraocular muscles, intraconal and retrobulbar fat invasion, eye bulb and optic nerve involvement, bulbar conjunctiva or sclera infiltration, eyelid involvement, proximal lacrimal pathways invasion [3,30] (Fig. 6). When dealing with such advanced-stage sinonasal tumors, a postoperative radio(chemo)therapy is adopted almost invariably, according to the final histology report. Orbital apex infiltration by sinonasal cancer deserves separate consideration since it has been reported how orbital apex involvement is dramatically related to poor prognosis regardless the treatment strategy adopted and extent of surgery [3]. A free-margins resection is virtually



Abbreviations: ON: optic nerve; OB: olfactory bulb; SS: sphenoid sinus; ICA: internal carotid artery

Figure 6. Contrast-enhanced MRI in coronal (**A**, T1 contrast-weighted and **B**, T2-weighted sequences) and axial (**C**, T1 contrast-weighted) views of a 51 year-old man affected by locally advanced well-differentiated squamous cell carcinoma involving the left orbit (white arrows indicate medial and inferior rectus muscles infiltration) and encroaching the anterior skull base. The patient underwent a bilateral endoscopic endonasal resection associated with skull base reconstruction and left orbital exenteration, followed by adjuvant irradiation (66 Gy). The contrast-enhanced MRI performed 3 years after treatment excluded recurrences of disease (panels **D**, **E** and **F**).

impossible in such cases due to the complex neurovascular anatomy of this site. Indeed, in such advanced cases, curative treatments are excluded and different forms of palliative surgery and/or chemoradiation should be adopted [3]. Tumors with cavernous sinus invasion, internal carotid artery encasement or massive intracranial involvement should be considered unresectable as well [33,38].

Prognostic significance of orbital invasion

To date, it is widely accepted that orbital invasion by sinonasal tumors affects negatively the survival rates, as summarized by data emerging from the largest case-series currently available in literature (Tab. III). Several worldwide case series have supported the evidence that progressive involvement of the orbital structures decreases survival rates [38-40]. Suarez et al. reported disease-specific survival rates of 41% in patients affected by sinonasal cancers with orbital invasion compared to 75% for those without orbital involvement [38]. Although a clear consensus regarding the oncological safety of orbital preservation has not yet been reached, trends encouraging orbit-sparing surgery are renowned since many years. In this regard, Carrau et al. found that orbit preservation, when a full-thickness periorbit infiltration was excluded, did not downgrade oncological outcomes, while a full-thickness periorbit invasion was associated with a decreased prognosis. Their results suggested that eye preservation, in the absence of orbital soft tissues invasion, did not compromise the local control rate [4]. In 2002, Imola and Schramm reported no differences in terms of survival rates between orbital preservation and

Table III. Literature review.

Authors	N. of cases	Degree of orbital invasion	Treatment strategies	Oncological outcomes	Conclusions
Carrau 1999 [4]	58	36% orbital invasion (bone and soft tissues)	Surgical resection + adjuvant treatment	NED 56% cases after orbital preservation NED 50% cases after orbital exenteration	Orbital sparing is possible when soft tissues are uninvolved, without affecting oncological outcomes
Imola and Schramm 2002 [40]	66	54 pt with bony wall or periorbital involvement 12 pt with intraorbital involvement	Surgery poRT in 44 cases	LRR 29.6% after orbital preservation LRR 33.3% after orbital exenteration	Selective orbital preservation does not seem to adversely affect survival or local control
Iannetti 2005 [36]	29	24.1% medial orbital wall invasion 20.7% extraconal fat invasion 37.9% intraconal or eyelid skin invasion	CFS poRT 37.9%	5y OS 71.4% with medial orbital wall invasion 5y OS 33.3% with extraconal fat invasion 5y OS 50.9% with intraconal fat invasion	Orbital exenteration is necessary in case of intraconal fat invasion
Ganly 2005 [49]	334	33.8% bone 16.5% periosteum 15% orbital contents	CFS poRT 48%	5y DSS 75% with no orbital invasion 5y DSS 40.7% with bone/periosteum invasion 5y DSS 44.4% with intraorbital invasion	Orbital contents invasion was a negative PF in univariate analysis, but not statistically significant in multivariate analysis
Patel 2003 [38]	1306	24.6% bone 10.5% periosteum 22.5% orbital content	CFS poRT 39%	5y DSS 66.2% with no orbital invasion 5y DSS 59.2% with bone/periosteal invasion 5y DSS 48.2% with orbital contents invasion	Orbital contents invasion is a negative PF in univariate analysis, but not statistically significant in multivariate analysis
Howard 2006 [39]	308	No orbital involvement in 56% of pt	CFS Adjuvant treatment 40% (mainly RT)	5y OS 52% with no orbital involvement 5y OS 45% with periosteal invasion 5y OS 14% with orbital involvement	Orbital spread is a negative PF
Suarez 2004 [37]	100	36% periosteum 14% deep orbital involvement	CFS Adjuvant treatment 55% (mainly RT)	5y OS 44% with no deep orbital invasion 5y OS 16% with deep orbital invasion	Deep orbital involvement is a negative PF
Safi 2017 [28]	52	100% invading the orbit beyond orbital periosteum	CFS Surgery + poRT	5y OS 14% after orbital preservation + poRT 5y OS 65.5% after orbital exenteration	In case of orbital content invasion, exenteration shows better survival rate than conservative surgery
Turri-Zanoni 2018 [3]	196	Grade 1: 44 pt Grade 2: 46 pt Grade 3: 49 pt Grade 4: 24 pt	27 pt orb. exenteration 112 pt orb. preservation 5 cases treated with CTRT *Grade 4 patients*: 11 pt orb. exenteration 13 pt orb. preservation	5y OS 84% for grade 1 5y OS 64.1% for grade 2 5y OS 48.9% for grade 3 5y OS 14.6% for grade 4	Orbital invasion represents a negative prognostic factor. Neoadjuvant chemotherapy can downstage the local extension of the tumor and maximize orbital preservation rates Cancers invading the orbital apex must be considered incurable

CFS: craniofacial surgery; RT: radiotherapy; poRT: postoperative radiotherapy; preRT: preoperative radioteraphy; CT: chemotherapy; CTRT: chemoradiotherapy; LRR: local recurrence rate; LCR: local control rate; DSS: disease specific survival; OS: overall survival; NED: non evidence of disease; PF: prognostic factor.

orbital exenteration in patients with tumor invasion limited to the bony orbital walls [41]. In 2006, Howard et al., as well, demonstrated that patients with preserved orbit didn't have worst prognosis when the orbital periosteum was not breached yet by the tumor; thus, removal of the infiltrated periorbit with the conservation of the orbital content could be oncologically feasible [40]. Therefore, sparing the soft tissues of the orbit when the periorbit have not been deeply transgressed by the tumor generally does not appear to adversely affect cure or local control [38]. On the other hand, when dealing with advanced-stage tumors with invasion of the orbit beyond the orbital periosteum, the orbital exenteration is considered as a safe oncological procedure with better oncological rates than conservative surgery [29]. In addition, recent reports have shown how orbital apex involvement appeared to be an independent prognostic factor, negatively impacting the survival rates and precluding any kind of curative treatment [3,33,42]. Turri-Zanoni et al. described 24 patients with orbital apex infiltration by sinonasal cancer, reporting a 95.8% rate of recurrence and death from disease within a mean period of 21 months [3]. Similarly, Nishino et al. described oncologic outcomes of multimodality treatments for patients with advanced-stage malignant tumors with orbital invasion, reporting significantly worse local control rates in patients with disease involving the orbital apex [42]. In conclusion, a multidisciplinary approach is mandatory for the correct management of sinonasal cancers invading the orbit and to thoroughly define precise indications to orbital exenteration.

Reconstruction of orbital defects

The main reconstructive goal is the support and positioning of the preserved eye, since it sits adjacent to the air-filled cavities of the maxillary, ethmoid and frontal sinuses. Other objectives are aesthetic restoration of bony and soft tissue defects, and skull base reconstruction of associated dural defects, when present [43]. Reconstructive options range from no reconstruction to grafts positioning, and, in selected cases, to free flap transfer, based on the extent of resection. Immediate reconstruction is recommended in order to improve healing and mitigate soft tissue contraction, especially if radiation therapy has or will be administered. Isolated papyracea defects and limited bony orbital floor defects, medial to the course of the infraorbital nerve, do not require rigid reconstruction, since the periorbit integrity itself is able to keep the position of the orbital content. Even in case of periorbital defects, the reconstruction is not routinely required since orbital stability is warranted by the intraorbital connective septal system and postoperative scar tissue is enough to restore the orbital continence [44]. To promote such healing process, a U-shaped silastic sheet can be placed to keep the orbital content into the orbital cavity and prevent its prolapse into the sinonasal region [13]. In selected cases, fascial grafts (temporalis or fascia lata), mucoperiosteum harvested from the middle turbinate or nasal floor/septum, or commercially available acellular dermis layer can be used to this purpose [33]. Larger defects involving the orbital floor must undergo rigid reconstruction to avoid post-operative enophthalmos, globe malposition, ptosis, diplopia and ectropion [41]. Titanium mesh or porous polyethylene implants can be used when post-operative irradiation is not scheduled (e.g. benign tumors) while bony free flap (e.g. scapular tip flap, iliac crest and fibular free flap) should be preferred in case of malignancies. Larger resections involving total maxillectomy, skull base removal, orbital exenteration and facial soft tissue removal require both structural and aesthetic reconstruction using distant free tissue transfer, such as chimeric anterolateral thigh flap [45], radial forearm flap or rectus abdominis flap. In addition to flap, prosthetic rehabilitation can be also helpful in these cases to restore form. Secondary procedures may be required for remodeling of the flap's soft tissues and to provide adequate space where prosthetics can be applied.

Functional outcomes

Functional sequelae which may be observed in case of orbital preservation may include enophthalmos, diplopia, lid ectropion, epiphora, canthal dystopia, exposure keratitis and visual loss. Imola and Schramm described a grading system to assess the eye function, which stratified cases as follows: grade I, functional vision without impairment; grade II, functional vision with impairment (chronic ophthalmological sequelae); and grade III, nonfunctional eye (blindness, nonserviceable visual acuity, intractable diplopia, patched eye, or delayed exenteration) [41]. In their study on 54 patients, eye function was reported as grade I in 54%, grade II in 37%, and grade III in 9%. The most common problem observed was orbit malposition due to lack of adequate rigid reconstruction of the orbital floor. However, the enophthalmos was not frequently associated with persistent diplopia, which was reported only in 9% of cases. Similarly, Turri-Zanoni et al. reported a case-series of 125 patients where the orbital preservation was achieved, obtaining functional eye without impairment in 63.2%, functional with impairment in 32.8%, and nonfunctional only in 4% [3]. Both of these studies concluded that postoperative radiation increased the risk of orbital sequelae, especially for optic atrophy, cataract formation, eye dryness, and ectropion. This is supported also by Rajapurkar et al. who described two cases of decreased visual acuity and radiation-induced retinopathy from a series of 19 patients with preserved orbit [46].

Table IV. Summary of evidences available in literature concerning the multidisciplinarymanagement of sinonasal benign and malignant tumours with orbital invasion.

Pathology	Rate of orbital invasion (%)	Multidisciplinary management	Orbital preservation
IP	2-4%	Recommended	Almost invariably
FOLs	12-15%	Recommended	Almost invariably
JNA	27-32%	Recommended	Almost invariably
Low grade cancer *(adenocarcinoma, ACC, low grade ONB, SCC);* chemoresistant tumor *(MM)*	35-45%	Mandatory	Highly selected cases (according to the grade of orbital invasion)
High grade cancer *(SNUC, SCC-G3, NEC, ONB grade IV, p53wt ITAC)*	50-80%	Mandatory	Selected case (according to the response to induction chemotherapy)

IP: inverted papilloma; FOLs: fibro-osseus lesions; JNA: juvenile nasopharyngeal angiofibroma; ACC: adenoid cystic carcinoma; ONB: olfactory neuroblastoma; SCC: squamous cell carcinoma; MM: mucosal melanoma; SNUC: sinonasal undifferentiated carcinoma; NEC: neuroendocrine carcinoma, p53wt ITAC, p53 wild type intestinal type adenocarcinoma.

Epiphora can result from stenosis of the nasolacrimal duct, lid malposition, or dry eye. Andersen et al. reported epiphora in 36% of cases [47] while Imola et Schramm found a decreased epiphora rate of 13% using a prophylactic stenting of the nasolacrimal duct [41].

Conclusions

Sinonasal benign and malignant tumors invading the orbit are rare and difficult to manage pathologies. An appropriate radiologic workup is paramount to assess the grade of orbital invasion and a thorough discussion with an expert radiologist can help in better defining it. To obtain complete excision of the tumor while reducing surgical morbidity and maximizing orbital preservation rates, an effective cooperation between otorhinolaryngologist, neurosurgeon, maxillofacial surgeon, and ophthalmologist is recommended, in order to select the best surgical strategy for each patient in a multidisciplinary perspective, as summarized in Table IV. In addition, based on the biology of the sinonasal tumor to treat, medical and radiation oncologists should be consulted in order to attempt multimodal therapies, including different schemes of induction chemotherapy and specific protocols of adjuvant chemoradiation. Contemporary studies show that invasion of the orbital apex is associated with reduced possibilities of complete tumor excision in both benign and malignant sinonasal tumors and adversely affects survival outcomes in case of cancers. Orbital preservation should be attempted, whenever feasible, and the reconstructive needs should be anticipated and addressed at the time of surgery so as to optimize functional and aesthetic outcomes of the preserved eye.

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Multidisciplinary approach to orbital decompression. A review

L'approccio multidisciplinare alla decompressione orbitaria. Una review

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SUMMARY

Endoscopic orbital surgery has become a highly evolving multidisciplinary surgical field thanks to development in technical skills of ophthalmologists and otolaryngologists. These advances expanded the clinical application of orbital decompression, with a growing body of literature describing the multidisciplinary management of thyroid eye disease and compressive optic neuropathy, since 1990. Although techniques have improved considerably, only few Randomized Control Trials (RCT) provide evidence to support recommendations in clinical practice. This review provides an overview of the current knowledge of orbital decompression to clarify which is the most standardized therapeutic strategy. In the literature, we observed several approaches with contradicting results and the comparison of different surgical techniques was biased by inclusion of patients at different stage of disease (active or inactive), different surgical indications (dysthyroid neuropathy or disfiguring proptosis) and measures of outcomes (such as different system for ocular motility evaluation). The timing of surgical decompression is one of the debated issues. One RCT focusing on Graves' orbitopathy showed how intravenous corticosteroids achieve better visual recovery than surgical orbital decompression; but in case of absent or poor response to medical therapy the patient should undergo surgery within two weeks. There is slight evidence that the removal of the medial and lateral wall (so-called balanced decompression) with or without fat removal could be the most effective surgical technique, with low complication rate, but an increasing number of authors are promoting, for selected cases, a pure endoscopic surgical approach (with removal of medial and infero-medial orbital wall), less invasive than the balanced one; the latter indicated to more severe proptosis or diplopia after endoscopic procedure. Three-wall decompression is chosen for high degrees of proptosis, but complications are more frequent. Timing of surgical orbital decompression, in particular when a concomitant optic neuropathy is present, is still to be determined. Additional ophthalmological procedures are needed to restore normal eye function and cosmesis. Strabismus surgery to address diplopia and lowering the position of the upper eyelid represent some of the additional steps for the final rehabilitation of Graves' orbitopathy. The main clinical outcomes including visual acuity, proptosis, and new-onset diplopia are changing. Recent studies focused on the development of imaging measurements in order to objectively evaluate the surgical results and QOL questionnaires are gaining increasing importance.

KEY WORDS: nasal endoscopy, orbital decompression, thyroid eye disease, compressive optic neuropathy

RIASSUNTO

La chirurgia endoscopica orbitaria rappresenta un ambito multidisciplinare in costante evoluzione grazie allo sviluppo delle tecniche sia in ambito oftalmologico che otorinolaringoiatrico. Tali progressi hanno esteso le applicazioni cliniche della decompressione orbitaria, con incremento del numero di lavori in letteratura, volti a descrivere la gestione multidisciplinare dell'orbitopatia tiroidea e della neuropatia ottica compressiva, a partire

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dagli anni '90. Sebbene le tecniche si siano evolute notevolmente, solo pochi studi controllati randomizzati mostrano evidenze a supporto di indicazioni per la pratica clinica. Questa review fornisce una panoramica delle conoscenze attuali sulla decompressione orbitaria, per chiarire quali siano le strategie terapeutiche maggiormente standardizzate. In letteratura, abbiamo osservato i diversi approcci con risultati contrastanti e il confronto delle varie tecniche chirurgiche è influenzato dall'inclusione di pazienti in stadio di malattia differente (fase attiva o inattiva), da differenti indicazioni alla chirurgia (neuropatia distiroidea o proptosi sfigurante) e metodi di misurazione dei risultati (come ad esempio vari sistemi per la valutazione della motilità oculare). La tempistica della decompressione chirurgica è un altro dei temi ancora oggi dibattuti. Uno studio clinico randomizzato ha mostrato come la terapia steroidea endovenosa consenta un miglior recupero visivo rispetto alla decompressione orbitaria chirurgica; ma in caso di scarsa risposta alla terapia medica il paziente dovrebbe essere sottoposto a chirurgia entro due settimane. C'è una lieve evidenza che la rimozione delle pareti mediale e laterale (cosiddetta decompressione bilanciata) con o senza rimozione del grasso orbitario rappresenti la tecnica chirurgica più efficace, con un basso tasso di complicanze. La decompressione a tre pareti è scelta in caso di proptosi di alto grado, ma le complicanze sono più frequenti. Un numero crescente di autori sta promuovendo, per casi selezionati, un approccio chirurgico puramente endoscopico (con rimozione della parete orbitaria mediale e infero-mediale), meno invasivo della decompressione bilanciata; quest'ultima appare indicata nei casi di proptosi più grave o di diplopia post-procedura endoscopica. La corretta tempistica della decompressione orbitaria è ancora da determinare, soprattutto se presente una concomitante neuropatia ottica. Procedure aggiuntive oftalmologiche sono necessarie per la normale funzionalità e cosmesi. La chirurgia dello strabismo per correggere la diplopia e l'abbassamento della posizione della palpebra superiore rappresentano alcuni dei passaggi successivi per la riabilitazione finale dell'orbitopatia di Graves. I principali outcome attualmente valutati includono acuità visiva, proptosi e diplopia di nuova insorgenza. Studi recenti si focalizzano sullo sviluppo di misurazioni sull'imaging per valutare i risultati chirurgici e i questionari sulla qualità della vita stanno acquisendo importanza sempre maggiore.

PAROLE CHIAVE: *endoscopia nasosinusale, decompressione orbitaria, orbitopatia di Graves, neuropatia ottica compressiva*

Introduction

Orbital decompression may be indicated for patients with orbital abscess, periorbital or orbital hematoma, neoplasm, cosmesis in patients with proptosis for other reasons, but the most common indication for orbital decompression is represented by Thyroid Eye Disease (TED), also called Graves' Orbitopathy (GO).

Unfortunately reaching the cure of GO, defined as both restoration of normal quality of life and complete regression of aesthetic and functional ocular impairment, is a rare occurrence in real-life patients, treated with medical therapy. Although the effort of preventive, immunosuppressive and novel targeted treatment, considering the complex pathogenesis and natural history of GO, the rate of patients that need ocular surgery is still elevated, making surgery a valid and often necessary therapeutic option in the multidisciplinary management of GO [1].

In 1990 Kennedy et al. introduced the transnasal endoscopic approach for orbital decompression.

Since then, endoscopic orbital surgery has become a highly evolving multidisciplinary surgical field thanks to development in technical skills and cooperation of ophthalmologists and otolaryngologists [2].

These advances expanded the clinical applications of endoscopic transnasal orbital decompression technique in the management of TED and compressive optic neuropathy (CON), leading to a growing body of literature in the otolaryngology and ophthalmology communities. In his first study, Kennedy reported a mean improvement of 4.7 mm in Hertel exophtalmometry measurement after inferior-medial wall decompression with transnasal endoscopic technique [2]. However, several early reports of endoscopic decompression described new-onset diplopia in up to 45% of cases [3]. The consequent technical refinement was represented by the preservation of an inferior-medial orbital bone strut in endoscopic orbital decompression that resulted in a considerable reduction in this complication [4]. This technical evolution was the result of a multidisciplinary team-work, as described by Goldberg, Shorr and Cohen in 1992 [5]. In fact, the expertise of otolaryngologist and ophthalmologist permitted to understand the importance of the orbital strut and suspensory ligament complex to preserve globe position after endoscopic surgery. The subsequent step has been represented by the preservation of a medial periorbital strip to reduce the medial rectus muscle prolapse into nasal cavity [6].

What the ophthalmologists earned from endoscopic approach, for example, was the improvement in visualization of the posterior medial wall, limiting the risk of optic nerve injury and maximizing the extent of decompression at the orbital apex: this is of paramount importance in case of rapidly progressive thyroid disease-related optic neuropathy. What the otolaryngologist learned from the oculoplastic surgeon was the direct visualization of the infra-orbital nerve that permits extensive (both medial and lateral to the nerve) inferior wall decompression in case of external transconjunctival and lateral canthal approach. This approach enables simultaneous three-wall decompression also, addressing a balancing effect because both the inferior-medial and lateral wall are decompressed, reducing the incidence of new-onset postoperative diplopia.

Thyroid Eye Disease

Orbital involvement in Graves' disease has a complex pathophysiology, resulting from the deposition of immune complexes that cause oedema and fibrosis of the extraocular muscles and orbital fat. The retro-orbital pressure increases and causes proptosis and exophthalmos, threatening the vision due to vascular impairment or stretching of the optic nerve.

GO, which is the main extra-thyroidal manifestation of Graves' disease, is a rare pathology and still represents a clinical and therapeutic challenge [7].

Although the role of TSH receptor activating autoantibodies (TSHRAb) on orbital adipogenesis has been widely demonstrated in literature, the complex pathogenesis of GO is not clear yet. A new promising pathogenetic mechanism has been recently discovered, based on an active "cross-talk" between TSH-R and IGF-1R in thyrocytes and orbital fibroblast, which lead to activation of an IGF-1R-dependent downstream intracellular pathway. Although GO is present in about 25% of Graves' Disease cases, fortunately, the sight-threatening variant is a rare occurrence [8].

Therapeutic management of TED

According to the recent Guidelines, the therapy of GO has to be gauged on two main parameters, Severity and Activity, which can be evaluated through validated scores, such as NOSPECS and Clinical Activity Score (CAS) [9]. The EUGOGO classification defines disease severity as sight-threatening, moderate-to-severe, and mild Graves' Orbitopathy [10] (Tab. I).

In case of mild GO, an oral daily dose of 200 mcg of Selenium appears to be effective as maintenance therapy, although its role in preventing orbitopathy has still to be clarified [11]. Furthermore, local measures, such as teardrops, ointments or gel, appear to be useful, particularly in alleviating ocular dryness or foreign body sensation. If diplopia impacts on the quality of life, using corrective prisms may be a valid option. Botulin injection has been tested too, with apparently transient benefits in reducing eyelid retraction [12].

Intravenous high-dose glucocorticoids represent the therapeutic cornerstone of Active GO. Indeed, in moderate-to-severe active GO, the first line approach consists in intravenous methylprednisolone, administrated weekly at initial dose of 0.5 g for 6 weeks, then 0.25 for other 6 weeks (4.5 g cumulative dose). This therapeutic scheme appears to have higher efficacy and fewer adverse effect then glucocorticoids oral administration. The optimal cumulative dose appears to be 4.5-5 g of methylprednisolone, but higher doses (up to 8 g) can be used for more severe forms [13]. Patients with sight-threatening GO, due to Dysthyroid Optic Neuropathy (DON) or severe corneal exposure, should be rapidly treated with high doses of intravenous glucocorticoids as first-line treatment. A commonly used regimen consists of giving 1 g of intravenous methylprednisolone for three consecutive days, that can be repeated on the subsequent week. It is important to strictly control clinical conditions because in case of absent or poor response, the patient should undergo orbital decompression within two weeks [9] (Fig. 1, Tab. II).

However, to achieve the reduction of relapse rates and the optimization of the final results, it seems necessary to resort to combinations of other current therapies, as the active disease could last 1-2 years and often a relapse occurs upon withdrawal of glucocorticoids [14].

Radiotherapy

Orbital radiotherapy, usually with a cumulative dose of 10 to 20 Gy per orbit, can be used as second-line therapy, when GO results to be still active after glucocorticoids treatment, particularly in case of diplopia and motility disorders. In randomized clinical trials, radiotherapy appeared to be as effective as oral glucocorticoid therapy and may have a synergic effect if combined with intravenous steroids. Although data on safety seem to be reassuring, further studies are needed to assess the real long-term effectiveness and safety, because of controversial for the theoretical concerns about carcinogenesis, especially for younger patients, and other side effects such as retinopathy and cataract [15-17].

Antiproliferative agents

Mycophenolate mofetil (MMF) inhibits the proliferative

Table I. Severity classification in Graves' Orbitopathy, recommendations and levels of evidence (from EUGOGO [10]).

Classification	Recommendation	Level of evidence
Sight-threatening GO: DON and/or corneal breakdown	Immediate intervention	IV, C
Moderate-to-severe GO: eye disease with sufficient impact on daily life (lid retraction $\geq$ 2 mm, exophthalmos $\geq$ 3 mm, moderate or severe soft tissue involvement)	Active: immunosuppression Inactive: surgical intervention	IV, C
Mild GO: minor impact on daily life (minor lid retraction< 2 mm, exophthalmos < 3 mm, mild soft tissue involvement, transient or no diplopia, corneal exposure responsive to lubricants)	Local measures to alleviate symptoms	IV, C

DON: Dysthyroid Optic Neuropathy; GO: Graves' Orbitopathy.

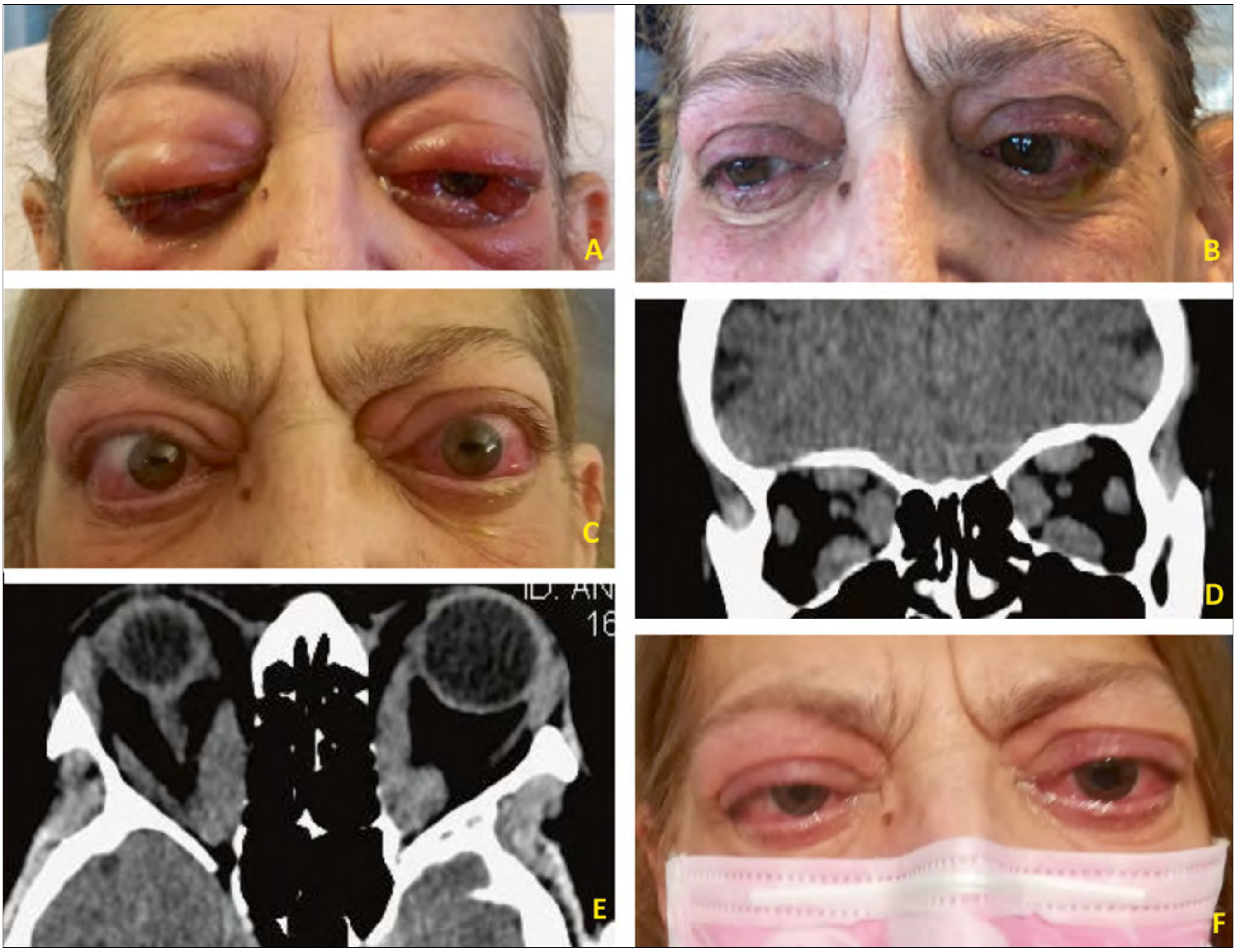

Figure 1. 63-year-old female patient, smoker, affected by active, sight-threatening GO, treated with administration of 1 g of intravenous methylprednisolone for three consecutive days. (**A**) Patient before therapy. (**B**) Two weeks after therapy. After thyroidectomy, a better control of hormonal levels was achieved. (**C**) Two months later, her visual acuity worsts to right eye: 4/20 left eye: 3/20 with anomalous colour vision test (dysthyroid optic neuropathy). (**D-E**) On CT-scans images, all the EOMs are enlarged with apex crowding. (**F**) After endoscopic bilateral endonasal optic nerve and medial wall decompression the visual acuity has greatly improved, and a 4 mm of proptosis reduction.
CT: computed tomography; EOMs: Extraocular muscles; GO: Graves' Orbitopathy.

responses of T and B lymphocytes and has a mechanism of a direct effect on orbital fibroblasts [18]; Cyclosporin, inhibits calcineurin pathway reducing IL-2, that is highly produced by T-cells activated in GO. Both MMF and Cyclosporin showed benefit in ocular symptoms and quality of life [19]. Methotrexate and Azathioprine have also been evaluated for utility in GO management as steroid-sparring agents, but more data are needed [20].

Targeted therapy

Several monoclonal antibodies have been tested as novel therapeutic options in second-line treatment for Active GO. Tocilizumab, a humanized monoclonal antibody directed against the IL-6 receptor, showed efficacy in terms of activity reduction [21]. A multicentre, randomized, trial versus placebo, showed that the use of tocilizumab in glucocorticoid-resistant GO showed a reduction in Clinical Activity Score (CAS) of at least 2 points, improvement in EUGOGO ophthalmic score and a bigger reduction of exophthalmos [22]. Most adverse effects tend to be mild and transient; however, a consistent risk of developing opportunistic infections has been noted during treatment for rheumatoid arthritis and need to be monitored [23]. Rituximab is a chimeric mouse-human monoclonal antibody, which targets the

Table II. Glucocorticoids and orbital decompression in Dysthyroid Optic Neuropathy (from EUGOGO [10]).

Management of DON	Level of evidence
GCs and surgical decompression are effective in patients with DON	III, B
High-dose i.v. GCs is the preferred first-line treatment for DON	III, B
If the response to GCs is absent after 1-2 weeks, prompt orbital decompression should be carried out	IV, C
Orbital decompression should be performed promptly in case of DON o corneal breakdown in patients who cannot tolerate GCs	III, B

DON: Dysthyroid Optic Neuropathy; GCs: Glucocorticoids; i.v.: intravenous.

B-lymphocyte antigen CD20. Two clinical trials reported contradictory outcomes: no benefit in one trial, when compared with placebo; a significant improvement in CAS, when compared with intravenous steroids, in the other [24,25].

Indications for surgery

Generally speaking, it is recommended to avoid surgery in Active TED, because it is evident that surgical procedures during this phase may increase orbital inflammation [26].

Urgent indications: surgical indication for orbital decompression can be considered in patients with active GO who are nonresponsive or intolerant to glucocorticoids, if waiting for spontaneous inactivation could be a risk for vision loss [27], in case of CON (estimated incidence 3-9% of TED patients) [28]. In fact, extraocular muscle enlargement could restrict the vascular supply to the optic nerve: this is the most well-accepted mechanism of DON. The diagnosis of DON remains still challenging and controversial, and possible clinical findings are represented by decreased visual acuity, a relative afferent pupillary defect, altered colour vision, optic disc abnormalities and visual field defects. In this case, the amount of orbital wall removal is particularly critical and should be achieved as complete as possible along the intraorbital portion of the optical nerve [29].

Extreme eye proptosis can also determine vision loss: persistent eyelid retraction caused by persistent inflammation and scarring of the eyelid retractors increasing corneal exposure, predisposing patients to ulceration and subsequent vision compromise.

Nonurgent indications: orbital decompression for disfigur-

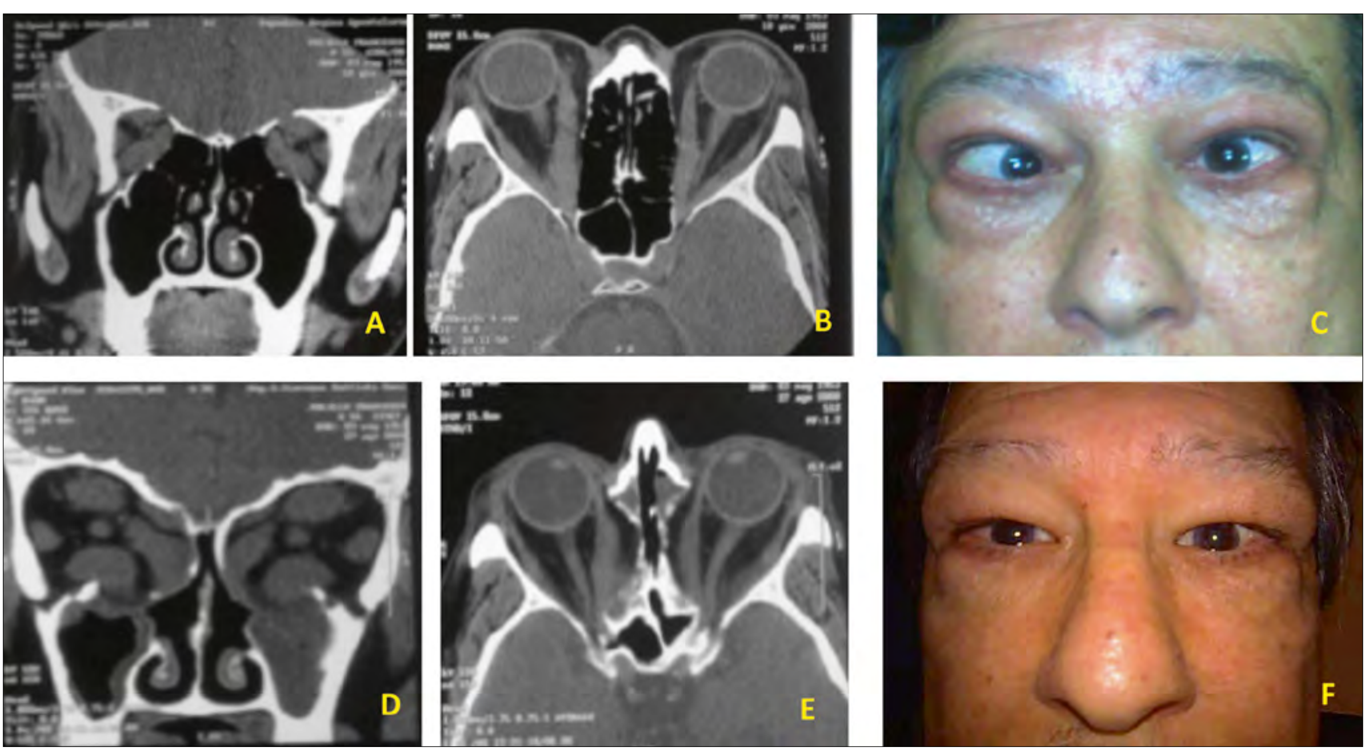

Figure 2. 65-years old, male patient affected by severe TED with proptosis and strabismus. (**A-C**) Pre-operative CT-scan images and appearance. (**D-F**) CT-scan images and appearance after bilateral endoscopic orbital decompression.
CT: computed tomography; TED: Thyroid Eye Disease.

Table III. Timing and the order for surgery in Graves' Orbitopathy (from EUGOGO [10]).

Timing and the order for surgery	Level of evidence
Surgical management should proceed in the sequence: orbital decompression, squint surgery, lid lengthening with blepharoplasty	III, B
Rehabilitative surgery should be performed in patients with inactive GO for at least 6 months	III, B

GO: Graves' Orbitopathy.

ing exophthalmos could be deferred until the orbitopathy has been inactive for at least 6 months [27]. Other nonurgent indications are represented by chronic retrobulbar pain or discomfort, congestion, ocular hypertension and diplopia (Fig. 2).
The majority of patients presents a good response to conservative treatments, only in 5% of cases an orbital decompression surgery is demanded in the 1st year after diagnosis, but in the ten years after diagnosis this rate rise up to 20% [28].
In relation to the staging of the surgical ophthalmic procedures for the rehabilitation of the patients affected by the TED, the decompression should be the first procedure performed, as it can affect ocular motility [30]. This is followed by eyelid surgery, which can be affected by both decompression and strabismus surgery [31]. Some have challenged this paradigm, suggesting that there is minimal change in upper eyelid position with decompression or strabismus surgery and that simultaneous upper eyelid and decompression surgery may be performed in order to shorten rehabilitation intervals [32] (Tab. III).
There are no absolute surgical contraindications to orbital decompression surgery; patients under anticoagulant treatment should discontinue the assumption preoperatively because of the major risk of bleeding intraoperatively that could impact negatively on surgery and the risk of postoperative haemorrhage. When a concomitant paranasal sinuses disease is present (sphenoidal and/or frontal rhinosinusitis), a parallel surgical opening of the involved sinuses could be addressed even if not needed for decompression surgery. Most of the studies show the efficacy and relative safety of orbital decompression [33]; however, the available studies do not allow any meaningful comparison of the available approaches [27]. Orbital decompression can be achieved with different surgical techniques: fat decompression, orbital floor or medial or inferior-medial wall decompression, orbital lateral wall decompression isolated or associated with the other wall decompression [31].

Multidisciplinary surgical approaches in orbital decompression

Transantral

Before the endoscopic era, the Walsh-Ogura transantral approach was the gold standard for treatment of exophthalmos in patients with Graves'disease [34].
This approach started with a sublabial incision in the oral vestibule mucosa, taking care to not injure the infra-orbital nerve during the exposition of the anterior wall of the maxillary sinus. Then an osteoplastic anterior maxillotomy is performed, by the temporary removal of a bony gusset that is replaced with microplates at the end of the procedure. The orbital floor and the lamina papyracea are then exposed and resected, resulting in orbital decompression and subsequent immediate reduction in proptosis.
It is important to preserve a bony bridge together with the infra-orbital canal, avoiding downward displacement of the eyeball and subsequent diplopia.

Complications

- hypoesthesia of the cheek, the lateral nasal ala, and the anterior teeth, due to lesion or temporary stretching of infra-orbital nerve in the bony canal inside the orbital floor or after its exit from the infraorbital foramen;
- paresis of extraocular muscles (inferior rectus, inferior oblique, possibly medial and lateral rectus muscles) and subsequent diplopia, due to lesions to nerve fibres that enter the muscles;
- haemorrhage due to injury to the infraorbital artery or infra-orbital branches of the ophthalmic artery;
- enophthalmos, if the entire orbital floor is resected.

Transnasal (Figures 3 and 4)

The endoscopic transnasal technique starts performing an uncinectomy and a maxillary antrostomy in order to obtain a good exposure of the posterior maxillary wall and orbital floor, and also to avoid obstruction due to inferior dislocation of orbital fat. Then a complete sphenoid-ethmoidectomy exposes the medial orbital wall from the sphenoid sinus down to the crista ethmoidalis and superiorly to the skull base. In some cases, it is possible to realize the resection of the middle turbinate for better visualization with subsequent cauterization of its postero-lateral remnant to avoid postoperative bleeding. The second step of the procedure is the removal of the bone from the inferior and medial orbital wall.
The lamina papyracea is then fractured with a blind dissector and elevated away from periorbita. Bone is thicker in the region of the orbital apex in the proximity of the annulus of Zinn, through which the optic nerve passes and

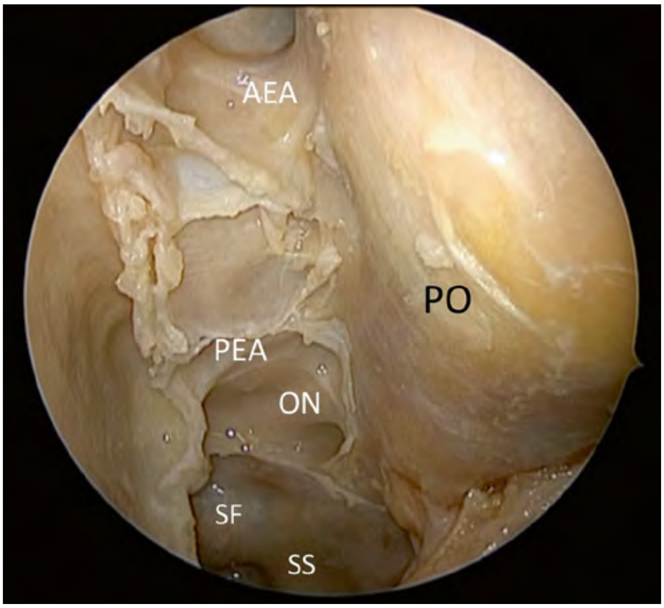

Figure 3. Anatomic dissection showing the periorbit (PO) after complete spheno-ethmoidectomy with the exposure of the Skull base from the I fovea ethmoidalis, anterior ethmoidal artery (AEA), Posterior ethmoidal artery (PEA); to the sphenoid sinus and the following structures: Optic nerve (ON), Interoptic carotid recess and sellar floor Sphenoid Sinus (SS).

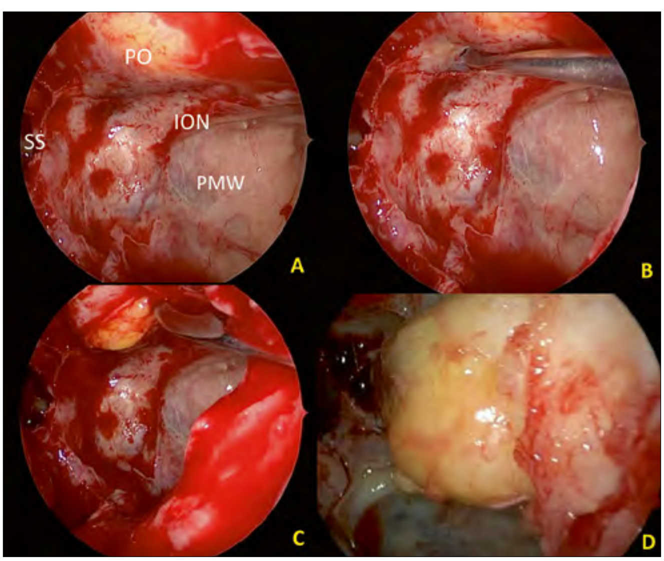

Figure 4. (**A-D**) Intraoperative view of left orbital decompression with the exposure of the sphenoid sinus (SS), Posterior maxillary wall (PMW), infraorbital nerve (ION), with incision of the inferior periorbit and the final fat ernjation.

where four extraocular muscles originate. Then, the periorbita can be elevated off the bony floor of the medial orbit. Only the portion of the floor that is medial to the infraorbital nerve is removed, preserving its canal as the lateral limit of dissection. Moreover, the preservation of a bony inferior-medial strut may reduce postoperative diplopia and help in improving proptosis [35]. The next step is the incision of the periorbita to enable extraconal orbital fat herniation into the ethmoid and maxillary cavities, avoiding lesions to the orbital contents, in particular of the medial rectus muscle. In order to decrease the risk of postoperative diplopia, it could be preserved the periorbital sling that covers the medial rectus muscle, as described by Metson and Samaha [6].

Complications

The more common complications of this kind of surgery include epistaxis, nasal adhesions, sinusitis, worsening of pre-existing diplopia or new-onset diplopia; pre-operative diplopia frequently does not resolve with surgery. Rare complications are represented by injury to the optic nerve and ophthalmic artery; otherwise, cerebrospinal fluid leaks rarely occur [36].

Bony removal, periosteum opening and fat resection

The techniques and extent of bony removal widely differ in the literature. Currently, for the floor the lateral extent removal has been limited to the space medial of the infraorbital nerve [2]. Anteriorly, some suggest leaving 10mm of bone under the globe to prevent hypoglobus [37]. The limits of medial wall removal differ depending on the surgeon and the clinical features. Anteriorly, the maximal extent is classically thought to be the posterior lacrimal crest [2]. Posteriorly, most descriptions involve dissection to the anterior wall of the sphenoid sinus; however, dissection can extend as far as the optic canal [2]. Many endonasal approaches describe canal decompression as part of the management for DON [38].

Superiorly, most authors describe dissection to the frontoethmoidal suture. At this level, it is critical to be aware of the skull base anatomy, as inadvertent entry into the cranial cavity through the fovea ethmoidalis has been reported [39].

Inferiorly, the inferior-medial orbital strut separates the medial and inferior walls and provides structure to the bony orbital cone. Authors have argued that removing this strut is important to allow for complete prolapse of the orbital tissue and maximal decompression. Others have suggested that leaving the strut (or part of it) intact is vital to avoid hypoglobus and important strabismus postoperatively [31,35].

The orbital periostium is unelastic and will minimize prolapse of orbital fat in periorbital spaces. For this reason, some suggest opening periostium completely after the bony decompression.

Other authors have suggested cross-hatching or linear incisions [31].

Extensive opening of the periosteum has been associated with greater rates of postoperative strabismus [37].

Medially, endoscopic surgeons have described the impor-

tance of leaving a strip of periosteum overlying the medial rectus and the inferior rectus to reduce the rate of eye inferior prolapse and strabismus [6].
The infraorbital nerve should be spared to avoid permanent anaesthesia dissecting the orbital floor only medial to the nerve or leaving a bony canal and dissecting on either side [31].

Lateral wall decompression
Lateral orbitotomy is an external approach first described by Krönlein in 1888 and since then has undergone some modifications. The original approach involved a curvilinear incision running towards the lateral canthus from the hairline [31]. Stallard and Wright modified the incision with a more acceptable postoperative scar running through the eyebrow [40]. Berke in 1953 proposed a canthal splitting lateral incision [41], while the first coronal flap to access lateral orbit was described in 1982 by Bonavolonta. Today, the most used approach is the lateral eyelid creased incision that provides excellent access and hides well in the eyelid crease [42].
The skin incision could be performed in the area of the lateral orbital rim, with possibility of injury to the ramus frontalis and ramus ocularis of the facial nerve, or in alternative, a pterional incision into the hairline could be realized without a cosmetic problem.
With a pterional incision, a scalp flap is formed and prepared until the lateral orbital rim is exposed, preserving the lateral palpebral ligament; temporalis muscle that overlies the lateral orbital wall is incised and bluntly pushed away. Microplates are needed for the reconstruction of the lateral orbital rim. With a saw, the bone at the lateral orbital rim is now separated. This is followed by the resection of the lateral orbital wall including parts of the zygomatic bone up to the greater wing of the sphenoid bone in the region of the inferior orbital fissure.
For the reconstruction of the lateral orbital wall, the temporarily separated bone is repositioned and fixed in place by microplates and the temporalis muscle is moved back and fixed. It could be necessary to insert drainage before closure layer by layer of the scalp.

Complications

- blunt shape of the lateral canthus due to detachment of the lateral palpebral ligament from the orbital rim;
- impairment of eye globe motility and diplopia because of injury to the lateral rectus and the inferior rectus muscles;
- anisocoria due to injury of the ciliary ganglion (laterally to optic nerve), during very extensive medial preparation;
- disorder of the mimetic musculature due to injury to the ramus frontalis or the ramus orbitalis of the facial nerve;
- sinking of soft tissue above the zygomatic arch because of incomplete repositioning of the temporalis muscle.

Optic nerve decompression
Many studies have reported the efficacy of medial wall decompression in optic compressive neuropathy. Transcaruncular, transorbital, transantral and endonasal approaches seem similar in the rate of DON improvement reported, range 75-90% [31]. The periosteum was described not incised, incised in the anteroposterior direction, radially incised. Despite the clinical efficacy of the medial wall optic nerve decompression, a few studies focus on pressure orbital changes [43].

Discussion

Most of the literature about orbital decompression consists of retrospective, cohort or case series studies. These papers provide useful descriptive information, but clarification is required to show the effectiveness of each operation related to different indications.
Orbital decompression is achieved by removing bony walls, orbital fat or both. It is an established procedure to correct exophthalmos for visual improvement in patients with optic neuropathy, corneal involvement and for the rehabilitation of patients with marked anterior positioning of the eyes. Several approaches are described with contradicting results, and the comparison of different surgical techniques was biased by inclusion of patients at a different stage of disease (active or inactive), different surgical indications (dysthyroid neuropathy or disfiguring proptosis) and assessment of outcomes (such as a different system for ocular motility evaluation).
The few Randomized Control Trials (RCTs) do not provide robust evidence to support recommendations for clinical practice. There is evidence only from available uncontrolled studies that the removal of the medial and lateral wall (so-called balanced decompression) with or without fat removal could be the most effective surgical technique, related to few complications [44].
The removal of the inferior wall through the antrum and transnasal removal of the medial wall had similar effects in reducing exophthalmos, but the second approach had a lower rate of complications, such as diplopia and infraorbital nerve damage [45].
The timing of surgical decompression is another debated issue and must be related to the failure of medical therapy. One of the few RCTs showed how intravenous corticosteroids achieve better visual recovery than surgical orbital decompression (56 *vs* 17%) [46]. Adverse outcomes were reported more frequently in the steroids group, i.e. weight gain and a Cushing-like syndrome, hypertension and tran-

sient diabetes; while side effects of surgery consisted of transient numbness of the facial skin in 4/14 participants or decrease in extraocular muscle motility. The beneficial effect of I.V. steroids on visual rehabilitation would appear to overcome the increased number of transient side effects in active TED with optic neuropathy.

In case of urgent orbital decompression, the main outcome is obviously represented by visual acuity: different studies have demonstrated high success rates with improvements in more than 82% of patients [28,33].

Medial and inferior-medial wall decompression is advisable in patients with severe posterior optic neuropathy, caused by apical crowding of the enlarged muscles, in particular of medial rectus.

For nonurgent orbital decompression, proptosis is the main outcome, orbital fat removal alone has been shown to reduce proptosis up to 4.7 mm, while decompression of the medial, inferior, and/or lateral walls could reduce proptosis up to 7.4 mm [28,33].

Lateral decompression allows for exophthalmos reduction causing less strabismus, especially with the incision of fascia temporalis. The literature suggests that three-wall decompression is chosen for high degrees of proptosis while two-wall for patients with less exophthalmos; fat removal in addition to bone removal could increase the effectiveness of the procedures [44].

The aim of orbital decompression surgery is not to create the biggest space with disruption of periorbital structures for maximal decompression, but to realize adequate decompression for relief of optic neuropathy or keratopathy caused by severe proptosis [47]. Moreover, cosmesis, was one of the most common indications for surgery and represented an important quality of life issue for patients [48].

Several studies suggest that three-wall decompression achieves the greatest reduction in proptosis but that complications are more frequent; for this reason, more conservative approach, such as balanced medial and lateral wall or endoscopic inferior-medial decompression may be preferable choices. The accuracy of measuring proptosis was also questioned. Although postoperative Hertel measurements were widely reported, they were inaccurate in particular when lateral canthotomy is performed, as these were made with a Hertel exophthalmometer using altered reference points, which may result in overestimation of improvement in proptosis [47].

Interestingly, diplopia can be considered both an outcome and a complication. In every kind of approach, new-onset diplopia could be present at different rates [33].

Many theories have been proposed to understand this phenomenon, for example, removal of the posterior medial wall, removal of the inferomedial strut, and the displacement of the extraocular muscle paths, but no one of these theories has been commonly accepted [49]. It has been suggested that preservation of inferomedial strut and a balanced orbital decompression causes less diplopia and some studies show new onset or worsening of diplopia ranges from 10 to 20% [50-52].

Although, some endoscopic surgeons described lower rates of strabismus with modifications to the periosteal opening medially. Additionally, higher rates of over 30% have been reported for balanced decompression. These rates could be technique dependant, both on the side of balanced decompression and medial decompression alone [31].

Finally, the comparison of induced diplopia rates after different orbital approaches is difficult to perform because of many factors: type of surgical indications, different measurements, the timing of outcome assessment, different criteria to define the condition.

In the study of Mourits et al. [49], authors used two tools to assess diplopia: ophthalmologist and orthoptist and determined clinically whether or not there was diplopia in any direction of gaze, while patients self-assessed their diplopia using the Gorman score. Using these criteria seemed to be a tendency for the swinging eyelid approaches to be associated with less induced diplopia. In the group of three-wall swinging eyelid decompression, the incidence of diplopia decreased, and the Gorman score improved. In some studies, the subjective response to treatment was measured using Terwee's GO-QOL, a validated disease-specific questionnaire to assess changes in visual function and changes in appearance [53].

Various attempts have been made in the literature to study radiographic-based and QOL-based outcomes after orbital decompression, in addition to the evaluation of clinical features.

An objective evaluation could be performed by the imaging measurements of radiographic-based outcomes; recent research has been focused on establishing the validity of an algorithm to determine various parameters, such as the measurement of the angle of the orbital apex, diameter of the extraocular muscles, exophthalmos and orbital volume [54-56].

Unfortunately, the use of radiographic-based outcomes is not assessed, and its specific role in outcome evaluation needs to be determined by further studies aimed to standardize analyzed parameters.

Probably, in the last years, the most important concept about outcome evaluation is the patient's point of view. For this reason, recently, many questionnaires about quality of life have been developed and validated. One of these is represented by Graves Ophthalmopathy Quality of Life (GO-QOL) scale that provides vision-related and appearance-related scores, which were assessed before, 6 weeks and 6 months after surgery [57].

Improvements in eyelid retraction and congested orbit did not predict the change in the appearance-related quality of life. As reported in previous studies, the correlation between clinical changes and quality of life outcomes is weak, also supporting the notion that subjective appraisals of appearance will predict psychological well-being better than clinical measures of severity. For example, patients with strabismus evaluated appearance as more important than other clinical factors [57].

A recent study has examined the impact of orbital decompression surgery on sinonasal-specific QOL evaluated by SNOT-22 administered preoperatively and one year after surgery, that showed a statistically significant improvement in sinonasal-specific QOL, in particular, improvements have been observed in the psychological domains of the test, confirming a preserved sino-nasal function even after fat prolapse into nasal cavities [58].

Conclusions and key notes

TED is the most common indication for orbital decompression in case of failure of medical therapies. The urgent surgical indications are represented by optic neuropathy and severe corneal exposure, while non-urgent surgical indications include diplopia, proptosis, orbital and retrobulbar pain, and ocular hypertension. In the case of optic neuropathy, bony removal in the region of the orbital apex is mandatory, reducing pressure on the optic nerve and leading to improvement in vision in patients with visual loss.

The main clinical outcomes include visual acuity, proptosis, and new-onset diplopia.

Recent studies focused on the development of imaging assessment in order to objectively evaluate the surgical results. QoL questionnaires are gaining increasing importance, based on patients' point of view.

The goal of orbital decompression is the reduction of proptosis, but additional ophthalmological procedures are needed to normal eye function and cosmesis. Strabismus surgery to address diplopia and lowering the position of the upper eyelid represent some of the additional steps for the final rehabilitation of GO.

A balanced decompression (combined external and endoscopic or only external approach) or pure endoscopic approach with the preservation of the anterior inferomedial orbital strut represents the gold standard to reduce the incidence of new-onset diplopia, but RCTs are required to confirm these data. Moreover, the orbital sling technique, obtained by the preservation of a strip of the periorbita overlying the medial rectus muscle is an additional technical trick to reduce diplopia.

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Multidisciplinary approach to lacrimal system diseases

Approccio multidisciplinare alle patologie del sistema lacrimale

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SUMMARY

Pathologies of the lacrimal drainage system range from benign to malignant lesions. However, independently of the etiological origin, the most common presenting symptom is represented by epiphora due to the dysfunction of the lacrimal system. Different diagnostic tools are now available, but for the most the first diagnostic approach is characterized by an ophthalmological visit, associated with nasal endoscopy, usually performed by an otolaryngologist. Frequently the diagnostic work-up is completed with a radiological exam (e.g. maxilla-facial CT or dacryocystography), whose role is still to be determined. Once a diagnosis has been made, different treatments are available in relation to the type of the disease, and commonly need close cooperation between an ENT and ophthalmic surgeon given the close anatomical structures involved. Taking into account all these aspects, the aim of this review is to highlight how a multidisciplinary approach to lacrimal pathologies is mandatory from diagnosis to treatment in order to offer the best clinical approach.

KEY WORDS: multidisciplinary approach, dacryocystorhinostomy, lacrimal pathology, nasolacrimal duct, lacrimal obstruction

RIASSUNTO

Le patologie della via lacrimale variano da malattia di natura benigna a maligna. Indipendentemente dall'origine etiologica, il sintomo di presentazione clinica più frequente è rappresentato dall'epifora, causata dalla disfunzione della via lacrimale. Oggigiorno sono disponibili diversi strumenti diagnostici per questo tipo di patologia ma, per la maggior parte della comunità scientifica, il primo step diagnostico è rappresentato dalla visita oftalmologica, associato a un'endoscopia nasale eseguita solitamente da un otorinolaringoiatra. Frequentemente, questo work-up diagnostico è completato da un esame radiologico (es: Tomografia Computerizzata o Dacriocistografia), il cui ruolo è ancora da determinare. Una volta eseguita una corretta diagnosi, differenti opzioni terapeutiche sono attualmente disponibili in relazione alla tipologia eziologica ed è necessaria, frequentemente, una stretta collaborazione tra otorinolaringoiatra e oculista, dati gli stretti rapporti anatomici delle strutture coinvolte.

Tenendo in considerazione gli aspetti sopracitati, lo scopo della presente review è di evidenziare come l'approccio multidisciplinare alla patologia delle vie lacrimali sia mandatorio dalla diagnosi alla terapia, in modo da offrire al paziente un approccio clinico ottimale.

PAROLE CHIAVE: *approccio multidisciplinare, dacriocistorinostomia, patologia della via lacrimale, dotto naso-lacrimale, ostruzione lacrimale*

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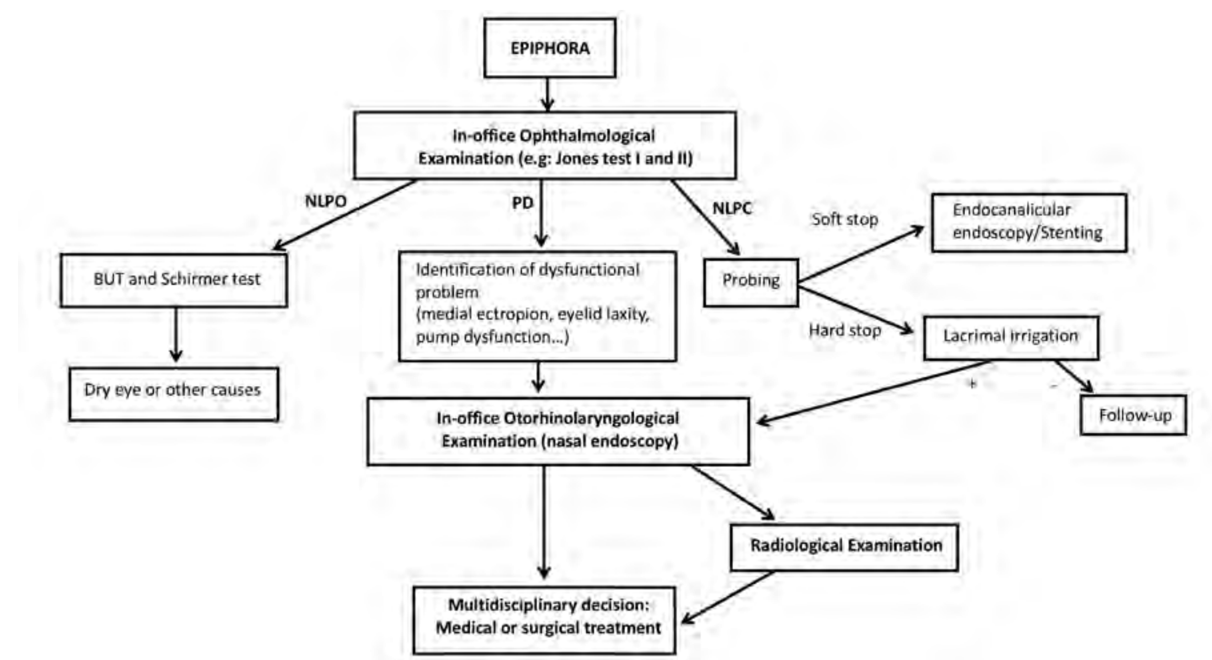
Introduction

The lacrimal drainage system (LDS) is a complex apparatus that is responsible for flow of tears from the eye (medial cantus) to the nasal cavity (inferior meatus). Any pathology of this system usually appears as watery eye, also known as epiphora, which is a common clinical sign that can be caused by different

factors that are mainly classified as reduced outflow (e.g. lacrimal obstruction, eyelid malposition), hypersecretion of tears and reflex tearing [1]. Among all these, lacrimal obstruction is the most common cause and can be distinguished in congenital, if it appears before the first year of life, and acquired forms [2,3]. Additionally, if considered the site of the obstruction, it can also be divided in proximal (punctum, superior, inferior and common canaliculus) and distal (or post-canalicular) lacrimal obstruction, which is the most common [2]. The latter form is most commonly encountered in middle-aged female patients in whom different local and systemic pathologies may cause lacrimal obstruction [1,4-12].
Regardless of its etiology, epiphora has substantial impact on the quality of life, thus making its correct approach fundamental [13,14]. In past years, lacrimal pathologies were mainly managed by an ophthalmologist due to the clinical presentation and the treatments that were available. Nowadays, with the advent of rigid endoscopes, the approach of these types of pathologies has radically changed, leading to cooperation with an otolaryngologist (ENT). Moreover, thanks to this technological implementation, not only has it permitted executing standard dacryocystorhinostomy through an endonasal endoscopic approach (END-DCR), but it has also gained a major role pre-operatively: in fact, endoscopic analyses of the nasal fossa permits direct and optimal identification of surgical landmarks and anatomical variations that can affect the surgery (e.g. nasal septum deviation, paradoxical middle turbinate). Additionally, endoscopic instrumentation can be used post-operatively, thanks to the importance of direct visualization of the healing process. Surprisingly, it has been reported that nasal examination is not usually performed by most ophthalmologists, with potential consequences on treatment outcomes [15].
In the past, several authors have tried to identify the best clinical practice for lacrimal diseases, but no one has taken into account the role of multidisciplinary consultation between an ophthalmologist and otorhinolaryngologist in the management of lacrimal pathologies. The aim of this review is to analyze the role of a multidisciplinary approach to lacrimal pathologies, from the diagnosis to treatment.

Diagnosis

The pathologies that may affect the lacrimal pathway are numerous and differential diagnosis between them can be challenging [16]. The finer aspects of a precise assessment of the lacrimal pathology is beyond the scope of this paper. However, most of the literature agrees that in-office ophthalmologic examination is the first diagnostic step that should be taken in case of suspicion of lacrimal pathologies (Fig. 1) [17]. In fact, clinical examination provides an assess-



BUT: break up time test; NLPO: naso-lacrimal pathways open; NLPC: naso-lacrimal pathway closed; PD: pump defect

Figure 1. Multidisciplinary diagnostic flow-chart for epiphora.

ment of lacrimal structures, eyelids, punctal position, meibomian gland, lacrimal gland and possible pathology of the ocular bulb, providing an initial differential diagnosis of the primary lacrimal pathway pathologies to secondary ones and its potential functional/obstructive nature [1]. Such an initial diagnostic step is a non-invasive, easy and low-cost way to establish an initial diagnosis, and if the result of this examination confirms a pathology of the eyelid, lacrimal gland, ocular bulb or meibomian gland, an otolaryngologist is not always required [16]. On the contrary, clinical examination of the nasal cavities by an otolaryngologist remains of major interest in case of both functional and obstructive lacrimal pathway pathologies [15]. In fact, even if in some lacrimal pathologies, like functional diseases, the available treatments are primarily performed by an ophthalmologist, the role of an otolaryngologist remain fundamental since he can provide an endoscopic assessment of the nasal fossa, excluding any form of influencing factors [15]. Similarly, in case of lacrimal obstructive pathologies, endoscopic assessment of the nose is important for diagnostic purposes (e.g. presence of neoplastic mass), direct evaluation of the endonasal space that can influence the decision of the treatment to be performed, and for identification of the potential surgical influencing factors such as the nasal septum deviation, nasal mucosa pathologies, paradoxal middle turbinate, and abnormalities of the nasal fossa [8].

As a result, to establish the best diagnosis for each patient affected with a pathology of the lacrimal drainage system, accurate and specific work-up is fundamental and needs to be done through multidisciplinary consultation between an ophthalmologist and otorhinolaryngologist.

In addition to this, different radiological studies are now available with the aim of precise identification of the lacrimal disease etiology: in particular, this diagnostic step is fundamental in case of neoplastic disease, since the clinical presentation of the tumor can be non-specific, such as medial cantus tender mass, bloody tears and epiphora, painless and with no endoscopic endonasal signs [11]. Nevertheless, its application in non-oncologic lacrimal pathologies is controversial [17]. A recent survey has demonstrated a relative lack of interest for lacrimal imaging among ophthalmic plastic surgeons [18]. However, there are times in which a specific diagnosis remains unclear and imaging of the lacrimal system may be used to help evaluate its function and anatomy. Specifically, Lefebvre et al. suggested that radiologic tools must be used in case of neoplastic suspicion and should be applied in case of re-operation or when there is suspicion of complicated anatomy [17]. The adjunctive information that can be obtained through radiological exams are important for both ophthalmic and ENT surgeons since they can provide the exact position of the obstruction and presence of anatomical malformation that can be missed with clinical/endoscopic exam [16].

At present, different imaging techniques are available (e.g. maxillo-facial CT, dacryocystography, MRI, dacryoscintigraphy, single-photon emission computed tomography); however, no unanimous consensus on the gold standard radiologic tool has been achieved [17].

Treatment

Given the large range of lacrimal pathologies described, analysis of their treatment needs to be divided into proximal and distal lacrimal pathologies, related to the site of the disease. A complete assessment of the possible treatments available for lacrimal pathologies is beyond the scope of this manuscript, although generally speaking collaboration between an ENT surgeon and ophthalmologist is mandatory in distal lacrimal obstructions, whereas in proximal pathologies it can be recommended in relation to the type of the disease. Conversely, in case of a pump defect or functional disease, multidisciplinary treatment is not generally required since these are primary ophthalmologic pathologies.

Proximal lacrimal obstructions

Lacrimal pathologies proximal to the valve of Rosenmuller are mainly divided into punctum (e.g. punctual stenosis, punctual membrane, cicatrizing disease) and canaliculus disease (e.g. stenosis, scarring and foreign bodies) [1]. If the former can be generally treated with punctoplasty, i.e. a surgical procedure with the aim of widening the tight punctum, canaliculus disease can be approached conservatively or surgically. In particular, a probing stenting of the proximal lacrimal pathway can be done and, if not successful, conjunctivodacryocystorhinostomy can be perfomed. The latter is a surgical procedure that creates a neo-passage from the conjunctiva to the middle meatus of the nose [19].

All the treatments described for proximal obstruction of the lacrimal pathway are generally performed by an ophthalmic plastic surgeon and the collaboration with an ENT is not always mandatory. However, conjunctivodacryocystorhinostomy is an approach in which the otolaryngologist can be helpful, since endoscopic assessment of the nasal cavity allows easy visualization of the correct position of the lacrimal tube and implementation of nasal co-interventions during the approach [20].

Nevertheless, these rules concern benign lesions since malignant ones require close collaboration with the ENT surgeon: in fact, even if a primary malignancy of the proximal lacrimal tract is rare, stenosis of the lacrimal pathway secondary to extrinsic compression due to sino-nasal, or-

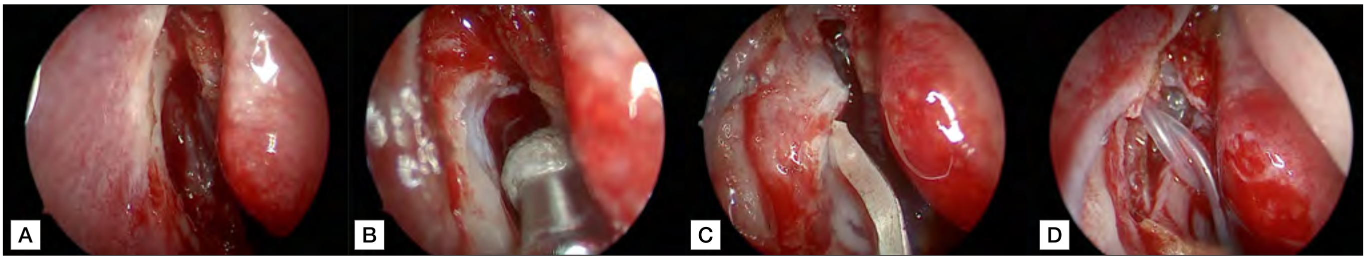


Figure 2. Endoscopic dacryocystorhinostomy surgical procedure. (**A**) Using 30° endoscope, the maxillary line is identified and a mucosal flap ("L-shaped") is raised posteriorly to expose the lacrimal bone; (**B**) the lacrimal bone is than removed using powered instrument; (**C**) while a Bowman's probe was used by an ophthalmologist to tent the medial sac, the ENT surgeon used its as a guide to make a vertical incision of the lacrimal sac; (**D**) the initial mucosal flap is reflected back and the ophthalmologist positioned a bicanalicular stent that is retrieved endonasally and looped.

bital and cutaneous malignancy can occur and needs to be treated in a multidisciplinary manner in order to eradicate the tumor and re-establish functional eye to nose tear flow.

Distal lacrimal obstructions

Distal acquired lacrimal obstructions present different treatments related to the etiology and age of the patient. In general, the most common location of the stenosis of this form is the nasolacrimal duct (NLD) [9].

If the congenital form is taken into account, lacrimal duct closure is usually caused by a mucosal membrane at the level of Hasner's valve or by a bony constriction of the NLD [21,22]. Congenital NLD obstruction is commonly managed conservatively: in particular, most patients experience spontaneous resolution of the pathology by the end of the first year, thanks to a bony development that allows an enlargement of the lacrimal duct [23]. Some clinicians usually prescribe a non-invasive procedure, Crigler's lacrimal sac compression, with which a simple inward lacrimal compression of the lacrimal sac enhances hydrostatic pressure within the system in order to overcome the common membranous obstruction [24]. As an alternative, a stenting-probing of the lacrimal system can be performed [25]. All these different approaches, commonly performed by an ophthalmic plastic surgeon, provide a success rate of up to 90%. In the event of challenging cases, endoscopic endonasal dacryocystorhinostomy (END-DCR) is an established procedure to address unmanageable congenital obstructions, making a multidisciplinary approach with an ENT a possibility in case of this refractive form [26].

Considering the adult form of distal lacrimal obstruction (DALO), the most common pathologies can be distinguished as oncologic and non-oncologic (primary and secondary) forms. Primary acquired and secondary, non-oncologic, diseases have several treatments available, both surgical and non-surgical, that can be performed by different clinicians. Among all, a recent review has pointed out that external dacryocystorhinostomy (EXT-DCR) and END-DCR present higher functional success rates compared to other techniques, and should be considered as treatments of choice [27]. In these cases, the collaboration between ophthalmic plastic and ENT surgeons is necessary because, if a END-DCR is performed, management of the proximal lacrimal pathway is required and needs the presence of the ophthalmologist (Fig. 2); conversely, if an EXT-DCR is performed, endoscopic direct visualization of the surgical landmark and potential anatomic variation can be helpful in order to decrease potential influencing factors of the surgical outcome [15].

If a secondary re-stenosis of the neo-rhinostomy occurs, END-DCR seem to be the treatment of choice since it provides direct visualization of intranasal abnormalities which cause surgical failure, with no superiority demonstrated over EXT-DCR [28]. In addition to this, a new endoscopic approach has been proposed, based on endonasal balloon dilatation of the stenotic neorhinostomy, with encouraging data [29,30] (Fig. 3). In general, it seems that both primary and secondary approaches to non-oncologic DALO would benefit from a multidisciplinary approach [28].

Malignancies of the distal lacrimal pathway have a wide range of histologies, with an epithelial origin the most common form. In general, treatment is based on complete and wide surgical resection, which commonly requires excision of adjacent structures. As a result, considering the necessary reconstruction of the lacrimal pathway and the potential combined approach to the orbital area, a multidisciplinary approach is indispensable [11].

Post-surgical management and follow-up

Following proper treatment, several post-surgical medical therapies are available, and, seem particularly useful in case of non-oncologic DALO. However, with the available data, the actual influence of adjunctive medical therapies is difficult to demonstrate [31], and endoscopic visualization of the healing process associated with nasal medication

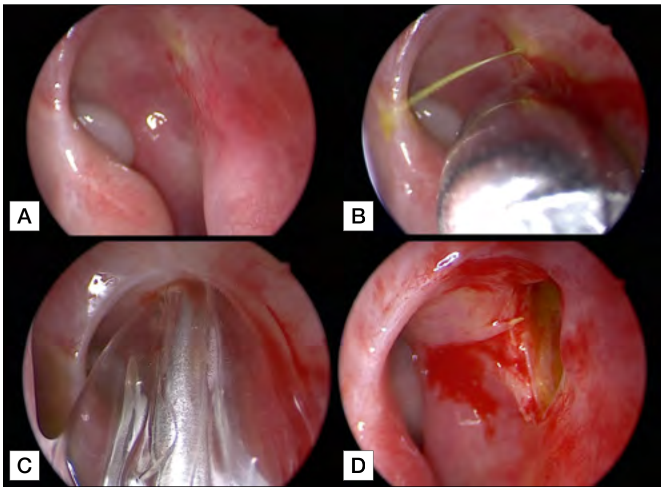


Figure 3. Using 30° endoscope, the stenotic neo-rhinostomy is identified thanks to soft lavage of the lacrimal pathway with fluorescein, performed by an ophthalmologist (**A**); identification of the exact position of the neo-rhinostomy thanks to "high" pressure lavage of the lacrimal pathway with fluorescein (**B**); pneumatic dilatation of the neo-rhinostomy using a trans-nasal balloon catheter (**C**); enlarged revised neo-rhinostomy (**D**).

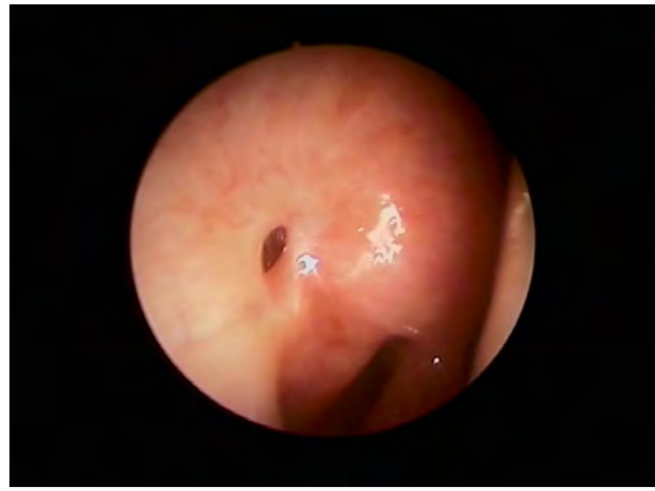


Figure 4. Endoscopic endonasal direct visualization of the neo-rhinostomy during a follow-up visit.

and lacrimal pathway irrigation remain the prevalent post-surgical management tools that can positively influence the surgical outcome of all forms of DALO. In fact, the periodic washing procedure of the lacrimal pathway and endoscopic treatment of the neo-rhinostomy can allow for better healing, and thus leading to better surgical outcomes [15]. As a result, post-surgical multidisciplinary approach remains of vital importance in long-term follow-up: in fact, on one hand the ophthalmologist can perform clinical evaluation of the lacrimal pathway, and on the other the ENT can endoscopically evaluate the neo-rhinostomy and provide additional information about the healing process (Fig. 4) [15]. At present, no definitive follow-up timing has been established, but it seems reasonable that this should be at least 6 months for non-oncologic DALO [27], up to 18 months for failure surgeries [32], and at least 5 years for oncologic DALO [11].

Conclusions

The correct approach to lacrimal drainage system pathologies can be challenging due to the location of this apparatus and the different diseases that can influence physiological lacrimal flow. Considering both its diagnosis and treatment,

Table I. Recommendations for multidisciplinary assessment.

Diagnosis	
Diagnosis of lacrimal pathway disorders	Multidisciplinary assessment "strongly recommended"
Treatment	
Pump defects (e.g. medial ectropion or eyelid laxity)	Multidisciplinary assessment "optional"
Functional diseases (e.g. Dry eye or other causes)	Multidisciplinary assessment "optional"
Proximal lacrimal obstructions	
Punctum diseases	Multidisciplinary assessment "optional"
Non-oncologic canaliculus diseases	Multidisciplinary assessment "recommended"
Primary/secondary oncologic canaliculus diseases	Multidisciplinary assessment "mandatory"
Distal lacrimal obstructions	
Distal congenital lacrimal obstruction	Multidisciplinary assessment "optional"
Non-oncologic distal acquired lacrimal obstruction	Multidisciplinary assessment "mandatory"
Oncologic distal acquired lacrimal obstruction	Multidisciplinary assessment "mandatory"
Post-surgical management and follow-up	
Post-surgical management and follow-up	Multidisciplinary assessment "mandatory"

a multidisciplinary approach with an ophtalmic plastic and ENT surgeons is frequently required, especially in distal forms, since such cooperation offers the best clinical approach available. In fact, even if most treatments of this apparatus are generally performed by an ophtalmologist, the additional information and surgical approach (END-DCR) that an ENT clinician provides can radically influence the decision making process and final success rate, making this cooperation of vital importance. Recommendations for multidisciplinary approach have been resumed in Table I.

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Surgical multidisciplinary approach of orbital complications of sinonasal inflammatory disorders

Approccio chirurgico multidisciplinare nel management delle complicanze orbitarie delle patologie infiammatorie naso-sinusali

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SUMMARY

Orbital infection complicating sinonasal inflammatory disorders may lead to serious sequelae, including blindness and death, if untreated. Communication between the otorhinolaryngologist, neuroradiologist, ophtalmologist, neurosurgeon and maxillo-facial surgeon is critical and time-sensitive for a successful treatment. The large majority of pre-septal cellulitis cases resolves after broad-spectrum antibiotic therapy. Also orbital cellulitis has been found responsive to pharmacological approach in most cases. The management of the subperiosteal abscess (SPA) is more controversial. An aggressive surgical approach is always recommended also in case of cavernous sinus thrombosis. In cases of surgical indication, debate is still open on the timing and the approach (endoscopic or external). The surgeon should be prepared to convert an endoscopic approach to an external one if needed and this should be included in the informed consent. Decompression of one or more orbital walls may be necessary if orbital pressure remains elevated. Immediate surgery is indicated in children with large SPA or orbital abscesses (OA), or in immune-compromised patients. Moreover, any worsening in the ophthalmological function must be carefully considered as a landmark in candidacy to surgery.

KEY WORDS: sinusitis, orbit, Chandler's classification, orbital abscess, orbital cellulitis

RIASSUNTO

L'infezione orbitaria come complicanza di una patologia infiammatoria nasosinusale può portare a gravi sequele, incluse cecità e morte, se non trattata. La comunicazione tempestiva e diretta tra l'otorinolaringoiatra, il neuroradiologo, l'oculista, il neurochirurgo e il chirurgo maxillo-facciale è fondamentale per garantire un trattamento di successo. Le celluliti pre-settali si risolvono con terapia antibiotica ad ampio spettro. Anche la cellulite orbitaria è responsiva al trattamento farmacologico nella maggior parte dei casi. Il management dell'ascesso subperiosteo (SPA) è invece controverso. Un approccio chirurgico aggressivo è sempre consigliato in caso di trombosi del seno cavernoso. Il timing e il tipo di approccio (endoscopico o esterno) sono oggetto di dibattito nella scelta chirurgica. Il chirurgo dovrebbe essere preparato a convertire un approccio endoscopico in uno esterno, se necessario. La decompressione di una o più pareti orbitarie può essere necessaria se la pressione rimane elevata. La chirurgia è immediata nei bambini con SPA o ascesso orbitario di grandi dimensioni o in pazienti immunocompromessi. Un eventuale peggioramento della funzione oftalmologica deve essere attentamente considerato come un fattore deponente per un trattamento chirurgico.

PAROLE CHIAVE: *sinusite, orbita, classificazione di Chandler, ascesso orbitario, cellulite orbitaria*

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Introduction

Despite differential diagnosis of orbital infection is broad, sinonasal inflammatory disorders are responsible for around 75% of cases. Being surrounded by sinuses on three sides, the orbit is susceptible to contiguous spread of infection, and notwithstanding the decreased incidence of this event in the antibiotic era, orbital infection without appropriate treatment may lead to serious sequelae, including blindness and death [1].

Chandler's classification distinguishes orbital complications according to the extent of infection into the orbital content and the surrounding structures [2]. Diagnostic work-up should include prompt radiological investigation, CT scan and MRI playing a complementary role in this setting [1].

A crucial point in the treatment of orbital complications is whether to choose a conservative or non-conservative (surgical) protocol. In cases of surgical indication, debate is still open on the timing and the approach (open or endoscopic). Overall, clear communication between the otorhinolaryngologist, neuroradiologist, ophtalmologist, neurosurgeon and maxillo-facial surgeon is critical and time-sensitive, both in treatment planning and performance.

A review of the literature was performed to thoroughly investigate on orbital complications of sinonasal inflammatory disorders, in particular to assess which are the indications to surgical treatment and when a multidisciplinary approach is recommended or optional in the management of such complications.

Anatomy

The orbital cavity has a pyramidal shape with four walls and an apex. The *superior wall* is made up by the inferior surface of the frontal bone and the lesser wing of the sphenoid. On this "roof", two depressions are clearly visible: the trochlear fossa and the supraorbital foramen, through which pass the homonymous vessels and nerve. The *inferior wall*, which hosts the infraorbital canal, separates the orbital cavity from the maxillary sinus. The *apex* represents the communication between the orbit and the middle cranial fossa, and is in close relationship with the lateral wall of the sphenoid sinus. It hosts the ophthalmic artery and vein, the optic and oculomotor nerves. The lamina papyracea (LP) of the ethmoidal bone represents the *medial wall*, and marks the bound between the orbital cavity laterally and nasal cavity medially, representing one of the most important landmarks in functional endoscopic sinus surgery [3]. Further details regarding the anatomic relationship between the orbit and the sinonasal cavity are depicted in Figure 1.

Physiopathology

Local complications of sinusitis could be orbital, intracranial and osseous. The orbit is susceptible to contiguous spread of infection as it is surrounded by sinuses on three sides. This is more relevant in children, because of their thinner bony septa and sinus wall, greater porosity of bones, open suture lines, and larger vascular foramina.

Indeed, infections can spread directly by penetration of the LP through its small bony dehiscence or extend directly by traversing through the anterior and posterior ethmoidal foramina. Since the ophthalmic venous system has no valves (Brechet's

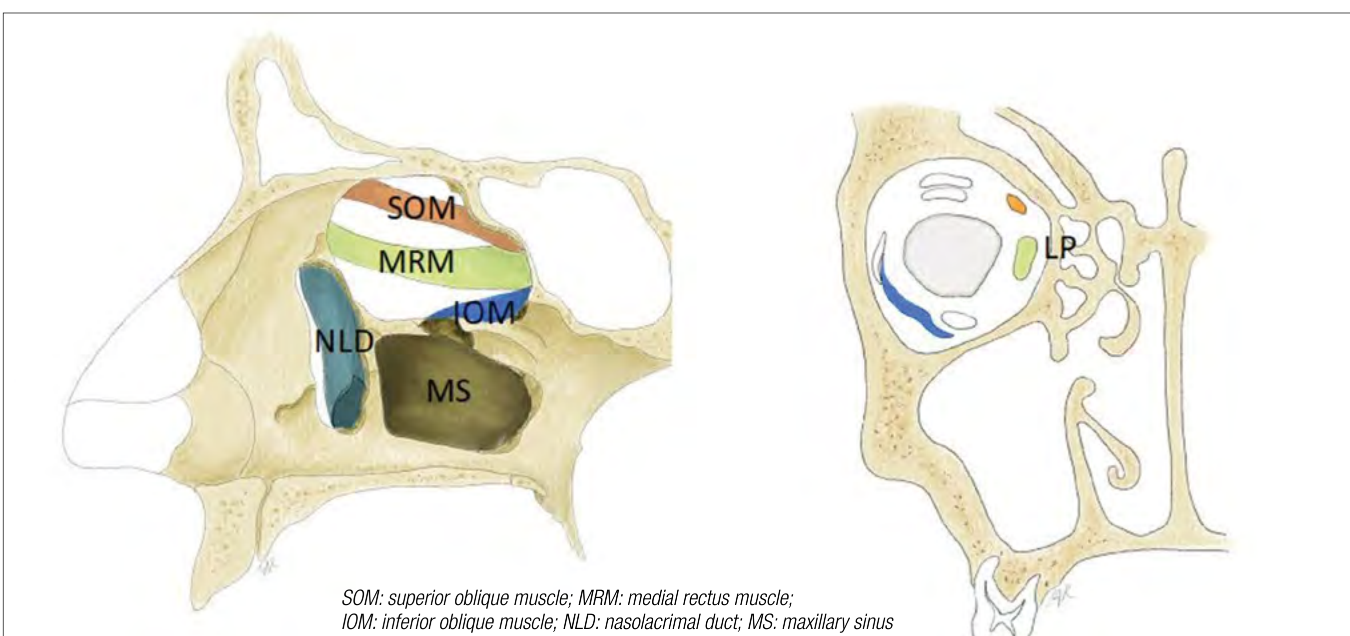

Figure 1. Lamina papyracea (LP) and its relationship with the orbital content (drawing realised by Elisa Aggazzotti Cavazza).

veins), the extensive venous and lymphatic communication between the sinuses and the surrounding structures enables retrograde thrombophlebitis. This is caused by an increase in pressure, due to the inflammation, that reverts the venous flow, which normally goes towards to the sinus. Although frontal sinusitis alone rarely causes orbital complications, communication from the frontal sinus to the orbit may occur in three sites of dehiscence in the frontal bone: behind the trochlear fossa, behind the supraorbital notch and at the junction of the middle and outer thirds of the sinus floor [2,4].

Differential diagnosis of orbital involvement includes bacteremia, facial infections, trauma, iatrogenic causes, tumors and dacryocystitis. However, sinusitis is responsible for a least 75% of cases [1].

Orbital complications

Orbital involvement is typically a complication of acute rhinosinusitis (ARS) and is associated, in order of decreasing frequency, with ethmoid, maxillary, frontal and sphenoid sinus infection. Despite oral and intravenous antibiotics have decreased the incidence of this event, orbital infection without appropriate treatment may lead to serious sequelae, including blindness and death. Chandler's classification (Tab. I) distinguishes orbital complications according to the extent of infection into the structures surrounding the orbit and the orbital content itself [2,3].

Preseptal cellulitis (PC) describes an infection limited to the skin and subcutaneous tissues of the eyelid, anterior to the orbital septum. The orbital septum is a membranous sheet that fuses with the levator palpebrae on the upper eyelid and with the tarsal plate on the inferior eyelid. It is the most common and least severe complication, especially in children, and results from impeded venous and lymphatic drainage from the obstructed sinus.

Orbital (or post-septal) cellulitis (OC) is an infectious process that occurs within the orbit, behind the orbital septum, that occurs when an increase in sinus venous pressure is transmitted to the orbital vasculature, resulting in transudation and leakage through the vessel walls. The orbital content shows diffuse edema, without abscess formation. *Subperiosteal abscess* (SPA) most commonly develops in the medial orbit when an ethmoidal sinusitis breaks through the LP or travels through the ethmoidal foramina, and create a collection in the subperiosteal space. A SPA could expand rapidly and may lead to blindness by compromising optic nerve function through several possible mechanisms: direct optic nerve compression, elevation of intraorbital pressure, or proptosis.

Orbital abscesses (OA) may occur inside or outside the muscle cone, when orbital cellulitis coalesces into a collection of pus. This rare condition occurs when OC diagnosis is delayed or in immunocompromised patients.

Table I. Chandler's classification.

I	Preseptal cellulitis
II	Orbital cellulitis
III	Subperiosteal abscess
IV	Orbital abscess
V	Cavernous sinus thrombosis

Cavernous sinus thrombosis (CST) results from the direct retrograde spread of infection from nasal cavities (sphenoid > ethmoid > frontal) through the superior and inferior ophthalmic veins, or also as an OC complication.

In a large review on 465 pediatric patients with orbital complications, nearly 50% had PC, 35% had OC, 15% had SPA and fewer than 1% had an OA [6]. This illustrates that in the antibiotic era, PC is the most common orbital complication of ARS. The most commonly isolated organisms in children are *S. pneumoniae, H. influenzae, M. catarrhalis,* and *S. aureus.* The adult population differs in the polymicrobial and anaerobic nature of the pathogens and in the most commonly odontogenic origin of infection.

Mucoceles of the paranasal sinuses represent another possible inflammatory source of orbital complication. Mucoceles are chronic cystic lesions, covered with columnar epithelium, that grow within the cavity of the sinus. They originate as an accumulation of mucoid secretion and desquamated epithelium inside the sinus with distension of its walls. The most frequent cause is the obstruction of the sinus ostium due to inflammatory processes, tumors or surgical interventions. The sinuses most commonly involved are the frontal, the ethmoid, the maxillary and the sphenoid, in decreasing order [7,8].

Clinical features

PC usually presents with eyelid swelling and erythema without impaired visual acuity. Diagnosis relies on clinical inspection and CT scans.which are only used when symptoms do not improve by 72 hours of antibiotic, since it is unusual for untreated PC to progress to OC.

Clinical presentation of OC may include orbital pain, proptosis and ocular motility impairment, without visual acuity symptoms. In PC the local examination, which may evoke pain and be difficult due to swollen eyelids, does not show globe displacement, as opposed to OC and SPA.

SPA is suspected when a patient with OC develops worsening proptosis and gaze restriction. The ability to distinguish colors may be used as a guide of disease progression because increasing intraorbital pressure causes loss of red/green perception before deterioration of visual acuity.

In children up to 9 years, SPA is likely to respond to antibi-

otic therapy, since it is usually due to a single aerobic pathogen. Also medial abscesses are highly amenable to antibiotic treatment, whereas more superiorly located abscesses (which tend to occur in older children) carry a greater risk of associated intracranial spread. Considering the lack of frontal sinus aeration in younger patients, especially patients with frontal sinusitis are more prone to intracranial extension through the diploic veins, which run across the orbit to the dural compartment.
OA may be clinically indistinguishable from OC. It may present with more severe proptosis, globe displacement, and ophthalmoplegia related to inflammation of the oculomotor muscles, and patients are more likely to appear toxic. Infection may extend to the orbital apex, causing decreased visual acuity, or intracranially.
CST is a potentially life-threatening complication; although in proximity to the orbit, it is de facto considered an intracranial complication. Even with rapid recognition and treatment, this condition may rapidly progress to loss of vision, meningitis, and death. Intracranial involvement may present with oculomotor nerve palsies, mental status changes, contralateral cranial nerve palsy, or bilateral orbital cellulitis. Headache is the most common symptom and generally precedes fever and periorbital signs.
It is of paramount importance that facial pain is interpreted considering the main sinonasal inflammatory entities [9]. Careful ophthalmologic and neurologic examination with attention to the cranial nerves should be performed, as the oculomotors nerves and the internal carotid artery could be involved. Around 60-70% of patients with CST will have an abnormal fundoscopic exam with papilledema or dilated retinal veins noted [10]. Extension of phlebitis into the cavernous sinus results in a progression of the process to the opposite eye, a distinguishing feature of CST.
Mucoceles may have variable presentation: a sphenoidal mucocele commonly presents with headache and visual loss, while in fronto-ethmoidal mucoceles, ophtalmic symptoms are frequent (proptosis, diplopia, reduced ocular motility and epiphora). Maxillary mucoceles may present with enophtalmos and globe proptosis [7,8,10,11].

Radiologic assessment

CT scan and MRI represent the two complementary imaging modalities for the assessment of the orbital cavity. Radiological appearance according to Chandler's classification is depicted in Table II.
It is possible to encounter clinical conditions whose radiological expressions overlap, especially when paranasal cavities do not seem involved. Differential radiological diagnosis includes the whole spectrum of infiltrative inflammatory pathologies, such as pseudotumor and sarcoidosis, especially as regards PC and OC. Not to forget is the metastatic infiltration of the retrobulbar adipose tissue, such as in breast cancer, which clinically expresses itself with enophthalmos instead of exophthalmos. When the cavernous sinus is involved, Toulouse-Hunt syndrome must be considered. Conversely, there are inflammatory diseases, such as fungal infections or mucoceles, whose radiological expression can be expansive rather than infiltrative, thus simulating the presence of a neoplasm. In post-traumatic infectious processes, orbital hematomas could simulate a mycetoma or abscess (both subperiostal and intra-orbital), especially in the subacute phase.
Another inflammatory lesion with radiological behaviour similar to expansive lesions is the mucocele. This pathology has the characteristics of a chronic process; therefore, local invasiveness predominates over diffusion in the perilesional soft tissues. Its content consists of proteinaceous mucous secretions, thus the cavity is completely obliterated, airless and expanded, with remodelling of the bone based on demineralization rather than erosion. CT scan is the method of choice; in MRI the T1 and T2 signal varies considerably, increasing the T1 hyperintensity and the T2 hypointensity in relation to the density of the secretions. In post-contrast images, the mucosal wall has a slight enhancement, which often becomes irregular if superinfection is present. Being a chronic process, the main radiological differential diagnoses are indolent lesions such as inclusion cysts (dermoid/epidermoid) or chronic post-traumatic hematomas (Figs. 2, 3).

Table II. Radiological features of the main orbital complications from sinonasal inflammatory disorders.

Chandler scale	Radiologic characteristics
Pre-septal cellulitis	Periorbital tissues swelling with paranasal sinuses involvement on CT. No contrast needed
Orbital cellulitis	"Stranding" of the intraorbital adipose tissue both at CT and MRI; contrast needed to differentiate edema from cellulitis and abscess
Subperiosteal abscess	DWI restriction of extraconal collections on MRI. Possible association with retrobulbar cellulitis or involvement of extrinsic muscles or optic nerve. Contrast needed
Orbital abscess	Same MRI features as SPA, but with intraconal location
Cavernous sinus thrombosis	Bulging of the cavernous sinus with reduced contrast enhancement on both CT and MRI

DWI: Diffusion-weighted imaging.

Management

In the treatment of orbital complications, a crucial point is whether to choose a conservative or non-conservative protocol. When planning the treatment, clear communication between the otorhinolaryngologist, neuroradiologist, ophtalmologist, neurosurgeon and maxillo-facial surgeon is critical and time-sensitive. Despite difficult in ill children with periorbital oedema, baseline eye examinations is critical: serial eye examinations should be completed by an experienced team member, preferably the same individual, since the treatment choices heavily relies on the validity of this examination.
According to a systematic review focusing on orbital complications, consensus has been found in the PC management: the large majority of cases resolve after broad-spectrum antibiotic therapy. Also OC has been found responsive to pharmacological approach in 77-100% of the pediatric population [10].
The management of the SPA is more controversial. In the pediatric population, some authors stated that surgery is not always the first choice. Garcia and Harris defined the criteria for management of patients with SPA. They found a 93% response rate in medically managed selected patients (< 9 years of age, with a medial, small SPA of nondental origin, and without optic nerve impairment, gas in abscess space, frontal sinusitis or chronic sinusitis) [12]. Other authors have sought to use medical therapy in all SPA patients without preselecting surgical cases, demonstrating that only 26% could be managed without surgical intervention [13].
Clearly, there are patients in whom immediate surgery is indicated, such as child with large SPA or OA, marked proptosis, multiple fields of restricted gaze, reduced visual acuity, afferent papillary defect or immunocompromised status. At the present state, however, there is no consensus on what ocular criteria predict the success of medical management [13].

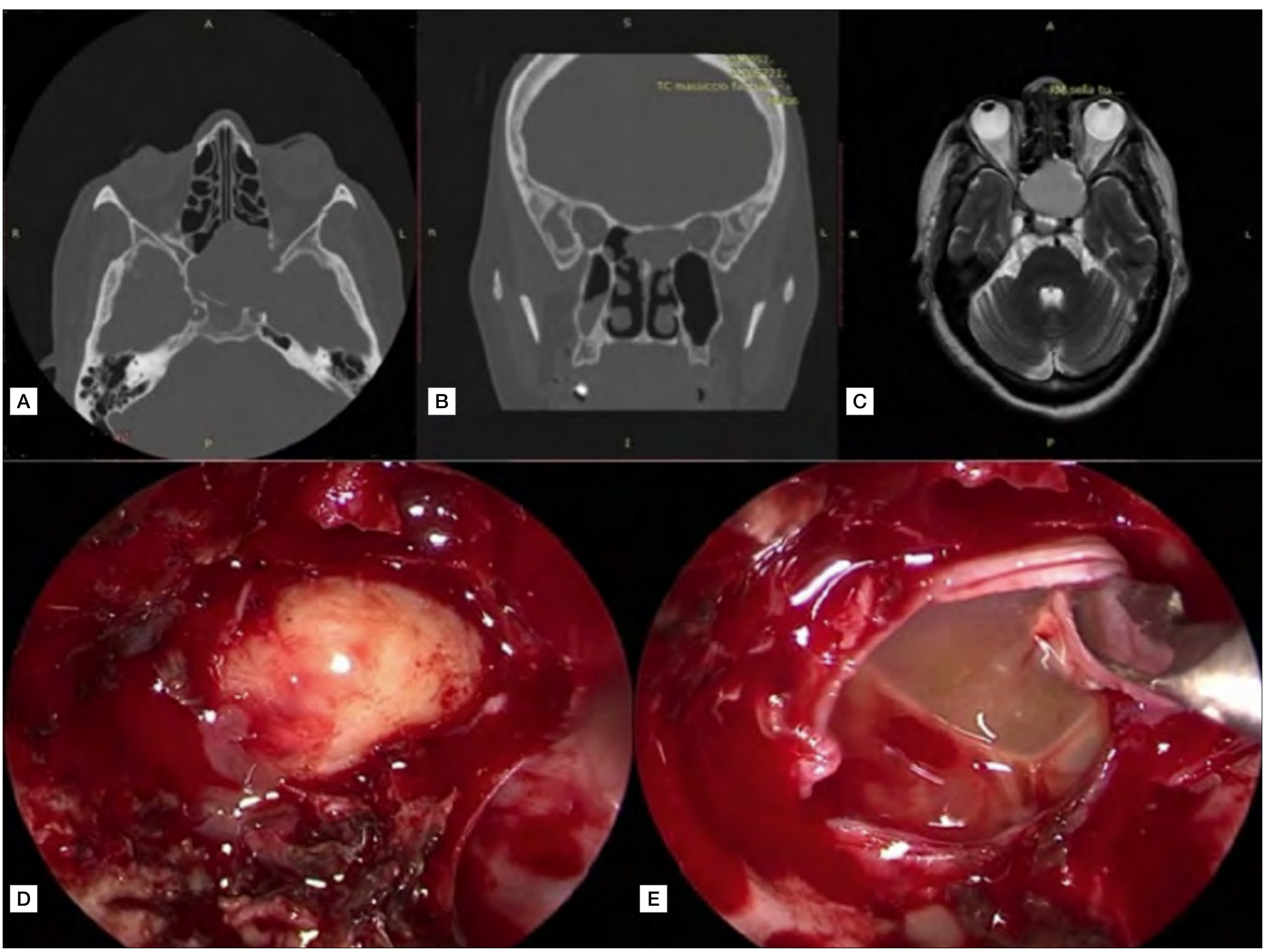

Figure 2. CT scan (**A** and **B**) and MRI (**C**) of a sphenoidal mucopyocele with bone erosion of optic foramen, lamina papyracea, orbital apex, carotid canal and sella turcica. Intraoperative view of the mucopyocele sac before (**D**) and after (**E**) its endoscopic drainage.

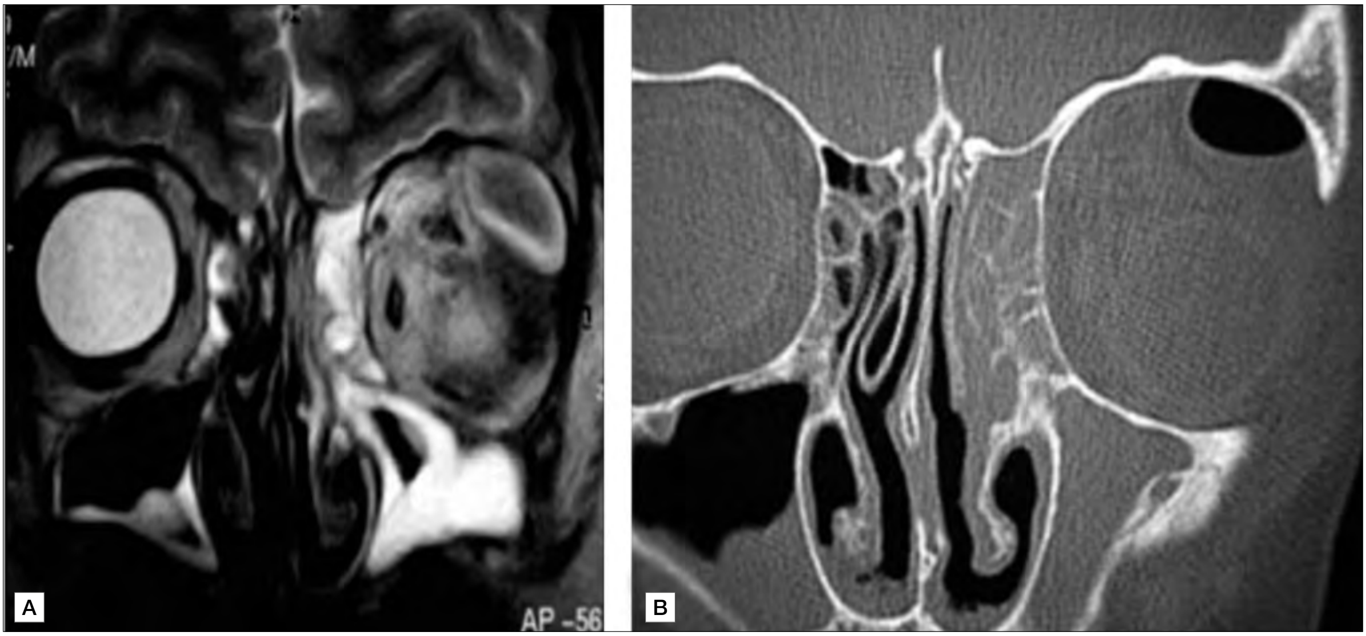

Figure 3. MRI (**A**) and CT scan (**B**) of left pansinusitis with orbital abscess.

Few studies in literature address management of OA, due to its rarity nowadays. In general, prompt antibiotic therapy in association with surgical drainage is mandatory. An aggressive surgical approach is always recommended also in case of CST, since neurological and vascular complications can be lethal, while the role of anticoagulants and steroids remains controversial. A proposal for a management algorithm for pediatric patients with SPA or OA is presented in Figure 4 [14].

Surgical techniques

The aims of surgical management of orbital complications include:

- draining the purulent collection;
- addressing the offending sinuses, enlarging their natural ostia;
- obtaining intraoperative cultures.

Decompression of one or more orbital walls may be necessary if orbital pressure remains elevated despite drainage procedure. Both endoscopic or external approaches may be performed, with the surgeon weighing the advantages and disadvantages of each approach. The surgeon should always be prepared to convert an endoscopic approach to an external one if needed and this eventuality should be included in the informed consent. In particular, external approaches could benefit from a multidisciplinary team, consisting of otorhinolaryngologist, ophthalmologist, maxillofacial surgeon, and neurosurgeon.

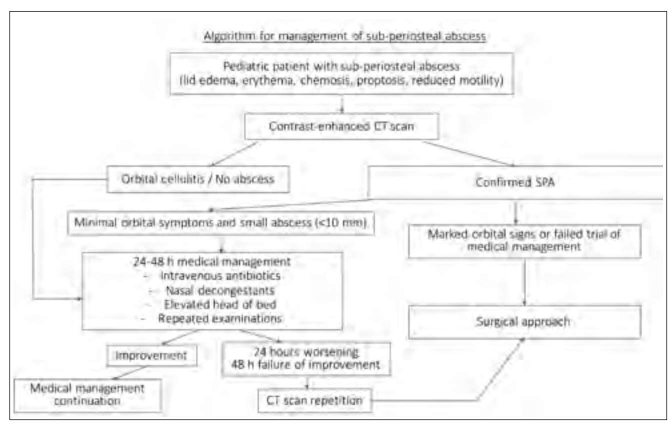

Figure 4. Management algorithm for pediatric patients with suspected subperiosteal or orbital abscess. CT, computed tomography; SPA, subperiosteal abscess (from Bedwell, Bauman, 2011 [14], mod.).

Historically, open drainage via Lynch incision, combined with external ethmoidectomy, was the preferred way for draining SPA and OA.

In 1993, Manning reported a successful endoscopic approach, consisting of ethmoidectomy, maxillary antrostomy and limited opening of the LP [15].

Since then, numerous studies have confirmed the endoscopic approach as a well-tolerated and effective method for management of medial SPA. The main limitation is related to the bleeding potential of the inflamed mucosa, which may seriously compromise visualization, especially in pediatric nose and even for experienced endoscopists. Meticulous dissection and identification of landmarks, possibly with the support of image navigation systems, should be employed to prevent injury to noble structures.

The endoscopic procedure for SPA involves anterior and posterior ethmoidectomy associated with frontal sinusotomy and maxillary antrostomy, with the aim of exposing the LP.

After the uncinated process is removed and the ethmoidal bulla is opened, the LP should be visualized and carefully skeletonized with through-cutting instruments in preparation for the abscess drainage. Sometimes pus can be seen streaming from the orbit during ethmoidectomy, through a natural dehiscence or a crack in the LP, especially when orbital pressure is elevated. Drainage of the pus may be initiated by cracking the LP with a Cottle or freer elevator. Access through the orbital medial wall may be allowed also by a diamond cutter, to reduce its thickness and facilitate removal, reducing the risk of periorbita damage.

It is advisable to preserve a few millimeters of LP anteriorly (just posterior to the bony canal of the nasolacrimal duct) to avoid injuring the trochlea of the trochlear muscle, while posteriorly the dissection should reach an imaginary line that corresponds to the sphenoethmoidal recess.

An incision of the periorbita is necessary to drain an OA. This should be done using a sharp sickle knife, with the tip of the knife remaining superficial; a horizontal incision is made from posterior to anterior, following a line between the lower third and the middle third of the periorbita, to preserve the medial rectus muscle. The intraconal adipose tissue is spread apart to ensure maximum drainage of the abscess collection with immediate decrease in intraorbital pressure. In both operations, there is no need to reconstruct the orbital wall since it is soon replaced by a thick scar tissue. In a patient with high intraorbital pressure the surgeon should be prepared to perform a wide orbital decompression in addition to the endoscopic drainage.

Despite the widespread adoption of endoscopic techniques, a role for open drainage remains. Occasionally, restrictive anatomy combined with florid inflammation may make endoscopic manipulation impossible. Tanna et al. in 2008 reported that 29% of patients who required SPA surgical drainage underwent a combined open/endoscopic approach, and a further 38% underwent open drainage only [16]. Those who underwent an open approach were more likely to have superolateral abscess, and demonstrated more extensive muscle involvement than the endoscopic group. Also Migirov et al. examined 22 children with medial SPA subjected to endoscopic versus open approach. The endoscopic group had no postoperative sequelae, whereas the external group experienced facial scarring, delayed healing, stitch abscess, unresolved diplopia, or recurrent cellulitis. The authors recommended exclusive use of endoscopic drainage for medial SPA with an external approach reserved for drainage of superior OA [17]. Another study by Yang and coworkers confirmed that in cases of laterally seated SPA or when OC is associated with ophthalmoplegia or visual loss, decompression and drainage of the orbit should be performed with no delay through an external approach [19]. Gavriel et al. found that location of abscess dictates the surgical approach: for more anterolateral collections, a combined approach is indicated, while for posterior localization an endonasal approach is more suitable [19].

Many approaches are indicated to perform external ethmoidectomy and/or anterior orbitotomy, although the most common remains the Lynch incision. A 2.5-3 cm curvilinear incision is made midway between the medial canthus and nasion, under the eyebrow and anterior to the lacrimal sac, taking care not to transect the supratrochlear and supraorbital nerves. A Z-plasty can be done to reduce scar retraction. The angular artery is encountered deep in the incision and it is ligated. The orbit is lateralized, taking care not to injure the periorbita, exposing the periosteum of the medial orbital wall. This is elevated and separated from the LP. It is important to identify the fronto-ethmoidal suture line, which works as a landmark corresponding to the level of the cribriform plate and the anterior and posterior ethmoidal foramina. Once the vessels are ligated, ethmoidectomy is obtained by perforating the LP immediately behind the posterior lacrimal crest, keeping below the fronto-ethmoidal suture; this ethmoidotomy provides direct access to the anterior ethmoid. Then ethmoidectomy is completed by opening the floor of the ethmoid bulla directing posteriorly [21]. In alternative, transconjunctival and transcaruncolar approaches have been described with excellent cosmetic outcomes, compared to the Lynch incision.

Conclusions

Although severe clinical evolutions are far less common in the post-antibiotic era, a worsening in the ophthalmological function must be carefully considered as a landmark in candidacy to surgical drainage. Orbital complications of sinonasal inflammatory disorders need a multidisciplinary counselling involving ophtalmologists, maxillo-facial surgeons and neuroradiologists (Tab. III).

Imaging and interpretation by a dedicated neuroradiologist is advisable for a correct diagnostic work-up and appropriate surgical approach. When considering endoscopic versus external approaches, the intraoperative availability

Table III. Final recommendations.

	Multidisciplinary approach
Pre-septal cellulitis	**Optional**
Orbital cellulitis	**Recommended** (ophtalmologist, maxillofacial, infectious disease specialist and neuroradiologist involved for differential diagnosis and appropriate medical therapy)
Subperiosteal abscess	**Optional**, depending on the location (mandatory maxillofacial and/or ophtalmologist cooperation for superior and lateral location)
Orbital abscess	**Optional**, depending on the location (mandatory maxillofacial and/or ophtalmologist cooperation for superior and lateral location, or for intraconal lesions)
Cavernous sinus thrombosis	**Recommended**
Maxillary mucocele	**Optional**
Sphenoidal mucocele	**Optional**
Frontal mucocele	**Optional**, depending on the location (recommended maxillofacial and/or neurosurgical cooperation for lesion extending to the anterior cranial fossa)

of ophthalmologist, maxillofacial surgeon or neurosurgeon is extremely helpful and encouraged, since the surgeon should always be prepared to convert to an external approach if needed.

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ENT and dentist cooperation in the management of odontogenic sinusitis. A review

La collaborazione tra otorinolaringoiatra e odontoiatra nel trattamento delle sinusiti odontogene

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SUMMARY

Odontogenic sinusitis represents by definition a border condition between otolaryngology and dental science and, from a holistic perspective, cannot be managed without a proficuous collaboration between specialists. This review focus on the different scenarios currently considered by international literature as related to odontogenic sinusitis and sinonasal complications of dental disease or treatment. Consequently, this review will cover all paranasal sinuses infections caused not only by dental disease (e.g. periodontitis and caries), but also by dental procedures (extractions, endodontics and the like), implantological procedures, pre-implantological (maxillary sinus grafting) and medication-related osteonecrosis of the jaw. After dealing with the odontogenic sinusitis diagnostic process and general principles of treatment, we will thoroughly cover odontogenic sinusitis scenarios treatment following an aetiology-based approach. This literature review shows that, albeit more prospective and rigorous studies are badly needed for determining the best treatment for each patient affected by odontogenic sinusitis, the sheer variety of scenarios that may be encountered should be enough to encourage mutual collaboration between ENTs and dentist. Such collaboration is required both to perfect diagnostic and treatment and to provide a solid scientific and medico-legal foundation for each intervention proposed to patients.

KEY WORDS: rhinosinusitis, paranasal sinus, endoscopy, computed tomography, Guidelines, dental implants, dental disease, maxillary sinus grafting, maxillary sinus, cone-beam computed tomography

RIASSUNTO

Le sinusiti odontogene rappresentano per definizione una condizione al confine tra otorinolaringoiatria e odontoiatria e, da un punto di vista olistico, non possono essere gestite in assenza di una proficua collaborazione tra specialisti diversi. Questa review si focalizza sui diversi scenari attualmente considerati nella letteratura internazionale come correlati alle sinusiti odontogene e sulle complicanze naso-sinusali di patologia o trattamento odontoiatrico. Conseguentemente, questa review andrà a trattare tutte le infezioni dei seni paranasali causate non solo dalla patologia di interesse odontoiatrico (es. parodontite e carie), ma anche conseguenti a trattamenti odontoiatrici classici (estrazioni, endodonzia, et similia), procedure implantologiche, procedure pre-implantologiche (rialzo del seno mascellare) e osteonecrosi del mascellare da farmaci. Dopo aver trattato la diagnosi delle sinusiti odontogene e i principi generali di terapia, ci focalizzeremo sulla gestione specifica dei singoli quadri di patologia. Questa revisione della letteratura mostra che, per quanto siano fortemente necessari un numero maggiore di studi prospettici per determinare il miglior approccio terapeutico per ciascun paziente affetto da sinusite odontogena, il mero numero di scenari diversi che si possono incontrare dovrebbe essere sufficiente a stimolare la mutua collaborazione tra otorinolaringoiatri e odontoiatri. Tale collaborazione è necessaria per perfezionare la fase diagnostica e di trattamento e per realizzare un solido fondamento scientifico e medico-legale per qualsiasi proposta terapeutica venga rivolta ai pazienti.

PAROLE CHIAVE: *rinosinusite, seni paranasali, endoscopia, tomografia computerizzata, linee guida, impianti dentali, rialzo del seno mascellare, seno mascellare, tomografia computerizzata cone beam*

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Introduction

Since it was first described in the Forties, odontogenic sinusitis (ODS) has represented a common ground for otolaryngologists and dental surgeons [1].

ODS is far from being the only condition where otolaryngology meets with other specialities, but it is somehow unique in this duality. Where most multidisciplinary teams are usually required for treatment, properly trained specialists should also cooperate for diagnosis [2].

No single specialist is usually capable of both correctly diagnosing an inflammatory process of the paranasal sinuses, adequately calibrating the tools recommended by international consensus [3,4], and evaluating the status of teeth and dental prosthetics alike, especially given the high complexity rate the latter achieved in the last decade [5].

Despite the term ODS referring literally to the inflammatory process of the paranasal sinuses due to diseased teeth, as in the first description of the condition, contemporary scientific literature stretched the term to include other loosely related causes [6]. As a result, ODS covers all paranasal sinuses infections caused not only by dental disease (e.g. periodontitis and caries) but also by dental procedures (extractions, endodontics and the like), implantological procedures, pre-implantological maxillary sinus grafting and medication-related osteonecrosis of the jaw (MRONJ). A composite figure, therefore, emerges, where a complex interplay between otolaryngologists and dental surgeons becomes most often mandatory to understand the bigger picture and correctly manage the patient.

ODS management becomes even more peculiar if we take into account that this protean group of sinonasal conditions lacks shared definition and diagnosis guidelines and the robust literature on the subject is plagued by extreme heterogeneity in defining cases and reporting outcomes. It has to be noted though that, despite guidelines on rhinosinusitis being extremely vague on this subject [3], ODS is almost universally considered a completely different condition from rhinosinusitis (RS), both in its acute and chronic forms, in terms of pathogenesis, microbiology and response to treatments [7,8].

A recent multidisciplinary consensus statement [9] addressed some issues in ODS management after careful revision of scientific literature. The shared statement emerging from the modified Delphi method consensus are resume in Table I and will be further integrated in the following sections of this review.

The most complete existing classification of ODS, defined as the group of sinonasal complications resulting from dental disease or treatment (SCDDT), has been proposed by our group in 2013 [10], and has been prospectively validated [11] and adopted by other groups, both nationally and internationally [12,13]. The classification (reported in Table II along with the number of patients treated at our institution from 2012 onwards) successfully tries to integrate different etiologies and possible (often multidisciplinary) treatments for possible ODS scenarios. In this review, after dealing with ODS diagnostic process and general principles of treatment, we will thoroughly cover ODS treatment following a similar aetiology-based approach:

- diagnosis of ODS;
- general principles of ODS treatment;
- ODS resulting from dental disease or dental treatments;
- ODS following maxillary sinus grafting;
- ODS following dental implants placement;
- ODS during medication-related osteonecrosis of the jaw (MRONJ).

Table I. Multidisciplinary consensus statements on odontogenic sinusitis (from Craig et al., 2020 [9], mod.).

Optimal management of ODS involves a shared decision-making process between the otolaryngologist, dental provider, and patient, where the benefits and risks of dental treatment and ESS are discussed
For complicated ODS (orbital or intracranial involvement), patients should undergo ESS, opening all diseased sinuses on CT scan
For ODS patients who have treatable dental pathology, and have minimal or tolerable sinonasal symptoms, primary dental treatment should be pursued
Oral antibiotics alone are not appropriate in the management of ODS due to dental pathology amenable to dental treatments
Once the dental pathology causing ODS has been treated adequately, patients should be followed for at least 1 to 2 months post-treatment to monitor for sinusitis resolution
Balloon sinus dilation may not be appropriate in patients undergoing sinus surgical intervention for ODS given the degree of inflammation and need for definitive sinus drainage
For ODS patients who have treatable dental pathology and have failed primary dental treatment, ESS should be pursued
For ODS patients who have treatable dental pathology, but have significant sinonasal symptoms, primary ESS combined with subsequent dental treatment should be pursued
For ODS due to maxillary dental implants, primary ESS should be pursued in efforts to preserve the dental implant

CT: computed tomography; ESS: endoscopic sinus surgery; ODS: odontogenic sinusitis.

Review

Diagnosis of ODS

As a recent systematic review of ODS literature confirmed [6], studies on the subject are hindered by the general lack of a diagnostic consensus. While RS diagnosis requires symptoms to be confirmed [3,4,14], many studies diagnose ODS only on the basis of radiological and, less frequently, endoscopic signs only [6]. Furthermore, not all authors agree on which etiologic scenarios to include under the term ODS (and

Table II. Sinonasal complications of dental disease and treatment classification, with treated cases since 2002.

Group	Class	Scenario	Proposed treatment	No. of patients	Rate (%)
I Preimplantological treatment complications	1a	Sinusitis following preimplantologic surgery	FESS + material removal + OAC closure	46	8.97%
II Implantological treatment complications	2a	Sinusitis with peri-implant osteitis and OAC	FESS + implant removal + OAC closure	49	9.55%
	2b	Sinusitis due to implant dislocation with OAC	FESS + implant removal + OAC closure	7	1.36%
	2c	Sinusitis due to implant dislocation without OAC	FESS + implant removal	26	5.07%
	2d	Implant dislocation without sinusite	implants removal (either endoscopic or transoral)	22	4.29%
III Classic dental disease or treatment complications	3 a	ODS with OAC	FESS + OAC closure	129	25.15%
	3b	ODS	FESS	234	45.61%

FESS: functional endoscopic sinus surgery; OAC: oro-antral communication; ODS: odontogenic sinusitis.

Table III. Summary of recommendations.

Clinical scenario	Multidisciplinary management
General ODS treatment principles	Mandatory - concurrent multidisciplinary management for OS with intraorbital or intracranial complications or patients with severe symptoms - two-step multidisciplinary management for conservatively treatable dental problems in patients with mild symptoms
Diagnosis of ODS	Strongly recommended
ODS resulting from dental disease or dental treatments	Mandatory - concurrent multidisciplinary management for existing or expected oro-antral communications - two-step multidisciplinary management for conservatively treatable dental problems
ODS following maxillary sinus grafting	Mandatory in case of graft infection and displacement for graft removal and OAC closure
ODS following dental implants placement	Strongly recommended for implant removal, mandatory for implant removal in case of primary ESS failure or for OAC closure
ODS during MRONJ	Recommended

ESS: endoscopic sinus surgery; MRONJ: medication-related osteonecrosis of the jaw; OAC: oro-antral communication; ODS: odontogenic sinusitis.

even on whether or not the term ODS should be used at all). Therefore it seems licit to include until further notice all the aforementioned etiologies. The strong recommendation emerging from the literature [7] is that both sinusitis AND the odontogenic focus need to be identified for a correct diagnosis of ODS. Consequently, a strict collaboration between the ENT surgeon and an oral surgery specialist is strongly recommended in order to combine the expertise required to avoid ODS overdiagnosis (blatantly inducing consequent overtreatment) and underdiagnosis (which is a known frequent cause of treatment failures in sinus surgery) (Fig. 1) [15,16]. While the clinical examination, both dental and otolaryngological, is straightforward, and the use of nasal endoscopy mandatory, the choice of imaging exams is more complex. Computed tomography (CT) and cone-beam CT (CBCT) are both commonly used for diagnosing sinusitis and identifying the dental problem [17,18], albeit with different peculiarities (as a general rule, standard CT scan provide a better resolution and contrast for the sinonasal cavities and a better visualization of soft tissues alike, while CBCTs – which represent nevertheless a continuously evolving technology – usually allow for easier diagnosis of dental conditions). However, dental specialists may further require employing techniques such as orthopantomography and periapical radiographs to complete the dental study. Such examination should surely be ordered only by the dental surgeon in selected cases, as not to expose the patient to unnecessary radiation.

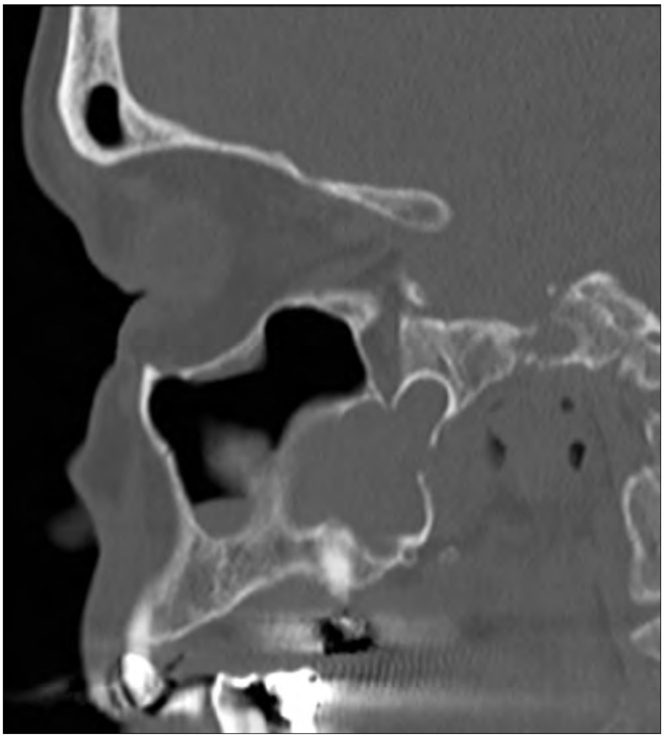

Figure 1. Sagittal CT image showing an odontogenic cyst extending into the body of the sphenoid sinus. Odontogenic sinonasal pathology could represent a matter of difficult differential diagnosis in some patients. A strict collaboration between otolaryngologist and dental specialist is often therefore required also in diagnostic terms.

General principles of ODS treatment

While it is almost impossible to cover in this review any single clinical picture and the grey areas in between in the galaxy of ODS, there are several general principles that should be taken into account when dealing with this group of conditions, some of which are also reported in Craig and colleagues' statement [9].

Patient with limited sinusitis symptoms and dental pathology amenable to conservative treatment should seek dental treatment, with endoscopic sinus surgery reserved for non-healing or relapsing patients. On the other hand, patients with severe symptoms or orbital/intracranial complications should be treated with a combined approach right from the diagnosis, thus allowing for sinus drainage and resolution of the etiological dental focus.

While endoscopic sinus surgery has an undebated role in ODS treatment, the extent of said surgery is still a matter of debate, since some authors [19,20] proposed that middle antrostomy is enough to warrant patient healing. While prospective validation of these approaches is required, at present opening all sinuses involved in ODS [21-23], while being the most frequent approach, is recommended only in case of ODS with orbital or intracranial complications [9]. Again, opening the maxillary sinus together with the anterior ethmoid, which represents another frequently adopted surgical choice aimed at restoring a good osteomeatal complex patency, needs further prospective validation before entering routine clinical use.

Last, before delving into the specific etiological pictures, it seems reasonable to raise a warning to the ENT specialist dealing with ODS, a warning that may sound redundant to specialists used to approach this condition. While ODS may appear as a "simpler" version of RS, where the aetiology can be rapidly identified without resourcing to endotypes and interleukin-mediated inflammatory responses, the interplay between teeth and sinuses is extremely complex, and dental causes are often elusive or uncertain. Furthermore, teeth represent an irreplaceable health asset for patients, while dental and/or implantological treatments impose hefty financial and healthcare costs, so any dental procedure, avulsions first and foremost, have to be supported by case-specific clinical evidence. Following these considerations, the statement "a shared decision-making process between the otolaryngologist, dental provider, and patient, where the benefits and risks of dental treatment and endoscopic sinus surgery (ESS) are discussed" opening Craig and colleagues' consensus [9] should become a mantra in treating ODS, not to turn the ENT-dentist dialogue into a dangerous Mexican standoff with the patient.

ODS resulting from dental disease or dental treatments

The most classic aetiology of ODS represents, at the same time, the widest and most diverse chapter to explore. Among dental conditions capable of inducing sinusitis it is worth citing periapical infections, caries-related tooth decay, unerupted teeth (Fig. 2) and odontogenic cysts infections; classic dental treatments which may lead to ODS are represented by failed endodontic treatments (either incomplete or overflowing into the sinus) and extractions (resulting in either oro-antral communications – OAC – or displacement of tooth/dental fragments/dental tools fragments into the sinonasal complex) [12,24].

While cases pertaining to this aetiology may appear extremely varied in presentation and sinus involvement, there are several standpoints than can help the collaboration between otolaryngologist and dental surgeon.

A simple but nevertheless fundamental distinction is between patients with and without OAC (Fig. 3), as originally proposed by Felisati et al. [10]. The former tend to uniformly require a combined approach for OAC closure and sinus drainage, that yields its best results when performed during the same surgical session [25,26]. The same principle applies whenever an iatrogenic OAC formation is expected during

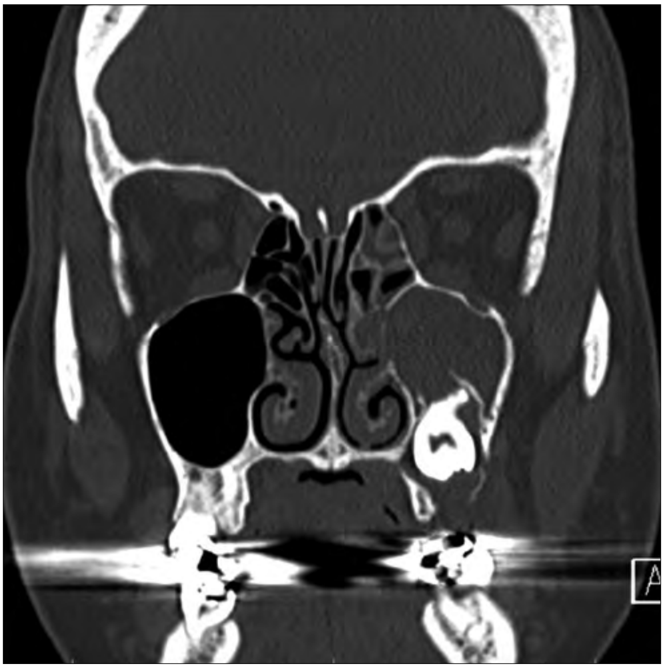

Figure 2. Coronal CT image showing unerupted teeth which determined a sinusitis process involving the ipsilateral maxillary sinus, ostiomeatal complex and, partially, anterior ethmoid sinus. Furthermore, the infection progressively led to the formation of oro-antral communication. A combined approach was performed in order to drain and ventilate the involved sinuses via an endoscopic approach and to remove the unerupted teeth and close the oro-antral communication from an intraoral approach.

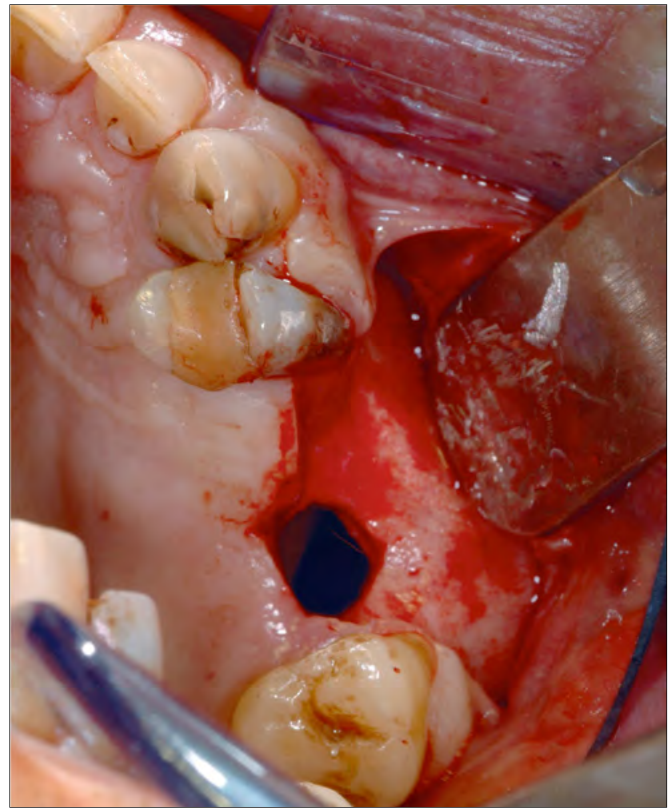

Figure 3. Intraoperative photograph of oroantral communication. A vestibular Rehrmann flap has been raised in order to provide a tension-free closure of the communication.

ODS treatment (e.g. when the dental surgeon planned the extraction of a tooth with roots extending into the maxillary sinus or when a large odontogenic cyst requires an intraoral approach for its removal). Also, in these cases, a combined intraoral-endonasal approach should be preferred.

Patient without OAC or where an iatrogenic OAC is not expected can be managed with ESS alone. In these cases, the dental treatment can be performed during a different surgical session, which should precede ESS in low to mild symptomatic patients and follow ESS in heavily symptomatic patients [9].

ODS following maxillary sinus grafting

Maxillary sinus grafting (MSG) is a common pre-implantologic procedure which gained increasing popularity from the mid-eighties in patients lacking enough vertical bone height to warrant safe dental implant positioning. The procedure aims at promoting osteoinduction and osteoconduction by positioning grafts (ranging from autologous bone to hydroxyapatite) underlying the maxillary sinus Schneiderian membrane from an intraoral approach. Implant placement might be immediate or delayed, i.e. following the consolidation of the newly formed bone, according to the initial bone vertical height before grafting. Immediate implant placement can be proposed only if the initial vertical bone height is enough to warrant implant stability, with the graft providing only a further reinforcement). Sinus complications may follow MSG mainly because of Schneiderian membrane perforation during the grafting, with consequent migration of the graft inside the sinus, or due to the unnoticed presence of otolaryngological contraindications to grafting. Given the significant disruption of the maxillary sinus homeostasis ensuing the sinus floor elevation, some authors postulated that a healthy sinus, with a patent ostium and efficient mucociliary clearance, was a basic requirement for avoiding sinusitis processes [27,28]. While the collaboration between otolaryngologist and dental surgeons in evaluating candidates to MSG in order to minimize complications is almost mandatory, this topic goes beyond the scope of this chapter (see also [29]). Nevertheless, treating ODS ensuing MSG is another matter of strict cooperation between these specialists. To navigate this scenario and evaluate the requirement of combined approaches, several points must be taken into account: 1) dislocation of grafting material into the sinus; 2) development of a sinusitis process; and 3) the presence of an OAC.

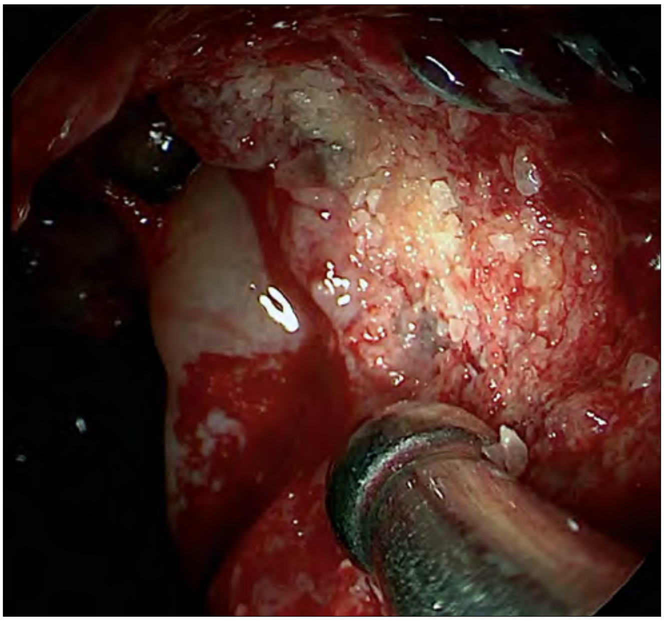

Figure 4. Endoscopic view of the right maxillary sinus obtained via a trans alveolar approach. A combined approach, both in operative and visualization terms, is required in post maxillary sinus grafting patients in order to completely remove the displaced and infected grafting material, in this specific case along with a non-osseointegrated implant.

First and foremost, if an acute infection follows MSG, appropriate imaging should be used to identify whether the grafting dislocated into the sinus. If the graft is still confined under the Schneiderian membrane, it will be up to the dental specialist to follow specific post grafting guidelines counselling whether trying to salvage the graft with appropriate antibiotic therapy or removing it via the same oral approach used when performing the MSG [27]. If the graft is displaced into the sinus, neither the oral approach nor nasal endoscopy is single-handedly enough to remove all the particles. In these patients, a combined approach is mandatory, with a wide antrostomy and oral access allowing the use of angled scopes and curved instruments to ventilate the sinus and remove the particles (Fig. 4). In our experience, a thorough particle removal, pivotal in maximizing therapeutic success rates in these patients, can be achieved only employing scopes and instruments both through the nose and the oral access, in order to allow the best maxillary sinus visualization [30].
Secondly, the specialist should investigate whether a sinus inflammatory process has taken place, with careful clinical evaluation of the patient coupled with endoscopy and/or appropriate imaging. Even in the few cases where sinusitis ensues MSG but without graft infection and displacement (e.g. if the sinusitis ensues months after the grafting, leaving enough time for osseointegration), an endoscopic endonasal approach is required to open the ostiomeatal complex and ventilate the sinus. As a general rule, if the graft is not displaced into the sinus, oral access for graft removal is not required.
Last, the presence of residual OAC communication must be properly evaluated also in post-MSG patients. A residual OAC, which often appears in correspondence to the bony window used for grafting, makes an intraoral approached closure mandatory.

ODS following dental implants placement

ODS may follow implants placement going awry for three main reasons: 1) implants may lose (or never achieve at all) osseointegration and dislocate into the mouth/sinuses leaving an OAC behind; 2) implants may dislocate into the sinuses, sometimes leading also to sinusitis, or 3) implants may develop peri-implant osteitis (or peri-implantitis) and act as a Trojan horse in allowing bacteria to reach the otherwise sterile sinusal spaces [31].
The first scenario requires a combined approach were sinus drainage is achieved endoscopically and OAC closure is performed transorally. Implants displaced into the sinuses may be retrieved either transorally or via nasal endoscopy according to position and surgeons' preference.
The second scenario, sinusal implant displacement, must be treated endoscopically in case of sinusitis, draining sinuses and removing the implant. In case of implant displacement without sinusitis, the retrieval can be performed either transorally, via a bony window or canine fossa access, or endoscopically [32,33].
Cases in which dental implants are, at least apparently, osseointegrated require the most careful planning and diagnostic workup (Fig. 5). While multidisciplinary statements suggest primary endoscopic surgery aimed at treating the patient without removing the implant [9], the surgeon must take into account that failure to recognize an unstable and infected implant is a frequent cause of treatment failure [10,34,35]. Indeed, unnecessary implant removal might enhance the risk of OAC and inevitably burdens patients with further oral rehabilitation costs. Intraoral radiographs, orthopantomography and careful dental clinical evaluation can help in minimizing risks at both ends of the spectrum, though only sharing the diagnostic and therapeutic plan with the patient allows tailoring the treatment. In these patients, multidisciplinary collaboration represents more of a diagnostic need than a therapeutic tool. For the sake of completion, it has to be noted that implant penetration in the maxillary sinus is not per se an indication to implant removal and does not necessarily imply the development of a sinusitic process over time [36].

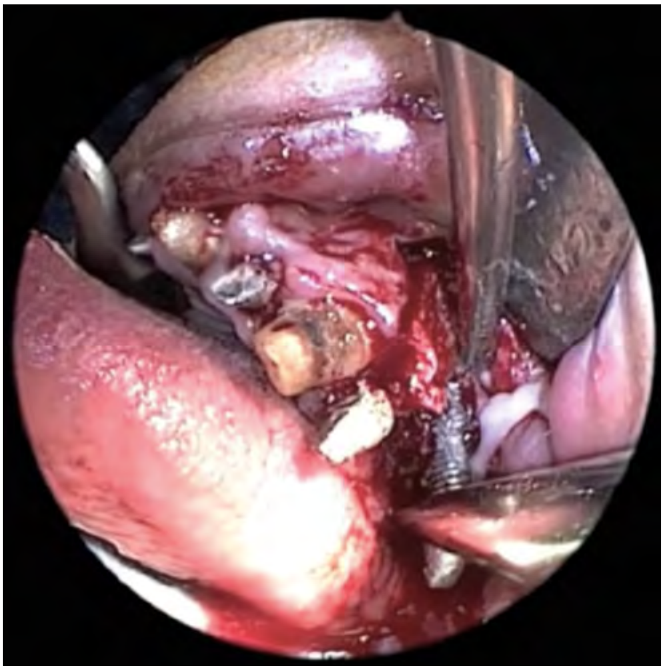

Figure 5. Intraoperative photograph showing the removal of an unstable dental fixture which developed a severe peri-implant infection, leading to sinusitis, in a patient with multiple infected implants.

ODS during medication-related osteonecrosis of the jaw (MRONJ)

OS following MRONJ is maybe the least studied scenario hereby presented, and the only scenario which is actually falling outside of Felisati classification [10]. Only three international groups presented MRONJ-related ODS cases in their series [12,37,38]. For these patients, intraoral access is recommended for removing necrotic bone [12] and should be coupled with an adequately calibrated antrostomy in order to explore, drain and ventilate the sinus removing any further foreign body [37,38]. While the cooperation with an oral surgeon seems based on solid scientific premises, MRONJ-related ODS requires at present further exploration to enhance patients' treatment.

Conclusions

ODS represent, by definition, a border condition between otolaryngology and dental science and, from a holistic perspective, cannot be managed without a proficuous collaboration between specialists.

Albeit more prospective and rigorous studies are badly needed for determining the best treatment for each patient, the sheer variety of scenarios that may be encountered should be enough to encourage mutual collaboration between ENTs and dentists, both for perfecting diagnostic and treatments and providing a solid scientific and medico-legal foundation for each intervention proposed to patients.

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Cooperation between ENT surgeon and dentist in head and neck oncology

Cooperazione tra otorinolaringoiatra e odontostomatologo in oncologia cervico-cefalica

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SUMMARY

Head and neck cancer (HNC) patients require specialized care throughout the continuum of cancer diagnosis, treatment, and survival. Cooperation between ENT and dentists is crucial, since all of the different anatomic areas affected by cancer have distinctive characteristics and the best results in terms of life expectancy and patients' quality of life can only be achieved through a multidisciplinary approach. The synergic cooperation of all health care workers in the early diagnosis of HNC allows a better prognosis for such patients. As soon as dentists diagnose a Potentially Malignant Disorder (PMD), patients should undergo complete ENT screening for detection of lesions in any portion of the upper aerodigestive tract. Before and after cancer diagnosis and before any oncologic treatment, it is critical that these patients undergo an accurate and complete dental and periodontal assessment to optimize treatment and minimize complications or side effects. Multidisciplinary ablative, reconstructive and prosthetic programing in Head & Neck oncologic surgery has become imperative to offer patients the best functional and esthetic outcome. An improvement in oral function and associated quality of life is strictly related to correct prosthetic rehabilitation. Finally, after surgery and/or radiotherapy (RT), the main objectives of dental treatment in these patients are the prevention and therapy of dental diseases and the side effects of oncological therapies involving the oral cavity.

KEY WORDS: potentially malignant disorder (PMD), oral care, osteoradionecrosis, oral mucositis, prosthetic implant, jaw reconstruction

RIASSUNTO

I pazienti affetti da tumori della testa e del collo (HNC) richiedono cure specialistiche lungo tutto l'iter diagnostico-terapeutico. La collaborazione tra otorinolaringoiatra e odontostomatologo risulta fondamentale, poiché le diverse sedi anatomiche coinvolte dalla patologia oncologica hanno caratteristiche peculiari, e i migliori risultati in termini di aspettativa e qualità di vita possono essere raggiunti solo attraverso un approccio multidisciplinare. La collaborazione sinergica di tutti gli operatori sanitari nella diagnosi precoce di tali tumori consente una prognosi migliore per questi pazienti; in quest'ottica, subito dopo la diagnosi di patologie odontostomatologiche potenzialmente maligne (PMD), i pazienti dovrebbero sottoporsi a uno screening ORL completo per l'individuazione di lesioni del tratto aero-digestivo superiore. È fondamentale che, dopo la diagnosi di carcinoma e prima di qualsiasi trattamento oncologico, questi pazienti ricevano una valutazione dentale e parodontale accurata e completa, per ottimizzare il trattamento e ridurre al minimo le complicanze o gli effetti collaterali. La pianificazione multidisciplinare ablativa, ricostruttiva e protesica nella chirurgia oncologica testa-collo è diventata indispensabile per offrire ai pazienti il miglior risultato funzionale ed estetico; un miglioramento della funzione orale e della relativa qualità di vita è infatti strettamente correlato a una corretta riabilitazione protesica. Infine, prima e dopo l'intervento chirurgico e/o la radioterapia, gli obiettivi principali del trattamento odontoiatrico in questi pazienti sono rappresentati dalla prevenzione e dal trattamento delle malattie dentali e degli effetti collaterali dei vari trattamenti oncologici a livello del cavo orale.

PAROLE CHIAVE: *disordini potenzialmente maligni (PMD), salute orale, osteoradionecrosi, mucosite orale, riabilitazione implanto-protesica, ricostruzione mandibolare, ricostruzione mascellare*

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Introduction

The term "head and neck cancer" (HNC) generally comprises malignant cancers which arise in the upper aerodigestive tract, and the complex anatomy makes the diagnosis and treatment of these cancers highly demanding. Cooperation between ENT and dentists is crucial to achieve good clinical practice, since all of the different anatomic areas have distinctive characteristics. Furthermore, the oral cavity can experience both the cancer itself and the side effects of cancer therapy of adjacent anatomic areas (i.e., the pharynx, sinuses, major salivary glands, the nasal cavity, and the ears). HNCs and their therapy can lead to devastating cosmetic and functional deficits with resultant psychological, physical, functional and nutritional detriments, thus a personalized medical approach and minimally invasive techniques can help to increase the quality of life of these patients. Furthermore, on the basis of more recent experience, the best results in terms of life expectancy and patients' quality of life can only be achieved through a multidisciplinary approach, beginning with prevention, and then early diagnosis, therapy and follow-up. This review has been written considering the most salient aspects of the clinical collaboration between otolaryngologists and dentists in the early diagnosis and management of the patient affected by head and neck cancer.

Diagnosis and management of potentially malignant disorders

Many different oral lesions can have an increased probability of evolving into cancer and constitute a heterogeneous group of diseases; historically, in 1978, WHO classified all these diseases as "oral lesions" or "oral conditions", considering the first as a disease of the oral mucosa and the second as systemic diseases, which can carry an increased probability to develop/evolve into oral cancer. The WHO classification was revised in 2007 and recently in 2017 introduced the term potentially malignant disorder (PMD), based on the field cancerization concept. All of these diseases have not only an increased probability to evolve into cancer in the affected oral mucosa, but in addition, other primary cancers can arise in any portion of the upper aerodigestive tract [1]. A multidisciplinary synergic approach in the early diagnosis of HNC provides a better prognosis for such patients, in terms of quality of life and life expectancy. As soon as dentists diagnose a PMD, patients should undergo complete ENT screening for detection of lesions in any portion of the upper aerodigestive tract [2]. Leukoplakia, erythroplakia, oral lichen planus and oral submucous fibrosis are the most frequent PMDs with some geographic and epidemiologic differences (Fig. 1).

The term *Oral Leucoplakia* (LP) describes a white patch or plaque, with an increased risk of malignant transformation (or, in a few cases, it can already be a cancer) having excluded (other) known diseases or disorders that are white (i.e. Frictional keratosis, Acute pseudomembranous candidiasis, Leukoedema, Lichen planus (plaque type) and Lichenoid lesion and reaction, Discoid lupus erythematosus, Hairy leukoplakia, Reverse Smoking). This definition is an exclusion diagnosis and a biopsy is mandatory to explore the pathology, which can range from squamous hyperplasia, to mild, moderate, or severe dysplasia/carcinoma in situ, or to carcinoma. LP is the most frequent PMD. Non-homogeneous lesions have a higher risk of dysplasia or cancer. Severe dysplasia, aneuploidy, loss of heterozygosis, HPV 16+, diameter wider than 2 cm, ventral tongue or floor of the mouth, female sex, age older than 50 years are all risk factors for further progression toward cancer [3]. Smoking habit is a risk factor for the onset of LP, nevertheless, LP in a non-smoking patient could have a higher risk of malignant transformation.

Erythroplakia (EP) is a clinical term that describes a red patch or plaque, with an increased risk of malignant transformation (or in many cases, its pathology shows severe dysplasia, carcinoma in situ or cancer) having excluded (other) known diseases or disorders that appear as red in color (i.e. Oral lichen planus, Discoid lupus erythematous, Pemphigoid and Pemphigus, Kaposi's sarcoma, Erythematous candidiasis, Hemangioma). It often appears as a mixture of LP and EP, known as erythroleukoplakia, since pure EP is rare. Optimum therapy and follow-up (recall) visits for leukoplakia are still debated since relapses and new localizations are frequent, whereas a more aggressive therapy (mainly surgery) and follow-up regimen are suggested for erythroplakia [4].

Oral lichen planus (OLP) is a mucocutaneous inflammatory disorder which can affect the skin and/or mucous membrane. Oral lesions are generally bilateral, white in color on an erythematous base, and typically reticular and/or radiate. The etiology of OLP is still unknown and all of the aspects of immunity have been detected as dysregulated, with an important role played by lymphocyte T cells. Clinical features can vary (reticular, plaque, atrophic erosive and desquamative gingivitis) and in many cases, pain and a burning sensation affect the patients, especially in its atrophic/erosive forms. On the other hand, when clinical and pathological features are not conclusively detected, a final diagnosis of Oral lichenoid lesions can be made [5]. The risk of transformation is around 1.4% per year and tongue lesions, erosive form and female sex are risk factors for

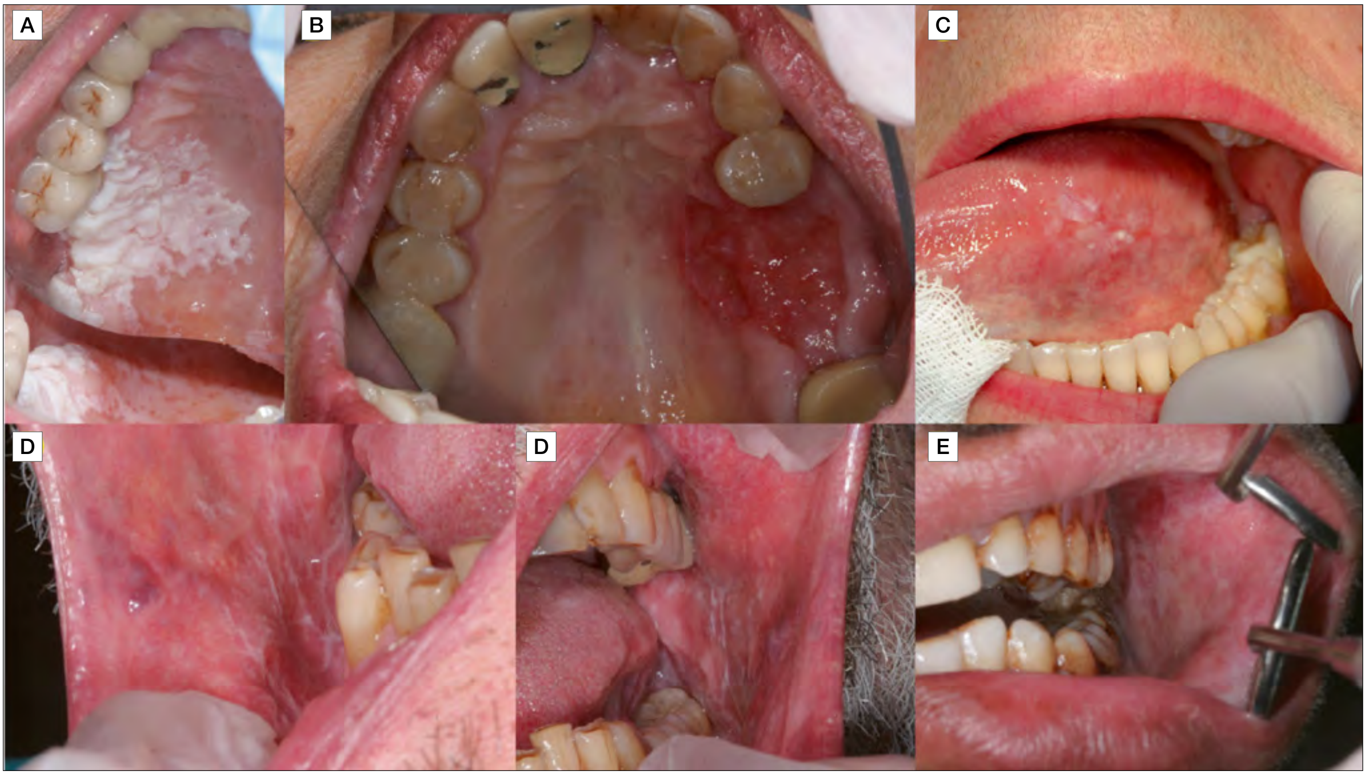


Figure 1. Potentially malignant disorders: the most common are: (**A**) leukoplakia; (**B**) erythroplakia; (**C**) leukoerythroplakia; (**D**) oral lichen planus (same patient); (**E**) oral submucous fibrosis.

transformation, thus OLP patients should undergo a strict clinical follow-up (recall visits every 3 months and biopsies must be performed whenever lesions become more suspicious) [5,6].

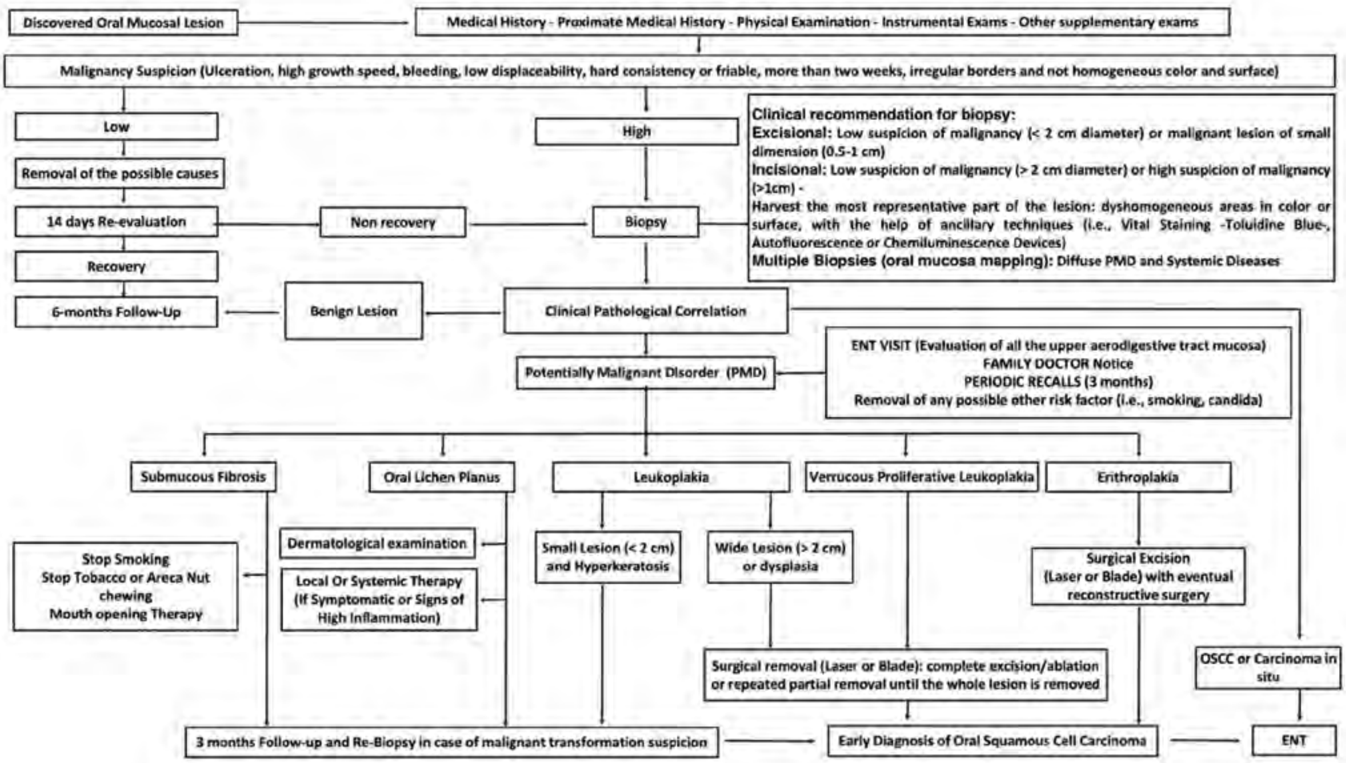
Oral submucous fibrosis is a progressive fibrotic degeneration of the oral mucous membrane predominantly seen in South East Asia and which affects young adults. It is mainly due to the areca nut and use of its derived products (chewing): these products, mixed with tobacco, are stored in the buccal vestibule and chewed. The affected mucosa appears initially inflamed and, with continuing carcinogenic stimuli, it becomes fibrotic, opaque and blanched and finally, movements of the tongue and of the buccal mucosa are impaired with a diminished opening of the mouth. Even though some medical therapies have been suggested [7,8], treatment should consider stopping areca nut chewing, monitoring for malignant transformation, and surgical procedures to improve mouth opening [9,10].

Diagnostic procedures

PMDs, and all pathological tissue removed from the oral cavity, should undergo histological examination to confirm the nature of the lesion. Biopsy can be performed either with a diagnostic-therapeutic purpose (Excisional biopsy) or with just a diagnostic purpose (Incisional biopsy) [11].

No criteria have been defined to choose between an excisional or incisional biopsy, but, since oral cancer therapy varies according to staging, excisional biopsy should only be considered for benign lesions or for small lesions (0.5-1 cm) highly suspicious for malignancy. An excisional biopsy with diagnostic and therapeutic purpose can also be performed in selected lesions less than 2 cm in width, if oncologic radicality can be guaranteed. In this case, the surgical specimen should include at least 1 cm of healthy tissue all around the lesion [12]. Biopsy can be performed either with a cold blade or with laser according to the experience of the surgeon, but the presence and sparing of delicate structures (i.e. arteries, nerves, gland ducts) should be considered.

Indications for incisional biopsy are: 1) lesions of large dimensions, 2) lesions with a high probability of malignancy which could not be completely removed, 3) lesions involving most of the oral mucosa, or 4) lesions that are difficult to reach. The experience of the authors is that incisional biopsy should be performed when malignancy is suspected, even for lesions with small dimensions (1-2 cm width), for at least two reasons: 1) small cancers could have already



ENT: Ear Nose Throat Doctor

Figure 2. Diagnostic-therapeutic flow-chart for Oral Mucosal Lesions, focusing on the clinical management of Potentially Malignant Disorders (PMD) and early diagnosis of Oral Squamous Cell Carcinoma (OSCC).

spread to the lymph nodes and 2) to facilitate the ENT oncologic surgeon in identifying the site of primary malignancy [13].

Incisional biopsy can include part of the healthy surrounding tissue in order to provide some information on possible infiltration, but the biopsy should be collected with the aim of giving the pathologist the most representative part of the lesion (often its center); on the other hand, necrotic areas in large lesions should be avoided because they do not provide useful information. However, during incisional biopsy, attention must be paid to preservation of the original characteristics of the lesion (site, dimensions, margins), in order to ensure the optimal conditions for possible radical excision in the case of malignancy. If the surgeon is unsure about the adequacy of the specimen, multiple biopsies can be performed. A diagnostic-therapeutic flow chart for oral mucosal lesions is proposed in Figure 2.

Diagnosis of intraosseous lesions of the mandible and maxillary sinus

Intraosseous lesions are often the result of problems associated with dentition. Bone biopsy indications mainly include those lesions that do not heal through traditional dental therapies, lesions that apparently have no correlation with dentition, and lesions not specifically identified by clinical and radiographic findings; these lesions can range from benign to malignant (i.e., maxillary sinus carcinomas to myxomas, ameloblastomas, sarcomas, keratocysts and odontogenic cysts). As pathologies in this region are difficult to reach or are in close proximity to important anatomic structures, e.g., tooth roots or nerves, they often represent a challenge [14] to perform a correct biopsy without damaging those structures. Two types of biopsy technique can be used for diagnosing endosseous lesions according to their radiological aspect. Radiolucent lesions, especially those which do not erode the cortex, require the creation of a bone window to be able to biopsy the lesion; all radiolucent lesions should be aspirated before biopsy to obtain valid information on the contents of the lesion such as fluid-filled, solid, vascular or without contents. Radiopaque lesions can be biopsied with special cylindrical drills (trephine drill) capable of coring the bone itself, with a depth indicator to reach the correct depth, and based on an earlier computed

Figure 3. Lateral approach to the right maxillary sinus with bone window repositioning technique.

tomography (CT) scan. At present, guided biopsy of osseous pathologies in the jawbone using a 3D-printed drilling template[14] allows a precise, minimally invasive approach, with an exact three-dimensional determination of the biopsy location before surgery. Moreover, an intraoral approach can easily be performed for intraosseous lesions of the maxillary sinus [15] through the execution of the biopsy on an outpatient basis with local anesthesia (Fig. 3). An important aspect of hard tissue biopsies is to prevent the lesion from invading soft tissues after the biopsy examination [16]; this can be achieved by careful management of the periosteum and by positioning resorbable membranes over the bone breach.

Oral evaluation and prophylaxis before oncologic treatment

It is critical that, after the cancer diagnosis (i.e., during the period of staging procedures) and before any oncologic treatment [17], these patients have an accurate and complete head, neck, oral, dental, and periodontal assessment to optimize treatment and minimize complications or side effects [17]. Assessment should include salivary gland function, the range of jaw opening and temporomandibular joint dysfunctions.

The presence of dental foci and poor periodontal status, in addition to influencing the healing of soft tissues, creates the risk of contamination of plates, screws and bone grafts in bone reconstructions. It is also essential to take into consideration that, after surgery and during adjuvant therapies, dental care is much more difficult. Patients often have considerable difficulty in opening their mouths and coordinating tongue and chewing movements, which are debilitated because of the therapies, and dental problems can be underestimated until they are of particular severity. Furthermore, other known risk factors such as irritation caused by ill-fitting dentures and other rough teeth surfaces must be explored and corrected. Pre-treatment dental care must be personalized and tailored to the patient's oral condition, ability, and specific expected toxicities from the planned anti-neoplastic regimen. The dentist must:

- detect and treat dental and soft tissue infections;
- set up maintenance and prophylactic measures and instruct the patient for the duration of the therapy;
- select healthy dental elements that will support future prosthetic rehabilitation;
- cooperate in the reconstructive choice;
- define the best prosthodontic rehabilitation choice for the patient on the basis of a multidisciplinary comparison.

In addition, at present, dentistry can make use of optical impression systems that can be coupled with three-dimensional reconstructions of CT data to carry out appropriate studies even in patients with advanced disease and in whom it is difficult or impossible to take traditional impressions. These technologies allow the design of temporary prosthodontic rehabilitations by simulating surgical resection and by designing the prosthesis, the temporary obturator or customized bone implants on the basis of the resection.

Currently, multiplanar reconstruction (MPR) and cross-sectional images associated with tridimensional (3D) reconstruction represent the most useful imaging modalities for diagnoses and surgical planning in the head and neck district. With the advent of virtual surgical planning, tumors in the orofacial district require optimization of the diagnostic radiological phase. First of all, whenever possible, it is advisable to have a cervical-maxillofacial district CT examination performed after removing both the fixed and mobile prosthetic metal objects from the patient's oral cavity. This aspect has particular importance, especially as a function of the localization of the tumor and its proximity to metal artifacts, in particular, if there is a fixed supported implant rehabilitation. Optimization of the radiological diagnostic path is therefore up to the clinician, who, according to his/her experience and according to the patient's general condition, will have to immediately request a series of radiological examinations necessary for the staging of the disease but also for the reconstructive programing, especially in cases where the maxillary or mandibular bones are involved. This last consideration translates into requiring a thin-slice CT scan (1 mm) of the maxillofacial complex and at the same time as the donor site [18]. Moreover, it is important to remember that a thin-slice CT scan of this region is of great help in identifying dental foci and in planning dental treatments before oncologic surgery.

Planning of maxillary and mandibular reconstruction, implant therapy and prosthetic rehabilitation

Multidisciplinary ablative, reconstructive and prosthetic programing in Head & Neck oncologic surgery has become imperative to offer patients, even the elderly [19], the best functional and esthetic result, especially when the stomatognathic system is involved. In our experience, this approach has also shown a greater adhesion and participation of patients in the therapeutic process as they are aware of the perspectives given and of the planned final result. Given the multifactorial challenges of maintaining quality of life, nutrition, and particularly oral intake, in this patient group, it is vital that interventions to support eating and drinking address the range of problems which interfere with the physical, functional and psychosocial aspects of opening the mouth, chewing, tasting and swallowing food. Each reconstructive method has distinctive characteristics and capabilities that can affect the subsequent phases of the patient's functional rehabilitation; the consideration of these complexities in jaw reconstruction is reflected in the wide variety of approaches and techniques that have evolved over the past century [20,21].

A primary reconstruction, where possible, generates significant benefits for a patient's residual quality of life and avoids major surgical procedures for secondary reconstruction. With the advent of virtual surgical planning, it is important to plan immediately what the targeted outcome will be, regardless of the timing in which the various steps will be addressed. Preoperative comorbidities can often be the main factor leading to poorer results and are optimized whenever possible. A range of reconstructive options will be available and patient participation in the selection of procedures should be emphasized.

The reconstructive and rehabilitative management of the maxilla and mandible have different characteristics and options depending on the type of resection that will be performed.

Maxillary reconstruction

Maxillectomy defects are complex and involve a number of anatomic structures such as the hard and soft palate, nasal cavity, maxillary sinus and, in some cases, extend to the orbit with various grades of functional impairment. In their systematic review, Bidra et al. [22] have concluded that a description of the defect based on six criteria (dental status, oroantral/nasal communication status, soft palate and other contiguous structure involvement, superior-inferior extent, anterior-posterior extent, medial-lateral extent of the defect) could be more objective and suitable for universal application in a classification system rather than a defect-based description alone.

The reconstructive choice (obturators, local/regional flaps, and microvascular free tissue transfer) depends primarily on the need to be able to clinically inspect the operated region and detect local recurrences. This aspect is strongly linked to the type and extent of the tumor. A prosthetic maxillary obturator, local and regional flaps are generally indicated for smaller defects, while microvascular grafts are highly recommended for larger defects (Fig. 4), with particular reference to defects requiring bone support [23]. An obturator is the only solution able to give the patient a better quality of life when a local, regional or microvascular surgical approach is not feasible due to the characteristics and dimensions of the lesion or to poor systemic-medical conditions [23]. Prosthodontic rehabilitation with a prosthetic obturator restores the missing structures and acts as a barri-

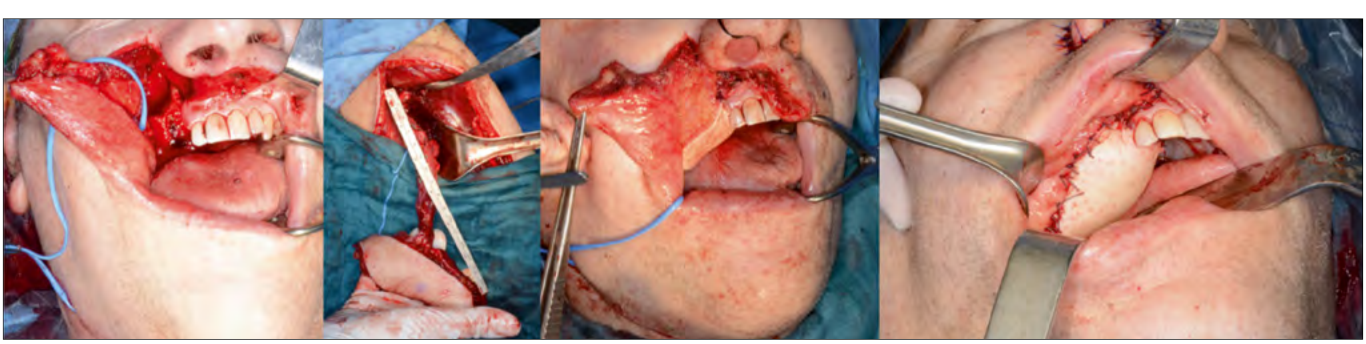


Figure 4. Maxillary reconstruction with fibula osteofasciocutaneous flap.

er to communication among the various cavities. The most common problem with prosthetic treatment is in attaining adequate retention, stability, and support. The size and location of the defect usually influence the amount of impairment and consequently the degree of difficulty regarding prosthetic rehabilitation. Residual dentition and the possibility of implant placement to stabilize the obturator play a key role. Advances in microvascular surgical techniques require comprehensive treatment planning guidelines for functional rehabilitation [24]. Free-tissue transfer offers the most effective and reliable form of reconstruction for complex maxillectomy defects. At present, a combination of reconstructive techniques using local flaps, free flaps and implant-prosthetic procedures allows satisfactory results to be obtained in both functional and esthetic terms. Zygomatic implantology and the advent of customized titanium subperiosteal implants represent new and important therapeutic options from both a reconstructive and rehabilitative point of view [25].

Mandibular reconstruction

Mandibular defects due to major surgery can be classified according to location and extent, as well as involvement of mucosa, skin, and tongue. From the point of view of bone, mandibular defects can be continuous or discontinuous in relation to the bone invasion by the tumor and the possibility of being able to perform a marginal or segmental mandibulectomy.

Vascularized bone flaps, in general, provide the best functional and esthetic outcome, with the fibula flap remaining the gold standard for mandible reconstruction in segmental mandibulectomy. This flap can be modeled with multiple osteotomies and can provide bone, muscle and skin for composite reconstruction. Oral tongue/floor of mouth squamous cell carcinoma with a depth of invasion up to 10 mm involves extrinsic muscles, and lingual neurovascular/lymphatic bundles require a "compartmental" hemiglossopelvectomy to improve locoregional control by "en bloc" removal of tumor and its pathways of spread [26,27]. Compartmental surgery (CTS) has been proposed in advanced lesions with the intent to remove the tumor en bloc, within the entire hemitongue and floor-of-mouth compartment, along with the tract between the primary tumor and neck lymph nodes, the T-N tract, and draining lymph nodes, thus standardizing the surgical technique and improving locoregional control [28].

The introduction of computer-assisted mandibular reconstruction (CAMR) with the pivotal role of virtual surgical planning has further increased the accuracy of the preoperative plan and gives greater precision to the surgical procedure and a reduction in surgical time [18]. At the present time, virtual surgical planning is a recognized technology for optimizing surgical outcome and minimizing operating time. Recent advances in mandibular reconstruction could be further refined through the application of the "two arches" concept. To optimize the outcome of the free fibula flap in mandibular reconstruction, the central portion of the mandible can be divided into upper and lower arches during preoperative evaluation and planning [29] in order to reconcile both the functional dental rehabilitation needs and the esthetic ones dictated by the lower edge of the mandible. CAMR allows osteotomy lines to be easily programed oblique to the long axis of the fibula and mandible in an attempt to increase the contact area between the two bone surfaces [30]. The combination of mandibular and fibular cutting guides and templates allows a precise and seamless surgical reconstruction; this technology is especially useful in minimizing operating time in complex defects where an osteofasciocutaneous flap is used for defect reconstruction and multiple osteotomies are required for bone modeling.

The possibility of accurately programing the position of the bone segments is also important in the patient's prosthetic rehabilitation; accurate occlusal restoration is definitely a key point to maintain stability over time without functional repercussions at the articular level; however, satisfactory rehabilitation only becomes achievable with a correctly positioned implant [31]. Dental implants in patients with fibula flaps are an appropriate and successful option for dental rehabilitation, even in those with risk factors such as smoking, alcohol use, and irradiation [32]. Implant virtual planning during CAMR must be considered an integral part of the reconstructive program to place fibular segments in the optimum position from both a functional and esthetic point of view regardless of their effective placement during surgery [31] (Fig. 5). Moreover, correct programing, in selected cases, can also allow the use of dental implants to stabilize the bone segments in reconstructions that require a double barrel fibula flap [31]. CAMR offers the possibility of programing and executing both mandibular reconstruction and prosthetic implant rehabilitation in a single surgical and prosthetic session called "jaw in a day". This procedure requires very accurate programing from both a surgical and implant-prosthetic point of view and careful coordination between all of the teams during surgery. We should remember how CAMR plays an important role in secondary mandibular reconstructions too. The possibility of programing reconstructions using the mirroring technique to restore good mandibular symmetry makes this type of reconstruction highly predictable from an esthetic and functional point of view. On the other hand, patients with advanced stages of oral cancer and reconstructed mandibles are nearly always additionally treated with radiotherapy and/

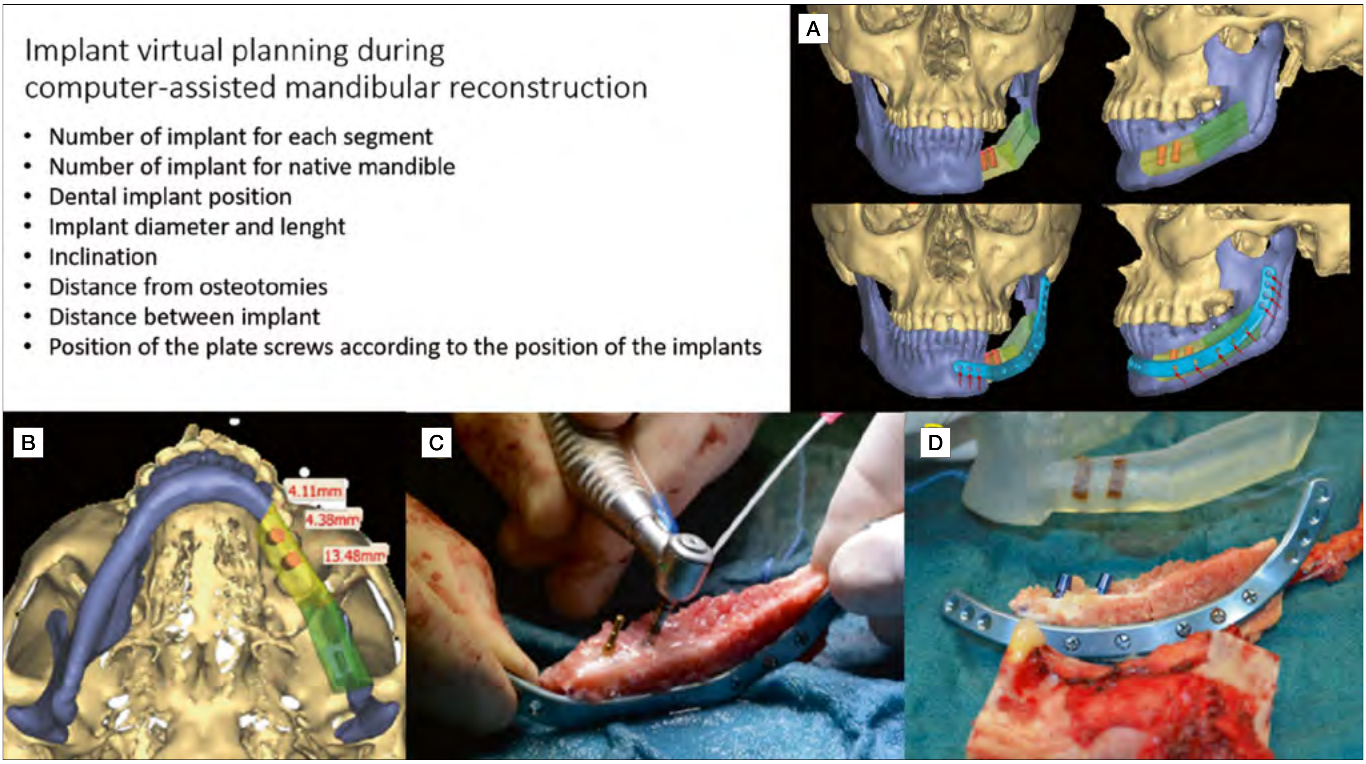


Figure 5. CAMR (**A**) with implant virtual planning (**B**); intraoperative positioning of implants into the fibula (**C**); final reconstructive complex (**D**): plate, fibula flap and dental implants.

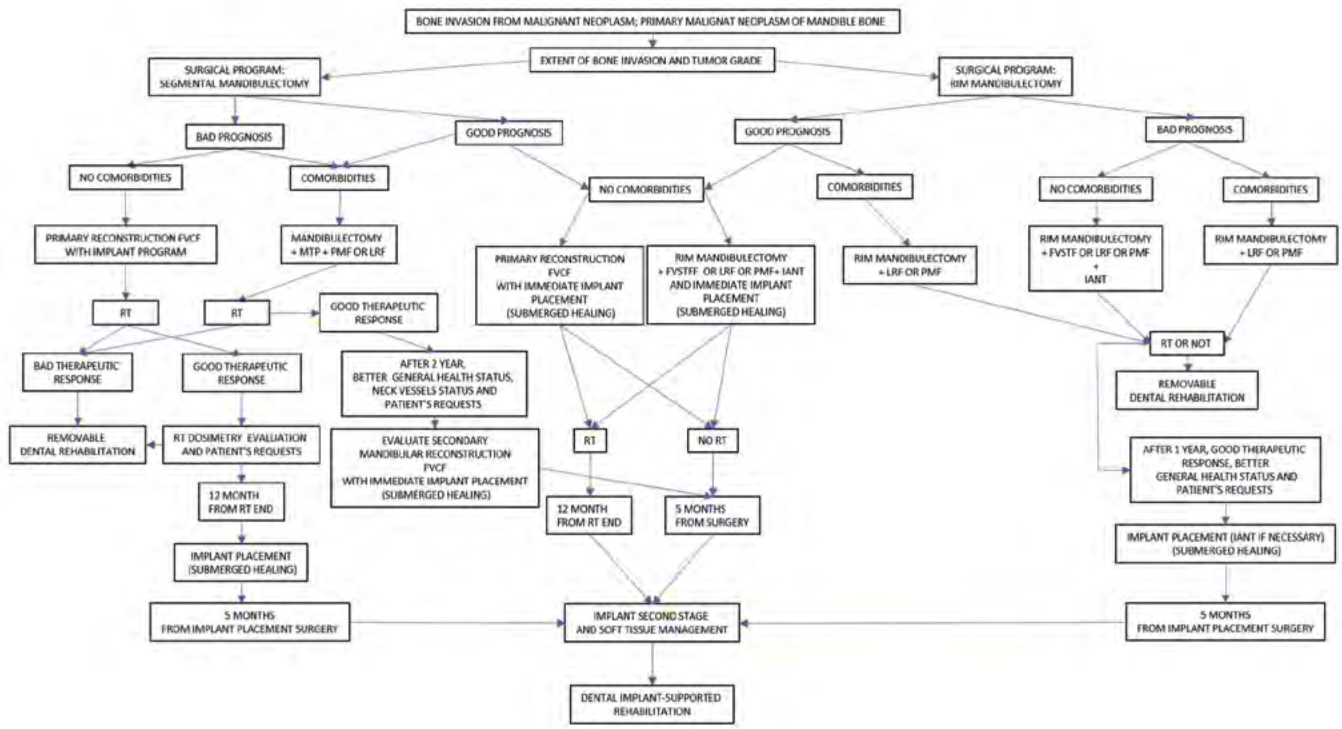
or chemotherapy. The combination of these treatment modalities increases the risk for impaired wound healing after secondary (pre)prosthetic surgery, despite precautions such as hyperbaric oxygen therapy. Therefore, the patient's need and desire for dental rehabilitation must be weighed against the risk of complications after (pre)prosthetic surgery.

Implant surgery and prosthetic rehabilitation

Improvement in oral function and related quality of life would be expected with correct prosthetic rehabilitation. The main problems that may hamper proper prosthodontic rehabilitation of these patients include a severe reduction in the neutral zone, an impaired function of the tongue, and a very poor load-bearing capacity of the remaining soft tissue and mandibular bone.

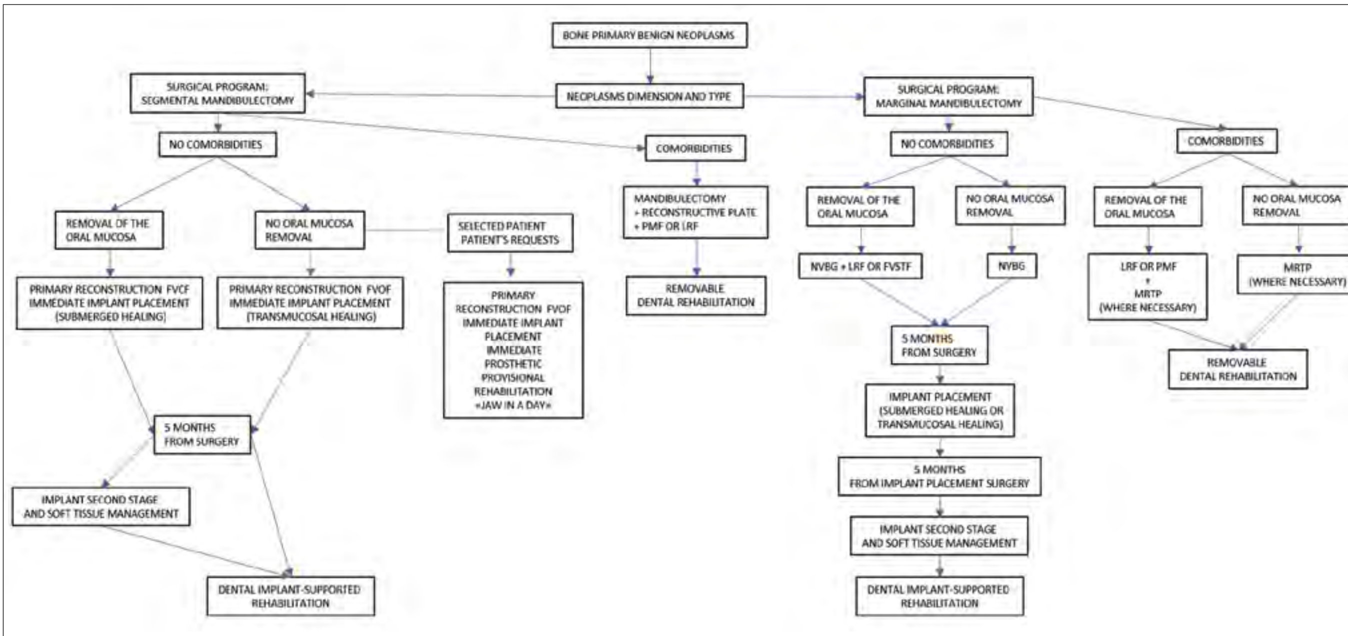
From a prosthetic rehabilitation point of view, it is very important to consider how radiation therapy can influence the reconstructive dental therapeutic program and procedures, although a definitive decision on radiotherapy (RT) is usually made after definitive histological examination. The evolution of implant hardware and improvement in treatment strategies during recent years have affirmed that dental implant-supported rehabilitation is a valuable treatment option for patients with a history of RT in the head and neck region [33,34]; one of the most debated aspects is when dental implants must be placed to have the least possible complications [34]. The presence of dental implants does not increase the risk of complications after surgery or during radiation treatment. Implants do not alter radiation dosimetry but do appear to positively impact early postoperative patient quality of life [31]. Based on the international literature [35-40] and personal experience [18,31,41,42], the authors recommend following what is reported in Figures 6, 7 and 8.

A further aspect that plays a fundamental role in patients reconstructed and rehabilitated with supported implant prostheses is the management of peri-implant soft tissue. The reconstructed soft tissue lacks the physiological properties and function of native mucosa. In reconstructions where an intraoral skin component is present, after implant-prosthesis restoration, excessive soft-tissue bulk, movement, chronic inflammation and hypertrophy are readily observed around implants and risk compromising the long-term success of the implant. Various clinical reports suggest different approaches, with contradictory results. A detailed soft-tissue analysis in these patients is essential. It is clear that normal attached gingiva and alveolar mucosa differ from soft tissue reconstructed with skin and muscle [36]. It is very important that these cases are treated and managed by specifically trained implantologists (Fig. 9).



FVCF: free vascularized composite flap; FVSTFF: free vascularized soft tissue flap; LRF: local/regional flaps; PMF: pectoralis major flap; IANT: inferior alveolar nerve transposition; MTP: mandibular reconstructive plate

Figure 6. Mandible malignant neoplasms with bone involvement: reconstructive and dental rehabilitative program.



FVCF: free vascularized composite flap; FVOF: free vascularized osteofascial flap; FVSTF: free vascularized soft tissue flap; LRF: local/regional flaps; PMF: pectoralis major flap; NVBG: non vascularized bone graft; MRTP: mandibular reinforcement titanium plate

Figure 7. Mandible benign neoplasms with bone involvement: reconstructive and dental rehabilitative program.

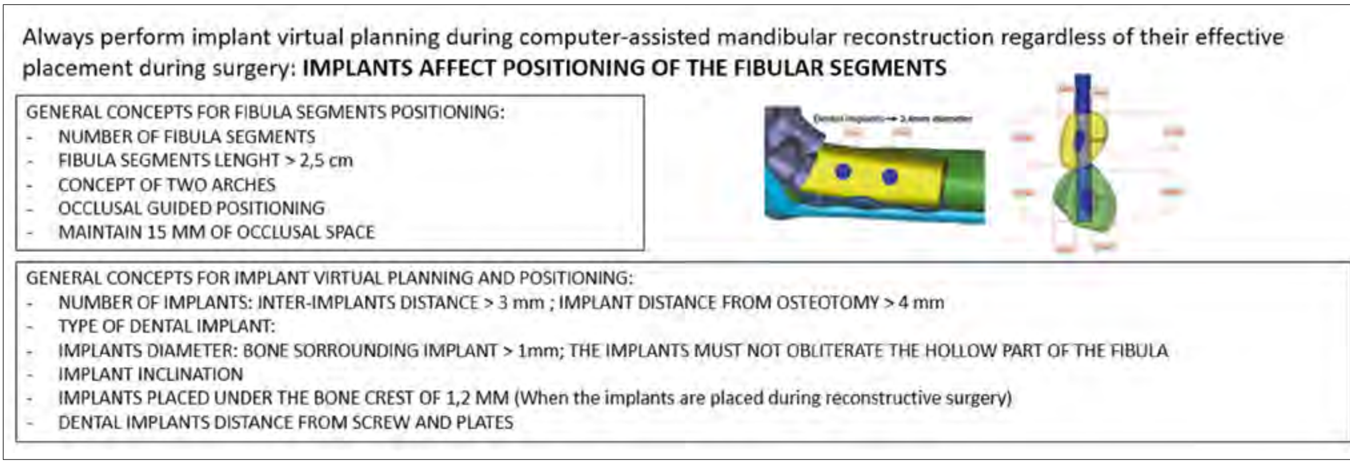


Figure 8. General concepts for fibula segments and dental implants planning and positioning.

Figure 9. Prosthetic implant supported rehabilitation after mandibular reconstruction with fibula free flap.

On the basis of the above considerations, the importance of a multidisciplinary approach is clear. To date, not all of the Italian national health care system offers oral rehabilitation after Head & Neck cancer treatment: the Italian health system does not consider the functional and esthetic rehabilitation of patients who have undergone impairments to the stomatognathic system due to radical surgery for tumor removal since prosthetic and implant rehabilitation is subject to prohibitively high costs. Moreover, it is necessary to train specific staff so that they have a complete knowledge of both the oncologic problems and the most suitable rehabilitation techniques for these patients (Fig. 10).

Management of radiotherapy complications and oral health supportive care

Radiotherapy (RT) now plays a fundamental role in the treatment of HNCs, and nearly 75% of all these patients undergo this therapy with curative, adjuvant, or palliative intent [43]. Unfortunately, RT, especially when combined with chemotherapy, may cause acute and/or late onset side effects on oral and maxillofacial tissue, and in particular, osteoradionecrosis (ORN), oral mucositis, hyposalivation, and dental caries [44]. The development of more accurate RT techniques (e.g. intensity-modulated radiation therapy

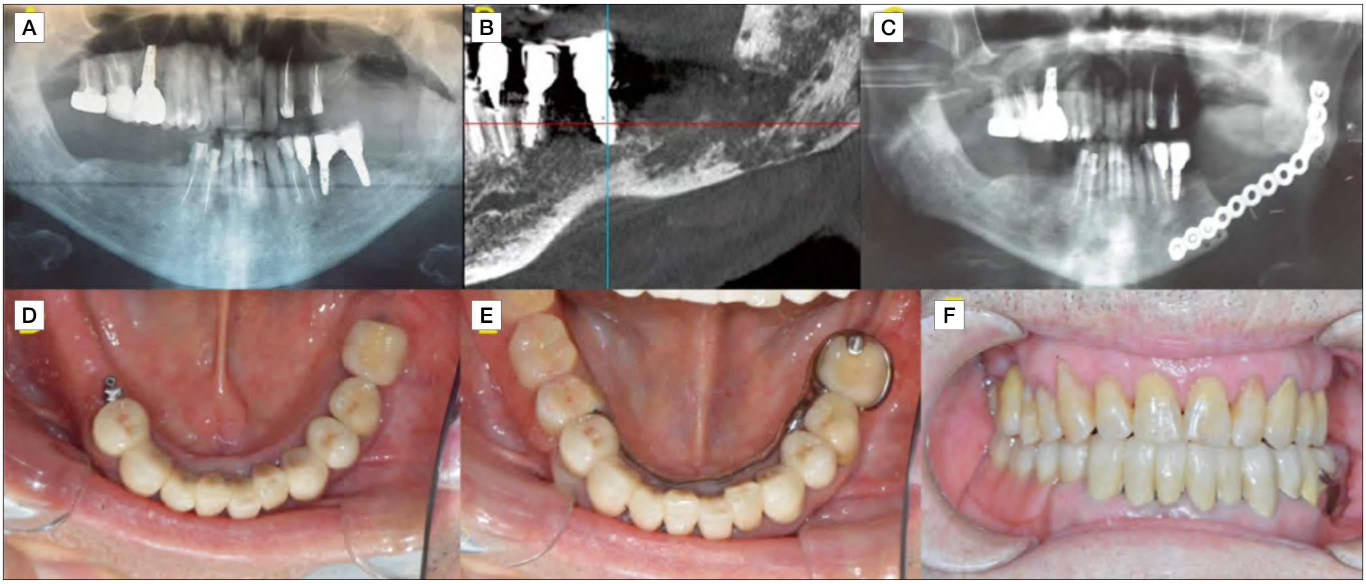


Figure 10. ORN of the left jaw (**A**); dental implant involvement in the ORN (**B**); orthopantomography after 3 months from surgery (left mandibulectomy, reconstructive plate with pectoralis major flap (**C**); conventional prosthetic dental rehabilitation (**D-F**).

(IMRT) has decreased the number of side effects in the oromaxillofacial district [45]; nevertheless, ORN remains the most important event which can sometimes impair a patient's quality of life.: it can occur in 2 to 22% of irradiated patients.

Osteoradionecrosis can be defined as irradiated exposed necrotic bone which has not healed over a 3-month period, in the absence of cancer recurrence [46]. Since teeth extractions are risk factors for ORN development [47], a thorough dental examination and removal of oral foci are generally recommended before starting RT to minimize the risk of ORN. The removal of oral foci before RT, taking advantage of the healing capability of unaffected bone and mucosa, seems to reduce ORN onset. No evidence-based guideline exists to help the clinician in the decision-making process, but some indications, mainly based on expert opinion, may be highlighted: impacted third molars with radiographic signs of pericoronitis, teeth with periapical lesions, unrestorable teeth, and teeth affected by periodontitis (Pocket Probing Depth (PPD) ≥ 5 mm, Clinical Attachment Loss (CAL) ≥ 8 mm, Grade 2 Tooth Mobility or worse, Grade 2 Furcation Involvement (FI) or worse) should be extracted. Every tooth extraction should be performed with antibiotic and antiseptic prophylaxis in order to prevent any possible socket infection and protect the reparatory mechanisms of the wound. Furthermore, a minimum interval of 15 days should elapse between the last extraction and the beginning of RT. In the case of ORN onset, its treatment can be non-surgical (encouraging oral hygiene improvement, prescribing local or systemic antibiotics, hyperbaric oxygen (HBO) therapy) [48] or surgical (debridement of necrotic bone, sequestrectomy, mandibular excision) [49].

Oral mucositis (OM) is an acute response to treatment that affects most patients receiving RT or chemotherapy for HNC. In patients receiving a typical 6- to 7-week course of RT, OM presents as erythema of the oral mucosa in the first 2-3 weeks of RT and progresses to ulceration and pseudomembranes as the dose of radiation increases [50]. The general long-term prognosis is reasonably good since most lesions resolve within 2-4 weeks after stopping RT or chemotherapy. Although OM is considered to be a self-limited injury in some patients, it could be a lethal injury in moderately to severely ill patients, which could lead to obligatory cessation of RT. Since an established treatment does not exist, OM prevention can be crucial. Benzydamine mouthwash can be used to prevent OM in patients with HNC receiving moderate dose radiation therapy (up to 50 Gy), without concomitant chemotherapy [51]. Although many studies had stated that sucralfate has no significant advantage for preventing OM in patients receiving chemoradiotherapy, a recent systematic review found that cancer patients treated with sucralfate mouthwash before receiving chemotherapy had a significantly reduced incidence of severe OM compared with controls [52].

Xerostomia and hyposalivation remain a significant burden for many individuals treated with RT. Several treatment strategies have been proposed for the management of xerostomia and they all aim to reduce patients' symptoms and/or increase salivary flow. Easy remedies are proper hydration, an increase in humidity at night-time, avoidance of irritating toothpaste and crunchy/hard foods, and the use of sugar-free chewing gums/candies. Medications include mucosal lubricants, saliva substitutes, and saliva stimulants. Hyposalivation and oral flora impairment are often the cause of a high predisposition to dental caries. Prevention of dental caries should be directed at the treatment of xerostomia-related complaints, oral hygiene, change of diet, control of cariogenic flora, and the use of frequent fluoride applications. With a daily topical 1.0% sodium fluoride gel application by custom-made fluoride carriers, caries occurrence can be greatly reduced. Due to the previously mentioned hyposalivation-related problems, fluoridation has to be continued on a lifelong basis (if hyposalivation persists), and high concentrations in toothpaste (5000 ppm fluoride) obviously fulfill the oral hygiene needs of these patients.

Tooth extractions performed after RT have been identified as the main risk factor for the development of ORN; for this reason, dentists should prevent dental diseases to minimize the number of extractions after RT [53]. Unfortunately, irradiated patients have a higher risk of developing dental caries and periodontal disease, which can give rise to oral foci and these are the main reason for tooth extraction in the general population. To prevent ORN and ensure that Head & Neck cancer patients have a higher quality of life, it is crucial to instigate a strict follow-up protocol, with a minimum frequency of every 6 months with continuous assessment of periodontal conditions and accurate caries detection.

The diagnostic procedure usually includes an assessment of the following:

- oral hygiene and plaque index;
- determination of sites with periodontal inflammation (bleeding on probing (BoP) or infection (suppuration); assessment of clinical probing depths;
- evaluation of existing reconstructions and vitality checks on teeth;
- examination for carious lesions. This is crucial in irradiated patients, due to their high risk of developing caries; early detection allows the clinician to easily restore a tooth, preventing the risk of developing oral foci.

This phase is followed by the scaling and root planning of periodontal sites, by assessing the motivation of the patient with regard to his oral hygiene, and a re-instruction on oral hygiene procedures.

Supportive care for oral health should include the measurement of salivary flow, since, when the salivary glands are within the irradiated field, irreversible damage to the salivary glands occurs in 63-93% of patients.

Conclusions

Head and Neck cancer treatment is intrinsically complex, and at the present time, it is necessary to create and make available measures capable of dealing with the disease in a multidisciplinary [54] way and with multimodality treatments. It is important to emphasize that it takes years of strict collaboration between ENT and dentists to reach a good working relationship, and garner sufficient experience and familiarity with oncological therapies. This also becomes possible through the organization of interdisciplinary training courses which, in addition to training new operators, allow continuous comparison and updating between the teachers themselves.

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Surgical multidisciplinary approach in the management of odontogenic or non-odontogenic neck infections

Gestione chirurgica multidisciplinare delle complicanze cervicali nelle patologie odontogene o non odontogene

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SUMMARY

In recent years, in our university hospital, the number of odontogenic and non-odontogenic abscesses has been rapidly increasing. We included 70 patients from January 4th 2018 to February 19th 2020 affected by the odontogenic ones. Deep neck infection can spread to the chest and is associated with high morbidity and mortality. The purpose of this mini-review is to demonstrate that, in case of complications, a multidisciplinary approach is needed to treat these infections, so that all practitioners should work together to achieve the patient's rapid recovery.

KEY WORDS: multidisciplinary team, head-neck, dental disease, abscesses

RIASSUNTO

Negli ultimi anni, nel nostro ospedale universitario, il numero di ascessi cervicali, odontogeni e non odontogeni, si è mostrato in rapido aumento. Dal 4 gennaio 2018 fino al 19 febbraio 2020 abbiamo valutato 70 pazienti affetti da ascessi di natura odontogena. Le infezioni degli spazi profondi del collo possono portarsi fino al torace ed hanno un alto tasso di morbilità e mortalità. Lo scopo di questo studio è di dimostrare che, in caso di complicanze, è richiesto un approccio multidisciplinare per trattare queste patologie. Quindi tutti gli specialisti coinvolti dovrebbero collaborare per ottenere una rapida ripresa delle condizioni del paziente.

PAROLE CHIAVE: *team multidisciplinare, testa-collo, patologie odontogene, ascessi*

Introduction

Dental infections are very common and are mainly due to dental caries. They affect mostly men, between the third and fifth decades, with underlying systemic disease (as diabetes), from a rural background, with poor oral hygiene and lack of dental care [1-3]. The clinical progression of these infections can lead to the appearance of an abscess. Deep neck abscesses of non-dental origin can be caused by peritonsillar or retropharyngeal abscess, sialoadenitis, epiglottitis, cervical lymphadenitis, jugular intravenous drug use and trauma, as well as iatrogenic causes including infection of surgical wounds [4]. The abscesses have many complications that affect the head-neck district. They are potentially lethal, and consist of upper airway obstruction, mediastinitis, necrotizing fascitis, thoracic empyema, jugular vein thrombosis, sepsis, orbital abscess and osteomyelitis [5-8].

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With the advent of modern antibiotics, the mortality rate associated with complications has significantly decreased [8]. The treatment of complications often requires a multidisciplinary surgical approach that can involve the otolaryngologist, the dentist, the maxillofacial and thoracic surgeons and sometimes the general surgeon.

Odontogenic neck infections

As Buckley et al., in the last few year, we have seen an increasing number of patients who went to the emergency room for neck abscesses due to dental infections [2]. The bacteria responsible for dental infection are often the ones of the dental plaque. In fact, Buckley [2] and Prabhu et al. [9] proved, from the pus samples, that Streptococcus Spp and Staphylococcus Aureus were the most common bacteria found. WHO Global Oral Health Data Bank reports that dental caries is still a major health problem in most industrialized countries as it affects 60-90% of school-aged children and the vast majority of adults [10]. It is one of the most frequent causes of consultation on dental issues. In most cases the origin of the infections are the inferior molars, and the periapical periodontitis is determined by caries in 90% of cases. (Figs. 1, 2) As Martins and Chagas said in their paper review, when the infections are immediately localized and diagnosed, the treatment is based on dental care such as endodontic therapy or removal of the infected part, usually one or more teeth, combined with specific antibiotic therapy, if necessary [11].

Pulp necrosis, caused by dental caries, represents the most common way of diffusion. The bacteria responsible for the caries, after causing septic pulpitis and pulp necrosis, reach the periapical region through the root canal region [12]. Pulp necrosis can also be caused by periodontal diseases: the periapical region's contamination happens after the propagation of the infective process through a deep periodontal pocket [13]. It is even possible a retrograde contamination of the apex: infective processes, passing through surrounding anatomical structures (for example a maxillary sinusitis or a cystic infected lesion), can extend to the periapical region of the adjacent tooth, causing its necrosis. Therefore, it is necessary to check the vitality of the teeth that could have been infected.

Regarding pericoronitis, the incomplete eruption of a tooth can promote the bacterial proliferation in the region between the crown of the tooth and the surrounding soft tissues. In case of more aggressive forms, it can extend to the outlying tissues [14].

Typical signs and symptoms of cervical complications from dental origin are fever, neck mass, lymphadenopathy, trismus and odynophagia. It is important to support clinical diagnosis with contrast-enhanced CT imaging and ultrasound.

Figure 1. Ludwig angina, bilateral submandibular phlegmon caused by lower molars caries.

Non-odontogenic neck infections

Deep neck infections of non-dental origin are mainly due to peritonsillar abscesses, adenoiditis, epiglottitis, sialadenitis and otomastoiditis. Peritonsillar abscess is the most common deep infection of the head and neck. Most cases are consequences of recurrent or chronic bacterial tonsillitis, leading to abscesses in the parapharyngeal space. It is most common in patients 20-40 years of age, with no gender predilection. Although rare in childhood, peritonsillar abscess has a greater risk of airway obstruction in paediatric population than in adults. Patients may present with changes in voice, odynophagia, drooling, dysphagia, trismus, and systemic symptoms such as malaise and fever. The most common pathogens are β-*Haemolytic Streptococcus*, *Pneumo-*

Figure 2. Left parapharyngeal and cheek phlegmon caused by upper third molar dysodontiasis.

coccus, Staphylococcus aureus and Haemophilus influenzae. Infection, that penetrates the fibrous tonsillar capsule and the peritonsillar space, may continue to extend into the masticator, parapharyngeal, or submandibular space. Imaging is not performed routinely as the diagnosis is clinical. However, CT with contrast agent is used if the diagnosis is uncertain, and typically shows fluid density with peripheral enhancement adjacent to an inflamed tonsil.

Infections of the retropharyngeal space generally result from the spread of infection from one site with a primary drainage route to the lymph nodes of the retropharyngeal space. In these cases, the causes can be otitis, pharyngitis, tonsillitis and infections of the oral cavity [5].

An abscess occupying the retropharyngeal space can also derive from adenoiditis. The retropharyngeal lymph nodes affected by the infection become enlarged and suppurate. On contrast-enhanced CT, a retropharyngeal abscess appears as a collection of low attenuating fluids that dilates the retropharyngeal space with enhancement of the peripheral border (Fig. 3).

Deep neck infections may also be due to sialadenitis, that are multifactorial diseases that can be acute or chronic. The most frequent cause of purulent sialadenitis is sialolithiasis. Salivary duct stones are present in sialadenitis which involves approximately 10-20% of parotid glands and 80-90% of the submandibular glands. Since obstruction of the salivary duct plays a significant role in sialadenitis, most cases occur in the submandibular glands, which are most frequently affected by sialolithiasis. CT is one of the main modalities for evaluation for sialadenitis and can demonstrate an enlarged salivary gland with increased attenuation, increased enhancement poorly defined borders, surrounding fat stranding, lymphadenopathy, and thickening of platysma and adjacent cervical fascia. Ultrasound is a valid alternative even if it turns out to be a less accurate examination. MRI makes it possible to distinguish acute and chronic sialadenitis.

The submaxillary gland can be the origin of an infectious process that reaches the perivisceral space directly or remains confined to the submaxillary lodge itself [15]. The different evolution depends on some anatomical variants. The middle cervical fascia can completely circumscribe the submaxillary lodge separating it from the perivisceral space. In other cases, the middle cervical fascia inserting itself on the hyoid bone (Charpy-Moresten anatomical variant) or on the sheath of the digastric muscle (Truffert anatomical variant), does not reach the medial aspect of the mandible resulting in a communication between the submaxillary lodge and the perivisceral space.

Due to a similar etiopathogenesis, a phlegmon or perivisceral abscess can originate from the parotid gland; the invasion of the perivisceral space is caused by the lack of a true capsule on the deep edge of the gland.

Bezold's abscess is a rare complication of acute otomastoiditis in which the infection erodes, through the medial cortex, the tip or internal surface of the mastoid and causes abscess formation in the sternocleidomastoid muscle that extends into the infratemporal fossa. Due to the depth of the cervical fascia that surrounds the sternocleidomastoid and trapezius muscles, the abscess is impalpable. As the mastoid sinus pneumatises late in childhood, Bezold's abscess occurs more frequently in adults. Due to its proximity to the internal jugular vein, the thrombosis is a possible complication [16].

Antibiotics

Antibiotic therapy for deep neck space infections is based on broad-spectrum antibiotics such as penicillin based,

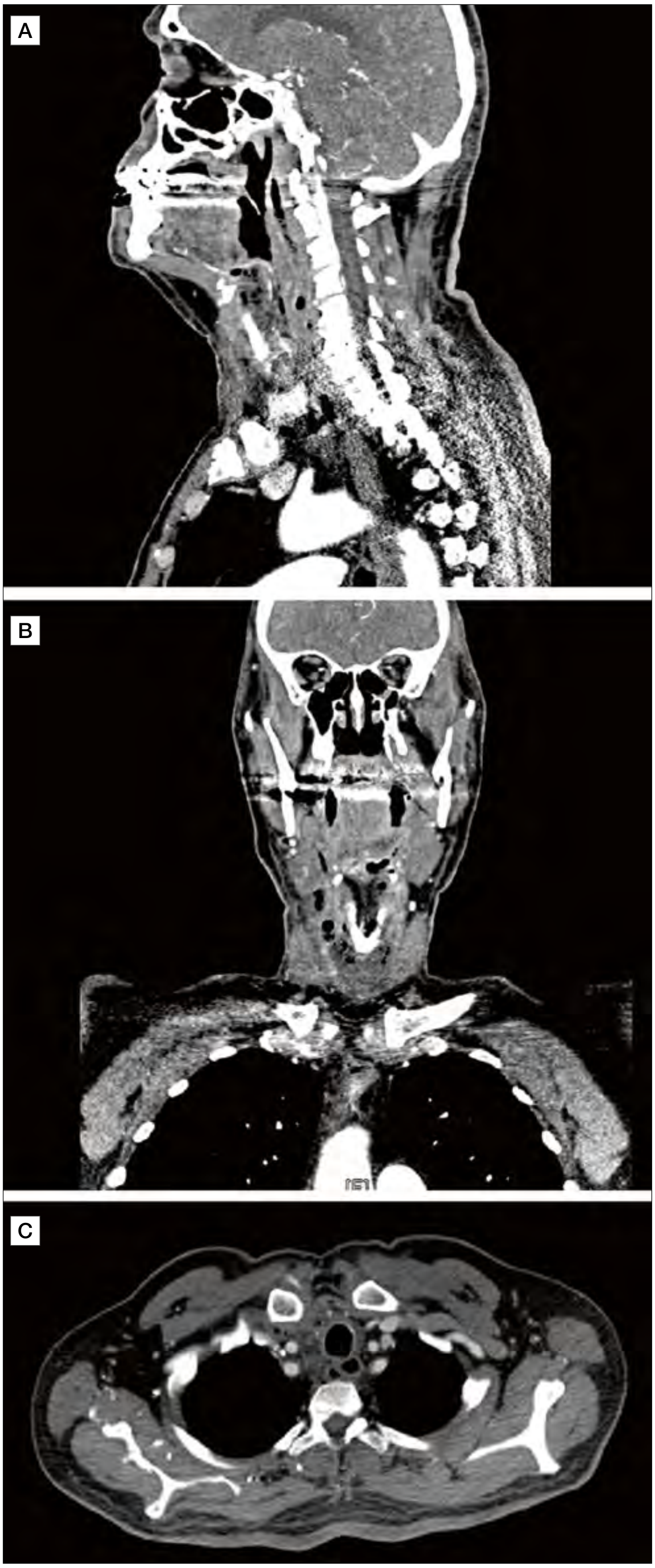

Figure 3. Odontogenic abscess of the upper right arch, partial obstruction of the upper airway. The head, neck and chest CT scan, with contrast medium, documented a phlegmon that reached the mediastinum, through the perivisceral space. (**A**) coronal plane; (**B**) sagittal plane; (**C**) axial plane.

clindamycin, and metronidazole [17]. The literature supports also the use of corticosteroids [18]. The antibiogram is also useful to test the material taken during the operation and to identify the bacteria and to start a target therapy. For this reason, beside surgery, supportive care is unavoidable.

Multidisciplinary management of deep neck infections

Without treatments, the infection can spread into surrounding tissues. When there is airway impairment, sepsis, descending infection, abscess larger than 3 cm, involvement of deep neck spaces or the failure of antibiotics therapy, surgical drainage is necessary. The airway management can be challenging. The main reason for ENT consultation is the evaluation of the air tract [19]. The purpose of the surgery is to eliminate the triggering cause, to drain the purulent material and preserve the airway patency. We need a laryngoscopy to evaluate the obstruction generated at the level of the oropharynx (glossoptosis) or the laryngo-pharynx (peripharyngeal oedema). Compared with elective intubation, emergency intubation is therefore associated with an elevated risk of complications and severe adverse events such as aspiration, a fall in oxygen saturation, or even death. For these reasons, according with Rombey and Shieren, it is better recommended to secure patient's airway via awake fiberoptic intubation and video laryngoscopy [20], that allow intubation of more challenging patients. They are performed under local anaesthesia and sedation and should be performed by an experienced anaesthesiologist. Fang et al. [21] and Ahuja et al. [22] showed that emergent awake tracheostomy should be considered in patients with impeding airway obstruction and is a safe and effective method to secure an airway in these patients. Some studies advocate early tracheotomy in severe deep neck infections in order to decrease the hospitalization in intensive care unit and related complications. Moreover, in severe cases of airway oedema, a prolonged intubation is required, and early tracheostomy can offer several benefits in ICU care compared to intubation such as for example avoiding laryngeal injury caused by prolonged intubation, facilitating nursing care, improving patient comfort by reducing the need for sedation, reducing the need for mechanical ventilation and making faster the discharge. Adley et al. evaluated scientific articles relating to a period of time of thirty years and said that there was a significant difference in favor of early tracheostomy in adults and pediatric group as early tracheostomy was superior regarding reduced duration of mechanical ventilation, with less mortality rates and less duration of stay in ICU [23].

In the case of abscesses of odontogenic origin, to treat the infections of cervical space a surgical approach in team with the dentist is almost mandatory, since in most cases it is necessary to perform the extraction of one or more dental elements. As Heim and Warwas proved quite recently, this better happens during the execution of an exploratory cervicotomy [24]. Odontogenic infections spread from mandible or maxilla into the sublingual, submandibular, or masticatory spaces and then into the parapharyngeal space. For this reason, the site of neck incision depends on the affected area. In any case the surgical incision should be placed in healthy skin, when possible, not at the site of maximum fluctuance, because these wounds tend to heal with an unsightly scar. It should be into a natural skin fold, in a dependent position.
Drainage of the submandibular space can be required a subperiosteal intraoral and an extraoral incision. For the external approach the incision should be done approximately 3 to 4 cm below the angle of the mandible. The incision is performed on skin and subcutaneous tissues, to the platysma. The platysma is divided with electrocautery or sharp dissection. Superficial and middle cervical fascia are cut in parallel to the inferior border of the mandible. The dissection continues in a superior-medial direction to enter the submandibular space.
Drainage of the lateral pharyngeal space is approached mainly through an external approach. In this case, neck dissection can be performed according to Paul André's approach [25]. Once reached the SCM muscle, the incision is carried down to the superficial and middle cervical fascia, and the carotid sheath is identified and opened. Dissection is carried superiorly along the vessels.
In order to reach abscesses affecting the perivisceral space up to the base of the neck, it is possible to extend the Paul André's incision or perform a horizontal or median arch-shaped incision about 3 cm above the sternum dimple. In this case, the perivisceral space surrounding the thyroid and larynx is reached after incision of the superficial and middle cervical fascia.
In people who have large retropharyngeal space abscesses, an external approach is needed. The carotid sleeve is mobilized medially, so it is possible to reach the deep cervical fascia and if necessary, the prevertebral fascia. In selected cases, with single-chamber and circumscribed abscess cavities, endopharyngeal access to the abscess is possible [26-31]. After the abscess has been drained, the drains are placed [32,33]. To date, it is not clear if it is better use passive drains than open ones. Passive drains are made of latex, polypropylene, or silastic rubber. These include Penrose drains and glove finger. They work by capillary action, gravity, overflow, or fluctuations of pressure gradients caused by body movement. To reduce the risk for ascending infection, passive drains should be covered with a sterile bandage that is placed and aseptically exchanged. if it does not, fluid can lead to severe skin irritation and excoriation in addition to increasing the risk for ascending infection [34].
Active drains, like Jackson-Pratt ones, are closed systems that collect fluid into a reservoir. This decreases the risk for ascending infection and can reduce exposure of hospital staff or other patients to contaminated fluid. Active drains apply an artificial pressure gradient to pull fluid or gas from a wound or body cavity [35].
Through the perivisceral space or the vascular space the infectious process can reach the anterior mediastinum, differently when the abscess involves the third or fourth cervical lodge, respectively the perivisceral space and the prevertebral space, it can reach the chest, causing posterior mediastinitis. In fact, Endo et al. classified descending mediastinitis according to the degree of diffusion of infection diagnosed by computed tomography. Localized descending mediastinitis, type I, is localized in the upper mediastinal space above the carina. Diffuse descending mediastinitis, type IIA, is extended to the lower anterior mediastinum and type IIB reach both anterior and posterior lower mediastinum [36].
Surgery is a complex procedure; thoracotomy and extended cervicotomy is the gold standard approach, as Corsten and Taylor assert in their papers [4,37]. The goal is to drain all the suppurated fluids, to save the organs from the close pus and fibrin collections. These operations give the chance to native tissues to regenerate consequently. Drainages and tissue stimulating dressings can be left in each corner of the affected areas after debridement. More recently, the armamentarium has been improved with a new technology that has shown promising results; the VAC-therapy seems to be associated to a faster resolution of the local tissue damage and some studies has encouraged to use this device more extensively [38].

Conclusions

The number of cervical deep infections has been rapidly increasing in the last years. Abscesses of odontogenic and non-odontogenic origin have a strong tendency to spread between the tissues and to invade the deep spaces of the neck down to the chest. The main reason for ENT consultation is the evaluation of the airway but in many cases, thoracotomy and extended lateral/anterior cervicotomy is required in order to drain all the suppurated fluids. In this scenario, a multidisciplinary approach involving the ENT surgeon, the dentist, the thoracic surgeon and the infectivologist, is the best option to treat such a challenging complication of several head and neck pathologies.

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When is a surgical multidisciplinary approach required in the management of head and neck non-melanoma skin cancer and in advanced head and neck pathologies involving skin?

Quando è indicato un approccio chirurgico multidisciplinare nel management dei tumori primitivi cutanei non melanocitari della testa e del collo e dei tumori localmente avanzati del distretto testa-collo con interessamento della cute?

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SUMMARY

Non-melanoma Skin cancer, including cutaneous squamous cell carcinoma and basal cell carcinoma, is the most common form of malignancy in the Caucasian population, and the skin of the head and neck is the site most involved. They should not be underestimated; in particular, high-risk lesions and advanced skin cancers require accurate diagnostic work up, aggressive surgical treatment and should be managed by the head and neck surgeon, the dermatologist and the plastic surgeon. Cutaneous head-neck malignancies are often overlooked or not routinely treated with a multidisciplinary surgical approach. Similarly, for primary head and neck cancers with involvement of surrounding skin, the involvement of the dermatologist and the plastic surgeon could better define an adequate diagnosis and treatment planning. The management of these patients presents both therapeutic and ethical problems, because the poor prognosis is burdened by facial disfigurement, open malodorous wounds and intractable pain. Therefore, in patients with advanced disease that is not candidate to radical surgery, palliative surgery with flap reconstruction could take place and could be proposed to improve quality of life.

KEY WORDS: non-melanoma skin cancer, head and neck cancer, multidisciplinary team, head and neck reconstruction, palliative surgery

RIASSUNTO

I tumori della pelle non melanocitari, che comprendono soprattutto il carcinoma squamocellulare e il carcinoma basocellulare, sono i tumori maligni più frequenti nella popolazione caucasica, e la cute della testa e del collo rappresenta la sede più coinvolta. Tali tumori non dovrebbero essere sottovalutati, in particolare le cosiddette lesioni ad alto rischio e i tumori cutanei avanzati richiedono un iter diagnostico più accurato e un trattamento chirurgico più aggressivo, che dovrebbe essere gestito coinvolgendo il chirurgo testa-collo, il dermatologo e il chirurgo plastico. Le neoplasie primitive cutanee del distretto testa-collo sono spesso trascurate e non sono routinariamente discusse in seno a teams chirurgici multidisciplinari. Allo stesso modo, per i tumori primari della testa e del collo con infiltrazione cutanea, il coinvolgimento del dermatologo e del chirurgo plastico può più efficacemente definire la diagnosi e pianificare il trattamento. La gestione di questi pazienti pone problemi sia terapeutici che etici, perché la prognosi infausta è gravata da importanti inestetismi facciali, ferite aperte maleodoranti e dolore intrattabile. Pertanto, anche nei pazienti con malattia avanzata non suscettibile di chirurgia radicale, la chirurgia potrebbe ugualmente trovare spazio, ma con finalità palliativa, al fine di migliorare la qualità di vita.

PAROLE CHIAVE: *tumori della cute non melanocitari, tumori testa-collo, trattamento multidisciplinare, ricostruzione del distretto testa-collo, chirurgia palliativa*

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Introduction

Non-melanoma Skin Cancer (NMSC) is the most common form of malignancy in the Caucasian population, and the skin of the head and neck is the site most involved. Basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (CSCC) make up the majority of these tumours [1], while a less frequent histotype is the neuroendocrine tumor that arise from Merkel cells, an insidious carcinoma originating in most of cases on the facial skin. Early stages should not be undervalued because of their propensity to local invasion and heterogeneity; therefore, inadequate treatment can lead local recurrences and uncontrolled skin cancer requiring complex surgery, high patient morbidity and even death [2]. Finally, personalized treatment should be tailored taking into account the best oncological outcome and the best aesthetic and functional results.

The anatomic complexity of the head and neck district and the overlap between the operating fields of the ENT surgeon, the plastic surgeon and the dermatologist, lead to an even more complex surgical approach to NMSC; nevertheless, the histological heterogeneity of tumors involving the skin of the scalp, the face and the neck, often requires a surgical multidisciplinary approach to these lesions, with the aim of a balanced outcome in terms of oncological radicality and aesthetical result. Usually, the dermatologist is involved in the management of small primary skin tumors, due to his predominant role in the diagnosis of these lesions; however, a complete dermatologic evaluation of the skin in all districts is often required by other specialists in case of systemic and diffuse tumors, such as Merkel cell carcinoma. On the other hand, advanced primary NMSCs of the head and neck, with their infiltrative growth pattern, may involve subcutaneous tissue, muscle, bones, peripheral nerves, and lymph nodes, thus requiring an ENT surgical approach. Finally, primary head and neck cancers originating from the epithelial surface of the upper aerodigestive tract (UADT) and from other structures of the head and neck district, such as salivary glands and bone, may extend to surrounding structures and involve the skin of the face and the neck; in these advanced cases, the cooperation between the ENT surgeon and the plastic surgeon often represents the most convenient approach in order to perform a radical and functional resection of the tumours and a concurrent reconstruction with favorable aesthetic results [3]. The management of these patients is complex and challenging for all the specialists involved and it poses both therapeutic and ethical problems, due to the extended resection and the reduction in terms of quality of life after such a surgery. However, although the oncologic radicality should always be the primary aim of the surgeon, patients with very advanced head and neck tumours, originating or extending to the skin, may be considered not eligible for a radical surgery (due to vascular infiltration, distant metastasis or extension to the skull base), but they may benefit from a "palliative surgery", a concept introduced about fifty years ago [4]. Thanks to advances in reconstructive surgery, in particular the use of regional and free flaps, palliative resection and reconstruction is now a reasonable treatment option [5].

A narrative review of the literature was performed to thoroughly investigate on both primary head and neck skin cancer and involvement of facial skin by head and neck tumours, in particular to highlight when surgical multidisciplinary approach is recommended.

Primary skin cancers

Non-melanoma skin cancers

Every year about 3.5 million of NMSC are treated all over the world and almost 75,000 new cases are diagnosed annually [6]. Skin cancer rates have been increasing since the '70s, passing from an incidence rate of 8 per 100,000 to 31 per 100,000 nowadays, with an increase of about 290% [7]. Risk factors for skin malignancy include cumulative sun exposure and/or sunburns, Fitzpatrick skin types I and II, ionizing radiation, acquired or inherited immunosuppression, genetic factors, presence of areas of chronic inflammation after burn or trauma. UVB radiations (290 to 320 nm) may cause direct DNA damage and are involved in aetiology of NMSC. In particular, intense and intermittent sun exposure during first years of life represent a risk factor for BCC and cumulative UV radiation dose seems to be associated with CSCC [8].

The *Basal Cell Carcinoma (BCC)* is an epithelial malignancy characterized by slow growth, that develops from epidermis basal layer. It has an age-adjusted incidence and prevalence of 226 and 343 per 100,000 persons per year, respectively; it presents locally destructive behaviour, but it rarely gives metastasis, occurring in approximately 0.003 percent to 0.1 percent of cases [9]. BCC is the most common skin malignancy all over the world, occurring in almost 80% of cases in head and neck region, with high prevalence on nose skin [10]. BCC is associated with intermittent recreational sun exposure, and genetic factors such as mutations in cell-cycle control genes (i.e. TP53, PTCH1, Sonic Hedgehog pathway) are common. Genetic syndromes like Gorlin syndrome and xeroderma pigmentosum also play a role in some BCCs [11]. Types of BCC are nodular (most common variant), superficial multifocal, sclerosing, infiltrative and morpheaform. About 20% of BCC show infiltrative growth pattern with high recurrence rate. Morpheaform BCC presents as a yellow plaque, similar to a scar, with indistinct margins, that extends widely intradermally. Ulcus terebrans is another aggressive type of BCC that invades underlying structures such as large vessels, bones and meninges; it could be fatal due to haemorrhage or infection [12].

Cutaneous Squamous Cell Carcinoma (CSCC) arises from keratinocytes with a locally destructive and metastatic potential. It affects 100/100,000 men and 50/100,000 women per year, representing the second most common skin cancer. Risk factors are similar to BCC, but specific factors are HPV infections, most commonly correlated to HPV 16 and 18, but also types 31, 33, and 38 have been implicated [13]. The most common gene mutations are TP53, mutations in the RAS family of human oncogenes (HRAS, KRAS) and PTCH1. Deletions in CSCC involve several chromosomes, including 3p, 9p, 9q, 13q, 17p and 17q, with a higher degree of genomic instability compared with BCC and more frequent presence of aneuploid cells [14]. The develop of SCC follows the classic pattern of cancers from precursor lesions (mild, moderate, severe dysplasia) to tumour progression, and subsequent metastasis. Histologic grades range from well differentiated, that show keratinization and dermal invasion of round tumour margin, to poorly differentiated without keratinization and cellular organization, with blurred borders and projections into surrounding tissues [15]. The risk of developing lymph node metastasis in patients with CSCC is 3 to 5%, but increases in high-risk patients with high rates (> 10 to 20%) [16]. Regional nodes can be divided into two groups: parotid (preauricular and parotid tail) and cervical nodes (levels I to V). The site of a CSCC is a determinant of the potential lymph node metastasis. For lesions in the lateral aspect of the head, metastases are commonly identified in parotid, level II and external jugular nodes. Parotid nodes represent the first echelon of lymphatic from the forehead, anterior scalp, temple, face and ear. Facial lesions tend to metastasize also to level I and II; while anterior lesions of the scalp, ear, temple, and forehead usually metastasize also to level II. Lesions posterior to the tragus usually metastasize to level V or to occipital nodes. Drainage to contralateral nodes occurs in 10% of patients, in particular in midline cancers [17].

Bowen disease, also referred as squamous cell carcinoma in situ, appears as a well demarcated, erythematous plaque that slowly enlarges. Ulceration and induration are hallmarks of the transformation to SCC. Progression to invasive SCC occurs at 5% per lesion per year. Treatment options include excision, electrodessication, and curettage [18].

Non-epithelial skin cancers

Merkel cell carcinoma (MCC) (Fig. 1) is a neuroendocrine tumour that, on the basis of histomorphology, gene expression profiling and molecular analyses, has been hypothesized to originate from Merkel cell precursors (potentially derived from epidermal stem cells or hair follicle stem cells), pre-B cells, pro-B cells or dermal fibroblasts. Because normal Merkel cells are terminally differentiated and do not undergo cell division, they are unlikely to be the cell of origin for MCC. Merkel cells derives embryologically from neural crest cells and are receptor cells to somatosensory afferents for touch discrimination. MCC has an occurrence rate of 0.6/100,000 people per year. The skin face is the most common location at about 25%. The risk factors are sun exposure, immunosuppression and polyomavirus (MCPyV) infection; this virus can be found integrated in the genome of more than 80% of tumours [19]. MCC carcinogenesis can be initiated by the clonal integration of the MCPyV genome or UV-mediated DNA damage caused by chronic exposure to sunlight, since UV exposure could also play a part in viral carcinogenesis by causing local immunosuppression. UV radiation induces the expression of inflammatory mediators and functional alterations in the antigen-presenting dendritic cells, which result in a cascade of events that modulate immune sensitivity. MCC clinically presents as a nodular lesion with rapid growth pattern, nontender, fleshcolored or blue-red colored and, due to the nonspecific presentation, clinical diagnosis of MCC is often delayed. Treatment consists of surgical excision with wide margins and particular attention to deep margin. Postoperative radiation is becoming accepted as the standard treatment. Before the advent of immunotherapy, no evidence supported adjuvant chemotherapy benefit [20]. However, over the last few years, the presence of PD-1 and PD-L1 has been demonstrated within tumour and immune cells. For the checkpoint inhibitors pembrolizumab and avelumab, responses of about 50% have been shown [21].

Dermatofibrosarcoma Protuberans (DFSP) is a rare low-grade soft tissue sarcoma; it is locally aggressive, with high rates of local recurrence but less than 5% tend to metastasize. DFSP affects 0.8 to 4 cases per million annually and most commonly arises in the 3rd decade of life, but also pediatric cases occur. Only 14% of DFSP involve head and neck. Patients with unresectable positive margins or metastatic disease may gain benefit from radiation or the tyrosine kinase inhibitors [22].

Malignant tumors of the adnexa (Fig. 2) derive from the pilosebaceous unit and sweat glands, eccrine and apocrine. Among them, tumours that show a predilection toward head and neck district are sebaceous carcinoma, primary cutaneous mucinous carcinoma, microcystic adnexal carcinoma and malignant cylindroma. Risk factors include previous irradiation and immunosuppression. Neck nodal metastasis are reported in 8% of cases but are often under-

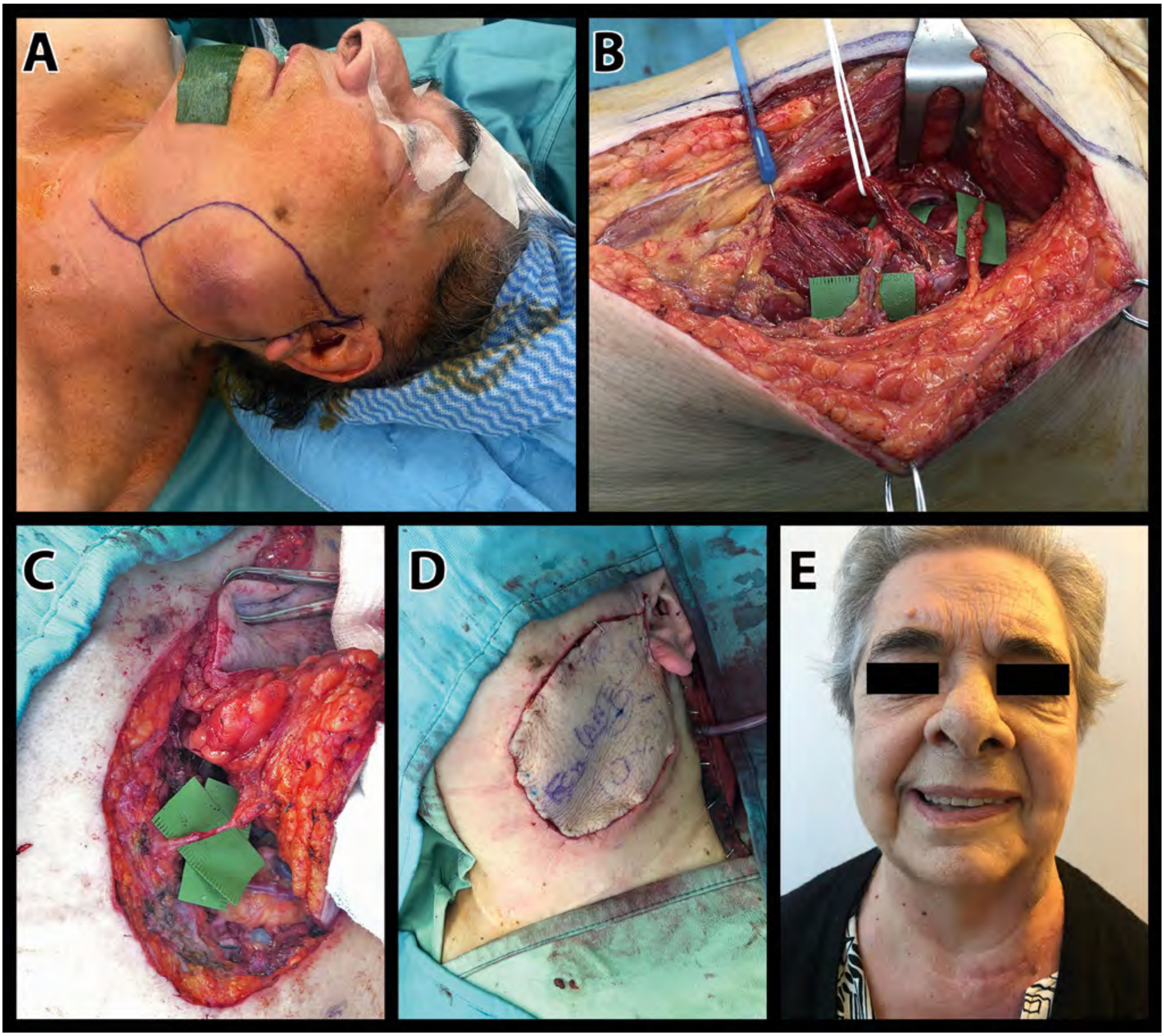

Figure 1. Eighty-three years old woman with parotid gland metastases of a cutaneous Merkel-cell carcinoma of the upper eyelid (treated 1 year before); the patient presented a clinical palsy of the inferior branches of facial nerve. (**A**) external appearance of the tumour; (**B**) harvesting of the ALT flap with preservation of the vascularized femoral-cutaneous sensory nerve for facial nerve reconstruction; dimensions: 9 x 8 cm; (**C**) insetting of the flap and distal anastomosis of the vascularized femoral-cutaneous nerve to the marginalis mandibulae nerve; the proximal anastomosis was performed on the inferior branch of facial nerve; (**D**) final result after vascular anastomosis; (**E**) functional result with smile after 6 months.

evaluated; distant metastasis incidence is quite rare. Local recurrence rate is about 6% after surgical excision. Surgery is the gold-standard, RT can be useful as adjuvant treatment for positive margins or presence of perineural invasion [23].

Diagnosis of primary skin cancers

Diagnosis of primary skin cancers is usually clinical, with subsequent histological confirmation. Following a thorough history and physical examination with palpation of draining lymph node basins, tissue biopsy (i.e., shave, punch, or excisional) remains the standard of care for diagnosing non-melanoma skin cancers [24]. However, in case of the sampling error with punch and shave biopsies, in 11 to 19% of cases a more aggressive histologic subtype may be missed [25,26]. Patients commonly report a remote history of a previously resected cutaneous malignancy, which may explain new-on-

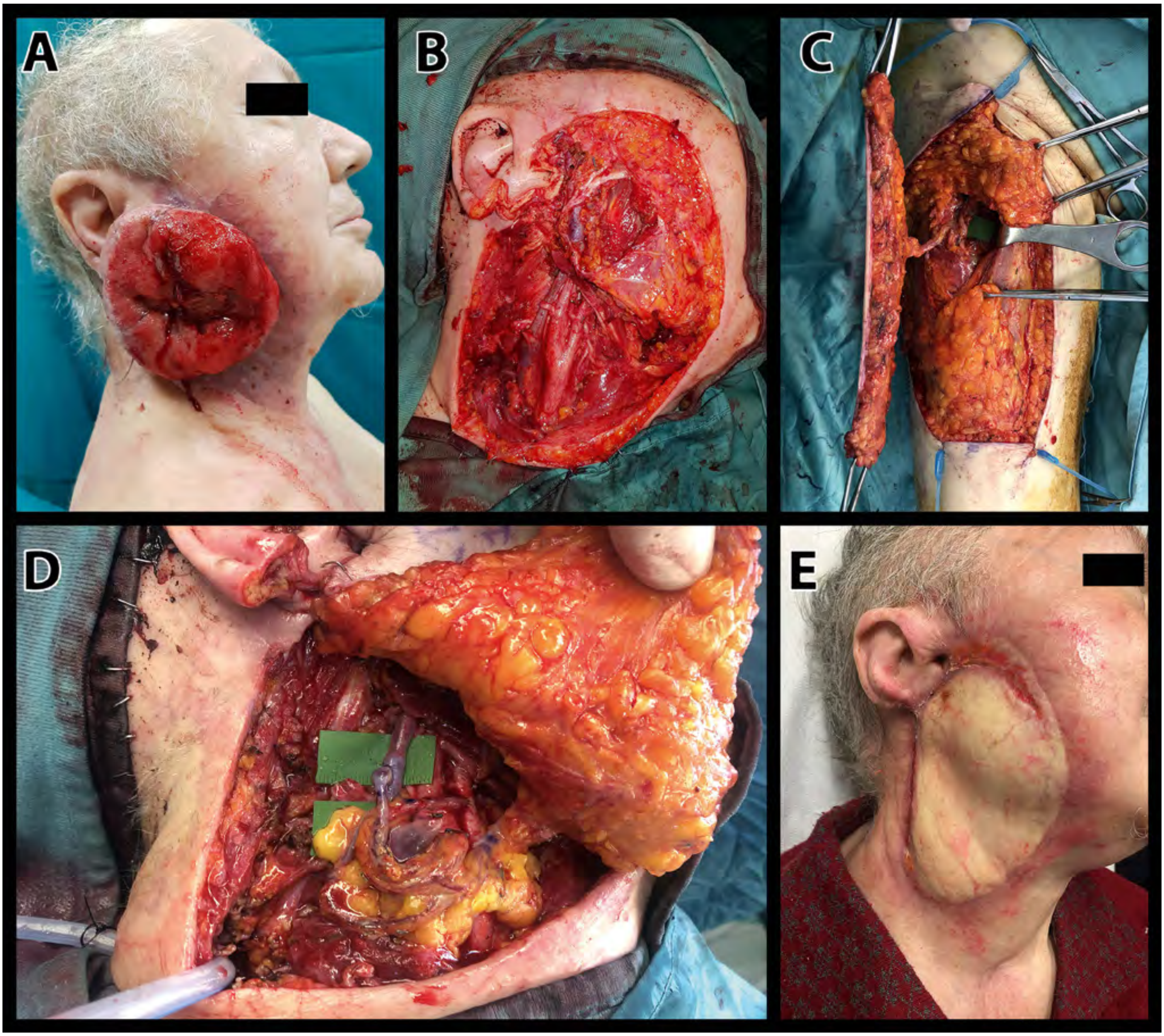

Figure 2. Seventy-nine years old woman with sebaceous carcinoma of the skin, extended to the external ear and parotid gland. (**A**) external appearance of the large tumour;(**B**) surgical resection of the tumour and total parotidectomy (with facial nerve preservation) extended to the lobule and the concha of the external ear; (**C**) ALT flap harvesting; dimensions: 13 × 10 cm; (**D**) insetting of the flap and anastomosis on the external carotid artery and internal jugular vein (double venous anastomosis); (**E**) Final result after 1 month.

set neck adenopathy, facial paresthesia, or a facial nerve paralysis. Complaints that suggest perineural invasion include facial weakness, hypesthesia, dysesthesia, and paresthesia. A recurrent lesion may present as a slow growing subcutaneous mass that invades the deep facial or neck musculature. A complete dermatologic examination is necessary for the patient with NMSC in order to find out eventual second primary tumours, especially in the suspect of a MCC, and dermoscopic examination of the lesions can be helpful in differential diagnosis [27]. MCC usually spreads to the regional lymph nodes; thus, sentinel lymph node biopsy (SLNB; that is removal and examination of the sentinel node) represents an important staging procedure and if the lymph nodes of the draining basin are clinically negative, it should be considered and planned at the same time as the wide local excision. The presence of occult nodal metastasis, in fact, is a strong prognostic factor and clinically occult nodal micrometastases are present in about 30% of patients [21].

The most widely adopted staging system for staging CSCC and BCC is the TNM Classification of Malignant Tumours, 8th Edition (Tab. I). Moreover, basing on clinical and pathological features, both CSCC and BCC are classified in Low-Risk Lesions and High-Risk Lesions, according to the risk of local relapse and locoregional diffusion. High-Risk BCC and CSCC require more accurate diagnostic work up and more aggressive surgical treatment [28]. As showed in Table II and Table III, BCC and CSCC share most of the prognostic factors, such as: location, poorly defined borders, recurrent lesion, immunosuppressed patient, site of prior radiotherapy, perineural involvement, and aggressive histologic subtype. Squamous cell carcinomas have a few unique high-risk features, including chronic inflammatory process (e.g., Marjolin ulcer), rapidly growing tumours, neurologic symptoms, poor differentiation, depth greater than 6 mm, lymphovascular invasion. For example, CSCC extending beyond subcutaneous fat (into deeper layers, such as the fascia, muscle, perichondrium, and periosteum) have an 11-fold higher risk of metastasis compared with more superficial tumours [29]; the presence of poor differentiation is associated with worse prognosis than well-differentiated CSCC, in particular local recurrence risk (7 *vs* 2%) and metastatic risk (7 *vs* 3%) [30]. Primary skin cancers involving sun-exposed areas of the head and neck do not usually require imaging for size assessment. In particular, low-risk T1 and T2 tumours rarely exhibit nodal metastasis and are staged primarily by clinical examination without additional imaging. However, the presence of adverse prognostic factors resulting from pathological examination, including those that increase T stage or those that increase risk classification, is often an indicator of aggressive behavior and may indicate additional imaging to assess occult nodal metastasis. These imaging modalities may include computed

Table I. TNM Staging of BCC and CSCC, AJCC 8th Edition.

T-staging	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor smaller than or equal to 2 cm in greatest dimension
T2	Tumor larger than 2 cm, but smaller than or equal to 4 cm in greatest dimension
T3	Tumor larger than 4 cm in maximum dimension or minor bone erosion or perineural invasion or deep invasion
T4a	Tumor with gross cortical bone/marrow invasion
T4b	Tumor with skull base invasion and/or skull base foramen involvement

N-staging BCC		**N-staging CSCC**	
NX	Regional lymph nodes cannot be assessed	**NX**	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis	**N0**	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE (-)	**N1**	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE (-)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE (-)	**N2a**	Metastasis in a single ipsilateral node 3cm or smaller in greatest dimension and ENE (+) or Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE (-)
N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE (-)	**N2b**	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE (-)
N2c	Metastasis in bilateral or contralateral nodes, none larger than 6 cm in greatest dimension and ENE (-)	**N2c**	Metastasis in bilateral or contralateral nodes, none larger than 6 cm in greatest dimension and ENE (-)
N3a	Metastasis in a lymph node larger 6 cm in greatest dimension and ENE (-)	**N3a**	Metastasis in a lymph node larger 6 cm in greatest dimension and ENE (-)
N3b	Metastasis in any node(s) and ENE (+)	**N3b**	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE (+); or multiple ipsilateral, contralateral, or bilateral nodes any with ENE (+); or a single contralateral node of any size and ENE (+)

M-staging	
M0	No distant metastasis
M1	Distant metastasis

Table II. BCC: prognostic factors for local recurrence or metastases.

	Low-risk	High-risk
Clinical features		
Location/size	Area L < 20 mm Area M < 10 mm	Area L ≥ 20mm Area M ≥ 10mm Area H
Borders	Well defined	Poorly defined
Primary *vs* recurrent	Primary	Recurrent
Immunosuppression	Negative	Positive
Site of Prior RT	Negative	Positive
Pathological features		
Subtype	Nodular, superficial	Aggressive growth patterns
Perineural involvement	Negative	Positive

Area H: "mask areas" of face (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/sulci, temple, and ear), genitalia, hands, and feet
Area M: cheeks, forehead, scalp, neck, and pretibia
Area L: trunk and extremities (excluding hands, nail units, pretibia, ankles, and feet)

Table III. CSCC: prognostic factors for local recurrence or metastases.

	Low-risk	High-risk
Clinical features		
Location/size	Area L < 20 mm Area M < 10 mm	Area L ≥ 20 mm Area M ≥ 10 mm Area H
Borders	Well defined	Poorly defined
Primary *vs* recurrent	Primary	Recurrent
Immunosuppression	Negative	Positive
Site of Prior RT or chronic inflammatory process	Negative	Positive
Rapidly growing tumours	Negative	Positive
Neurologic symptoms	Negative	Positive
Pathological features		
Degree of differentiation	Well or moderately differentiated	Poorly differentiated
Acantholytic, adenosquamous, desmoplastic or metaplastic (carcinosarcomatous) subtypes	Negative	Positive
Depth: thickness or level of invasion	≤ 6 mm and no invasion beyond subcutaneous fat	> 6 mm or invasion beyond subcutaneous fat
Perineural, lymphatic, or vascular involvement	Negative	Positive

Area H: "mask areas" of face (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/sulci, temple, and ear), genitalia, hands, and feet
Area M: cheeks, forehead, scalp, neck, and pretibia
Area L: trunk and extremities (excluding hands, nail units, pretibia, ankles, and feet)

tomography (CT) of the neck and/or magnetic resonance (MR) imaging with contrast enhancement. Stage III-IV cancers routinely undergo imaging prior to therapy, including a neck CT and/or MR imaging with contrast enhancement, as well as other modalities, such as a positron emission tomography (PET)-CT scan. CT is generally preferred over MRI for evaluating the primary tumour, the status of the lymph nodes, and the presence of bony invasion. MRI is better for the detection of perineural spread, dural invasion, and orbital disease. Patients with bulky lymph node metastasis should also be evaluated for distant metastasis with a CT scan of the chest [31,32].

Management of primary skin cancers

Low-risk NMSC and small MCC could be managed by a single specialist (usually plastic surgeon or dermatologist), without multidiciplinary surgical approach. Surgical excision is the gold standard and margin assessment is mandatory. In this way, 5-years disease-free survival is 95-98% for BCC and 92% for CSCC [33,34]. Management of high-risk NMSC and larger MCC is more complex. Surely, the treatment of choice is surgical removal, whether by conventional surgery or Mohs micrographic surgery. Recommended margins range from 4 to 6 mm for low-risk BCC and CSCC to 10 to 15 mm for high-risk lesions [35]. These wider margins are impractical for all regions of the head and neck, but only for those with such substantial tissue laxity as to allow closure of resultant large defects. Therefore, very extensive skin lesions, including certain highly aggressive tumours, such as those invading bone, major nerve branches, or with involvement of the parotid gland, are typically best approached with a multidisciplinary surgical team, involving the head and neck surgeon [36,37]. Lesions with nodal spread at diagnosis should be multidisciplinary treated as well. Nevertheless, cutaneous head-neck malignancies are often overlooked or not routinely discussed in a multidisciplinary surgical approach involving both the head and neck surgeon and the dermatologist and the plastic surgeon [38].

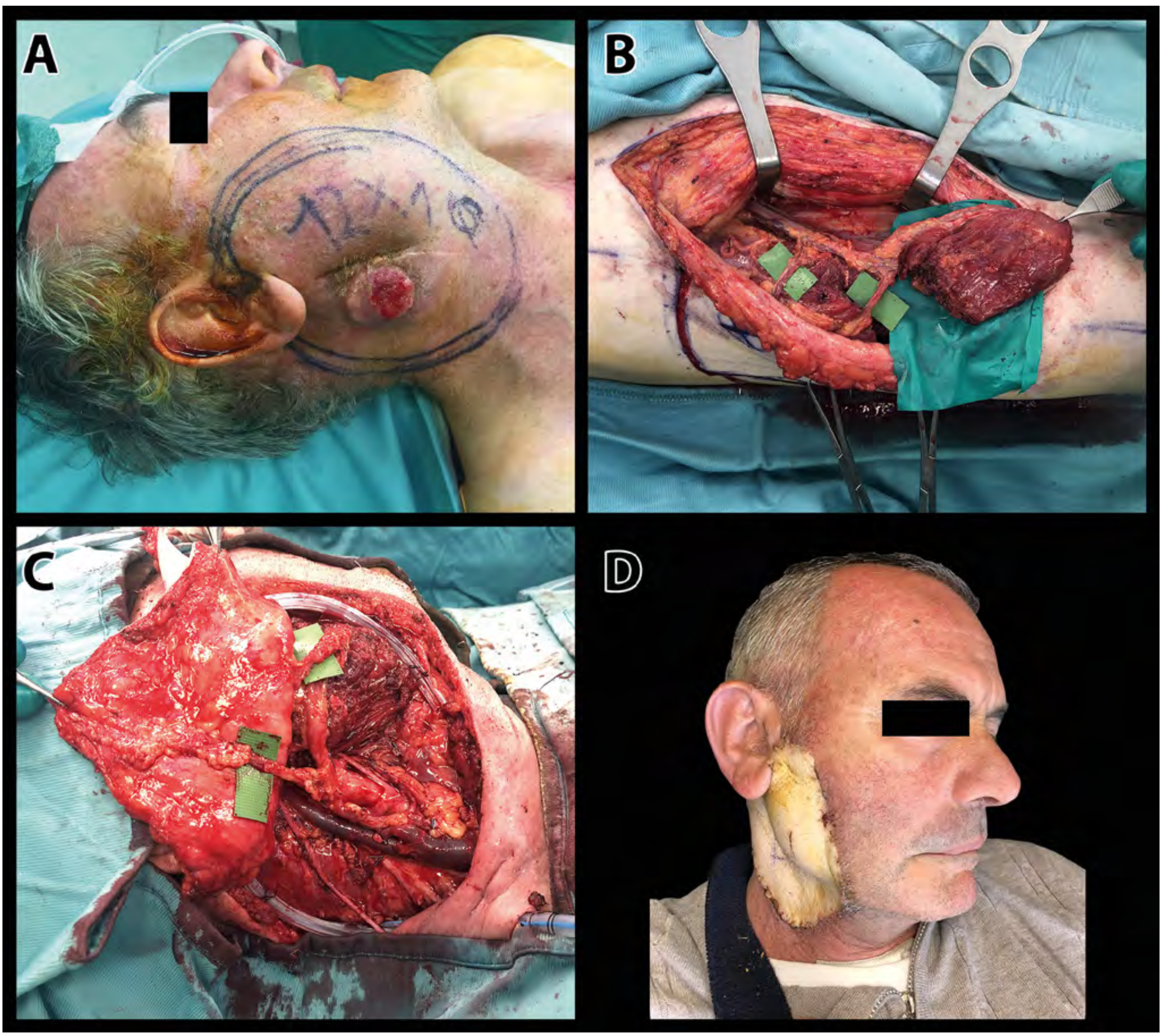

Figure 3. Fifty-four years old man with adenocarcinoma of the parotid gland extended to the skin of the parotid region. (**A**) external appearance of the tumour; (**B**) harvesting of the double pedicled chimeric ALT flap with a skin paddle and vastus lateralis paddle; dimensions: 12 x 12 cm; (**C**) insetting of the chimeric flap and vascular anastomosis; (**D**) final result after 1 month.

Surgical management of all skin malignancies is dictated by the location and extent of the tumour. Small lesions of the face and neck can be excised elliptically in the plane of skin tension with excellent aesthetic results and surgical defects resulting from resection can be closed primarily after wide undermining. However, skin grafts are best suited to the part of the face with minimal facial motion, such as the tip or lateral aspect of the bridge of the nose, the temple or the parotid region where facial movement is minimal with excellent cosmetic results (Fig. 3). Local flaps are preferred to repair larger surgical defects or those requiring full-thickness reconstruction, because they provide the best functional and aesthetic outcome. Primary closure of the donor site defect usually can be accomplished with ease with proper planning of local skin flaps. The blood supply of facial skin and soft tissues is extremely rich because the terminal branches of the external carotid artery provide a major source of blood to the facial skin, which allows use of axial flaps. In addition, an extensive subdermal anastomotic network facilitates the use of random flaps. Examples of axial skin flaps are nasolabial, glabellar, Mustardé cheek, and temporal forehead. Examples of random flaps are cervical, rhomboid, and bilobed. If local flaps are not suitable, consideration should be given to regional or free flaps for appropriate repair of large surgical defects (Figs. 4,5). Moreover, we have to highlight the role of neck dissection in the management of skin cancer. In case of cN+, neck dissection is mandatory; in case of cN0, a recent manuscript stated that elective neck dissection should be performed in case of T3-T4 disease, regardless of other risk factors [39].

Head and neck cancers with skin involvement

Head and neck squamous cell carcinomas (HNSCC) represent a group of aggressive tumors, genetically complexed and difficult to treat. Males are affected significantly more than females, with a ratio ranging from 2:1 to 4:1, between 50 and 70 years old [40]. Exposition to carcinogens, e.g. tobacco smoke and alcohol abuse, and human papilloma virus (HPV) infection are considered the most important etiological factors [41]. Approximately 30 to 40% of patients with HNSCC present with stage I or II (early stage disease). Five-year overall survival in patients with stage I or II disease is typically from 70 to 90 percent. Loco-regionally advanced (stage III-IV) HNSCC is associated with a high risk of both local recurrences and distant metastases. Combined modality approaches (surgery, RT, and/or chemotherapy) are generally required to optimize the chances for long-term disease control [42,43]. Skin involvement by non-cutaneous head and neck cancer is an infrequent finding, with a reported incidence of 9-11% [44]. It is usually associated with locally advanced diseases, either primary head and neck tumours and recurrent ones. Therefore, skin invasion always indicates a T4 tumour, regardless of tumour site (major salivary glands, oral cavity, paranasal sinuses) and it is a sign of poor outcome. In fact, patients with direct skin invasion have a 7-months median survival. According to the same authors, involvement of facial skin is prognostically better for duration of survival than involvement of neck skin [45].

Diagnosis, staging and prognostic factors

Diagnosis of head and neck tumours involving the skin, is initially clinical based on detailed history and accurate physical examination. If a primary tumour is identified, its site of origin, visual characteristics, palpatory findings, and physical signs of local extension and invasion of adjacent structures should be noted, and biopsy should be performed. Imaging plays an integral role in the evaluation of head and neck tumours. Imaging can help define the extent of the primary tumour as well as the presence, volume, and location of regional and distant metastases. In addition, imaging is helpful in detecting synchronous or metachronous primary tumours that may not be evident clinically. CT and MRI can complement each other to enhance the anatomic definition of selected tumours. PET/TC is particularly helpful in evaluating patients with advanced head and neck cancers for distant metastases and post-therapy recurrence [46].
When a surgical reconstruction with locoregional or microvascular free flap is required, in case of large resection, an ultrasound perforator assessment is needed by a radiologist experienced in the evaluation and study of perforator vessels. Radiologist using Doppler technique performs an analysis of best perforator, selecting the vessel with the largest caliber, and marking on the skin its fascial emergency site and subcutaneous direction, in order to evaluate the orientation of cutaneous island flap, creating a preoperative mapping in order to optimize the reconstructive procedure [47-49].

Management of head and neck cancer with skin involvement

Surgical management of head and neck malignancies with skin involvement poses several problems about the management of these patients because the poor prognosis is burdened by facial disfigurement, open malodorous wounds, and intractable pain. Chemoradiation is often considered the standard of care for patients with inoperable disease. However, it does not adequately address the abovementioned problems related to skin involvement, whereas extensive skin involvement is often amenable to surgery. Moreover, open wounds treated with chemoradiation will often enlarge and become more problematic. Yamazaki et

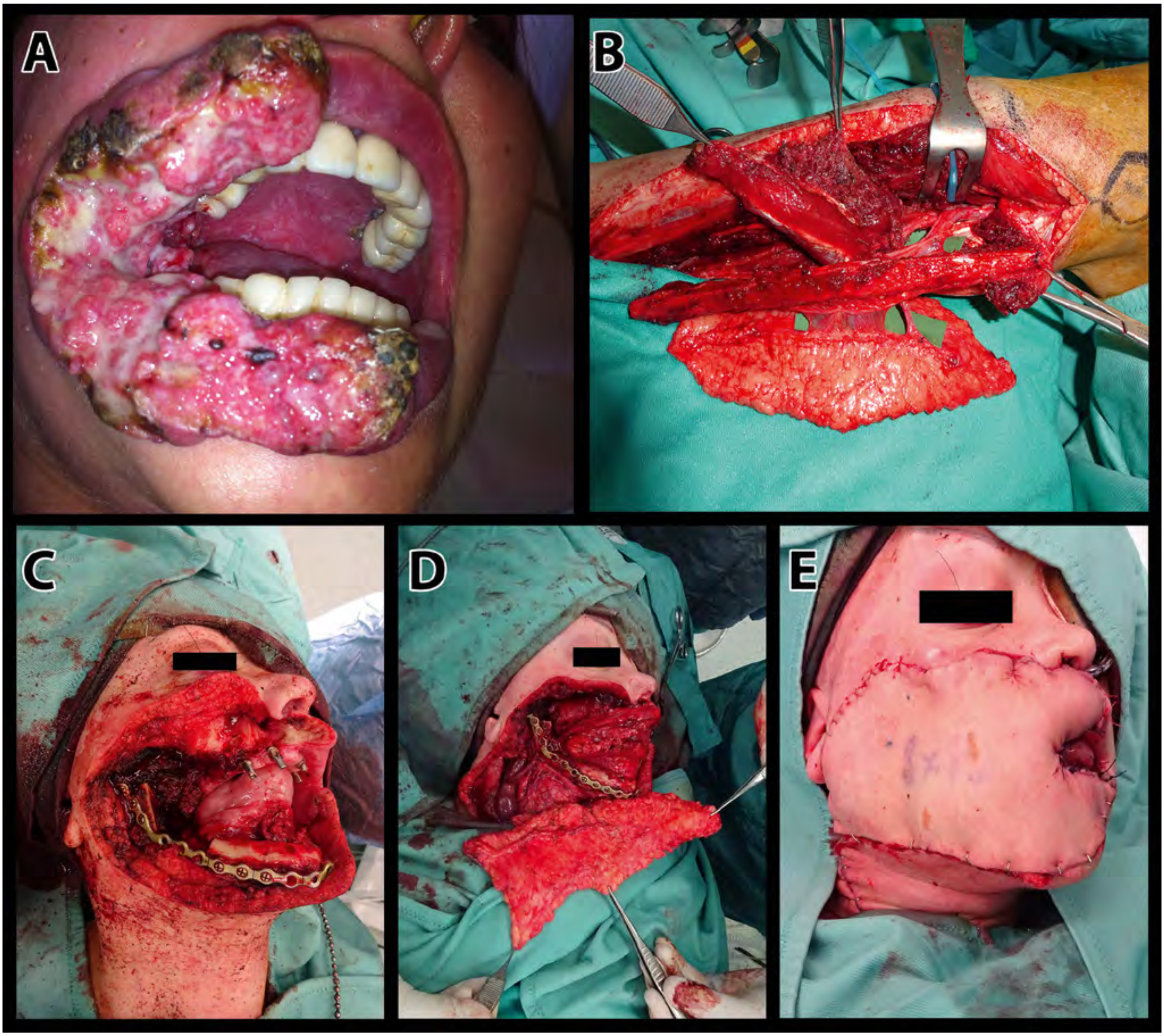

Figure 4. Young thirty-five years old woman with squamous cancer of the upper lip and buccal mucosa extended to the mandible and the skin of cheek. (**A**) external appearance of the large tumour; (**B**) harvesting of the osteocutaneous fibula flap; dimensions: 20 x 8 cm; (**C**) result after the tumour resection; the mandible titanium plate was applied before the resection in order to guide the osteotomies; (**D**) mandible reconstruction with the fibula flap and face resurfacing with a large DIEP flap; dimensions: 28 x 10 cm; (**E**) immediate final result.

al. aimed to elucidate the influence of skin invasion in patients with recurrent head and neck cancer treated with re-irradiation using stereotactic radiotherapy. They described that the skin invasion positive group showed a lower response rate, a lower local control and a lower progression free survival than the skin invasion negative group [50]. In this scenario, thanks to reconstructive advances by use of microvascular free flaps, perforator or not, single or multiple, salvage surgery with curative intent is an effective option offering good oncological outcomes (in terms of overall survival, relapse and metastasis free survival and salvageability) and functional results. At this purpose, a close cooperation between otolaryngologist and plastic surgeon should be encouraged. In patients with persistent or recurrent disease that is not amenable to radical surgery, palliative surgery with reconstruction with regional or free flaps could take place and could be proposed to improve quality of life and quality of death. In a pioneering case

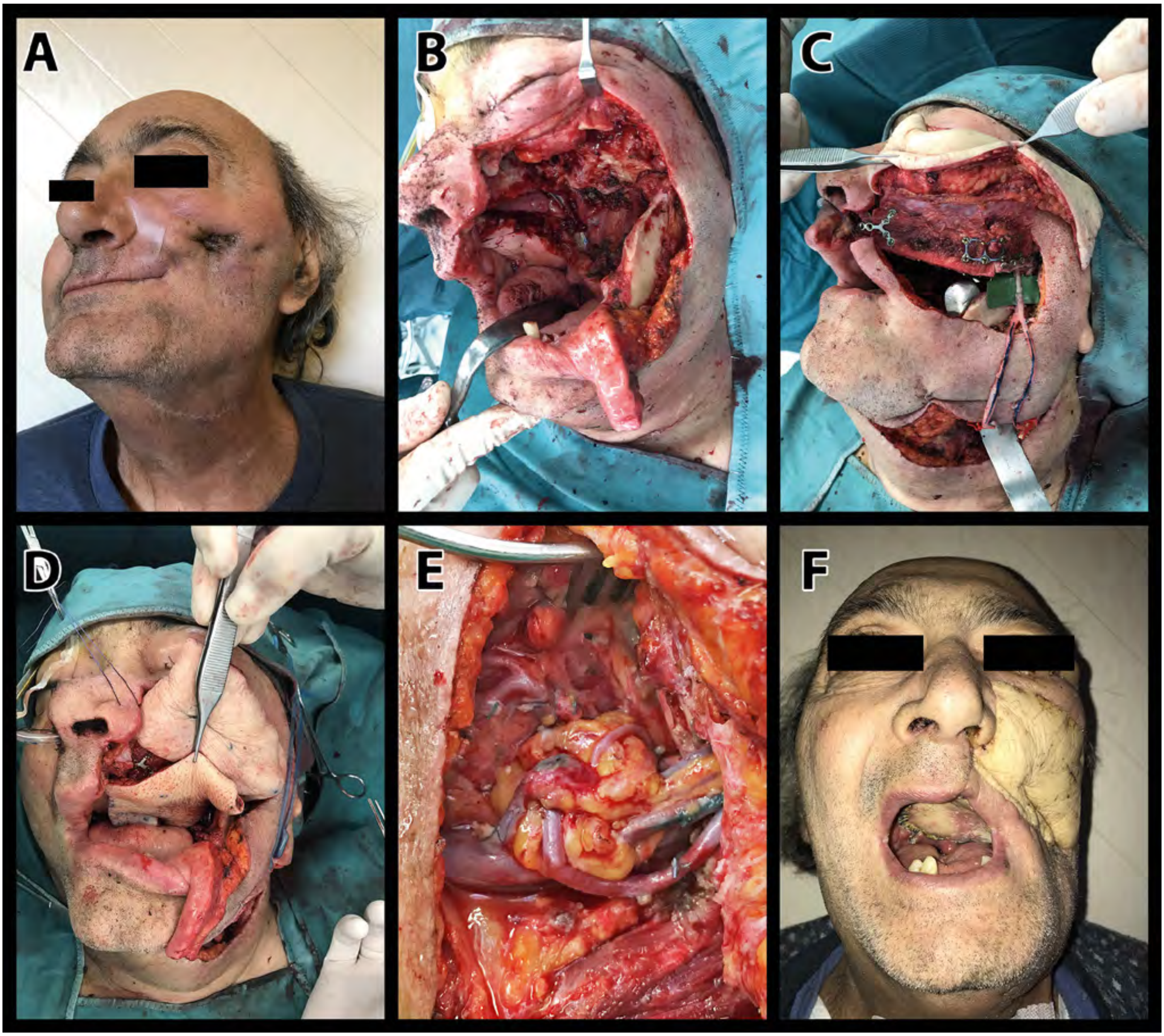

Figure 5. Sixty-four years old man with relapse of oral cavity cancer extended to the left maxillary sinus and the zygomatic skin. (**A**) external appearance of the tumour; (**B**) surgical result after extended total left maxillectomy; (**C**) insetting of the osteocutaneous fibula flap; dimensions: 17 x 7 cm; cutaneous paddle was used for the reconstruction of the oral cavity; (**D**) a second ALT flap was used to resurface the zygomatic region; (**E**) detail on the anastomosis of both the pedicles on the external carotid artery and jugular vein, with fat as stabilization; (**F**) final result after 1 month.

series, reported in 1993, in which 13 patients underwent palliative resection, there was an increased survival of 20 months beyond the median survival of the other patients. Thanks to the common use of microvascular free flaps in head and neck surgery, the prognosis of these patients has improved, as well. Jang et al. reported a median survival of 9.5 months (range: 1-30 months) [51]. Stravianos et al. reviewed a case series of 31 patients: all patients underwent surgical resection with free flap reconstruction, the most common being the radial forearm (78%). With this form of management, the authors reached a mean survival of 23 months, and six patients were still alive at follow up of 4.5 years [52]. Furthermore, this approach does not obviate the opportunity to undergo further chemoradiation.

Conclusions

Multidisciplinary surgical approach in the management of

Table IV. Recommendations.

Indication	Surgical multidisciplinary approach
Low-risk NMSC	Optional
Recurrent NMSC	Recommended
Very extensive NMSC (T3, T4a, T4b)	Strongly recommended
Nodal metastasis at diagnosis	Strongly recommended
Head and neck cancer with skin involvement	Strongly recommended

head and neck carcinomas involving the skin and high-risk primary skin cancer of head and neck district, is strongly recommended. Low-risk NMSCs and small MCC are routinely treated in some regions by community practitioners and dermatologists; however, national cancer networks should establish an integrated approach involving both the head and neck surgeon and the plastic surgeon to care for patients with certain high-risk CSCC and BCC and large MCC (Tab. IV). Cooperation between otolaryngologist and plastic surgeon is extremely helpful in order to better plan surgical treatment, including safe oncological excision and careful and accurate reconstruction, with a good aesthetic result.

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Multidisciplinary approach to nose vestibule malignancies: setting new standards

Approccio multidisciplinare ai tumori maligni del vestibolo del naso: verso la definizione di nuovi standard

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SUMMARY

Nose vestibule malignancies, mainly SCCs, are considered rare neoplasms. In the present paper, we review the current state of the art concerning classification and treatment, and describe current evidence supporting a paradigm shift. In the current AJCC classification nose vestibule is considered part of nasal cavity/ethmoid. In daily clinical practice, nose vestibule lesions are often misclassified as skin primaries. This leads to an underestimation of the real incidence and to a mis-management. When nose vestibule primaries are correctly classified as nose primaries, the current AJCC TNM appears inadequate for prognostic stratification and an old staging system described 4 decades ago by Wang has been demonstrated to be more reliable in the literature and is preferred in centers with the largest volume of cases treated. The principles of Wang classification should be applied and nose vestibule acknowledged as a new distinct subsite of nose and paranasal sinuses by the AJCC/UICC. Surgery, External Beam RadioTherapy (EBRT) and Interventional RadioTherapy (IRT, BrachyTherapy BT) are the current therapeutic options for nose vestibule (NV) SCC. Increasing evidence demonstrates that IRT, with a proper multidisciplinary approach, is at least equivalent to surgery and EBRT for treatment of the primary lesions in terms of oncological outcomes, but markedly superior in terms of cosmetic and functional results, supporting HDR (high dose rate) IRT as the new standard for the treatment of the primary lesion in these malignancies. To optimize the advantages of IRT as primary therapeutic modality we set up a new approach to the implantation phase of IRT exploiting the anatomic planes of esthetic and functional nose surgery and the potential of intensity modulated and image guided brachytherapy to avoid septal and alar perforation (anatomic implantation).

KEY WORDS: nasal vestibule carcinoma, brachytherapy, total rhinectomy, interventional radiotherapy

RIASSUNTO

I tumori maligni del vestibolo del naso, principalmente SCC, sono considerati neoplasie rare. Nel presente lavoro, rivediamo lo stato attuale dell'arte per quanto riguarda la classificazione e il trattamento, e descriviamo le evidenze attuali a supporto di un cambiamento di paradigma. Nell'attuale classificazione AJCC il vestibolo del naso è considerato parte della cavità nasale/etmoide. Nella pratica clinica quotidiana, le lesioni del vestibolo del naso sono spesso erroneamente classificate come primarie della pelle. Questo porta a una sottovalutazione della reale incidenza e a una cattiva gestione. Quando i tumori primitivi del vestibolo del naso sono correttamente classificati come a origine dal naso/seni paranasali, l'attuale AJCC TNM appare inadeguato per la stratificazione prognostica e un vecchio sistema di stadiazione descritto 4 decenni fa da Wang ha dimostrato di essere più affidabile ed è preferito nei centri con il maggior volume di casi trattati. I principi della classificazione di Wang dovrebbero essere applicati e il vestibolo del naso dovrebbe essere riconosciuto dall'AJCC/UICC come una nuova sottosede distinta di naso e seni paranasali.

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La chirurgia, la radioterapia a fasci esterni (EBRT) e la radioterapia interventistica (IRT, BrachyTherapy BT) sono le attuali opzioni terapeutiche per il carcinoma del vestibolo del naso (NVSCC). Sempre più evidenze dimostrano che la IRT, da effettuarsi in un contesto rigorosamente multidisciplinare, è almeno equivalente alla chirurgia e all'EBRT per il trattamento delle lesioni primarie in termini di esiti oncologici, ma nettamente superiore in termini di risultati estetici e funzionali, supportando l'HDR (high dose rate) IRT come nuovo standard per il trattamento della lesione primaria in questi tumori maligni. Per ottimizzare i vantaggi della IRT come modalità terapeutica primaria abbiamo impostato un nuovo approccio alla fase di impianto della IRT sfruttando i piani anatomici della chirurgia estetica e funzionale del naso e le potenzialità della brachiterapia a intensità modulata e guidata dalle immagini, per evitare la perforazione del setto e dell'ala (impianto anatomico).

PAROLE CHIAVE: *carcinoma del vestibolo nasale, brachiterapia, rinectomia totale, radioterapia interventistica*

Introduction

The present work is a critical review of the state of the art concerning nose vestibule squamous cell carcinomas (SCC) with the aim to outline recent evidence supporting a paradigm shift in the domains of classification (1), treatment strategy (2), and therapeutic technique (3, brachytherapy implantation technique).

Nose vestibule malignancy, current classification and misclassification

The nasal vestibule (NV) is defined as that part of the anterior nasal cavity that is lined by squamous epithelium up to the limen nasi, which is the muco-cutaneous junction [1]. SCC of the nasal vestibule (NV) is a relatively rare condition believed to account for about 1% of all head and neck malignancies. Primary epithelial malignancies, ad in particular SCCs, of the nasal vestibule, according to the AJCC/UICC staging system [2], are classified together and assigned the same topography code (C30.0) than those of the rest of the nasal cavity (nasal cavity proper). A Danish group recently estimated, as a rounded down approximation, an annual incidence of squamous cell of the nasal vestibule of 0.41 per 100.000 inhabitants [3]. Anyway, the absence in the AJCC classification of a specific topography code for nose vestibule malignancies which most often are not discriminated from all the other nasal cavity primaries, as well as the frequent misdiagnosis and misclassification of these lesion as cutaneous neoplasms are likely to produce a relevant underestimation of their incidence. When TNM staging system is concerned, staging criteria for the primary lesion (T) according to AJCC are the same as nasal cavity proper and ethmoid, but anatomical features and peculiar pattern of spread make such criteria clearly inadequate for nose vestibule [1-6]. In fact skin invasion through the nasal valve (mostly deep to alar and superficial to lateral nasal cartilage) is very frequent among SCC of the NV, and makes most of them cT4a for AJCC. On the other hand, paradoxically, bony invasion, which, according to the AJCC, can be present also in cT1 ethmoid/nasal cavity lesions, is typical only of the bulkiest, most difficult to treat and with the worst prognosis, vestibular SCC [1,4-6]. Wang, back in 1976, outlined that "there is no acceptable classification for tumors of the nasal vestibule" and proposed a classification of primary lesions (T), specific for the nose vestibule [7] (Tab. I). Wang classification has been reported to predict prognosis better than more recent AJCC/UICC T classification and remains the most used for nose vestibule malignancies [1,4-6,8,9] even if it can result difficult to apply (especially for the distinction between T2 and T3, see Table I).

Rethinking classification and staging of nose vestibule malignancies

Basing upon the above considerations a shared international standard for classification and staging of nose vestibule malignancies and in particular SCC is needed. We propose 2 modifications of the current TNM.

1. Define the nose vestibule as the portion of the nasal cavity extending from the pyriform aperture to the external skin of the nose, cheek, superior lip, and assign a specific topography code as a site distinct from nasal cavity proper/ethmoid and from maxillary sinus, which are currently the two sites with different T classification criteria for nose and paranasal sinuses. It will allow to better define the incidence and also to better consider the peculiar aspects of malignancies of the nose vestibule.
2. Set up specific T classification criteria for the newly de-

Table I. Staging of the primary lesions of the nose vestibule according to Wang.

T1	The lesion is limited to the nasal vestibule, relatively superficial, involving one or more sites within
T2	The lesion has extended from the nasal vestibule to its adjacent structures, such as the upper nasal septum, upper lip, philtrum, skin of the nose and/ or nasolabial fold, but not fixed to the underlying bone
T3	The lesion has become massive with extension to the hard palate, buccogingival sulcus, large portion of the upper lip, upper nasal septum, turbinate and/ or adjacent paranasal sinuses, fixed with deep muscle and bone involvement

Table II. A preliminary proposal for redefinition of T classification in nose vestibule malignancies.

T1	The lesion is limited to the nasal vestibule internal surface (skin and or mucosa)
T2a	The lesion invades superficial structures outside the nasal cavity (skin and subcutaneous) and in particular upper lip, philtrum, skin of the nose and/or nasolabial fold, but does not destroy cartilage, nor invades bony structures, nor structures beyond the plane of the pyriform aperture (septum, lateral wall, turbinates, etc.)
T2b	Disruption of cartilages is evident, without invasion of bony structures, nor of structures beyond the plane of the pyriform aperture (septum, lateral wall, turbinates, etc.)
T3	The lesion extends beyond the pyriform aperture (septum, lateral wall, turbinates, etc.)
T4a	The lesion invades bony structures as hard palate, nasal bones, frontal process of the maxilla, ethmoid, and the orbit
T4b	Tumor invades any of the following: orbital apex, dura, brain, anterior and middle cranial fossa, cranial nerves other than (V2), nasopharynx, or clivus

fined subsite, starting from the Wang classification, to better define prognosis and guide treatment selection. A hypothetical draft of the new T classification is reported in table II, considering that, in our experience, cartilage is not usually disrupted in the early phases, but somehow guides tumor spread (posteriorly along the septum, superficially below the alar and above the lateral cartilages to the skin of the dorsum, inferiorly to the superior lip) to different areas of the midface (Fig. 1).

Current treatment options for nose vestibule SCCs: evidence supporting brachytherapy as the new standard for treatment of the primary lesion

Oncological outcomes

Surgery, External Beam RadioTherapy (EBRT) and Interventional RadioTherapy (IRT, BrachyTherapy BT) are the current therapeutic options in clinical practice [3,9-14], as there are not clear evidences of superiority for any modality. Recent papers focusing on the comparison between surgery and IRT [4] and on IRT alone [5,15,16] showed that brachytherapy as primary treatment of the T is not inferior to surgery as for oncological results (OS over 90% in cT1 and cT2 according to Wang).

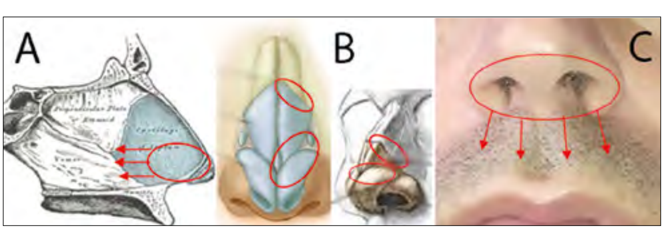

Figure 1. Preferential pattern of local spread of malignancies arising in the nose vestibule. Cartilagineous structures are not usually disrupted in the early phases, as tumor spread rather occurs along them to different areas of the face. Posterior spread along the septum for primaries of the columella and anterior septum is shown in **A**. Preferential pattern of spread of primaries of the lateral side of the vestibule, between alar and lateral cartilages or (more rare) between lateral cartilage and nasal bones is shown in **B**. Spread of primaries from columella and inferior side of the vestibule is shown in **C**.

In the absence of oncological evidences supporting one versus another modality, functional issues become fundamental for treatment selection.

Cosmetic outcomes

Among such functional issues there is for sure the aesthetic appearance, which have obvious social implications and can be deeply impacted by any therapeutic procedure involving the nose and the nose vestibule in particular [1,4,6]. In fact, reconstruction of the nose tip, which shares the cartilaginous framework with the vestibule after ablative surgery, is notoriously extremely difficult for at least 2 reasons:

- it is the most exposed and noticed area of the entire body, where light and human eyes always land. Therefore, minimal imperfections, scars, color mismatches, and deformities exhibit the highest esthetical and social impacts;
- it is practically impossible to faithfully reproduce the complex pattern of relieves and hollows created by the nose cartilage and underlying maxillary and nasal bones using surgical procedures. Free flaps, which have drastically changed head and neck surgical oncology in the last few decades, do not have a resolutive impact here. According to several authors [3,12,18] bone anchored prostheses remain the best option under an esthetical point of view in case of total rhinectomy defects.

Therefore, anatomical preservation of the osteocartilaginous framework is the most successful option in midface and nose vestibule malignancies from an aesthetic point of view [4,12]. If we consider in addition that nose cartilage itself is generally pretty resistant to radiation, the markedly better cosmetic results reported for high dose rate (HDR) IRT (Fig. 2) when compared to surgery (Fig. 3) [4] can be easily explained. For the same reasons also EBRT, with similar survival figures than IRT [3,13,14], is considered a valid alternative option also under an esthetical point of view [8,10,12,19,20] and is probably the most frequently recommended primary treatment in Western countries at present [10,19].

Functional outcomes

The nose is primarily part of the respiratory system, being the first section to be passed through by inhaled air. Thus, the nose has evolved multiple physiologic strategies to regulate flow speed, temperature, and humidification (somehow conditioning the inhaled air headed to bronchi and alveoli) of the inspired air, as well as to tightly modulate its ability

Figure 2. Pretreatment findings (**A, B, H, I**), catheter positioning (**C, D, L, M**) and postoperative results (**E, F, G, N, O**) in 2 patients treated by primary brachytherapy are shown. Case 1 came to our observation with a primary SCC arising from the columella without a clear cartilagineous involvement (cT1 stage according to Wang). Plastic tubes were placed parallel along the main axis of the nose (**C, D**) with a complete coverage of the tumor volume. The patient is currently alive with no evidence of disease (60 month follow up) (**E**). The aesthetic result appears very good (**F, G**) (pictures have been taken 9 months after treatment). Case 2 displayed a bulky primary SCC (cT2 according to Wang classification, pN1 after concomitant neck dissection), involving all the walls of the nasal vestibule and infiltrating the skin of the nasal dorsum and of the superior lip, and alar and septal cartilages (**H, I**). The patient underwent primary brachytherapy and bilateral selective neck dissection. At the time of neck surgery plastic tubes were placed parallel along the main axis of the nose (**L, M**) with a complete coverage of the tumor volume). The patient is currently alive with no evidence of disease (30 month follow up). The aesthetic results appear acceptable (**N, O**) (pictures have been taken 7 months after treatment) with no further loss of cartilage deriving from IRT.

Figure 3. Preoperative findings (**A, B, E, F, G**) and postoperative results (**C, D, H, I, L**) in 2 patients treated by primary surgery are shown. Case 1 came to our observation with a primary SCC arising from the limen nasi and spreading to the tip and the alar skin with cartilagineous involvement (**A, B**) (T2 stage according to Wang). R0 resection was performed, with the preservation of nostril rims, but the aesthetic result without a prosthesis 12 months after surgery is not satisfactory at all (**C, D**). Case 2 displayed at physical exam (**E**) and at MR imaging (**F, G**) a SCC of the columella spreading towards the superior lip (T2 stage according to Wang). 6 weeks after the R0 resection, the results of the primary closure are objectively better (**H, I, L**) but still not fully satisfactory for the patient.

to protect and defend itself and the respiratory system as a whole. Among such physiologic strategies, there are the maintenance of adequate intranasal resistances within the physiologic variations due to the nasal cycle [21], the sneeze reflex [22], and the complex immunological and mechanical defensive system constituted by nasal mucosa, with all its cellular components (both in the ciliated epithelium and in the stroma) and by the mucous itself. One of the most characteristic and well-known expression of such defensive system is the mucociliary clearance.

Disruption of any of the above-cited physiologic functions can be secondary to gross anatomic variations, as after oncological surgery, or to other pathological processes involving and impairing one or more of the above cited mechanisms, mainly at the level of nose mucosa, as in case of irradiation, which notoriously harbours well known acute and, most of all, late toxicities.

For this reason, knowing that, under a cosmetic point of view, evidence supporting EBRT *versus* IRT is lacking, we recently compared the 2 irradiation modality as for outcomes on nasal function [15]. The nasal functions are notoriously affected by irradiation [23-25], and many complaints, as crusting [25], dry nose [26], dysosmia [24,27], dysgeusia [24], in patients with a previous irradiation of nasal region, are clearly linked to the disruption of physiological mechanisms by mucosal toxicity of radiotherapy [26,28,29]. Most of these previous data have been recently confirmed with specific test after EBRT but not after IRT [15], with a substantial preservation of nasal function and cytological findings. The rapid dose fall off of the IRT, exploited also in the adjuvant/perioperative setting [30,31], with a drastic reduction of the irradiated mucosal surface inside the nasal/paranasal cavities, may be decisive factors. Nevertheless such favourable toxicity profile is well known and exploited also in geriatric population [17].

The new standard
Such evidence, together with the confirmation of oncological effectiveness, which remains of course the most relevant argument, supports the establishment of interstitial IRT as the new standard for the treatment of the primary lesion in cT1 and cT2 (according to the Wang staging) NV SCCs. Still, it must not be forgotten that IRT is a multidisciplinary tool at the border between surgery and radiotherapy, and close cooperation between surgeons and radiation oncologists during every phase, from the recommendation of treatment and implantation in the operating theater to the prescription and dose painting at the radiotherapy department, is mandatory to perform high-quality IRT [6].

Implantation technique for nose vestibule primaries

The aim of functional and, even more, cosmetic preservation of patients with nose vestibule carcinoma passes as written above through the preservation of the nose tip cartilaginous framework not already eroded by tumour growth. It is well known also from laryngeal oncology [32] that cartilage itself is particularly resistant to tumour invasion also because it is devoid of blood vessels and fed through the interstitium by direct diffusion from vascularized perichondrium [33]. In fact, as blood vessels are brought in by ossification, probability of invasion drastically increases. Nose cartilages, differently from laryngeal ones, and thyroid cartilage in particular, do not usually get ossified even in the elderly, and in fact, as observed above, direct invasion is very late in nose vestibule SCCs. This fact and the resistance and the low toxicity of radiotherapy on nose cartilages [4,15,34-37] are clear advantages for the cosmetic results after irradiation of these malignancies.
However, the main reported long-term toxicity of IRT in this area is known to be chondronecrosis and consequent septal and even alar perforations [13]. These sequelae are reportedly more frequent when an interstitial delivery is chosen, than in endocavitary/mold technique [13], suggesting that chondronecrosis is likely due to the mechanical damage and interruption of the perichondrium which feeds the cartilage by the implants, more than to the dose to cartilage itself. Starting from this assumption, we modified our implantation technique following the principle to avoid as much as possible the piercing of the perichondrium and of the cartilages. To this aim, we leave the implantation phase of nose vestibule SCCs to skilled nose surgeons who brings the plastic tubes along the subperichondral planes, which are the main dissection routes of the functional and aesthetic surgery of the nose (Fig. 4). This implies that the planes of the implant are ideally the subpericondral planes themselves and that the final geometry of the implant is dictated primarily by the anatomy of the nose tip (and not by the Paris system rules). Such anatomic implantation technique resulted in no septal perforation in our series (39 cases by now) with markedly better functional and cosmetic results than in previous series [13]. The "anatomic" implantation technique may contravene the "classical" Paris system [38] whose rules and principles remain valid to obtain an optimal dose distribution, especially with LDR linear sources, but the potential of the intensity dose modulation, thanks to the stepping source brachytherapy treatment planning combined with the image guided IRT, can improve dose distribution after "anatomic" implantation in order to obtain optimal local control, which in fact is not inferior to other brachytherapy series [4,6,9,13,15,16].

Figure 4. The plastic tubes ideally lie along a subperichondral route, cartilages and perichondrium should not be disrupted and the tubes pass from a submucosal to a subcutaneous plane through the junction between alar and lateral cartilages. Such an implant is particularly fit for a primary lesion invading skin along the same route. More rarely the primary can reach skin through the junction between nasal bone and lateral cartilages, also in this case the implant should follow the same route as malignancy (drawing realised by Nicola Tsatsaris).

Conclusions: towards new standards

The evidence and the considerations expressed above push for a paradigm shift in different management phases of nose vestibule carcinomas:
- *Diagnosis and staging*. Nose vestibule should be considered a distinct site of nose and paranasal sinuses, with specific T staging and criteria borrowed from the most used Wang staging (Tab. I) with some improvements (Tab. II);
- *Treatment choice.* There are three options available for the treatment of the primary lesion in nose vestibule SC-

Cs (surgery, EBRT, IRT), without any clear difference in term of oncological outcomes, but IRT (administered with HDR) offers clear advantages in terms of cosmetic and functional results and we consider it the standard for cT1 and cT2 (according to Wang) primary lesion. When there is indication to neck treatment (elective or therapeutic) we recommend concomitant neck dissection, to be performed in the same session as implantation, being IRT a localized treatment, and in case or local/regional recurrence EBRT remains a fully available option;
- *IRT technique.* The main long term toxicity of IRT on the nose vestibule, which is chondronecrosis deriving from mechanical damage to the perichondrium, can be avoided by an anatomic implantation of the plastic tubes which should lie along the subperichondral planes, exploited for the surgical dissection in the rhinoseptoplasty. Dose distribution can be optimized by intensity modulation and image guidance.

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Border areas in head and neck pathologies: professional liability in the multidisciplinary approach

Implicazioni medico-legali nel trattamento delle patologie di confine della testa e del collo

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SUMMARY

Discussing border areas in Head and Neck pathologies means addressing diseases' convergence point of different specialities and professionalisms guided by a common goal: patient health. Starting from the concept of a border, it becomes possible to define the content of a new model of team responsibility: no longer that of the team leader who, as a new Agamemnon, takes on the role of scapegoat when things go wrong, even for errors not directly attributable to his supervision, but that of a *primus inter pares*, a King Arthur with the Knights of the Round Table, committed like the others, each with his wealth of experience and knowledge, to pursue the same goal. A member of this team assumes the role of spokesperson for diagnostic and therapeutic solutions within a process of acquiring consent that recovers the dimension of verbal and non-verbal communication with the patient. In such a context, in which criminal liability can be challenging to identify based on the principle of *in dubio pro reo* and civil liability in some countries has already transferred the burden of compensation from the professional to the healthcare facility. In most, no-fault compensation systems appear consistent.

KEY WORDS: medical malpractice, multidisciplinary approach, professional liability, team liability, otorhinolaryngology

RIASSUNTO

Discutere di zone confine nelle patologie del distretto testa-collo significa affrontare il tema di quelle malattie che costituiscono il punto di convergenza di specialità e professionalità differenti guidate da un obiettivo comune: la salute del paziente. Muovendo dal concetto di confine, diviene possibile definire il contenuto di un nuovo modello della responsabilità di équipe: non più quello del team leader che, novello Agamennone, assume il ruolo di capro espiatorio quando le cose vanno male anche per errori non direttamente riconducibili al suo operato, ma quello di un primus inter pares, di un Re Artù con i Cavalieri della Tavola Rotonda, impegnato lui al pari degli altri, ciascuno con il proprio bagaglio di esperienze e conoscenze, a perseguire lo stesso obiettivo. Un componente di questo team assume il ruolo di portavoce delle soluzioni diagnostico-terapeutiche all'interno di un processo di acquisizione del consenso che recuperi la dimensione della comunicazione verbale e non verbale con il paziente. In un siffatto contesto, in cui la responsabilità penale può essere di difficile individuazione in base al principio dell'"in dubio pro reo" e la responsabilità civile in alcuni paesi ha già provveduto a trasferire il peso del risarcimento dal professionista alla struttura sanitaria, la soluzione più coerente appare quella propria dei sistemi di no fault compensation.

PAROLE CHIAVE: *colpa medica, patologie di confine, responsabilità professionale, responsabilità di équipe, otorinolaringoiatria*

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Introduction: contents and limits of the concept of "border"

The first book of Rome's history, Titus Livy, tells the legend of Rome's founding and the epic fratricidal clash between Romulus and Remus. It narrates the tale of Remus being killed by Romulus because he dared to climb in mockery a furrow ploughed by his brother, who later entrusted his memory to posterity with the following epitaph: "So from now on, it will happen to anyone else who will pass through my walls". Centuries later the Swiss philosopher Rousseau wrote, "The first who, having fenced off a land, dared to say, 'This is mine', and who found people so naïve as to believe him, was the true founder of civil society". Therefore, the concept of border is associated with the concept of property, but this only a part of it. The Romans coined the word *limes* to refer to the frontier – to the final edge not to be crossed so as not to incur dangers that are difficult to manage. For Emperor Augustus, the *limes* is Teutoburg. In 9 AD, the defeat of Varus' legions at the hands of rebellious Germanic tribes led by the traitor Arminius, once an officer of the Roman auxiliaries but in fact, a leader of the Cherusci insurgents caused Caesar Octavian such despair that he advised his successor Tiberius not to extend the borders of the empire and to stay inside the *limes*.

As reported in the Encyclopedia Britannica, the Latin term *limes* was initially used in agriculture to separate fields cultivated with vineyards, which later became a symbol of the last Roman advanced outpost. The word *limes* has roots in two possible Indo-European derivation *lemmas*. The first is *lik(c)/leik(c)*, which refers to the concept of "bending, going sideways", hence the meaning of "oblique" (and therefore, a demarcation line, which is almost never straight and clear in fields dedicated to cultivation). The second is *li*, which indicates the "flowing" of a watercourse; a damp place; rich in water (in ancient Greek: *leimon*; marsh); turbid; muddy; in a sense related to *limus*; full of filth; a place difficult to cross; marked by a bad smell emanating from decomposition or from droppings collected there [1]; and marked by fear of contracting contagious diseases, to which historians acknowledge the contribution given to the strengthening of the borders between states. In its original meaning, in the sense of *limes*, a border is not only a border between neighbouring and culturally homogeneous fields, but also represents the equivalent of a marshy terrain, in which one can become entangled because of its changing characteristics, or the evolution of a possible battleground between two or more orders that are eager to assert the right of possession or expansion.

Considering pathologies as a border territory in nosographic frameworks means addressing the issue of diseases that attack a complex of well-defined organs located within a well-defined area of the body and attract the interests of different disciplines. The discussion on these pathologies and the responsibilities of caregivers cannot be traced back to the usual interpretative schemes that are appropriate for criminal and civil doctrine on health liability. Instead, they deserve to be addressed using new instruments modelled on recent legislative contributions. This was first done in the United Kingdom, followed by France and Italy, to extend the *limes* of medical action while avoiding exacerbating its pitfalls.

Pathologies as a border territory in head and neck surgery: new horizons and new and old dilemmas

If we wanted to search for the progenitor of the concept of the pathologies as a border territory, it could perhaps be useful to turn to the notion of focal pathology. The notion is clearly a didactic reference that is helpful in underlining the general influence of local disease. This is precisely the case of a focal odontostomatogenic disease, which affects a single dental element, yet its effects reverberate elsewhere toward other medical areas, such as nephrology, cardiology, neurology, and otorhinolaryngology. This is also the case with tonsillitis and its long-term repercussions, such as nephrological or cardiological effects.

However, in its original meaning, the concept of focal pathology also encompasses the origin of the concept of pathology as a border territory. In the past, a focal pathology would have involved different teams of caregivers, each one acting within their respective fields and their own disciplines' "boundaries" as rigid interpreters of the diagnostic-therapeutic schemes of their own sectors. Today, focal pathology engages the same teams with their valuable expertise but obliges them to a shared multidisciplinary approach to facilitate early diagnosis and correctly plan subsequent therapeutic processes.

The focus is not only the disease that alters the homeostasis of the organism and produces harmful effects on contiguous or even distant organs. It is also its multiplicity of expression – even if only potential – that attracts and concentrates the interests of different specialities, which have been moving into increasingly smaller anatomical limits, despite the fact that these specialities cultivate competencies that are not entirely homogeneous.

Therefore, it is becoming increasingly common a multidisciplinary approach to design and implement the best diagnostic-therapeutic strategies for different pathologies, such as pituitary adenomas; in this specific example, the optimal planning of preoperative diagnosis, management and treatment involves a team of endocrinologists, neurosurgeons, ENT, neuro-ophthalmologists and neuroradiologists; in order to improve surgical results, minimize complications and facilitate follow-up [2].

In the preoperative evaluation and in the surgical management, the team members are equally important protagonists even if with different timing and approaches; but it is important underline that this cooperation and co-responsibility does not mean that no boundaries exist. On the contrary, the "boundaries"are designed by the skills and areas that one single team member would add to achieve the optimal result conform to the "personalized" solution in specific disease in a specific patient.

As in the evolution of the limes of the Roman Empire, this simply means that the substantial prohibition of Augustus to go beyond the border was followed by Hadrian's intuition to "integrate" the *limes* (and therefore to expand its extension). In the progress of medical knowledge, the time of rigid and solitary sectors has been replaced by the concept of multidisciplinarity, confrontation, and dialogue between several "performers" who all have highly qualified knowledge. These performers do not throw themselves into virtuosic "solos" but are part of an "orchestra" capable of playing at the right time and constructing music with which the strings of each individual instrument vibrate at their best.

An example of this approach can be found in the field of head and neck neoplasms. Once a battleground between potentially involved disciplines, it has become a reference model for other oncological specialities faced with the same dilemmas of optimal treatment in other anatomical-functional districts. Today, the multidisciplinary approach in the diagnostic-therapeutic strategy of head and neck tumours is considered essential and demands that surgeons, oncologists, radiotherapists, pathologists, radiologists together study the history of an individual patient and meet to offer the patient a personalized solution. It is no coincidence that several EU Member-State legislations require the participation of multidisciplinary teams (i.e., tumour boards established in referral centres) to offer different specialist skills to guarantee strategic clinical choices for patients with head and neck cancers [3]. Not by chance, cancer is a focal pathology. It settles in on the part of the body but involves the entire organism and requires the skills of multiple specialities, which are in constant dialogue and have the sole objective of ensuring that the patient receives coordinated, effective, and personalized care.

Which model of responsibility for the interpreters of therapeutic-diagnostic treatment in pathologies which require a multidisciplinary approach?

Antic responsibilities: from the responsibility of Agamemnon to that of King Arthur and his Knights

The modern idea of responsibility – of Kantian derivation [4] – is to see a subject responding only to actions with a programmed and desired result, while we shun the idea of having to answer for actions that do not depend on our decision and happen in the shadow of our actions [5]. In complex organizations, such as health care facilities, the modern idea of responsibility is often put to severe tests. Patients could be damaged, and tracing the exact cause can be difficult or even impossible in many circumstances.

Homeric heroes of ancient Greece solved this problem in a radical way. The Homeric hero answered for acts not under his direct control. In addition to paying for what he did, he also pays for what was not strictly related to his intentions and actions. Agamemnon's responsibility [4] for having stolen the beloved Briseis from Achilles does not end with the dutiful economic compensation assured by Agamemnon himself towards Achilles, but extends to the whole Greek army, which was scattered for Achilles' abandonment of the battlefield. Agamemnon is forced to make public amends in front of Achaeans' assembly to bring Achilles back into battle and reverse the fate of war.

Agamemnon's responsibility is very reminiscent of the responsibility model once attributed to the so-called team leader based on the legal principle of "non-reliance". By virtue of his position as coordinator and the most experienced member (his *auctoritas*), the team leader must trust neither his collaborators nor other members of the team, who are reduced to the rank of mere executors of his directives. Therefore, he responds, solely, to the mistakes possibly made by them in executing his orders. This is a model that once seemed to be tailor-made for figures similar to the team leader, such as the head of a care unit (in the past called the "primary") or as the health director of a hospital company. Such a figure's "public" role so to speak [6] ended up being a pole of attraction for most disparate claims and unloading forms of objective responsibility (i.e., of an organizational nature), which the hermeneutical tools of law had not been able to canalize otherwise.

The evolution of the law is the result of a very different interpretation of the concept of "team" and was borrowed from the experience of team games, which has led to the abandonment of the "non-reliance" scheme in favour of the opposite principle of "entrustment". Within a team, each member fulfils a valuable role and participates with their own skills to realize results. In such a scenario, the team leader must trust the skills of his collaborators (colleagues or companions, not only those belonging to the same unit or department). The leader must maintain the obligation to supervise the correctness of others' choices and conduct and, therefore, the obligation of corrective intervention in the takeover. This is especially so when the group is faced with situations of particular difficulty. However, this solution continues to be permeated by the spirit of Agamemnon's responsibility because it is still associated with the need to identify the "guilty party" for the consequences of an action. Such consequences have so many "unknown fathers", and all of them are indoctrinated within a complex organization such as that of a health facility as if it were not possible to imagine an alternative to the so-called objective responsibility that would not proceed with the inevitable identification of a scapegoat, a San Sebastian by Mantegna, who pays for all.

And yet, among the models of responsibility forged by the law of the ancients, there is one from ancient legendary tales that seem to be made specifically to define the responsibilities of multidisciplinary groups called to confront for the treatment of pathologies as a border territory and more: King Arthur and the Knights of the Round Table. The legend of King Arthur is not only a story of one man's ability to draw a sword that is stuck in the rock, but it is above all a story of the handover of responsibility from Agamemnon to a group. The Round Table is a material representation of this passage – a geometric place of plane positions equidistant from a fixed point at the centre of the plane. Every position of the geometric place is important, and each one of them would not exist without those positions. King Arthur sits at the Round Table like any other knight. Most important of all, it is not King Arthur's position but the centre of the table that makes all others equal because of its inherent equidistance to them. In a healthcare organization that aims to guarantee the safety of care, the centre position of the Round Table belongs to the patient.

Therefore, with the personalization of care, the centrality of the patient has become a new benchmark to measure and evaluate a new model of healthcare responsibility to which all team members are called upon. In this model, subjectivity (i.e. liability) is not attributed to a scapegoat once identified in the team leader or director. Instead, the healthcare organization itself is a subject that acts equally with team members.

Inapplicability of the team responsibility scheme to the "board" responsibility model: towards the end of the "team responsibility" concept?

A healthcare team can be defined as a group of several specialists and professionals who cooperate and thus contribute to the pursuit of the common goal of patient care. This multidisciplinary activity is carried out both synchronously by professionals of the same or different hierarchical levels and diachronically – i.e., in chronologically distinct but always interdependent phases. Interaction in time and space configures the rule of teamwork. The growth of specialist knowledge, technological innovation, the multiplicity of healthcare figures have caused the paradigm of the single doctor to wane [7].

Various definitions of teams have appeared in the literature, but the results are not entirely satisfactory. Three models of professional cooperation have been outlined: the ward team, the surgical team (or team in the strict sense), and the team in the broad sense [7]. The first is characterized by a work team that is only apparently monodisciplinary since it is not only composed of doctors with the same specialization who work in a hierarchically organized working relationship, but also of other independent professionals, such as nurses, technicians, rehabilitation therapists, and psychologists. A surgical team involves an activity carried out synchronously by hierarchically organized health workers with different specialities and skills. Finally, the team in a broad sense corresponds to a form of multidisciplinary diachronic cooperation – i.e., not contextual [8].

In this context, heterogeneous and difficult-to-assimilate forms of health cooperation/interaction come together. However, beyond all these scholastic definitions, the fact remains that it is quite difficult to reconstruct the chain of decisions and to weigh the possible roles of each health-worker in the determinism of possible damage suffered by a patient. In the attempt to trace the person responsible for an action – an action produced by one or more members of a multidisciplinary team and the consequent damage – one would in fact risk being trapped in the dilemma of the "hunting pellet". In this situation, it is not clear which of the "hunters" present at a "hunting scene" can be held responsible for the mistakenly firing the lead shot extracted from a victim's body since the victim does not remember anything. From the position of the hunters and ballistics data, it is at most possible to conclude that hunter A has a 55% chance of being the shooter and hunter B has a 45% chance of being the shooter.

In criminal proceedings, the inochentism principle applies in such a dilemma. Therefore, *in dubio pro reo*, an absolutory solution could be found for both hunters, given the failure to exceed the threshold of reasonable doubt calibrated on probabilistic percentages close to certainty and not oscillating around the values of the case. In civil law, the guilty principle applies, whereby *in dubio pro misero*, according to the percentage threshold assigned *a priori* to the probability of guilt, two different conclusions could be

reached: the attribution of responsibility to both hunters, albeit in a proportionate manner, or the recognition of responsibility by the person who has exceeded the limit of 50% + 1 of such probability [9].
Just try to imagine the consequence of this dilemma in both the work of a multidisciplinary otolaryngological and neurosurgical team that has been recruited to treat a patient with a pituitary adenoma with a transfenoidal approach resulting in a liquor fistula. The decision making side could involve a "tumour board" composed of otolaryngologists, radiotherapists, oncologists, eidologists, histopathologists, nutritionists, phoniatrists, and rehabilitators to achieve the best strategy of contrasting a laryngeal neoplasia that has relapsed. The limits of the team liability model are not restricted to the narrow space of the so-called "uncertain causality" [10], but are even more evident when one examines the content of the performance of each member of a multidisciplinary team.
In fact, it has been wittily observed that by forcing the concept of a guarantee position, especially in the criminal field, for which each health worker is invested with the function of guarantor of the health of the patient, the simple unweighted transposition of a term such as "team" or "multidisciplinary team" from the purely medical field to a metalegal field has occurred with the sole purpose of extending the horizon of punishability. The team was intended as a form of cooperation between different medical specialties and various other professions but has become a source of a mixed guarantee positions. Precisely, one guarantee position is related to the protection of the patient's health, which is in fact the content of the health service required of each health care worker, and another extended guarantee position results from the expansion of the concept of "guarantor" towards the other team members' actions [11].
In this way, the rationale of the division of tasks is altered, and the inclination towards mutual trust and respect is eroded, even though it should be the founding element of a team in the pursuit of a positive goal. It would also undermine the personal nature of criminal responsibility. As medical activity is risky in itself, the errors of others could always be considered predictable. Therefore, each team member could be required to monitor and supervise the work of others. Thus, one would risk being charged to answer for the culpable conduct of third parties caused by an unfortunate event, in a *bellum omnium erga omnes,* which indeed is the exact opposite of the concept of teamwork.
Therefore, such an eccentric distortion in applying this concept of team and guarantee position in favour of the patient would always result in an unfavourable outcome being attributed to all professionals who were a part of the treatment. In the criminal field, this introduces a form of joint liability, which could perhaps be digested by the compensatory logic present in the system of civil liability but is certainly alien to modern criminal law anchored in guilt for the fact [11].
And in fact, it has already occurred that the otolaryngologist is recognized as responsible for not having correctly intubated a patient, replacing the anaesthesiologist (also considered responsible) or the anaesthetist for not having correctly tracheostomized a patient by replacing the otolaryngologist (to which responsibility has also been attributed). Therefore, it is easy to understand how the scheme of team responsibility offers itself to such distortions and many others that one would hope to be overcome. Certainly, the current application of this scheme with the double profile of protection of the patient's health and control of everyone's actions is not well suited in areas of multidisciplinary commitment.
Consider a tumour board where the discussion on the interpretation of eidological and histopathological data and on the direction that a certain meaning attributed to one cause or another could direct the clinical decision. Who would be responsible for an interpretation that later turns out not to be in line with the reality of the case examined? Is it the eidologist, the histopathologist, the otolaryngologist, the radiotherapist, or all of them, and in what proportions? Looking at this team as a modern revision of King Arthur's liability scheme and the Knights of the Round Table, we can only conclude that the hermeneutics of team liability should be considered as fading and that this is certainly not the area of criminal or civil restorative justice, which should provide an appropriate answer to these questions.

A solution to the dilemma of responsibility: the role of the health care organization as a provider of health care and the legislator's response in this regard

Due to the intuition of those who work in the world of clinical risk management, a predominant role in the determinism of unfavourable events is attributable to the organizational context in complex systems such as healthcare organizations [12-14]. In fact, it has been estimated that the contribution of human action in the determinism of damage to a person receiving a healthcare service within a structure is equal to 20-30% [15]. Even when the damage event can be attributed to the human factor, it must not be seen as an expression of the "monad" of the medical staff, but as a consequence of the treatment process that proved to be defective.
Organizational theories have highlighted how an accusatory approach directed exclusively at the professional is certainly reassuring as if they were holding the "smoking gun" of the error that has just occurred, but this conceals organizational inefficiencies that are hidden behind the verification of an accident. To believe in human error is certainly

a relief, at least because it leads to the certainty that it is an error, which can be controlled and charged (with guiltiness attributed) to a person. However, it prevents us from directly approaching the system to learn about the shortcomings and imperfections that could cause the same adverse events to occur again. The culpability approach has the sole purpose of shifting the responsibility for the performance failure in to an individual or several professionals and in fact might benefit the same flawed structure by deferring its reorganization, which is usually very demanding from an economic point of view [16,17].

It is no coincidence that the so-called health structure responsible for the "organizational shortcomings" was invented some time ago in legal literature [12]. The term was created to emphasize the role of the structure's organizational activity causing an adverse event but from an equally blameworthy perspective. The aim was splitting up the damage caused by organizational deficit into the causal contribution attributable to the collective action of the structure and the damage attributable to the individual health professional. Thus, this contributes exclusively to shift the focus from the health professional – the last causal link in a complex organizational process – to the institutionally delegated person in charge of the management choices capable of directing and guiding the organization of activities within the structures [12].

Following this path, the common law systems of the UK/USA [18] and Italian legislators have developed liability reforms in an attempt to divert the claims of harmed patients from the liability of the professional to the liability of the healthcare facility [19]. In the UK, the system has been in place since 1995 following the institution of the National Health Service Litigation Authority to administer the fund established by the National Health Service to assist Health Service organizations and bodies sharing costs arising from negligence, health care, and professional liability in general. In Italy, after a draft reform was carried out in 2012, it required a new law in 2017, which attempted to overturn the logic of the criminal sphere, proclaiming that events due to errors of any degree are not punishable as long as they occur in the context of activities carried out in compliance with the recommendations contained in codified guidelines or good clinical care practices [20]. In the civil sphere, it established a shift of the burden of compensation from health workers to public and private health care companies [14].

In France, the responsibility of the structure in the occurrence of adverse events related to assistance has been contemplated since the introduction of the law dated 4th March 2002. The advantage of the French system essentially lies in the fact that the victim of an adverse health event is exempted from the burden of proof when the event has occurred during or following risky treatment and when a disabling condition of certain severity (permanent impairment of more than 24%) has occurred, which grants the victim access to compensation from a special compensation fund. It is a solution borrowed from experiences in New Zealand, where for some time now, not only has the weapon of criminal judgement been inoperative, but a system of no-fault compensation for the damage suffered has also been in place, allowing the patient to quickly obtain adequate remuneration.

The objective of ensuring the safety of care is achieved by balancing the different needs: the protection of the victim, who deserves to be compensated for additional damage suffered, and the protection of the professional, which is the last link in a system that deserves to be reviewed and perfected [14]. In a system set up in this way, the health care professional confidentially reports system dysfunctions worthy of being studied and corrected, and the damaged patient receives rapid compensation for the discomfort or impairment suffered. The structure promotes a constant policy to improve the quality and safety of care, there is no need to hunt for the scapegoat, and everyone cooperates to keep the interest of the patient's health at the centre of attention. Therefore, it can be well understood how such a system is the best organizational and regulatory response to the dilemma of responsibility in the multidisciplinary approach because it is the most functional tool to maintain the climate of effective collaboration, which is essential to the integration of several professional skills involved to address focal pathologies in their broadest sense.

Information to the patient at the time of "boards": who is responsible, and what are the repercussions?

For years, the subject of informed consent has been the matter of dedicated conference sessions, and it has been debated whether the correct form of this legal principle should be written or verbal. Among the supporters of the written form are minimalists, who are inclined to minimize communicating information and receiving consent, as well as rigorists, who are inclined towards the preparation of detailed forms. When COVID-19 appeared, the verbal form came back into vogue, but mostly only for precautionary reasons because of the possibility that the virus could remain active on surfaces for several hours/days. It has acted as a stimulus for the development of new ways of recording informed consent (i.e., audio-video recordings) [21]. Therefore, it is clear that new ways of communication need to be created. And this is even more valid for multidisciplinary contexts, such as boards, where many actors and authors of a diagnostic-therapeutic choice refer to the patient.

First, it is necessary to identify a single clinical reference for the patient – a spokesperson to whom the task of providing information to the patient and collecting consent to the services should be entrusted. This professional figure will act as a hinge that reports the patient's thoughts and questions to the multidisciplinary team and promotes the combined answers. In such a reorganization of the informed consent acquisition process, the dimension of the interview and non-verbal language will be able to recover a thus-far compressed space, and the use of written forms will no longer be the basic instrument for the registration of informed consent. Instead, it will constitute a useful tool to integrate the verbally communicated information.
Since it is addressed to the patient, the tool must be thought usable, easy to read, and easy to understand with drawings and images. Therefore, it will be necessary to initiate the spokesperson's training in verbal and non-verbal communication beforehand so that he or she can positively accomplish such a delicate task. At the same time, it will be necessary to revise the forms used and adapt them to the recipient's needs (the patient). They should be made more functional to receive and understand the information contained that was already displayed during the interview. Finally, it will be essential to promote audit activities within multidisciplinary teams to analyze clinical cases and adverse events that have occurred during care, as well as decision-making processes, the level of patient involvement, and patient satisfaction with the care in a continuous review program that aims to constantly improve the quality of care.

Conclusions

Creating a culture of safety within a multidisciplinary team requires an investment in leadership by each member. This investment is based on one assumption: none of the components can achieve success alone, even within an advanced technological process. The creation of a common governance structure in the organization of an operating team or a tumour board, in which every professional is valued and feels involved in leadership, is fundamental to exploit the commitment and expertise of each of them to ensure patient safety [22]. This is certainly the best approach to multi-organ pathology governance because involving everyone in a process aimed at quality in best interests of the patient allows the implementation of main positive actions capable of overcoming the *limes* while respecting its content through the integration of skills.

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