Surgery for Malignant Maxillary Tumors Involving the Middle Cranial Fossa

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ABSTRACT

The purpose of this study was to evaluate the disease-free survival (DFS) of patients with maxillary malignant tumors invading the middle cranial fossa (MCF) who underwent a lateral or anterolateral skull base resection. This study was a retrospective analysis in a tertiary referral center and included 62 patients with maxillary malignant tumors invading the MCF (stage T4b) treated with surgery with or without postoperative radiotherapy. All patients had sharp pain and involvement of at least one branch of the trigeminal nerve. Twenty-eight patients had not been treated previously, and 34 had previously been treated elsewhere. The MCF dura was infiltrated and resected in 36 cases, and in nine of these, there was an intradural extension of the tumor, with temporal lobe and/or cavernous sinus invasion. Thirty-six patients underwent reconstruction with a temporalis muscle pedicled flap, and 26 patients with a free flap. There was a 22% overall rate of postoperative complications, but no intraoperative deaths. The median follow-up time was 49 months (range 2 to 186). Overall DFS was 33.9% and was higher for untreated patients (46.4% versus 23.5%) and for patients in whom clean margins were achieved (51.4% versus 12.5%). The survival time for patients who died of disease was 9 months for squamous cell carcinoma and 38 months for adenoid-cystic carcinoma. All patients experienced anesthesia in the territory of the resected trigeminal branches, but their pain vanished, and their quality of life improved. Lateral skull base surgery may achieve satisfactory oncologic results for patients with low-grade tumors, with improved quality of life for almost all patients.

KEYWORDS: Maxillary malignant tumors, middle cranial fossa, skull base surgery, quality of life

Malignant tumors of the paranasal sinuses are rare, accounting for only 3% of all head and neck malignancies. As a consequence, no report of a randomized clinical trial about different treatments has been published, and the chance to perform such a trial is remote. However, the combination of surgery and

chemo-/radiotherapy seems to offer better local control than radiotherapy alone.^{1,2} Surgical treatment of paranasal sinus cancers have for many years remained little more than a piecemeal resection. Lizars of Edinburgh, in 1826, proposed the entire removal of the superior maxillary bone, and performed the first resection in

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1829. He accurately described the procedure, but a portion of the tumor, attached to the pterygoid process, could not be detached.³

Öhgren, in 1933, divided maxillary tumors with his famous line in “topographically more benign tumors” (anteroinferior) “from those of more malignant character” (superoposterior).⁴ Actually, the superoposterior extension of a maxillary sinus tumor has always made its radical resection very difficult and uncertain with an only anterior transfacial approach,⁵ so that tumors with this extension have always been classified as T3 or T4 in all following American Joint Committee on Cancer-International Union Against Cancer (AJCC-UICC) classifications.

Ketcham et al in 1963⁶ were the first to report a series of patients undergoing a combined transcranial and transfacial approach for tumors of the paranasal sinuses involving the anterior skull base. Today, anterior craniofacial resection is the standard treatment for these tumors, and the prognostic factors have been quite well established.^{7,8}

On the contrary, the prognosis of maxillary malignant tumors with extension to the infratemporal (ITF) and middle cranial fossa (MCF) is not so clear. Given the low incidence rate, the variety of histological types, and the exacting surgery, few centers have extensive experience with the treatment of these tumors, thus preventing any meaningful analysis of outcomes.

The aim of this retrospective report is to analyze the results of a monoinstitutional series of patients with maxillary malignant tumors involving the MCF and the indications and contraindications for this challenging surgery.

PATIENTS AND METHODS

Patients with maxillary malignant tumors involving the ITF and MCF, who underwent a lateral or anterolateral craniofacial resection at the Istituto Nazionale per lo Studio e la Cura dei Tumori of Milan between 1990 and 2006, were included in this study.

Patient charts, operative notes, follow-up clinic notes, and radiological (computed tomographic scan, and/or magnetic resonance imaging) and pathological reports were analyzed for each patient. Radiographic study results and pathological reports were used to assess the site of origin of the tumor (only maxillary sinus) and the clinical and pathological involvement of the MCF. Histological diagnosis was always based on a transnasal or transmaxillary biopsy or on the specimen from previous surgery performed elsewhere.

Patients underwent a lateral or anterolateral craniofacial resection and a subtotal or total maxillectomy, but a detailed description of the surgical techniques is beyond the scope of this study. All patients were oper-

ated upon by the same surgeons (G.C., head and neck surgeon, and C.L.S., neurosurgeon).

All patients had a regular follow-up after surgery for at least 2 years or until their death. Disease-free survival (DFS) was measured from the date of surgery to the date of disease recurrence or death; in the absence of either event, the time was measured from the date of surgery to the date of last follow-up available. The median follow-up time was 49 months (range 2 to 186). Patients who died of other causes and were without evidence of disease at 24 months or later were considered cured (NED). In contrast, patients who were alive with disease at last follow-up were considered dead of disease (DOD).

RESULTS

Overall, the study included 63 patients. One subject was excluded from the analyses because he died postoperatively of anuria. Patient ages ranged from 15 to 76 years (mean age, 48 years), and the male/female ratio was 1 (31/31). The main disease characteristics are described in Table 1.

All tumors were in stage T4b according the AJCC-UICC 2002 classification. Patients with recurrent disease were staged at the time of recurrence. Four patients presented with cervical lymph node metastases (undifferentiated carcinoma, adenoid cystic carcinoma, adenocarcinoma and squamous cell carcinoma, one each), and underwent neck dissection together with primary tumor resection. Eight patients developed neck metastases during follow-up together with primary tumor recurrence and/or distant metastases. None of these patients died from nodal metastases per se.

Table 1 Disease Characteristics of the Patients

	No.	%
Prior treatment		
No	28	45.2
Yes	34	54.8
Tumor histology		
Sarcomas*	17	27.4
Adenoid cystic carcinomas	15	24.2
High-grade salivary tumors†	12	19.3
Squamous cell carcinomas	7	11.3
Undifferentiated carcinomas	4	6.5
Low-grade salivary tumors‡	2	3.2
Others§	5	8.1
Total	62	100

*Osteosarcoma 7, chondrosarcoma 3, rhabdomyosarcoma 2, leiomyosarcoma 1, fibrosarcoma 1, liposarcoma 1, third-grade sarcomas 2.

†High-grade adenocarcinoma 9, high-grade mucoepidermoid carcinoma 1, myoepithelial carcinoma 1, clear cell carcinoma 1.

‡Low-grade adenocarcinoma 1, low-grade mucoepidermoid carcinoma 1.

§Hemangiopericytoma 1, plasmacytoma 1, malignant ameloblastoma 1, malignant meningioma 1, solitary fibrous tumor 1.

All patients experienced sharp pain from involvement of at least one branch of the trigeminal nerve, and this pain was one of the first reported symptoms. Twenty-five patients showed invasion of the hard and/or soft palate, with bleeding oral ulceration in 11 cases. Twenty-eight patients (45.2%) had received no previous treatment. Four of these patients (with osteosarcomas) underwent planned preoperative chemotherapy. Thirty-four patients (54.8%) had previously been treated elsewhere with surgery (14), surgery and radiotherapy (15), or radiotherapy or chemoradiotherapy (5). Thirty-three patients underwent planned postoperative radiotherapy (three with adenoid-cystic carcinoma and macroscopic residual diseases were treated with fast neutrons).

The surgical technique was a classic ITF intracranial approach for tumors involving only the MCF (39 cases), and an anterolateral approach for tumors involving both middle and anterior cranial fossa, with total ethmoidectomy and resection of the cribriform plates (23 cases). The greater wing of the sphenoid was always eroded by the tumor and removed together with the root of the pterygoid process, thus entering into the MCF. The MCF dura was infiltrated and resected in 36 cases; in nine of these patients, there was also an intradural extension of the tumor, with temporal lobe and/or cavernous sinus invasion. A subtotal petrosectomy with dissection of the carotid artery was performed in four cases, but no carotid artery was sacrificed. In 25 cases, there was involvement of the orbital apex (22 orbital exenterations), in 16 there was involvement of the mandible (segmental resection of the vertical branch was performed with condylectomy), and in six there was involvement of the parotid gland (radical parotidectomy was performed in all cases, with sacrifice and reconstruction of the facial nerve in two cases). The pterygoid plates were always partially or totally destroyed by the tumor and were resected together with pterygoid muscles, thus achieving a complete cleaning of the ITF. In 19 patients, the tumor involved the lateral wall of the nasopharynx and the eustachian tube. In all cases, a subtotal (25) or total (37) maxillectomy was also performed through a transfacial approach (classic or modified Weber-Fergusson incision, tailored according to the extension of maxillary involvement). Total maxillectomy included the resection of the hard palate.

Macroscopic and microscopic clean margins have been achieved in 35 cases (56.5%), close margins in 24 (38.7%), and macroscopic residual disease remained in 3 (4.8%).

All patients underwent reconstruction, with a temporalis muscle pedicled flap (36 cases) and with a free flap in 26 cases (21 rectus abdominis, two lateral thigh, two latissimus dorsi, and one fibula). As a rule, reconstruction with the temporalis muscle was performed in cases without total maxillectomy and orbital

exenteration, namely where the dead space to be filled was smaller. The anterior skull base was always reconstructed with a pedicled pericranial flap. No bone or alloplastic material was used for reconstruction of the floor of MCF, and problems with brain herniations were not observed.

There were no intraoperative deaths in this series. One patient died 15 days after surgery of anuria (the patient had renal transplantation 4 years prior to this surgery). There were 14 postoperative complications (22%): four soft tissue infections, five partial flap failures, three cerebrospinal fluid leaks, one meningitis, and one pneumonia.

The cosmetic appearance was very good in patients without orbital exenteration, facial nerve sacrifice, and/or mandibulectomy. In these cases, despite the best reconstruction, some facial disfigurement was unavoidable. Obviously, all patients had anesthesia in the territory of the resected trigeminal branches, but their pain vanished. Some months after surgery, almost all patients complained of disesthesia in the territory of the resected trigeminal branches; however, all reported an improvement in their quality of life.

OUTCOMES

Overall, 46 patients (74.2%) experienced a tumor recurrence. Twenty-two of these suffered a local recurrence, six patients had local and neck recurrences, eleven patients presented with local and distant metastases (mainly lung), and seven patients presented with distant metastases as the sole site of recurrence. Excluding three patients with macroscopic residual disease, the time elapsed between surgery and recurrence was similar for patients in whom clean margins had been achieved (15 months, range 4 to 64), and patients with close margins (14 months, range 2 to 43). Conversely, there was a great difference in time to recurrence between patients with squamous cell carcinomas (median interval 3 months) and patients with adenoid-cystic carcinomas (16 months, range 4 to 34). Overall, 28 patients (45.2%) were cured of their primary tumor.

Thirty-nine of 46 patients who had recurrences underwent symptomatic therapy or palliative chemotherapy and/or radiotherapy. Seven patients were treated with surgery and/or radiotherapy for local-regional recurrence (5) or isolated lung metastasis (2), and five of these (two adenocarcinomas, two osteosarcomas, one chondrosarcoma) are alive and NED with a long follow-up (54 to 94 months).

DFS was observed in 21/62 patients (33.9%; Table 2) and was significantly better for previously untreated patients (13/28, 46.4%) than for those with recurrent tumors (8/34, 23.5%). The DFS was 51.4% (18/35) for patients in whom clean margins have been achieved, and 12.5% (3/24) for patients with close

Table 2 DFS Rates According to Prior Treatment and Histological Type

	NED (%)	DOD (%)	Mean Survival in Months for NED Patients (Range)	Mean Survival in Months for DOD Patients (Range)
Prior treatment				
No	13/28 (46.4)	15/28 (53.6)		
Yes	8/34 (23.5)	26/34 (76.5)		
Squamous cell carcinomas	3/7 (42.8)	4/7 (57.2)	49 (30–83)	9 (6–12)
Undifferentiated carcinomas	0/3 (0)	3/3 (100)	—	8 (2–14)
Adenoid-cystic carcinomas	2/15 (13.3)	13/15 (86.7)	72 (40–104)	38 (9–72)
High-grade salivary tumors	2/12 (16.7)	10/12 (83.3)	70 (35–106)	40 (20–134)
Low-grade salivary tumors	2/2 (100)	—	179 (173–186)	—
Osteosarcomas	6/8 (75.0)	2/8 (25.0)	93 (33–150)	5.5 (5–6)
Chondrosarcomas	2/3 (66.7)	1/3 (33.3)	72 (43–101)	18
Rhabdomyosarcomas	2/2 (100)	—	78 (35–122)	—
Other sarcomas*	0/5 (0)	5/5 (100)	—	12 (3–28)
Other	2/5 (40.0)	3/5 (60.0)	53 (39–68)	28 (18–35)
Overall	21/62 (33.9)	41/62 (66.1)	85 (30–186)	28 (2–134)

*Leiomyosarcoma 1, fibrosarcoma 1, liposarcoma 1, third-grade sarcomas 2.

DFS, disease-free survival; NED, no evidence of disease; DOD, died of disease.

margins. The rate of clean margins was the same for untreated patients and recurrences but was lower for high-grade than for low-grade tumors (44% versus 75%). The DFS was 42.8% for squamous cell carcinomas, 66.6% for chondrosarcomas, 75% for osteosarcomas, and 13.3% for adenoid-cystic carcinomas. It is important to underline that four patients with adenoid-cystic carcinoma died from distant metastases without primary recurrence. Therefore, 40% of patients with this tumor were cured at the primary site. The DFS for patients with or without dural involvement was 29.6% versus 38.4% and for patients with tumor in the cavernous sinus DFS was 25%. The only patient with large temporal lobe invasion died for primary tumor relapse.

The median survival time for NED patients was 86 months (range 30 to 186), and for DOD patients this was 28 months (range 2 to 126). The survival time for DOD patients with squamous cell carcinomas was 9 months (range 6 to 12), and for patients with adenoid-cystic carcinomas, it was 38 months (range 9 to 72).

DISCUSSION

For many years, maxillary malignant tumors invading the ITF and MCF were considered inoperable. In the 1970s and 1980s, great enthusiasm took the place of the previous skepticism about surgical treatments for these tumors, and numerous papers and books appeared regarding the technical details of lateral skull base surgery.^{9–12} Those works demonstrated that tumors of the MCF may be extirpated, though complications are not infrequent. However, none of those studies reported oncologic long-term results. Follow-

ing this, other works have been published about results in lateral skull base surgery for tumors,^{13–17} but almost all started from a technical point of view (surgical approach) and contained some biases: small number of patients treated by each author, a variety of locations of origin of the primary tumor (paranasal sinuses, parotid, nasopharynx, oropharynx, orbit) and various extents of local invasion (extracranial and intracranial together), a mixture of benign and malignant tumors, and insufficient length of follow-up. Actually, it is well known that a short follow-up can be misleading with some tumor types, like adenoid cystic carcinoma. Therefore, the reported rates of DFS vary widely (0 to 70%).^{14–18}

In the series of 35 patients presented by Pitman et al,¹⁴ there were only adenoid-cystic carcinomas, and no more than 34% of these had intracranial invasion.

Carrillo et al¹⁵ reported a DFS higher than 70%, but their series of only 21 malignant tumors was very heterogeneous, as three patients had small tumors of the external auditory canal (two T1 and one T2), two patients had tumors of the oropharynx, and only one had intradural extension of the tumor. Despite these small numbers, the authors concluded that patients with dural involvement had a worse prognosis.

Llorente et al¹⁶ analyzed a series of 40 patients with lateral skull base tumors managed with a subtemporal-preauricular approach. Twenty-one of these patients had malignant tumors, and only 14 had skull base involvement. The overall 5-year estimated survival of patients with malignant tumors was 39%, but the authors conclude that this surgery offers satisfactory oncologic results only in the absence of intracranial involvement.

In addition, the series of Bigelow et al¹⁷ (25 patients) has a heterogeneous composition (five primary tumors in the oropharynx, four in the nasopharynx, three in the temporal bone, two in the parotid, etc.). Only nine patients had dural involvement, two of which exhibited intradural extension. The 5-year DFS was 25%.

In the series of Irish et al,¹⁸ patients were divided according to anterior, middle, or posterior fossa involvement. The cases with MCF extension (with or without anterior fossa invasion) numbered only 13 (17%). The dura was involved in 40% of these patients, and none of these patients was living after 4 years.

Therefore, the ethical question is whether this challenging surgery is worth all of the effort and expense or if it is more an issue of satisfying the egos of surgeons than the interests of their patients.

This study tries to answer this question. Unlike the majority of previously reported series, for which the focus was the surgical approach, it leaves out surgical technical details, focusing on oncologic long-term results. These data are quite numerous and very homogeneous, as this investigation takes into consideration only malignant tumors with a primary location in the maxillary sinus and only cases with involvement of the MCF with a long follow-up for survivors. Moreover, all patients in this study were operated upon at the same institution and by the same surgeons. All patients were in stage T4b, meaning that they were “unresectable” according to AJCC 2002 classification, which makes the clinical suitability of this classification disputable.

The overall DFS for our patients was 33.9%. This rate may appear low in comparison to those reported by other authors, though it is quite impossible to compare the rates because of the aforementioned inconsistencies between studies. For example, Fordice et al¹⁹ stated a higher DFS for patients with adenoid-cystic carcinoma and perineural invasion of minor (unnamed) nerves in comparison with patients with involvement of major (named) nerves, which is the case for all of our patients.

The DFS was very different across histological types; it was high for low-grade salivary tumors and osteo-, chondro-, and rhabdomyosarcomas; intermediate for squamous cell carcinomas; and, at first sight, disappointing for undifferentiated carcinomas, high-grade salivary tumors, and adenoid-cystic carcinomas. However, we must remember that adenoid-cystic carcinoma is a tumor with a long natural history. Patients with primary and/or distant recurrence may survive many years (up to 72 months in our series). For this reason, the comparison of the quality of life before and after surgery is fundamental. All of our patients had sharp pain, with trigeminal involvement; many of these had bleeding and smelling ulcerations in their mouth, and almost all would have these problems in the near future without tumor resection. None of those who recurred in

the site of the primary tumor had bleeding ulcerations, as the recurrence was deep and covered by the reconstruction flaps.

Therefore, we believe that we must take into consideration not only the quality of life (or remaining life), but also the quality of death for these patients. In other words, we think that for some of these patients, we may use the term *symptomatic surgery*.

All of our patients reported an improvement in their quality of life after surgery, in particular the disappearance of pain. Pitman et al¹⁴ wrote: “Surgery appears to be ultimately palliative for most patients with adenoid-cystic carcinoma of the sinonasal tract. Thus, the morbidity of surgery should be tempered by this fact with consideration given to the preservation of functioning major neurovascular structures that are involved by the tumor.” Bigelow et al,¹⁷ dealing with trigeminal branches, stated: “Improvements in intraoperative monitoring, as well as the ability to monitor nearly all the cranial nerves along with the prevailing attitude among most cranial-base surgeons to maximize functional and cosmetic results when possible, should lead to a significant increase in the preservation rate of these nerves.”

We agree only partially with these statements. Obviously, some nerves are essential for a good quality of life (second, third, fourth, sixth, and seventh cranial nerves). We believe that every effort should be made to preserve these nerves when they function normally before surgery, and, with regard to the orbit, it must be exenterated only when there is an intraconal involvement. These structures are so important for the quality of life that one must carefully weigh the pros and cons before their sacrifice, even if at the cost of close margins at the level of cavernous sinus and Gasser's ganglion. We generally make this decision after a discussion with the patient. As a rule, we are more aggressive in low-grade and untreated tumors because we believe that a radical resection has greater likelihood to ultimately cure these patients. In contrast, we are more conservative in high-grade tumors and in relapses, because for these patients the surgery is more likely to be symptomatic. Although large invasion of the temporal lobe is a contraindication to surgery, the involvement of the dura and cavernous sinus reduces the rate of DFS, and surgery may be suitable for low-grade tumors.

On the contrary, it is our opinion that the involved trigeminal branches (mainly the second and third) must always be resected. In the majority of cases, they are already compressed and infiltrated by the tumor, but, when not involved, face the risk of possible future local relapse and progression of disease. Thus, the consequent pain will frustrate the goals of our “palliative surgery.”

The different DFS between untreated and previously treated patients (46% versus 23%) proves once

again that the first treatment must be more suitable than possible, as it is often the only treatment.

Finally, we offer a few words regarding the ethicality of surgery in comparison with neutron radiotherapy. Douglas et al²⁰ report a 5-year actuarial local-regional control in 59% of patients without involvement of the cavernous sinus, base of skull, or nasopharynx, whereas the local-regional control was significantly lower for patients with tumors involving these sites (15%).

CONCLUSION

Surgery for maxillary malignant tumors invading the MCF can be performed with low morbidity and mortality, improving quality of life of patients with sharp preoperative pain and offering satisfactory oncologic results for patients with low-grade tumors. No patient with undifferentiated carcinoma was cured and their survival was short, such that the indication for surgery for these patients must be carefully evaluated. The results for squamous cell carcinoma were quite good, but the survival for patients with recurrence was short. The most interesting tumor is adenoid-cystic carcinoma. The ultimate cure rate for these patients was very low, but the local cure rate (which means quite asymptomatic survival) was 40%. Moreover, patients with local and/or distant metastases had a long survival.

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