PROGNOSTIC FACTORS IN SINONASAL TUMORS INVOLVIN THE ANTERIOR SKULL BASE

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Abstract: *Background.* Anterior craniofacial resection is a standardized procedure for the treatment of ethmoid and frontal orbital tumors with intracranial invasion.

Methods. A retrospective review of 100 patients with sinonasal tumors involving the anterior skull base who underwent combined craniofacial surgery at the Hospital Central de Asturias.

Results. The most frequent pathologic entity was adenocarcinoma (53 cases) and other epithelial tumors (29 cases). Five-year actuarial survival according to the Kaplan–Meier method was 40%. Factors such as involvement of surgical margins, orbital periosteum involvement, frontal sinus invasion, or spread into the dura had no significant effect on survival. Survival, however, was affected by the histologic findings of the tumor ($p = .03$), brain involvement ($p = .04$), deep soft tissue involvement of the orbit ($p = .003$), involvement of the sphenoid sinus ($p = .001$), previous treatment ($p = .05$), and postoperative recurrence ($p = .0000$). Neither the INT staging system nor the UICC system showed statistical prognostic significance. After multivariate analysis and Cox regression analysis, only recurrence after craniofacial resection, involvement of soft tissues of the orbit, and invasion of the sphenoid sinus significantly influenced survival.

Conclusions. Standard staging systems did not statistical prognostic significance. Only involvement of critical areas was reliable as predictor of an unfa outcome. © 2003 Wiley Periodicals, Inc. *Head Ne* 136–144, 2004

Keywords: craniofacial resection; paranasal sinuses; tumors; tumor staging; prognostic factors

The poor prognosis associated with mal tumors of the paranasal sinuses is mainly sequence of local recurrences in the base skull. Furthermore, the tumor is frequently to have affected the median portion of the a cranial fossa when the diagnosis is estab This has been observed to occur in about 75% of the esthesioneuroblastomas[1] and a as 38% of the adenocarcinomas.[2] Anterior c facial resection is a standardized procedure treatment of ethmoid and frontal orbital with or without intracranial invasion. In th two decades, a number of modifications and sions of the classic approach have been des which have allowed better control of the minimizing the cosmetic defects. Tumors

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region can differ with respect to histologic features, grade, and extent of involvement, which further complicates survival analysis. The purpose of this article is to study the prognostic factors that might have implications for patient management, as well as to present our experience with different approaches and their indications.

PATIENTS AND METHODS

The medical records of all patients who received an anterior craniofacial resection at our institution between 1986 and 2001 were retrospectively reviewed. A total of 100 patients were included and evaluated in this series. Only patients with sinonasal tract tumors invading the anterior skull base were included. Selection criteria for considering candidates for this procedure included the CT or MRI demonstration of involvement of the cribriform plate or the roof of the ethmoid, and/or the sphenoid sinus, with or without unilateral or bilateral orbital extension. Tumor growth into the cavernous sinus, deep invasion into the frontal lobes, and bilateral involvement of the optic nerves were considered contraindications for an anterior craniofacial resection.

The UICC classification system (edition published in 2002)[3] and the staging system proposed by Cantu et al[4] (INT system) (Table 1) were used to validate the usefulness of both systems as prognostic factors in our series. According to the UICC-AJCC staging, 4 tumors were staged T2, 28 T3, 18 T4a, and 50 T4b. According to the INT classification system, 28 tumors were staged T2, 32 T3, and 40 T4.

At diagnosis, four patients with different histologic types (adenocarcinoma, neuroesthesioblastoma, and two undifferentiated carcinomas) were seen with nodal metastasis in areas I and/or II.

The most common procedure used was the craniofacial resection of the ethmoid (84 cases), whereas 8 patients were submitted to different frontal orbital resections for neoplasms involving the frontal sinus, frontal bone, or/and the orbit. Finally, eight patients received an anterior craniofacial resection and an infratemporal approach, including a total maxillectomy (Table 2). A standard bifrontal craniotomy was performed in 18 cases, whereas 52 patients received a transfrontal craniotomy according to the technique previously described by us.[5] Twenty-two patients underwent a modified subcranial approach from that described by Raveh et al,[6,7] most of the time consisting of a transfrontal craniotomy in continuity with the inner part of the orbital rim and the nasal bones. In eight cases with limited extension into the nasal cavity, the tumor was resected through the intracranial approach, with occasional endoscopic assistance. A bifrontal craniectomy was used in the case of large involvement of dura and bony structures of anterior skull base and/or brain invasion. This approach was also used in the case of a very small frontal sinus, which precluded a transfrontal craniotomy. Tumors with bilateral invasion of the ethmoid and extension or not to the orbits were managed with a subcranial approach. When, in addition to the bilateral involvement of the ethmoid, there was an important intracranial extension, the subcranial approach was enlarged, tailoring a wider osteoplastic flap as described by Pinsolle et al.[8]

All the tumors were large, and most of them disrupted at least the roof of the ethmoid. In 67

Table 1. Comparison of UICC and INT staging systems.

UICC System of staging	
T1	One subsite
T2	Two subsites or adjacent nasoethmoidal site
T3	Medial wall/floor orbit, maxillary sinus, palate, cribriform plate
T4a	Anterior orbit, skin of nose/cheek, anterior cranial fossa (minimal), pterygoid plates, sphenoid/frontal sinus
T4b	Orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V_2, nasopharynx, clivus
INT System of staging of ethmoidal tumors	
T1	Tumor involving the ethmoid and nasal cavity, sparing the most superior ethmoidal cells
T2	Tumor with extension to or erosion of the cribriform plate, with or without erosion of the lamina papyracea and without extension into the orbit
T3	Tumor extending into the anterior cranial fossa extradurally and/or the anterior two thirds of the orbit, with or without erosion of the anteroinferior wall of the sphenoid sinus, and/or involvement of the maxillary and frontal sinus
T4	Tumor with intradural extension or involving the orbital apex, the sphenoid sinus, the pterygoid plate, and the infratemporal fossa

Table 2. Surgical procedures.

Craniofacial resection ethmoid (CFR)	84	Bifrontal craniectomy	18
		Transfrontal craniotomy	52
CFR ethmoid + maxillectomy/ infratemporal fossa	8	Subcranial approach	22
Frontal orbital resections	8		

patients, other areas were involved, such the orbital periosteum, the sphenoid sinus, the optic nerve and anterior clinoid process, and the anterior part of the middle cranial fossa. Eleven patients underwent orbital clearance at the time of the craniofacial resection, and 39 received resection of the orbital periosteum with preservation of the eye.

In 45 cases, dural involvement made mandatory its resection and reconstruction with lyophilized dura or with a pericranial free graft. At operation, some degree of brain involvement was found in 28 cases, the intracerebral extension being resected.

Bilateral involvement of the ethmoid was observed in 19 cases, making necessary the use of a modified subcranial approach. Finally, the frontal sinus was primarily or secondarily invaded in 25 patients (Table 3).

A large-sized pericranial flap was used for reconstruction of the anterior skull base in patients subjected to a subcranial approach or receiving a bifrontal craniectomy. The temporalis muscle flap was used in 16 patients for reconstruction of the orbit after exenteration or for closure of defects in the palate after an associated total maxillectomy, and alloplastic bone replacement material or calvarial bone served to give contour to the orbital rim, frontal region, and nose when these bone structures were removed (six cases). Finally, extensive resections of frontal bone, orbit, and facial skin were repaired through the use of parascapular free flaps in three patients.

Statistical analysis of data was performed using SPSS 10.0 (Chicago, IL). Survival curves were calculated using the Kaplan–Meier product limit estimate. Deaths from causes other than the index tumor or its metastases were not considered treatment failures, and these patients were censored in all analysis involving the length of survival. Differences between survival times were

Table 3. Tumor extension at diagnosis.

Structures involved	No. cases
Ethmoid	92
Cribriform plate	85
Dura	45
Orbital periosteum	36
Brain	28
Sphenoid	28
Frontal sinus	25
Ethmoid bilateral	19
Deep involvement of the orbit	14

Table 4. Histologic diagnosis of tumors.

Type	No.
Adenocarcinoma	
Squamous cell carcinoma	
Undifferentiated carcinoma/ neuroendocrine tumor	
Neuroesthesioblastoma	
Sarcomas	
Melanoma	
Adenoid cystic carcinoma	
Basal cell carcinoma	
Miscellaneous	

analyzed by the log rank method. Multiva Cox proportional hazards models were us examine the relative impact of either var demonstrated to be statistically significa univariate analysis or those variables lik have an effect on outcome.

RESULTS

The cohort of 100 patients was composed of 8 and 17 women. Their ages ranged from 3–81 y with a median age of 57 years. Of the 100 pa the various pathologic entities included epit tumors in 82, esthesioneuroblastoma in 9, dif types of sarcomas in 6, and miscellaneous t in 3 (Table 4). Preoperative treatment inc surgery (n = 18), radiotherapy (n = 3), c therapy (n = 1), and combinations (n = 5) the 27 patients.

From patients surgically treated else (n = 22), no one received craniofacial appro but only minor procedures, such endoscopic or paranasal surgery (n = 16). In the total gro

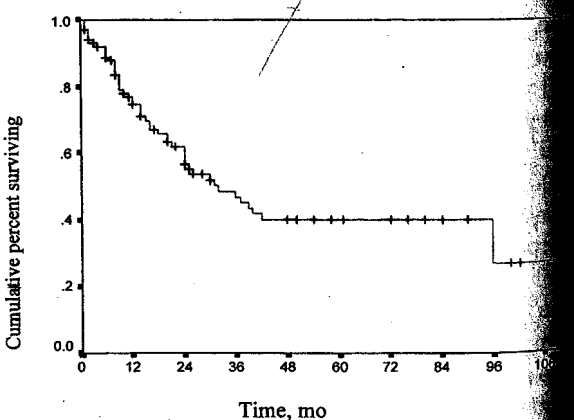

FIGURE 1. Kaplan–Meier representation of survival over all cases.

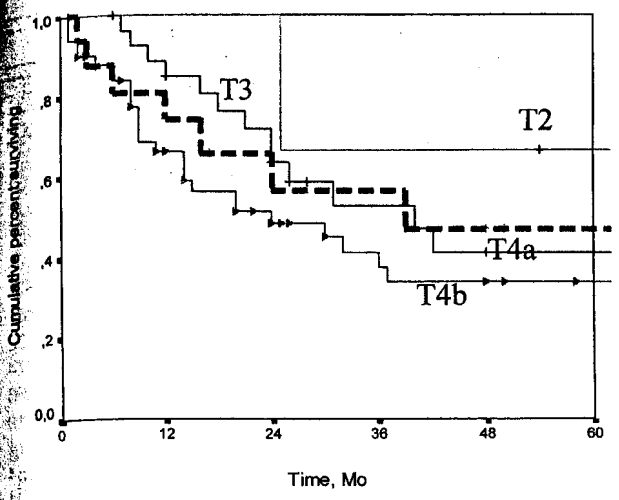

FIGURE 2. Kaplan–Meier representation of survival following UICC distribution (log rank, $p = .2774$).

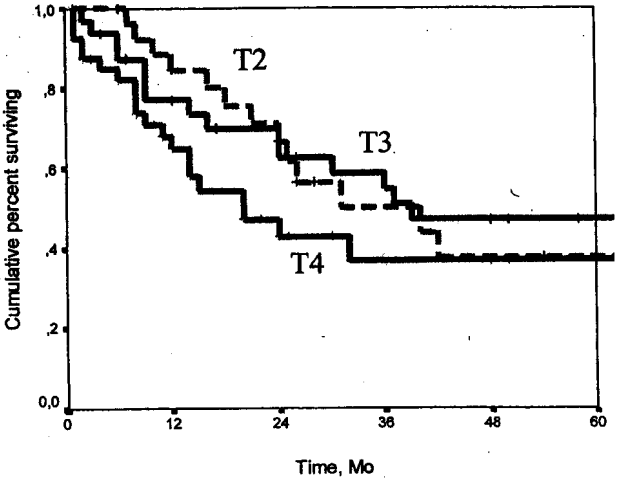

FIGURE 3. Kaplan–Meier representation of survival following INT distribution (log rank, $p = .3174$).

patients with some preoperative treatment, the histologic types included epithelial tumors ($n = 20$), different types of sarcomas ($n = 3$), esthesioneuroblastoma ($n = 2$), and miscellaneous tumors ($n = 2$).

After craniofacial surgery, further treatment was given to 55 patients, mainly radiotherapy. Additional craniofacial surgery for recurrent disease or complications was performed in eight patients, between one and three times.

The cancer-specific actuarial survival for this group of patients was 40% at 5 years, which dropped to 27% at 10 years (Figure 1). Among the 56 patients who had a recurrence, patterns of failure included the following: locoregional ($n = 51$), distant ($n = 5$), and a combination of them ($n = 10$). Most of the recurrences were both intracranial and extracranial, whereas five were exclusively intracranial and six extracranial.

From these patients, a total of 17 were salvaged with additional surgical treatment. To date, 45 patients are alive without disease, 50 patients died of disease, and other 5 patients died of unrelated causes.

The prognostic difference according local stages was not statistically significant both with the UICC and INT systems. A more clear separation among the curves was evident for the UICC system, although survival of T3 patients was slightly below T4a. On the other hand, in the INT system of staging, the clinical outcome for patients with T2 and T4 was almost the same (Figures 2 and 3).

All four patients who showed neck nodes died soon, independently of the histologic findings of the tumor or the T stage.

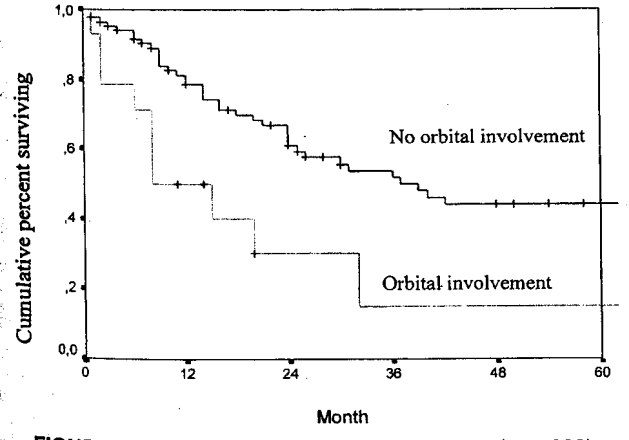

FIGURE 4. Survival by deep orbital involvement ($p = .003$).

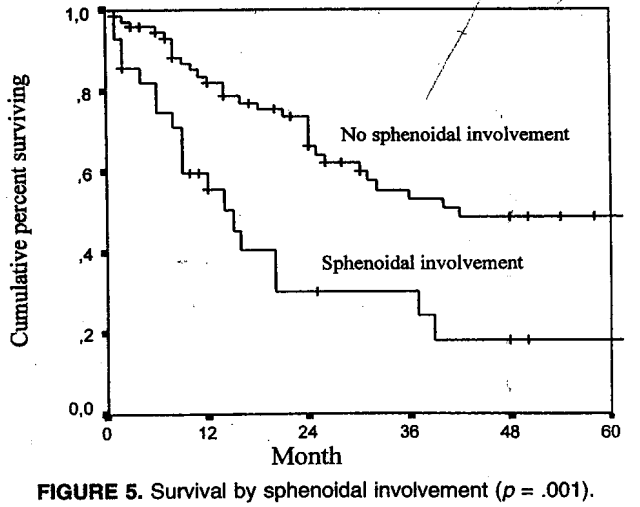

FIGURE 5. Survival by sphenoidal involvement ($p = .001$).

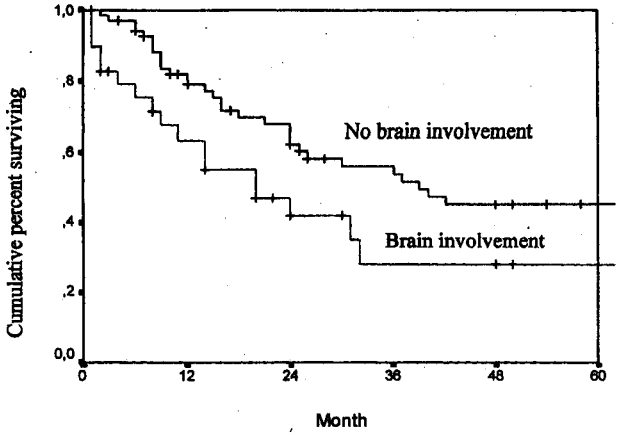

FIGURE 6. Survival by brain involvement ($p = .04$).

Table 5. Results of univariate analysis on survival.

Variable
Postoperative recurrence
Involvement of sphenoid
Deep involvement of the orbit
Involvement of brain
Histologic findings
Previous treatment
Involvement surgical margins
Involvement frontal sinus
Involvement cribriform plate
T stage (UICC)
Type of approach
Involvement orbital periosteum
T stage (INT system)
Postoperative treatment
Involvement of dura

Factors that affected survival were deep involvement of the orbit ($p = .003$) (Figure 4), involvement of the lateral wall of the sphenoid sinus ($p = .001$) (Figure 5), brain involvement ($p = .04$), and postoperative recurrence ($p = .0000$). Patients who received orbital exenteration did not improve their outcome compared with those with periosteal invasion in whom the eye was spared ($p = .19$). On the other hand, neither orbital periosteum involvement nor frontal sinus invasion had statistical significance on survival. With regard to intracranial involvement, patients who had no evidence of spread into the dura had similar 5-year actuarial survival than patients with such involvement ($p = .41$). Nevertheless, the 5-year survival for patients with brain involvement was 23%, significantly worse than that of patients in whom this structure was unviolated (48%) (Figur (Table 5).

Survival was significantly affected by histologic findings of the tumor ($p = .03$). F year actuarial survival was 71% in patients esthesioneuroblastomas, 65% in squamous carcinomas, 31% in adenocarcinomas, 17% undifferentiated carcinomas, and 0% in mel mas requiring a craniofacial resection. Figu shows actuarial survival for different histo types when the cohort was four or grea Significant differences in survival were f between esthesioneuroblastomas and undiff tiated carcinomas ($p = .04$), squamous cell c noma and undifferentiated carcinoma ($p = .0$

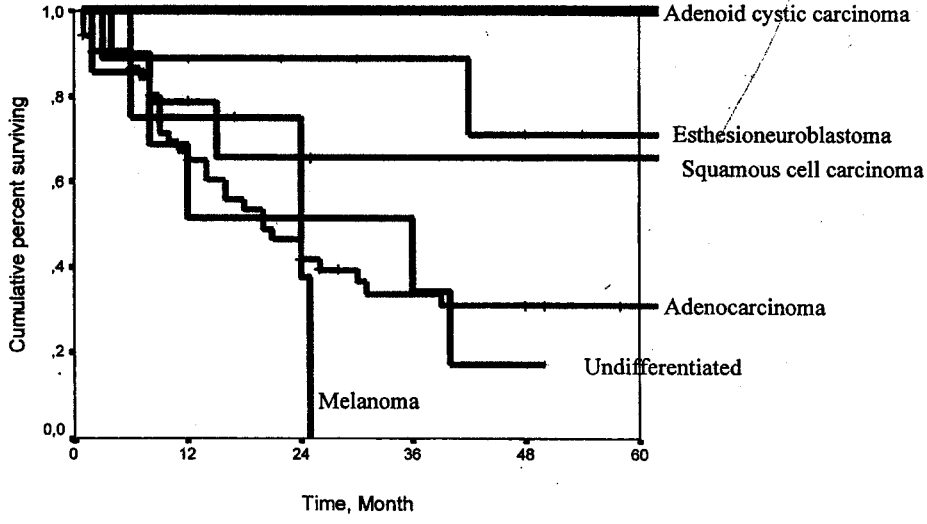

FIGURE 7. Kaplan–Meier survival by histologic type.

Table 6. Survival by type of approach.

Type of approach	% 5-year survival
CFR ethmoid	38
CRF ethmoid + exenteration	23
CFR ethmoid + total maxillectomy	60
CFR ethmoid + total maxillectomy + exenteration	33
Subcranial approach	53

Abbreviation: CFR, craniofacial resection.

Survival in our series was not significantly affected in those patients with positive margins compared with those with negative ones ($p = .07$). Postoperative treatment ($p = .33$) and type of approach used ($p = .28$) (Table 6) also did not affect the outcome of patients. Survival in our series was significantly affected in those patients who underwent salvage surgery compared with those who received their initial treatment at our institution (35% vs 55% 5-year survival, respectively) ($p = .05$). Multivariate analysis and a Cox regression analysis have identified factors that significantly affected survival of the patients. They are recurrence after craniofacial resection ($p = .001$), deep involvement of the orbit ($p = .037$), and involvement of the sphenoid sinus ($p = .024$).

DISCUSSION

Surgical Considerations. The craniofacial approach to the sinonasal tract has significantly improved survival of patients with tumors. Indications for craniofacial resection of ethmoidal tumors have not been clearly defined. This approach is indicated in all patients with esthesioneuroblastoma, because tumor extension along the olfactory rootlets is present in all patients despite radiologic studies showing disease limited to the nasal cavity.[9,10] Some authors extend this indication to other histologic tumor types,[11,12] whereas others only consider a craniofacial resection in tumors with extension to[13] or erosion of the cribriform plate.[13,14] On the basis of different observations, involvement of the orbit, dura mater, brain (limited), hard palate, and infratemporal fossa are not contraindications for craniofacial resection. On the other hand, involvement of an only seeing eye, bilateral orbital apex involvement, optic chiasm involvement, massive bony skull base destruction, massive brain involvement, invasion of the clivus or sella turcica, and tumor extension into the cavernous sinus and carotid artery are considered contraindications for craniofacial surgery for malignant lesions.[15]

The intracranial approach through the frontal sinus (transfrontal craniotomy), as classically designed,[16,17] involves a partial or total removal of the anterior and posterior walls of the frontal sinus, with the drawback of risk of osteomyelitis in the case of replacement of a devitalized anterior wall of the sinus. We have modified this technique using an osteoplastic frontal flap that has been used in a variety of pathologic conditions of the frontal sinus to avoid this problem.[5]

We have enlarged this procedure in the case of bilateral ethmoid involvement through a modification of the subcranial approach with removal of the anterior wall of the frontal sinus in continuity with a part of the orbital rims and the nasal bones. The subcranial approach[6,18,19] can be tailored in different ways. The size of the frontal bone and the amount of the orbital rims included in the flap are determined by the amount of exposure that will be needed.[8] The use of a subcranial approach is essential in tumors involving both sides of the ethmoid, particularly if there is progression into the orbits, and provides wide access to the anterior fossa with minimal frontal lobe retraction.

There is a trend in surgery to ward minimally invasive procedures, such craniofacial resection using the transcranial route only,[6,11,14,20] endoscopically assisted or not, with the aim of avoiding facial incisions.

For soft tissue repair, the temporalis muscle is very useful in reconstructing the orbit after exenteration[21] or the palate after an associated total maxillectomy.

Overall survival after craniofacial resection of ethmoid ranges between 40% and 50% at 5 years.[13,22,23] Comparison of long-term results is difficult, because indications vary widely from one author to another. Series that include significant number of cases without cribriform plate involvement show an overall cure rate of about 60% to 70%[11,14,18,24,25]; when there is intracranial invasion, survival drops to less than 30%.[4,11]

Both recurrence rate (12% vs 60%)[26] and disease-free survival (82% vs 38%)[27] have improved after the use of craniofacial resection of the ethmoid compared with the precraniofacial era. However, it is not well established whether craniofacial resection of the ethmoid improves the outcome of patients with tumors that do not involve the bony structures of the anterior skull base. This is important because most of the time a craniofacial resection implies a bilateral loss of the olfaction

(contralateral preservation of the olfactory nerve can be achieved very seldom[28]) and a higher risk of other complications than an ethmoidectomy through a paranasal approach. Multiinstitutional randomized studies need to be addressed to provide an answer to this question.

Factors Related to Tumor Invasiveness and Stage. Intracranial extension has been recognized as the most adverse prognostic factor in malignant sinonasal tumors.[29] Comparison of those individuals with no dural invasion to those with either dural or brain invasion reveals a significantly worse prognosis in the last group.[15,30] Dural invasion alone seems for most of the authors to be detrimental to survival, decreasing 5-year survival from 68% to 25% in a series of 63 adenocarcinomas[22] and from 83% to 22% in patients undergoing craniofacial resection.[31] Furthermore, local control is affected in the case of dural invasion, with a decrease from 91% to 64% in 73 patients receiving a craniofacial resection.[32] Nevertheless, in our series no effect of dural invasion on survival was observed.

The potential of cure decreases dramatically with extensive brain invasion,[23,33] although similar chances of survival as with dural invasion have been observed in the case of limited brain involvement.[30] In contrast, few reports show no difference in survival when comparing patients with and without dural and brain involvement,[1,14] possibly because of a large number of esthesio neuroblastomas in the series.[1] Although it is generally admitted that invasion into the frontal lobes carries a bad prognosis, patients with limited involvement of the brain can be cured, as is shown in this series.

Orbital involvement has a significant impact on survival, particularly if the apex is affected[13] and is not reversed by exenteration. Of more importance, tumor grade and orbital invasion were the only significant independent variables adversely affecting survival in McCaffrey et al's series.[1] Many authors have reported poorer survival in those patients requiring orbital exenteration than those who did not.[15] Moreover, Lund et al[23] have compared survival of a group undergoing resection of the involved orbital periosteum with those undergoing orbital exenteration, showing that preservation of the orbit does not adversely affect outcome. Therefore, the eye can be spared in the absence of extensive periorbital involvement by tumor without sacrificing local control or survival. Our results confirm this observation, which has important implications for quality of life.

Classification of malignant ethmoid t according to Cantú[4] (INT system) is based most commonly accepted unfavorable prog factors. UICC T4 tumor classification is too despite its having been divided in two groups last edition. Patient distribution among dif UICC stages was less balanced in our serie with INT classification, but unexpectedly we to detect with the last one an association w clinical outcome. Although it did not re significant values, a progressive worsening prognosis was shown to occur from to T2–T4 the UICC system, with the exception of T3 a tumors. There is a rationale for both classifi systems, but the limitations of our series ar as occurs with most of the others, it includes histologic types with different degree of aggr ity, a small number of most of the histologic different places of origin in a number of tu different nonsurgical adjuvant therapies prior treatment in a significant part of the Multiinstitutional studies with a large num tumors of the most common histologic type similar schedules of treatment have to b dressed to validate staging systems. Further the combination of molecular prognostic fa histopathologic, and clinical characteristic system of mathematical scores possibly wi vide more accuracy in the individual evalua the expected outcome of patients.

Prognosis by Histopathology. In a compi of 1001 cases of craniofacial resections of th moid corresponding to different series,[1,14,15,24,33–36] adenocarcinoma was the most fre histologic diagnosis (27.6%), followed by mous cell carcinoma (18.2%), esthesioneur toma (13.8%), and sarcomas (12%). In our there is a still higher incidence of adenoca mas, which represent 53% of craniofaci proaches. Tumor histologic findings play portant role in treatment outcome; howeve prognostic effect of histologic findings is diffi establish, because of the high number of di pathologic conditions and the small num most of the histologic types. This is a limita this study, in which all the groups exce epithelial tumors are small. On the other han possible that the survival associated w particular histologic type is affected by the tiveness of adjuvant therapy on a given hist type. For instance, the responsiveness of a carcinoma to radiation therapy is different that of squamous cell carcinoma, and possib

histologic response to adjuvant therapy has some influence on tumor recurrence.

Generally, the prognosis of esthesioneuroblastomas and chondrosarcomas is better than for the other histologic types, each of them showing a 5-year survival usually greater than 75%.[1,13,15,23,27,35,37] Patients with well-differentiated adenocarcinomas and adenoid cystic carcinomas show better 5-year survival (between 40% and 60%)[13,15,22,23,35] than those with squamous cell carcinomas (25% to 50%),[1,15,23,35] survival being the poorest in high-grade sarcomas, melanomas, and undifferentiated carcinomas.[15,30] Although disease-free survival remains stabilized in most histologic types between 5 and 10 years after of the treatment, in adenoid cystic carcinoma and chondrosarcoma, the survival falls significantly in this period, which entails a lifetime risk.[23]

Factors Related to Treatment. In this particular location, surgical margins are difficult to evaluate; this explains the similar incidence of local recurrences in both positive and negative margins.[14,15] As in advanced lesions clear margins do not guarantee cure, and wide en bloc resections are rarely achieved, many authors consider postoperative radiation therapy for nearly all their patients.[15,35]

Previously treated patients have an unfavorable prognosis,[13] and for this reason some authors advocate immediate anterior craniofacial resection when a diagnosis of ethmoidal malignant tumor has been made so that an inadequate surgical or radiotherapeutic treatment does not jeopardize the potential of cure. Our results support this assumption, and survival in our series was significantly affected in those patients who underwent a craniofacial resection as salvage compared with those who where newly diagnosed and received their initial treatment at our institution. Nevertheless, the level of significance did not reach the same level as recurrences after craniofacial resection, possibly because some patients did not have extensive recurrences from a low-stage ethmoidal tumor previously treated endoscopically or through the paranasal approach.

One of most adverse prognostic signs, as shown by the multivariate analysis, was recurrence after craniofacial resection. Although some authors have noted similar survival between these groups,[15,33] in general the success of salvage surgery is limited, particularly after craniofacial resection.[4] Failures are predominantly at the primary site and unresectable.

CONCLUSIONS

One hundred patients with different malignant tumors involving the anterior skull base underwent combined craniofacial surgery. Survival was affected by the histologic findings of the tumor, brain involvement, deep involvement of the orbit, involvement of the sphenoid sinus, previous treatment, and postoperative recurrence. Nevertheless, neither the INT staging system nor the UICC system showed statistical prognostic significance. The diversity of the site of origin, histologic diagnosis, extent of tumor invasion, and treatment protocols make any attempt at reporting meaningful survival statistics for comparison with other series difficult. Multiinstitutional studies with a large number of tumors of the most common histologic types and similar schedule of treatment have to be addressed to validate prognostic factors and staging systems.

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