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HEAD AND NECK ONCOLOGY

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Craniofacial resection for malignant tumours involving the anterior skull base

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Abstract Ethmoid malignant tumours are rare, but nearly all at least approach or involve the lamina cribrosa. An anterior craniofacial resection is almost always mandatory for a radical resection. While almost everything has been written about technical details, few studies reported meaningful analysis about prognostic factors and long-term results, for a series of reasons: the infrequency of these tumours, the variety of histologies, small patients cohorts presented by each author, a medley of untreated and pre-treated patients, the lack of a universally accepted classification. We perform a review of the literature in the light of our experience of 330 anterior craniofacial resections for ethmoid malignant tumours. We present our classification of ethmoid malignant tumours (called INT, Istituto Nazionale Tumori). It turned out to be more prognostic than AJCC–UICC classification.

Keywords Craniofacial resection · Skull base surgery · Skull base tumours · Ethmoid tumours · Classification

Introduction and literature overview

Malignant tumours involving the anterior skull base mostly originate in the paranasal sinuses, in particular in the ethmoid and nasal cavity, from the epithelium or glandular tissues. The most frequent histologic types are squamous cell carcinoma, undifferentiated carcinoma, and adenocarcinoma. Adenoid-cystic carcinoma is less frequent, while mucoepidermoid, acinic cell carcinomas and sarcomas are uncommon. A rare but typical tumour of this region is esthesioneuroblastoma. Anterior skull base may be also involved by an advanced tumour of the skin of the face or scalp, or by a tumour of the orbit and/or maxillary sinus with ethmoidal extension.

Malignant tumours of the nasal cavity and paranasal sinuses account for only 3% of head and neck tumours, and about 0.5% of all malignancies. As nearly all the ethmoid tumours at least approach the lamina cribrosa, an anterior craniofacial resection is almost always mandatory for a radical resection. Fortunately, ethmoid tumours account for about 20–30% of all paranasal malignancies.

Surgery still remains the cornerstone in the treatment of these tumours. The literature about anterior craniofacial resection is very large. In 1954 Smith [41] reported a case in which the craniofacial concept was applied for the first time. A neurosurgeon, and a head and neck surgeon, working in conjunction, resected en block an ethmoid-orbital tumour with cribriform plate and anterior wall of the sphenoid sinus in the specimen. Smith and colleagues' work did not receive a warm welcome. Only in 1963, when Ketcham [22] published his paramount paper reporting a series of 17 anterior craniofacial resection, this surgical procedure became a touchstone for the treatment of malignant tumours approaching the lamina cribrosa. Between 1966 and 1973 Ketcham et al. [23–25, 47] published four additional papers with a larger series of patients.

After Ketcham and colleagues' works a lot of papers on anterior craniofacial resection have been published, and nowadays this kind of surgery is widely recognized as the gold standard for malignancies approaching or involving the cribriform plate. Several technical details have been presented over the course of the past 40 years. We can summarize them in four variants:

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1. A classic double approach, as presented by Ketcham (transcranial and transfacial [22–24, 47].
2. An only trancranial approach [31].
3. An only transfacial approach [32].
4. A subcranial approach [34] avoiding any facial incision.

As regards technical details of anterior craniofacial resection, we refer to specific papers [9, 13, 16, 22, 31, 34, 38, 39].

Considerations about prognostic factors, statistics and long-term results

The main goals of every surgical resection of head and neck malignant tumours are, at least, clear margins and monobloc specimen. While clear margins must be a dogma, monobloc resection is not. Actually, in anterior craniofacial resections for malignancies it is sometimes necessary to forgo the second goal to better achieve the first, as the deep margins may be better overlooked and resected after the removal of the vegetating component of the tumour. However, we must avoid as much as possible a piecemeal resection.

As far as clear margins are concerned, we ought to resect at least one layer of uninvolved tissue all around the tumour; however, in some instances it is difficult to reach this purpose. Actually, toward the skull base the uninvolved tissue may be the lamina cribrosa, or the dura (when the lamina cribrosa has been destroyed). On the contrary, an intradural extension of the tumour makes it very difficult to reach a real radicality, also with a partial frontal lobe resection. A good radicality is also impossible when the tumour involves the orbital apex, as we may achieve few millimeters of sound tissue at the most, also cutting the optic nerve close to the chiasma. Finally, a tumour eroding the anterior–inferior wall of the sphenoid sinus is quite easily resectable; on the contrary, when the tumour involves or destroys the superior–posterior–lateral walls and spreads to the cavernous sinus, the sella turcica and the clivus, it is impossible to achieve its complete removal.

Until 50 years ago tumours involving skull base structures have been considered inoperable. Nowadays, advances in surgical approach coupled with new reconstructive microvascular techniques have enabled experienced surgical teams to resect nearly all types of malignant skull base tumours. However, oncologic unresectability is a concept that every experienced surgeon must always bear in mind.

The complex anatomy of skull base makes the surgical procedures for resection of tumours in this region very difficult and hazardous; it requires a skilled skull base surgical team, consisting at least of head and neck surgeons, neurosurgeons, and microvascular plastic surgeons. Neuro-anestesiologists and specialists in intensive care medicine are also fundamental. A spirit of willing cooperation makes each component of the team both to learn and to teach each other. For example, the neurosurgeon may learn the unusual concept of monobloc resection, and the head and neck surgeon may learn a different concept of radicality, because of impossibility to resect some centimetres of uninvolved tissue in the brain.

Despite this co-operation, craniofacial resection is not without complication. Intra- and post-operative mortality has became quite low (4,7%; 19), but major complications (wound infection, meningitis, CSF leakage, intracranial abscess, pneumocephalus, and orbital problems) are rather frequent (33%; 15, 17, 19, 28). Only a large experience makes the team able to overcome intra- and post-operative difficulties. Rarely like in this surgery the learning curve is so important. In our experience, the peri-operative mortality was dramatically high in the first 30 cases (20%), and it decreased to 1% in the following 300 patients [9, 43].

While almost everything has been written about technical details, few studies reported meaningful analysis about prognostic factors and long-term results of malignant tumours involving the anterior skull base [18, 21, 29, 48]. Moreover, the results reported from all the authors are difficult to interpret to draw any definitive conclusion for a series of reasons: most authors present a small number of patients, with a variety of histologies, not enough to draw any meaningful conclusions; in some papers there is a combination of benign and malignant tumours [29, 38]; the percentage between untreated and previously treated patients is different (from 39% [28] to 54% [9]); the location and extent of the tumour are not the same; the majority of papers report malignant tumours of paranasal sinuses, while in others the most frequent primary location is the skin [15].

For example, there is a great difference between American and European series under the histologic point of view. Squamous cell carcinoma is the most frequent histologic type in almost all American series [17, 21, 31, 35, 40], followed by sarcoma, and esthesioneuroblastoma. This last rare tumour and basal cell carcinoma of skin origin are the prevalent histology in the series presented by McCaffrey [30] and Dias [15], respectively. On the contrary, Intestinal Type Adeno-Carcinoma (ITAC), very unusual in American series (5–17%), is the most frequent tumour in all European series (27–74%; 9, 26, 29, 36, 44). In an Australian paper [7] the percentage of adenocarcinoma is 37%. It is a strange occurrence, as ethmoid ITAC is a professional disease, clearly correlated with wood and leather dusts exposure and with the level of dust concentration in the inhaled air [1, 2, 6, 37]. Ninety percent of our 115 patients with ethmoid ITAC had previously been exposed to wood or leather dusts (16.3% only for a short time and long before the onset of disease; [6]. A possible explanation of the different rates of adenocarcinoma between North American and European series may be a wider use of dusts aspiration devices and masks by American wood or leather workers.

Another problem in analysing long-term results is the small number of patients treated by each author, not allowing any indisputable statistical analysis of prognostic factors. A paper [33] reporting the results of an International Collaborative Study Group in which about as many as 1,307 patients collected from 17 institutions tried to overcome this difficulty. The histology of the primary tumour, the status of surgical margins, and intracranial extension turned out to be independently significant predictors of recurrence-free survival and disease-specific survival.

As regards histology, there is a general consensus about a better prognosis for patients with esthesioneuroblastoma, whereas patients with undifferentiated/anaplastic tumours fare worse. However, we must remember that tumours like esthesioneuroblastoma and ITAC need a very long follow-up. Two relapses of esthesioneuroblastoma after 12 and 14 years from a craniofacial resection and radiotherapy occurred in our patients. Two more patients treated for an ITAC presented with a local relapse (or new tumour with the same histology) after 15 and 18 years, respectively.

The importance of histologically negative margins in improving cure rate is quite universally accepted [20, 33]. However, this pathological characteristic cannot be overemphasized, as sometimes it is difficult to state. When the matter in hand is a mucinous tumour like an adenocarcinoma, it is nearly impossible to preserve a real monobloc of the specimen, and it is necessary to send to the pathologist some peripheral samples to control the radicality [24]. Moreover, toward the cranial fossa and the orbit the radicality is often a thin layer of uninvolved tissue (dura or orbital periosteum). In these cases, according to common rules for radicality, did we achieve an R0 or close margins? Other authors [40] did not find a prognostic value for the status of margins.

All the authors agree about a bad prognosis when the tumour involves the brain. Only a few of them [9, 44] report a better cure rate for patients with only dural involvement in comparison with those with brain infiltration. Most papers [12, 27, 40, 48] do not make this distinction, and report the same prognosis for both intracranial extension. For this unreported difference in prognosis in the original series of some participating institutions, also the International Collaborative Study Group [33] was unable to enter into details about the grade of intracranial extension affecting prognosis. A following analysis of the set of patients with paranasal sinus tumours [20] found a different outcome according to intracranial extension. The authors wrote: ''For recurrence-free survival, only brain invasion was significant, presumably because a resection margin can still be achieved when either bone or dura is involved, but this is less likely when brain parenchyma is involved''.

Furthermore for orbital extension of the tumour and for the possibility to spare the eye there are different opinions. Ketcham himself was prone to conservative surgery in his first paper [22], but 10 years after he advocated a more aggressive attitude [24]. Nowadays, many authors [13, 29, 45] assert the possibility to spare the orbit when there is involvement of the lamina papyracea but the inner face of the periosteum is intact. However, the paper of the International Collaborative Study Group [20] reports disease-specific survival figures with orbital involvement of 40.7% (periosteum/bone) and 44.4% (intraorbital contents) compared with no orbital involvement of 75%. Authors' conclusion is somewhat sibylline: ''This is consistent with previous reports in the literature that orbital involvement correlates with a poorer survival outcome''.

As far as previous treatment is concerned, some authors [9, 44] report a worse prognosis for pre-treated patients, whereas other authors [40] did not find any difference. Previous radiotherapy was found to have a negative effect on post-operative complications [33] and on recurrence-free survival [20]. Apart from a possible treatment selection bias, primary radiotherapy may be used more likely for patients with associated medical comorbidity and larger tumours, previous radiotherapy does not allow post-operative radiation therapy that is generally accepted as a standard treatment after a craniofacial resection.

So, some important questions are still open. Many mono-institutional series are too small, and the population of the international series [20, 33] is heterogeneous according to histologic composition, previously treated patients, site and extension of the tumour, surgical technique, and pre- and post-operative radiotherapy.

Moreover, in addition to the previously reported difficulties, another main problem in presenting the long-term results was the lack of an international clinical classification. So, most authors classified their patients only according to a pathologic staging. Furthermore the aforementioned international papers [20, 33] do not report any clinical staging of patients, due to heterogeneity in reporting T stage by every single institution. Actually, ethmoid carcinomas were staged only in the fifth edition of both the AJCC [3] and UICC [42] TNM classifications of malignant tumours in 1997. In the sixth edition of both AJCC [4] and UICC [46] classifications we may find a different definition of T categories, including nasal cavity and ethmoid sinus in a nasoethmoid complex; thus, finding a solution for the difficult distinction of the site of origin of tumours of this region. The new AJCC–UICC classification divides T4 tumours into T4a and T4b, resectable and unresectable, respectively.

Materials and results

At the *Istituto Nazionale per lo Studio e la Cura dei Tumori* of Milan (INT) we began to perform anterior craniofacial resections for malignant tumours in 1987. Till 1990 we treated only 30 patients. Since then, our Institute became the most important centre for these tumours in Italy. Till now we have operated 330 patients. This is probably the largest mono-institutional series in the world, and it allows us to draw meaningful

conclusions. Our surgical technique is a classic transcranial and transfacial double approach [8, 41]. The different expertises of co-authors of this paper and their close co-operation allow us to perform a standard anterior craniofacial resection as a routine operation, lasting less than 3 h. We use loupes, without microscope and endoscope.

Five years overall survival of our patients according to histology was: esthesioneuroblastoma 79%, adenoid-cystic carcinoma 68%, adenocarcinoma 44%, squamous cell carcinoma 21%, and melanoma 0%. The prognosis was significantly better for untreated patients than for relapses after previous treatment.

In the absence of an international staging system and on the basis of our experience with anterior craniofacial resections, we developed in 1993 and presented in April 1997 an original classification for malignant ethmoid tumours [8] based on the most commonly accepted unfavourable prognostic factors (involvement of dura mater, intradural extension, involvement of the orbit and, in particular, of its apex; invasion of maxillary, frontal and/or sphenoid sinus, and invasion of the infratemporal fossa and skin; Table 1). We applied this classification (called INT, Istituto Nazionale Tumori) to 91 consecutive malignant naso-ethmoid tumours, and we realized that it worked, satisfying one of the main goals of tumour staging, namely the progressive worsening of prognosis for different classes [9]. In 1999 we examined 123 patients and compared our classification with the 5th AJCC–UICC classification. We demonstrated again the prognostic value of INT classification, while AJCC–UICC classification turned out to be without any prognostic value [10]. After the publication of the 6th AJCC–UICC-2002 staging system we performed a new evaluation of 241 patients with malignant ethmoid tumours treated with an anterior craniofacial resection, and staged them according to the AJCC–UICC-1997 classification, AJCC–UICC-2002 classification and INT classification [11]. We used Kaplan–Meier curves and Cox models to investigate the prognostic value of each classification system on disease-free survival (DFS) and overall survival (OS). We measured the prognostic discrimination capability of each classification by using an index of agreement between each classification and DFS or OS time. Only the INT classification showed a progressive worsening of the prognosis with increasing stage, both for untreated and previous treated patients, and when it was applied to the whole series and to patients with adenocarcinoma. The index of prognostic discrimination favoured the INT classification, while both the 5th and 6th AJCC–UICC classifications seemed to have limited prognostic value.

Table 1 INT classification of malignant ethmoid tumours

T1	Tumour involving the ethmoid and nasal cavity sparing the most superior ethmoid cells
T2	Tumour with extension to or erosion of the cribriform plate, with or without erosion of the lamina papyracea and without extension into the orbit
T3	Tumour extending into the anterior cranial fossa extradurally and/or into the anterior two-thirds of the orbit, with or without erosion of the antero-inferior wall of the sphenoid sinus, and/or involvement of the maxillary and frontal sinus
T4	Tumour with intradural extension, or involving the orbital apex, the sphenoid sinus, the pterygoid plate, the infratemporal fossa or the skin

The better performance of INT classification is due to the fact that it takes into account the possibilities and limitations of the standard surgical treatment for ethmoid malignant tumours (i.e. craniofacial resection) to achieve radical resection, and it assembles in the same stage tumours with the same chances of clear margins. On the contrary, AJCC–UICC classification put together different tumours. For example, a tumour involving the medial wall of the orbit, even if without any orbital extension, is classified T3, like a tumour involving the maxillary sinus and destroying the palate. In the AJCC–UICC stage T4a we may find tumours with "minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses". First of all, it is not easy to understand what "minimal extension to anterior cranial fossa" means. A tumour with intracranial extension at least is attached to the dura; but involvement of the dura makes a tumour to be in the stage T4b. Moreover, sphenoid involvement is not clearly defined, because a detailed description of its extent is lacking; as we have aforementioned, there are in the same definition tumours easily resectable and tumours unresectable. Finally, both a tumour involving only the dura and a tumour invading the brain are T4b; also in this case there is the same bias about resectability.

Conclusions

In their swan-song in 1985, Ketcham and Van Buren [23] stated some fundamental principles about craniofacial resection for paranasal malignant tumours:

1. "Cancer involving the ethmoid and sphenoid frontal sinus complex can be successfully eradicated by a combined transcranial and transfacial surgical dissection."
2. "Survival rates of 44–58% with a 3% hospital mortality rate in patients whose previous surgery or radiotherapy was largely unsuccessful suggest that this cosmetically acceptable surgical endeavour should be used more often by the head and neck surgeon in treating paranasal sinus cancer."
3. "Utilizing the principles of antibiotic prophylaxis, strict attention to principles of tumour removal and surgical technique, and the talents of the combined surgical and neurosurgical team, this aggressive

surgical approach to the paranasal sinuses can be safely and successfully carried out. The approach described herein has the following advantages: it allows accurate evaluation of intracranial tumour extension while protecting the intracranial contents, it essentially avoids cerebrospinal fistulization, it provides adequate exposure for hemostasis, facilitates en bloc tumour resection, selectively conserves the orbital contents, and provides patient survival rates up to 58% for paranasal cancer that involves the ethmoid and sphenoid frontal sinus complex.''

These statements made 20 years ago are still valid.

We may conclude that craniofacial resection and post-operative radiotherapy is still the gold standard for the treatment of tumours involving the anterior skull base. The role of endoscopic resection for some small tumours is still under discussion, and everyone might be careful in leaving the main street of craniofacial resection for the treatment of malignant tumours involving the anterior skull base. We cannot find in the literature large series of malignant tumours resected by endonasal–endoscopic approach with long-term results [5, 14].

For the aforesaid reasons it is sometimes difficult to interpret long-term results. In the literature there are not randomized trials, and probably they will never be possible. The common use of a prognostic clinical classification might be at least the beginning in presenting comparable results.

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