Endoscopic Endonasal Approaches for Malignant Tumours Involving the Skull Base

Paolo Castelnovo · Mario Turri-Zanoni ·
Paolo Battaglia · Maurizio Bignami ·
Andrea Bolzoni Villaret · Piero Nicolai

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Abstract The treatment of skull base malignancies has evolved significantly during recent decades, requiring the contribution of multidisciplinary teams. Surgery, which plays a pivotal role, ranges from traditional external procedures to endoscopic endonasal approaches (EEA). Recent reports have demonstrated that EEA is feasible, safe, and able to achieve the radical resection of selected lesions, while minimising the morbidity in patients. At the present time, the major criticisms that are made focus on oncologic outcomes, in view of the limited number of patients studied and the short/intermediate follow-up of larger series, which have grouped together different histologies associated with different prognoses. An extensive review of the pertinent literature is addressed here in order to analyse the endoscopic surgical techniques employed, the evolution of indications and the oncologic outcomes. The promising results that have emerged seem to indicate that EEA, when properly planned and performed by experienced surgeons, has nowadays acquired an accepted role with precise indications in the whole armamentarium available for the treatment of skull base malignancies.

Keywords Sinonasal cancers · Skull base · Endoscopic endonasal approach · Craniofacial resection · Skull base reconstruction · Cranio-endoscopic approach

Introduction

Sinonasal malignancies are uncommon, comprising only 3 % of head and neck cancers, and they have traditionally been associated with poor prognosis. The anatomical proximity of the nasal cavity and paranasal sinuses to the skull base, brain, orbit and carotid artery makes complete surgical resection a challenging and sometimes impossible task. In addition, sinonasal cancers tend to be asymptomatic at their early stages, presenting more frequently only when extensive local invasion has already occurred. A major advance in the management of sinonasal malignancies in the past was craniofacial resection (CFR), introduced by Ketcham et al. [1] in the 1960s. By including the anterior skull base (ASB) in the surgical specimen, this intervention has dramatically improved local control of tumours encroaching upon the roof of the ethmoid [2]. However, this approach has been associated with a morbidity and perioperative mortality that is not negligible [3, 4]. The increased expertise of skull base teams (neurosurgeons and otorhinolaryngologists) in endoscopic procedures and improved imaging diagnostic systems, together with the technological refinement of endoscopic equipment, have all contributed to gradually expand the indications for endoscopic endonasal approaches (EEA) for resecting malignant tumours in selected cases. The first endoscopic experiences in sinonasal malignancy treatment emerged in the late 1990s and were limited to lesions involving the naso-ethmoidal box, but not encroaching upon the ASB [5]. Over the past decade, data from several centres worldwide have demonstrated that the EEA can be extended to include the dura of the ASB (ERTC, endoscopic resection with transnasal craniectomy), from the posterior wall of the frontal sinus back to the sphenoid planum and between the orbits [6]. Hence, the extent of the

P. Castelnovo · M. Turri-Zanoni (✉) · P. Battaglia ·
M. Bignami
Department of Otorhinolaryngology, Ospedale di Circolo e
Fondazione Macchi, University of Insubria, Varese, Via
Guicciardini 9, Varese, Italy
e-mail: tzmario@inwind.it

A. Bolzoni Villaret · P. Nicolai
Department of Otorhinolaryngology, Spedali Civili di Brescia,
University of Brescia, Brescia, Italy

endoscopic resection can be tailored to fit specific tumour characteristics (histotype, site of origin and proximity to critical areas) while preserving uninvolved structures, thus reducing functional sequelae as a consequence [7•]. When the EEA is not feasible, due to massive intracranial extension of the tumour, it can be associated with a transcranial approach to obtain better control of the upper margins [8]. Overall, the golden point for the skull base procedures is to choose the best surgical corridor toward the pathology. The endoscopic endonasal corridor is to be preferred when it provides the most direct access to the tumour but entails the least manipulation of neural and vascular structures; if nerves or vessels need to be mobilised to reach the tumour, an alternative approach should be considered. Based on this statement, we believe that the surgical choice should be made without any fundamentalism, and the surgical team should be experienced in all the different procedures in order to be able to perform ‘multiportal’ surgical approaches. Moreover, to optimise outcomes, endoscopic resections of sinonasal and skull base tumours should be performed only by teams of surgeons with longstanding experience in the endoscopic management of inflammatory diseases and CSF leak repair together with a thorough knowledge of the surgical oncologic principles necessary for the management of malignancies. In this review, major series reporting results concerning the EEA, with or without craniectomy, for the treatment of sinonasal and ASB cancers, will be addressed. Pre-operative workup, indications and exclusion criteria, surgical techniques, post-operative management and adjuvant therapy will be analysed. Oncologic outcomes, the evolution of indications and open issues are also discussed.

Pre-Operative Assessment

The pre-operative diagnostic workup includes fine-cut computed tomography (CT) with triplanar reconstruction of the paranasal sinuses and MRI scan with gadolinium enhancement in all cases. In patients suffering from claustrophobia, a CT scan with contrast medium can replace the MRI. In addition, ultrasound examination of the neck, chest X-ray and bone scintigraphy are performed to rule out systemic dissemination of the disease. To the same purpose, a total body PET scan is preferred in cases of aggressive histotypes (i.e., malignant melanoma and neuroendocrine carcinoma). Biopsy analysis of the sinonasal lesion is a crucial step in order to clearly identify the specific histotype of cancer and subsequently to plan the correct therapeutic strategy. When dealing with rare and particularly aggressive histotypes, a second histopathological opinion is mandatory for reaching the correct diagnosis. In the large majority of cases (squamous cell

carcinoma, olfactory neuroblastoma and adenocarcinoma or other salivary gland tumours), the standard therapy is surgery followed by adjuvant radiotherapy (RT), if required. In contrast, in cases of mesenchymal or haematolymphoid tumours, neuroendocrine carcinoma and undifferentiated carcinoma, the first-line therapy is chemotherapy associated or not with RT, leaving the surgical option only for the persistence/recurrence of disease. Moreover, all patients scheduled for a purely EEA have to be informed about the possibility of switching to a combined cranio-endoscopic resection (CER) intra-operatively, if deemed necessary.

Indications and Exclusion Criteria

The EEA allows the resection of small- to intermediate-sized sinonasal tumours (stages T1–T3) and also selected T4a–T4b lesions. According to the site of origin, extension and histotype of the tumour, the endoscopic resection can be performed unilaterally (resection extended antero-posteriorly from the posterior wall of the frontal sinus to the planum sphenoidale and latero-laterally from the nasal septum to the lamina papyracea) or bilaterally (resection extended from one lamina papyracea to the opposite one). Contraindications for an exclusively EEA include: infiltration in nasal bones and palate; massive involvement of the frontal sinus; massive involvement of the lacrimal pathway or of the bony walls of the maxillary sinus (with the exception of the medial one); extension into the infratemporal fossa; and involvement of the orbit content (Fig. 1). Remarkably, focal contact or suspected infiltration of the tumour with ‘high risk’ areas, such as the lamina papyracea, the cribriform plate or the roof of the ethmoid and the dural layer of the anterior cranial fossa, are not considered contraindications. In cases of ASB involvement and intracranial extension, massive infiltration of the dura over the orbital roof or brain parenchyma infiltration, detected both in the pre- or intra-operative settings, requires combining an endoscopic approach with an external one (CER). At present, the only intradural structures that can undergo endoscopic transnasal resection are the olfactory bulb and tract.

Surgical Techniques

The target of EEA is the radical removal of the lesion with negative margins, as in traditional procedures. The cornerstone of oncological surgery that focused on ‘en-bloc’ resection to avoid the risk of tumour spilling is now debated, gradually being replaced by the concept of ‘disassembling’ of the lesion, having under view the limits

Fig. 1 Contraindications for an exclusively endoscopic endonasal resection of anterior skull base malignancies. *BP* brain parenchyma, *NB* nasal bones, *HP* hard palate infiltration, *FS* massive involvement

of the frontal sinus, *LWms* lateral bony wall of the maxillary sinus, *OC* orbit content and lacrimal pathway

between normal and diseased mucosa. Although the surgical technique varies slightly from one patient to another according to the site of origin and extent of the lesion, endoscopic endonasal resection (ER) comprises of six main surgical steps:

Tumour Origin Identification

The surgical procedure usually starts with disassembling the tumour using powered instrumentation and/or cutting instruments. The lesion is gradually debulked starting from the core, in order to identify clearly its site of origin. In this phase, it is crucial to preserve the surrounding anatomical structures, since these are useful landmarks for orientating the subsequent surgical steps.

Surgical Target Setting

Removal of the posterior 2/3 of the nasal septum is performed to gain better exposure of the surgical field and to optimise the endonasal manoeuvrability of the dedicated instruments, using the two-nostrils four-hands technique [9]. In this step, the removal of the sphenoid rostrum is crucial to expose the postero-inferior margin of the dissection. The septal branches of sphenopalatine arteries are isolated and coagulated to reduce bleeding and to improve visibility. The frontal sinus is approached by Draf type IIb sinusotomy in the case of monolateral ER, whereas Draf type III median sinusotomy is performed if the ER involves both sides. The frontal sinusotomy represents the antero-superior margin of the dissection, allowing precise identification of the beginning of the anterior cranial fossa.

Centripetal Removal

Once the postero-inferior and antero-superior margins of the resection are exposed, a subperiosteal dissection of the nasoethmoidal-sphenoidal complex is subsequently performed unilaterally or bilaterally (according to the extension of disease), to expose the lateral margin(s) [10]. The lamina papyracea is included in the dissection when the tumour is in close proximity to or frankly involved in it. When required by the extension of disease, endoscopic medial maxillectomy type III can be performed, to achieve good control of the whole maxillary sinus. This surgical phase has to be associated with naso-lacrimal duct exposure and resection, just below the lacrimal sac. Superiorly, the dissection is continued in the antero-posterior direction, by resecting the olfactory fibres and the basal lamella of the ethmoidal turbinate, to mobilise the monoblock. The entire nasoethmoidal-sphenoidal complex is now isolated and pushed towards the central part of the nasal fossa (centripetal technique) to extract it transorally or through the nasal vestibule. The surgical margins are checked by frozen section and, if necessary, the dissection is continued until free margins are obtained.

Skull Base Removal

According to the extension of the disease, the endoscopic resection can also be extended to include the ASB (ERTC, endoscopic resection with transnasal craniectomy). Completion of the ethmoid roof exposure with removal of bony partitions is performed using a drill with a diamond burr. The ASB resection can be performed monolaterally or bilaterally according to the extension of disease and to the

particular histotype of the tumour. The anterior and posterior ethmoidal arteries are exposed, cauterised with bipolar electric forceps, and dissected. The crista galli is carefully detached from the dura and removed with blunted instruments, avoiding dura iatrogenic lesions.

Intracranial Work

The key point for subsequently performing an optimal skull base reconstruction is to properly dissect the epidural space over the orbital roof(s) laterally, the planum sphenoidale posteriorly and the posterior wall of the frontal sinus anteriorly, before starting the resection of the dura itself. The dura is then incised and circumferentially cut with angled scissors or a dedicated scalpel, far enough away from the suspected area of tumour spread (Fig. 2a). The falx cerebri is clipped in the anterior portion before its resection, to avoid sagittal sinus bleeding; then, its posterior portion at the level of the spheno-ethmoidal planum is resected. The arachnoid plane over the intracranial portion of the tumour is then dissected and separated from the brain parenchyma (Fig. 2b). The specimen, including the residual tumour, the ASB and the overlying dura together with one or both of the olfactory bulbs, is removed through the transnasal route. The dural margins are sent for frozen sections. In cases of small-sized tumours, the dural resection can be performed by leaving the ethmoidal complex attached to the skull base at the level of the olfactory grooves in a monoblock fashion.

Reconstruction Time

The resulting skull base defect is reconstructed by the endoscopic endonasal multilayer technique, performed preferably using autologous materials. In our experience, the fascia lata and/or the iliotibial tract (ITT) possess the best characteristics in terms of thickness, pliability and strength [11]. For the first intradural layer of duraplasty, the graft has to be at least 30 % larger than the dural defect and split anteriorly on the midline to adjust to the falx cerebri in cases of bilateral resection (Fig. 2c). The second layer, intracranial and extradural, needs to be precisely sized and tacked between the previously undermined dura and the residual ASB bone. Pieces of fatty tissue are placed to eliminate the dead space between the second and third layers and to flatten the residual denuded ASB. The third extracranial layer has to cover all the exposed ASB, but must not overlap the frontal sinusotomy(ies). The borders of the second and third layers are properly fixed with fibrin glue. In the case of a tumour sparing the nasal septum and without multifocal localisations (e.g. not in the case of intestinal-type adenocarcinoma, ITAC), for the third layer of the skull base reconstruction, it is also possible to use a

mucoperiosteum/mucoperichondrium pedicled nasoseptal flap (Hadad-Bassagasteguy flap, HBF) [12]. Its use facilitates rapid healing of the surgical cavity, especially in patients who require adjuvant irradiation.

At the end of the procedure, in selected cases, the frontal sinusotomy(ies) can be stented with rolled Silastic sheath(s) to allow subsequent frontal sinus debridement with no risks for the duraplasty. The surgical cavity is packed for about 48 h.

For lesions filling the frontal sinus or encroaching the ASB with intradural extension over the orbital roof or with brain parenchyma infiltration, the EEA has to be combined with an external approach (CER, cranio-endoscopic resection) [8]. The procedure is performed by two surgical teams (neurosurgeons and otorhinolaryngologists) working simultaneously through a transnasal and transcranial corridor, respectively. The EEA allows mobilising the ethmoidal labyrinth in a monoblock, by removing the nasal septum and rostrum and dissecting the sphenoid posteriorly and the lamina papyracea laterally. The transcranial approach consists in a subfrontal (or frontal) craniotomy, the size and shape of which depends on the surgical requirements. The craniotomy is carried out a few millimetres above the orbital upper arches in order to obtain an approach to the frontal skull base as broad and tangential as possible, to reduce as much as possible any excessive retraction of the cerebral parenchyma and thus avoid excessive kinking of the pericranium flap during the ASB reconstruction. A bony ‘volet’ including the anterior and posterior wall of the frontal sinus is removed. After detaching the bony flap from the dural layer and clipping the sagittal sinus emissaries to control the bleeding, the exposed dura is incised, the cerebral falx is dissected, and the intracranial portion of the tumour is carefully resected from the brain parenchyma. With a diamond burr, the superior portion of the fronto-ethmoidal–sphenoidal bony complex is isolated. Finally, the intracranial dissected lesions, together with the ethmoidal box, are extracted transcranially by the two-physician surgical team co-operating through the different approaches. The dural defect is rebuilt by suturing the dura mater to the temporal fascia or fascia lata. The ASB defect is reconstructed using a galeoperiosteum flap that is folded over and fixed by means of button sutures to the remaining sphenoidal border and to the orbital process of the frontal bone (medial edge). In this phase, the simultaneous endoscopic endonasal approach is useful to make sure that the duraplasty grafts are correctly placed, without any dehiscence. The bony flap is put back into place and fixed with titanium plaques and screws. The galea-cutaneous flap is then relocated and fixed with a button suture. At the end of the procedure, the EEA is especially useful for completing the skull base reconstruction. Indeed, the endoscope makes it possible to verify the watertight closure and to apply a

Fig. 2 Surgical steps of the endoscopic transnasal craniectomy (ERTC). **a** Resection of dura and olfactory bulb, **b** endoscopic view of the anterior skull base defect, extended from the posterior wall of the frontal sinus back to the sphenoidal planum and between the orbits, **c** endonasal skull base reconstruction using layers of

autologous materials. *FS* frontal sinus, *RoE* roof of ethmoid, *CG* crista galli, *dm* dura mater, *1* intradural layer, *2* intracranial extradural layer, *3* extracranial layer placed overlay, *FL* frontal lobe, *OB* olfactory bulb, *O* orbit, *ITT* iliotibial tract

connective tissue in overlay fashion (temporal fascia or fascia lata), for reinforcing the ASB reconstruction.

Post-operative Management

All patients who undergoing skull base reconstruction require a brain CT scan on the 1st post-operative day to rule out complications and to evaluate the extent of pneumocephalus, and they must observe complete bed-rest keeping the head in a 20° elevated position until the 3rd post-operative day. Nasal packing is gradually removed within 48 h. Intravenous third-generation cephalosporin therapy is started the day before surgery and continued for at least 5 days. Nasal irrigation with saline solution and application of mupirocin ointment twice daily is recommended for at least 1 month. Post-operative RT is planned in the case of significant skull base involvement (pT3), intracranial extension and dural infiltration (pT4a-b), margins close to the orbital content or the frontal sinus, and in cases of unresectable residual disease [7•]. All cases of olfactory neuroblastoma (ONB) receive adjuvant RT [13]. Post-operative RT is indicated in all patients receiving CER as a primary treatment, except for cases of mucosal melanoma where the role of RT is unproven [14]. Chemotherapy is added to RT in the cases of histotypes with a high risk of systemic dissemination of the disease. All patients have to be followed according to a protocol that includes monthly endoscopic examinations and MRI every 4 months during the 1st year, endoscopic examination and MRI every 2 and 6 months, respectively, during the 2nd year, and, thereafter, both examinations at 6-month intervals.

Outcomes

To date, there have been several studies that attest to the efficacy of EEA, associated with transcranial approach if

required, for the treatment of malignant neoplasms of ASB. Stammberger et al. [15] reported the earliest study on 36 patients affected by different histotype cancers, who were managed strictly via the endoscopic endonasal approach. The authors concluded that the outcomes were similar to those achieved with open approaches, obtaining 100 % disease-free survival for all eight ONB cases reported. Goffart et al. [16] reported 78 patients undergoing endoscopic resection of sinonasal malignancies, with adenocarcinoma being the most common histotype encountered. In this case-series, the 2- and 5-year survival rates of the whole group were 73.1 and 52.3 %, respectively, while the adenocarcinoma group exhibits a significantly better prognosis than other histological types with 2- and 5-year survival rates of 89.8 and 63.8 %. The authors concluded that patients who could be treated purely endoscopically (66/78) had a significantly better survival rate than those treated by an external and endoscopic approach. Both of these early studies set the stage for many additional experiences accrued over the last 10 years, supporting the efficacy of EEA for the management of ASB cancers (Table 1) [13, 15–24]. Roh et al. [17] reported the first US experience on a series of 19 patients with sinonasal malignancies, 13 of which were managed exclusively by the EEA. The overall and disease-free survival rates were 78.9 and 68.4 %, respectively, with a mean follow-up of 32 months.

The two largest series, reporting on 184 and 120 patients, respectively, who underwent an endoscopic approach to resect sinonasal and ASB cancer, were published almost concomitantly. The former one collected the data we acquired during our 10-year experience in two tertiary care Italian centres [19], while the latter summarised the oncologic results in a cohort of patients treated at the M.D. Anderson Cancer Center in Houston over a 16-year period [20]. Both series included patients in whom endoscopic surgery was used either alone (72.8 vs. 77.5 %) or in combination with frontal or subfrontal craniotomy

Table 1 Case-series of endoscopic surgery for sinonasal and skull base malignancies

Author, Year	No	Histology (%)	Stage (%)	Surgical approach	Survival rate
Stammberger 1999 [15]	36	50 % carcinoma 22 % ONB 14 % melanoma	Not shown	36, ER	DFS: 100 % (ONB)
Goffart 2000 [16]	78	51 % ADC	Not shown	66, ER 9, CER 3, CFR	5-year survival: 52.3 %
Roh 2004 [17]	19	Not shown	Not shown	13, ER 6, CER	OS: 78.9 % DFS: 68.4 %
Castelnuovo 2007 [13]	10	100 % ONB	30 % Kadish A 40 % Kadish B 30 % Kadish C	10, ER	OS: 100 %
Lund 2007 [18]	49	30 % ADC 22 % ONB 22 % melanoma	Not shown	49, ER (converted into CFR in 3 cases)	5-year OS: 88 %
Nicolai 2008 [19]	184	37 % ADC 13.6 % SCC 12 % ONB 9.2 % melanoma	28 % pT1 14 % pT2 17 % pT3 9 % pT4a 19 % pT4b	134, ER 50, CER	5-year DSS: 81.9 ± 3.9 %
Hanna 2009 [20]	120	17 % ONB 14 % ADC 14 % melanoma 13 % SCC	25 % pT1 25 % pT2 21 % pT3 29 % pT4	93, ER 27, CER	5-year DSS: 87 %
Folbe 2009 [21]	23	100 % ONB	10.5 % Kadish A 58.9 % Kadish B 26.3 % Kadish C 5.3 % Kadish D	22, ER 1, CER	OS: 100 %
Jardeleza 2009 [22]	12	100 % ADC	50 %, pT2 40 %, pT3 10 %, pT4	12, ER	5-year DFS: 91.6 %
Batra 2010 [23]	25	24 % SCC 20 % ONB 20 % melanoma 20 % SNUC	56 % pT3 44 % pT4	25, ER	5-year OS: 58.6 % 5-year DFS: 51.7 %
Van Gerven 2011 [24]	44	100 % ADC	2 % pT1 59 % pT2 11 % pT3 20 % pT4a 7 % pT4b	44, ER	5-year OS: 63 % 5-year DSS: 82 % 5-year RFS: 60 %

ER endoscopic resection, *CER* cranio-endoscopic resection, *ONB* olfactory neuroblastoma, *ADC* adenocarcinoma, *SCC* squamous cell carcinoma, *SNUC* sinonasal undifferentiated carcinoma, *ER* endonasal resection, *CER* endonasal resection combined with transcranial approach, *CFR* craniofacial resection, *5-yr*, five years, *OS* overall survival, *DSS* disease-specific survival, *DFS* disease-free survival, *RFS* recurrence-free survival

(27.2 vs. 22.5 %). The distribution of patients in relation to histology reflected the variable prevalence of histologies found in various geographical areas. In the Italian series, adenocarcinoma was the most frequent lesion (37 %),

while ONB was prevalent (17 %) in the US experience. With no major differences in the mean follow-up time (34.1 vs. 37 months), the 5-year disease-specific survival in the two series for the entire patient cohort was also quite

similar: 81.9 vs. 87 %. Interestingly, Nicolai et al. found a statistically significant difference in 5-year disease-specific survival between patients treated with endoscopic surgery alone compared to those who received CER (91.4 vs. 58.8 %; $P < 0.001$), although this observation was not confirmed by Hanna et al. As pointed out by these authors, this variability can reflect the different criteria used for patient selection for the different approaches, with the US group being more inclined to reserve an endoscopic approach for patients with relatively earlier disease stage and no or limited skull base invasion. Moreover, the Italian study analysed the 5-year disease-specific survival by stratifying patients into four subgroups according to the histotypes with comparable biological aggressiveness, finding values of 78.6 % for adenocarcinoma and squamous cell carcinoma, 100 % for ONB, 0 % for mucosal melanoma, and 92.4 % for other miscellaneous subtypes. The absence of facial incisions and osteotomies, less post-operative pain, decreased hospitalisation time, improved visualisation of tumour borders and reduced morbidity and mortality rates are commonly cited as the major advantages of endoscopic resection over the external approach [25]. Furthermore, when resection of the skull base is performed transnasally, retraction on the frontal lobes with the ensuing possibility of complications is avoided. On the other hand, the transnasal resection of the dura, with consequent endoscopic duraplasty, increases the likelihood of CSF leak. In the Italian series, the CSF-leak rate was 4.3 % and represents the most frequent major complication, as in the M.D. Anderson Cancer Center experience, which reported a CSF leak rate of 3.3 % (4/120) [19, 20]. However, a recent report performed by our group, focusing on skull base reconstruction after endoscopic surgery for malignancies of the sinonasal tract, demonstrated that the occurrence of CSF-leak is clearly related to the learning curve of the surgical team and to the refinement of the surgical technique, with progressive decrease of this complication over time [26•].

Several publications analysing the efficacy of endoscopic surgery in a specific histology have concentrated on adenocarcinoma. The Belgian experience, on a series of 44 patients treated with endoscopic resection followed by RT, obtained a 5-year overall survival of 83 % with a mid-term follow-up (mean: 42 months) [27], reduced to 63 % 3 years later, with a longer follow-up (mean: 61 months) [24]. In this case-series, local recurrences occurred in 36.3 % of cases, some being localised even in areas that were quite different from the initial presentation. Of note, if the tumour was unilateral, no contralateral dissection was undertaken. For this reason, and on the grounds of our experience, we prefer to include the entire bilateral ethmoid labyrinth in the resection. This policy can be justified by the fact that the exposure to wood dusts, which is almost

invariably associated with adenocarcinoma, renders all the mucosa of the nasoethmoidal complex vulnerable to developing adenocarcinoma foci [28].

Future Directions

The EEA has nowadays acquired an accepted role with precise indications in the whole armamentarium available for the treatment of sinonasal and skull base malignancies [29], and has to be considered one of the therapeutic options, together with the other surgical approaches and radio-chemotherapy, in a perspective of oncologic multimodal therapy capable of achieving radical and complete treatment of the pathology, while minimising the morbidity for the patient [30]. However, changes in clinical practice should be rooted in methodologically sound evidence. At the moment, the levels of evidence in endoscopic cancer surgery are mainly level 3 (case series) and level 4 (expert opinion). In the next decade, we will have to reach higher levels of evidence. Since prospective studies contrasting the results of the endoscopic and craniofacial resections are difficult to carry out, given the rarity of the disease together with ethical issues, the creation of a large database would favour the analysis of several variables in a significant number of patients. For this purpose, a website may permit the collection of information of large series of patients (clinical history, imaging data, pathological findings, types of surgical management and post-operative treatment) from different centres worldwide and particularly of rare neoplasms, which will increase our knowledge of their biological behaviour [7••]. The final step will be to perform a collaborative, multicentre, randomised, controlled trial on a large cohort of patients, with a precise stratification of the study population into homogeneous groups according to the stage of disease and histotype, to validate the endoscopic endonasal approach in the management of sinonasal and skull base malignancies. This is a unique opportunity for international and interdisciplinary collaboration that will result in benefits for a wide range of patients affected by sinonasal and skull base tumours.

In fact, there are still open issues and questions, which could and should be answered [31••]. Longer follow-ups are needed in order to have meaningful information on the outcome of those tumours that can relapse well beyond the usual 5-year period. Stratification of survival data by histology and stage is required to have a better understanding of the impact that these variables have on outcome. Recent advances in histopathological differential diagnosis between poorly differentiated neuroendocrine carcinoma and ONB seem to be crucial to properly plan adjuvant or neoadjuvant treatment and also to predict the prognosis of patients [32]. The role of neoadjuvant and/or adjuvant

therapies (radiotherapy, chemotherapy, biological modifiers) also needs to be explored with the intent of identifying patients who can benefit from these therapies, thus avoiding over-treatment in those with a less aggressive disease. In this respect, primary cisplatin-fluorouracil-leucovorin chemotherapy (PFL) followed by surgery and radiation has been proposed for advanced stage (T3–T4) intestinal-type adenocarcinoma, with significant improvement of disease-free survival, in the presence of wild-type TP53 or still-efficient p53 protein [33]. For systemic diseases, such as mucosal melanoma, the study of molecular abnormalities related to the biology of cancer might lead to the development of tailored target therapies to improve the outcome of this devastating disease [34]. Moreover, when evaluating long-term outcomes, EEA should be compared with traditional external approaches not only in terms of safety and efficacy but also of quality of life (QoL). To this purpose, prospective QoL evaluation should also be included in the pre- and post-treatment assessment of these patients [35, 36]. Incorporating a QoL questionnaire into the standard of care of patients with skull base cancers will enable the surgeon to better understand, in a more holistic fashion, the impact of treatment on the daily life-style of these patients and consequently identify the best treatment option for a given patient.

Conclusions

The endoscopic resection of sinonasal malignancies is an expanding technique. The role of transnasal endoscopic resection for low-stage (T1–T2 or Kadish A–B) sinonasal malignancies is now practically well established, whereas, for advance-stage lesions with skull base involvement and/or focal dural infiltration, a longer follow-up and larger case-series are needed in order to validate this approach. In these latter cases, when an extensive involvement of the intracranial structures is present, the endoscopic endonasal corridor can be safely associated with a transcranial approach. The encouraging overall and disease-specific survival rates reported in the recent studies published suggest that, for well-selected cases and with appropriate use of adjuvant/neo-adjuvant therapies, the endoscopic endonasal resection technique could produce acceptable oncologic outcomes in the management of sinonasal and ASB cancers, at the same time minimising the morbidity for the patient.

Compliance with Ethics Guidelines

Conflict of Interest Paolo Castelnovo, Mario Turri-Zanoni, Paolo Battaglia, Maurizio Bignami, Andrea Bolzoni Villaret, and Piero Nicolai declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Ketcham AS, Wilkins RH, Van Buren JM, et al. A combined intracranial facial approach to the paranasal sinuses. *Am J Surg*. 1963;166:698–703.
2. Lund VJ, Harrison DFN. Craniofacial resection for tumors of the nasal cavity and paranasal sinuses. *Am J Surg*. 1988;156:187–90.
3. Ganly I, Patel SG, Singh B, et al. Craniofacial resection for malignant paranasal sinus tumors: report of an international collaborative study. *Head Neck*. 2005;27(7):575–84.
4. Ian G, Snehal GP, Bhuvanesh S. Complications of craniofacial resection for malignant tumors of the skull base: report of an international collaborative study. *Head Neck*. 2005;27:445–51.
5. Stammberger H, Anderhuber W, Walch C, et al. Possibilities and limitations of endoscopic management of nasal and paranasal sinus malignancies. *Acta Otorhinolaryngol Belg*. 1999;53:199–205.
6. Castelnovo P, Dallan I, Battaglia P, Bignami M. Endoscopic endonasal skull base surgery: past, present and future. *Eur Arch Otorhinolaryngol*. 2010;267(5):649–63 Review.
7. •• Lund VJ, Stammberger H, Nicolai P, Castelnovo P et al. European position paper on endoscopic management of tumours of the nose, paranasal sinuses and skull base. *Rhinol Suppl*. 2010; (22):1–143. *Extensive review of recent literature concerning endoscopic management of sinonasal and skull base tumours, focusing on patient workup, surgical techniques, post-operative care and outcomes.*
8. Castelnovo PG, Belli E, Bignami M, et al. Endoscopic nasal and anterior craniotomy resection for malignant nasoethmoid tumours involving the anterior skull base. *Skull Base*. 2006;16(1):15–8.
9. Castelnovo P, Pistochini A, Locatelli D. Different surgical approaches to the sellar region: focusing on the “two nostrils four hands technique”. *Rhinology*. 2006;44(1):2–7.
10. Castelnovo P, Battaglia P, Locatelli D, et al. Endonasal micro-endoscopic treatment of the malignant tumours of paranasal sinuses and anterior skull base. *Oper Tech Otolaryngol*. 2006;17(3):152–67.
11. Villaret AB, Schreiber A, Battaglia P, Bignami M. Endoscopy-assisted iliotibial tract harvesting for skull base reconstruction: feasibility on a cadaveric model. *Skull Base*. 2011;21(3):185–8.
12. Hadad G, Bassagasteguy L, Carrau RL, et al. A novel reconstructive technique after endoscopic expanded endonasal approaches: vascular pedicle nasoseptal flap. *Laryngoscope*. 2006;116(10):1882–6.
13. Castelnovo P, Bignami M, Delù G, et al. Endonasal endoscopic resection and radiotherapy in olfactory neuroblastoma: our experience. *Head Neck*. 2007;29(9):845–50.
14. Lund VJ, Chisholm EJ, Howard DJ, Wei WI. Sinonasal malignant melanoma: an analysis of 115 cases assessing outcomes of surgery, postoperative radiotherapy and endoscopic resection. *Rhinology*. 2012;50(2):203–10.
15. Stammberger H, Anderhuber W, Walch C, Papaefthymiou G. Possibilities and limitations of endoscopic management of nasal

- and paranasal sinus malignancies. *Acta Otorhinolaryngol Belg.* 1999;53(3):199–205.
16. Goffart Y, Jorissen M, Daele J, et al. Minimally invasive endoscopic management of malignant sinonasal tumours. *Acta Otorhinolaryngol Belg.* 2000;54(2):221–32.
 17. Roh HJ, Batra PS, Citardi MJ, et al. Endoscopic resection of sinonasal malignancies: a preliminary report. *Am J Rhinol.* 2004;18(4):239–46.
 18. Lund V, Howard DJ, Wei WI. Endoscopic resection of malignant tumors of the nose and sinuses. *Am J Rhinol.* 2007;21(1):89–94.
 19. Nicolai P, Battaglia P, Bignami M, et al. Endoscopic surgery for malignant tumours of the sinonasal tract and adjacent skull base: a 10-year experience. *Am J Rhinol.* 2008;22(3):308–16.
 20. Hanna E, DeMonte F, Ibrahim S, et al. Endoscopic resection of sinonasal cancers with and without craniotomy: oncologic results. *Arch Otolaryngol Head Neck Surg.* 2009;135(12):1219–24.
 21. Folbe A, Herzallah I, Duvvuri U, et al. Endoscopic endonasal resection of esthesioneuroblastoma: a multicenter study. *Am J Rhinol Allergy.* 2009;23(1):91–4.
 22. Jardeleza C, Seiberling K, Floreani S, Wormald PJ. Surgical outcomes of endoscopic management of adenocarcinoma of the sinonasal cavity. *Rhinology.* 2009;47(4):354–61.
 23. Batra PS, Luong A, Kanowitz SJ, et al. Outcomes of minimally invasive endoscopic resection of anterior skull base neoplasms. *Laryngoscope.* 2010;120(1):9–16.
 24. Van Gerven L, Jorissen M, Nuyts S, Hermans R, Vander Poorten V. Long-term follow-up of 44 patients with adenocarcinoma of the nasal cavity and sinuses primarily treated with endoscopic resection followed by radiotherapy. *Head Neck.* 2011;33(6):898–904.
 25. Batra PS. Minimally invasive endoscopic resection of sinonasal and anterior skull base malignant neoplasms. *Expert Rev Med Devices.* 2010;7(6):781–91.
 26. • Villaret AB, Yakirevitch A, Bizzoni A, et al. Endoscopic transnasal craniectomy in the management of selected sinonasal malignancies. *Am J Rhinol Allergy* 2010; 24(1):60–5. *This case-series specifically addresses the problems related to the anterior skull base defect reconstruction after endoscopic endonasal resection of sinonasal malignancies. The procedure entailed acceptable morbidity, with progressive decrease of surgical complication over time.*
 27. Bogaerts S, Vander Poorten V, Nuyts S, et al. Results of endoscopic resection followed by radiotherapy for primarily diagnosed adenocarcinomas of the paranasal sinuses. *Head Neck.* 2008;30(6):728–36.
 28. Bonzini M, Battaglia P, Parassoni D, et al. Prevalence of occupational hazards in patients with different types of epithelial sinonasal cancers. *Rhinology.* 2013;51(1):31–6.
 29. Nicolai P, Castelnovo P, Lombardi D, et al. Role of endoscopic surgery in the management of selected malignant epithelial neoplasms of the naso-ethmoidal complex. *Head Neck.* 2007;29(12):1075–82.
 30. Harvey RJ, Winder M, Parmar P, Lund V. Endoscopic skull base surgery for sinonasal malignancy. *Otolaryngol Clin North Am.* 2011;44(5):1081–140 Review.
 31. •• Nicolai P, Castelnovo P, Bolzoni Villaret A. Endoscopic resection of sinonasal malignancies. *Curr Oncol Rep* 2011; 13 (2):138–44. *Recent review of indications and outcomes in the management of anterior skull base malignancies, with discussion on the pros and cons of the endoscopic paradigm.*
 32. Cohen ZR, Marmor E, Fuller GN, DeMonte F. Misdiagnosis of olfactory neuroblastoma. *Neurosurg Focus.* 2002;12(5):e3 Review.
 33. Bossi P, Perrone F, Miceli R, et al. Tp53 status as guide for the management of ethmoid sinus intestinal-type adenocarcinoma. *Oral Oncol.* 2013;49(5):413–9.
 34. Turri-Zanoni M, Medicina D, Lombardi D, et al. Sinonasal mucosal melanoma: molecular profile and therapeutic implications from a series of 32 cases. *Head Neck.* 2012. doi:[10.1002/hed.23079](https://doi.org/10.1002/hed.23079).
 35. Amit M, Abergel A, Fliss DM, Gil Z. The clinical importance of quality-of-life scores in patients with skull base tumors: a meta-analysis and review of the literature. *Curr Oncol Rep.* 2012;14(2):175–81.
 36. Castelnovo P, Lepera D, Turri-Zanoni M, et al. Quality of life following endoscopic endonasal resection of anterior skull base cancers. *J Neurosurg.* 2013 (in press).