ORIGINAL ARTICLE

Lymph Node Metastases in Malignant Tumors of the Paranasal Sinuses

Prognostic Value and Treatment

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Objective: To assess the frequency of nodal involvement and its prognostic value in malignant tumors of the paranasal sinuses, particularly in maxillary sinus squamous cell carcinoma.

Design: Retrospective review.

Setting: Tertiary cancer center.

Patients: The medical records of 704 consecutive patients surgically treated for malignant tumors of the paranasal sinuses from January 1968 to March 2003 were reviewed. The tumors were staged according to American Joint Committee on Cancer–International Union Against Cancer 2002 classification. Only patients with clinically positive nodes underwent a neck dissection.

Main Outcome Measures: Lymph node metastases (at presentation or during follow-up, occurring alone, or with concurrent local recurrence and/or distant metastasis). Also analyzed were local recurrence (occurring alone or with concurrent distant metastasis), distant metastasis (occurring alone), and overall survival.

Results: The tumor site was the ethmoid sinus in 305 cases and maxillary sinus in 399 cases. At baseline, 5 patients (1.6%) in the ethmoid sinus group and 33 (8.3%) in the maxillary sinus group presented with positive nodes ($P < .001$); during follow-up, nodal recurrences (alone or simultaneous with T and/or M recurrence) occurred in 15 and 51 patients, respectively, and the corresponding 5-year incidence estimates were 4.3% and 12.5% ($P = .001$). The highest incidence of node metastases was found in maxillary sinus squamous cell carcinoma, particularly in T2 tumors. Five-year overall survival estimates were 45.3% for patients with N0 tumors and 0% for those with N+ (N1, N2, or N3) ethmoid sinus tumors, and 50.6% and 16.8%, respectively, for patients with maxillary sinus tumors.

Conclusions: Lymph node metastases are a poor prognostic factor for patients with malignant tumors of the paranasal sinuses. The incidence of these metastases is low, particularly in ethmoid sinus tumors. A prophylactic treatment of the neck in patients with N0 tumors (surgery or radiotherapy) might be considered in T2 squamous cell carcinoma of the maxillary sinus and in undifferentiated carcinoma of the ethmoid sinus.

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MALIGNANT NEOPLASMS of the paranasal sinuses are very rare (about 3% of head and neck malignant tumors). Moreover, there is a great variety of histologic types. Consequently, few medical centers have treated so many patients that they are able to draw indisputable conclusions about prognostic factors and long-term results. To our knowledge, 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 radiotherapy seems to offer better local control than radiotherapy alone.[1,2] The treatment of the primary tumor is so challenging that often the problem of lymph node (LN) metastases has been considered to be of minor importance. Fortunately, the incidence rate of LN metastases is low,[3] even if it is difficult to state its real rate for the variety of histologic types, site of origin, and extension of the primary tumor in each published series. Obviously, patients with clinically positive LNs require treatment of the neck. Yet, the treatment of patients with an N0 neck is still unclear. In the literature, statements like these may be found:

"Elective neck irradiation is probably unnecessary for patients with early-stage disease."[2(p821)]

"In general, elective treatment of regional lymph nodes in patients without clinical evidence of lymph node metastases is not indicated."[3(p822)]

"Therefore, our present policy is to consider elective neck irradiation in patients with T3-4 squamous-cell carcinoma of the maxillary sinus."[4(p541)]

"Based on the 28.9% rate of neck recurrence and the poor median survival of patients who recur in the neck, we recommend prophylactic ipsilateral neck irradiation in patients with T1-T4 squamous cell carcinoma of the maxillary sinus."[5(p283)]

In light of these controversial statements, we analyzed our series of patients treated for malignant tumors of the paranasal sinuses to assess the frequency of nodal involvement and its prognostic value according to tumor site (ethmoid or maxillary sinus), extension, and histologic traits.

METHODS

This study involved 704 consecutive patients with malignant tumors of the paranasal sinuses treated at the Istituto Nazionale per lo Studio e la Cura dei Tumori (INT) of Milan, Italy, from January 1968 to March 2003. Excluded were patients with malignant tumors of the skin with secondary invasion of the sinuses, tumors of the nasal vestibule, tumors of the nasal cavity involving only the inferior turbinate and/or the inferior septum (cartilage and/or vomer), and primary tumor in the sphenoid sinus or in the frontal sinus.

All patients, with either primary or recurrent tumors primarily treated elsewhere, underwent tumor resection with curative intent. Patients with clinically positive LNs also underwent neck dissection, possibly followed by postoperative radiotherapy in cases of extracapsular spread.

Individual information, as obtained from clinical, radiological, and surgical procedures, was retrieved from a prospective clinical database. In particular, data on age at surgery, sex, tumor site and histologic characteristics, T and N stage, surgical procedures, adjuvant treatments, occurrence of neoplastic events, and death were considered.

Tumor site was classified as maxillary or ethmoid sinus. Ethmoid sinus tumors included lesions originating in the middle and/or superior turbinate, or in the superior septum (vertical lamina of the ethmoid), according to anatomical attribution of these structures. Tumors involving more than 1 sinus were classified according to their epicenter.

Tumor stage of the lesion treated at INT was assessed by means of standard cranial radiograms and conventional tomography (stratigraphy) until 1975 and by means of computed tomography thereafter; magnetic resonance imaging was often used after 1986. Tumor stage for both carcinoma and noncarcinoma tumors was defined according to the 2002 American Joint Committee on Cancer–International Union Against Cancer TNM classification.[6]

The event of main interest was LN recurrence (occurring alone or with concurrent local recurrence and/or distant metastasis). Also analyzed were local recurrence (occurring alone or with concurrent distant metastasis), distant metastasis (occurring alone), and overall survival. Time to event occurrence (tumor recurrence or death) was computed from the date of surgery performed at INT to the date when the event was first recorded, or censored on January 1, 2005, for event-free patients at that date. The statistical analysis of tumor recurrences was performed in a competing-risks framework[7] by computing the crude cumulative incidence curves, which were compared by means of the Gray test.[8] Survival curves were estimated with the Kaplan-Meier method and compared by means of the log-rank test.

We used SAS statistical software (SAS Institute Inc, Cary, North Carolina) and the S-Plus (StatSci, MathSoft, Seattle, Washington) Design (available at: http://lib.stat.cmu.edu) and Cmprsk (available at: http://biowww.dfci.harvard.edu/~gray/) libraries to perform the modeling and statistical calculations. Considered significant were the 2-sided *P* values below the 5% conventional threshold.

Table 1. Main Patient and Disease Characteristics According to Tumor Site[a]

Characteristic	Ethmoid Sinus	Maxillary Sinus
Total patients, No.	305	399
Age, median (IQR), y	58 (49-65)	58 (48-67)
Sex		
Female	89 (29.2)	175 (43.9)
Male	216 (70.8)	224 (56.1)
Presentation		
Primary	195 (63.9)	226 (56.6)
Recurrent	110 (36.1)	173 (43.4)
Tumor histologic characteristic		
Adenocarcinoma	153 (50.2)	18 (4.5)
Esthesioneuroblastoma	27 (8.9)	0
Adenoid cystic carcinoma	24 (7.9)	91 (22.8)
Melanoma	11 (3.6)	0
Sarcoma	15 (4.9)	59 (14.8)
Squamous cell carcinoma	33 (10.8)	156 (39.1)
Undifferentiated carcinoma	17 (5.6)	26 (6.5)
Mucoepidermoid carcinoma	1 (0.3)	27 (6.8)
Other	24 (7.9)	22 (5.5)
T stage, AJCC-UICC 2002 classification		
T1	27 (8.9)	0
T2	46 (15.1)	156 (39.1)
T3	85 (27.9)	37 (9.3)
T4A	66 (21.6)	134 (33.6)
T4B	81 (26.6)	72 (18.0)
N stage		
N0	300 (98.4)	366 (91.7)
N1	3 (1.0)	23 (5.8)
N2A	1 (0.3)	6 (1.5)
N2B	1 (0.3)	2 (0.5)
N2C	0	1 (0.3)
N3	0	1 (0.3)

Abbreviations: AJCC-UICC, American Joint Committee on Cancer–International Union Against Cancer TNM classification[6]; IQR, interquartile range.

[a] Data are presented as number (percentage) unless indicated otherwise.

RESULTS

The series of 704 study patients included 305 with tumors of the ethmoid sinus (43.3%) (hereinafter, ethmoid sinus group) and 399 with tumors of the maxillary sinus (56.7%) (hereinafter, maxillary sinus group). The main series characteristics according to tumor site are summarized in **Table 1**. The 2 groups were well matched for age, sex, presentation, and T stage. Overall, the median age was 58 years, the male-female ratio was 1:7, and primary cases were prevalent (59.8%) compared with recurrent cases (40.2%). Among the latter, primary treatments (alone or in combination) were as follows: surgery (80 cases [72.7%]), radiotherapy (73 cases [66.4%]), and chemotherapy (21 cases [19.1%]) in 110 patients in the ethmoid sinus group;

Table 2. Crude Cumulative Incidence (CCI) Estimates for the 3 Investigated Events According to Tumor Site

Event	Ethmoid Sinus				Maxillary Sinus			
	First Events, No.	CCI Estimate (SE), %			First Events, No.	CCI Estimate (SE), %		
		2-Year	5-Year	N>1		2-Year	5-Year	N>1
All events	205			7	297	297	297	12
T or T/M	152	40.3 (2.9)	51.1 (3.0)	3	160	32.4 (2.4)	38.8 (2.5)	4
N	15	4.3 (1.2)	4.3 (1.2)	3	51	10.9 (1.6)	12.5 (1.7)	8
N alone	5	NE	NE	1	31	NE	NE	5
N/T	8	NE	NE	2	17	NE	NE	3
N/M or N/T/M	2	NE	NE	0	3	NE	NE	0
M	12	2.7 (1.0)	3.6 (1.1)	0	19	3.6 (0.9)	4.9 (1.1)	0
Second malignant neoplasm	3	NE	NE	1	1	NE	NE	0
Death for unrelated condition	23	NE	NE	NA	66	NE	NE	NA

Abbreviations: M, distant metastasis; N, lymph node relapse; NA, not applicable; NE, not estimated; N>1, second or subsequent lymph node relapse; T, local relapse.

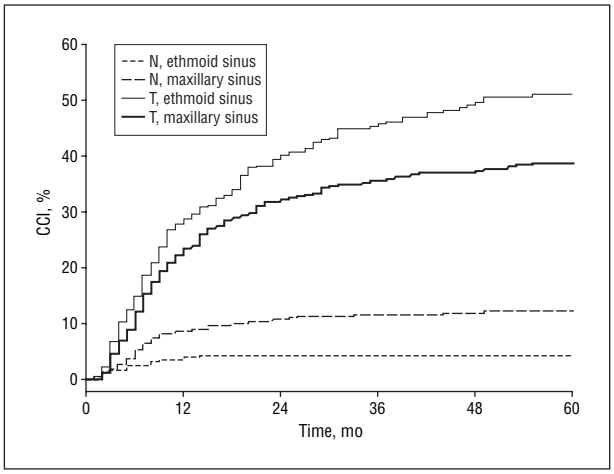

Figure 1. Crude cumulative incidence (CCI) estimates of local recurrence (T; occurring alone or with concurrent distant metastasis) and lymph node recurrence (N; occurring alone, or with concurrent local recurrence and/or distant metastasis) for patients in the ethmoid sinus and maxillary sinus groups.

and surgery (116 cases [70.7%]), radiotherapy (88 cases [53.6%]), and chemotherapy (14 cases [8.5%]) in 173 patients in the maxillary sinus group.

Regarding histologic characteristics, intestinal-type adenocarcinoma (ITAC) was the most frequent histologic type in the ethmoid sinus group (50.2%), whereas squamous cell carcinoma (SCC) was the most frequent in the maxillary sinus group (39.1%). Esthesioneuroblastoma was present only in the ethmoid sinus group (8.9%). Adenoid-cystic carcinomas (ACC) and sarcomas were more frequent in the maxillary sinus group than in the ethmoid sinus group (22.8% vs 7.9%, and 14.8% vs 4.9%, respectively). Non-ITAC adenocarcinomas (hereinafter, ADE) have been found only in the maxillary sinus.

The tumors of most patients in both groups were staged as N0 at baseline; nodal involvement was less frequent in the ethmoid sinus group (5 cases [1.6%]) than in the maxillary sinus group (33 cases [8.3%]; χ^2 test; $P<.001$). Considering those in the maxillary sinus group with SCC, nodal lesions were found in 16 of 156 patients (10.3%), and 11 of those 16 were patients whose tumors were staged as T2, 1 whose tumor was staged as T3, 3 whose tumors were staged as T4a, and 1 whose tumor was staged as T4b. Four of 26 patients (15.4%) with undifferentiated carcinoma (UC) presented with nodal lesions, and 13 of 217 patients (6%) presented with other histologic types.

Regarding surgical treatment at our institute, 258 anterior craniofacial resections were performed; 52 ethmoidectomies with only transfacial approach; 271 limited, subtotal, or total maxillectomies; 55 maxillectomies extended to middle cranial fossa (lateral craniofacial resections); and 68 maxillectomies with infratemporal fossa dissection (extracranially). Eighty patients underwent an orbit exenteration. Surgical resection achieved clean margins in 545 cases (77.4%); there was macroscopic residual disease in 38 cases (5.4%) and close margins or microscopic residual disease in 121 cases (17.2%). The surgical procedure that achieved the highest rate of clean margins was anterior craniofacial resection (88%). Almost all transfacial ethmoidectomies were performed before 1987 (when we began to perform anterior craniofacial resections), and this procedure achieved the lowest rate of clean margins (57%).

For the reconstruction after standard anterior craniofacial resections, a pedicled pericranial flap was used (in 206 cases). For larger resections requiring more complex reconstructions, either the pedicled temporalis muscle or a free flap were employed (in 156 and 40 cases, respectively). Patients with smaller resections did not undergo any reconstruction (obturator). After surgery (performed at our institute), 161 patients overall underwent planned postoperative radiotherapy on the site of the primary tumor, with a median dosage of 60 Gy (range, 45-70 Gy).

As of January 2005, the median duration of follow-up (interquartile range) was 109 months (range, 60.0-170.0 months). Fifty-two patients (7%), alive without recurrence, were lost to follow-up before the fifth year, with a median duration of follow-up of 38 months (range, 19.5-49.5 months).

Information on events recorded during follow-up and corresponding crude cumulative incidence estimates according to tumor site are shown in **Table 2** and **Figure 1**. The most frequent neoplastic event was local recurrence, and its incidence was significantly higher in the ethmoid sinus group (51.1% at 5 years) than in the maxillary sinus group (38.8% at 5 years) ($P=.001$). Relatively rare were dis-

Table 3. Crude Cumulative Incidence (CCI) Estimates of Lymph Node Recurrence According to Tumor Site and Other Disease Characteristics

Characteristic	Ethmoid Sinus			Maxillary Sinus		
	First Events, No.	CCI Estimate (SE), %		First Events, No.	CCI Estimate (SE), %	
		2-Year	5-Year		2-Year	5-Year
Tumor histologic characteristic						
Adenocarcinoma	5	3.3 (1.4)	3.3 (1.4)	4	22.2 (10.1)	22.2 (10.1)
Esthesioneuroblastoma	2	NE	NE			
Adenoid cystic carcinoma				3	1.1 (1.1)	2.3 (1.6)
Melanoma	1	NE	NE			
Sarcoma				3	NE	NE
Squamous cell carcinoma	1	NE	NE	32	18.7 (3.1)	20.7 (3.3)
Undifferentiated carcinoma	4	25.5 (11.9)	25.5 (11.9)	3	8.0 (5.6)	13.0 (7.4)
Mucoepidermoid carcinoma				1	NE	NE
Other	2	NE	NE	5	13.6 (7.6)	18.2 (8.6)
AJCC-UICC 2002 classification						
T2				30	15.4 (2.9)	18.0 (3.1)
T3	7	8.3 (3.0)	8.3 (3.0)	2	NE	NE
T4A/B	8	4.2 (1.7)	4.2 (1.7)	19	8.9 (2.0)	9.4 (2.1)
Nodal status at baseline						
N–	13	3.7 (1.1)	3.7 (1.1)	39	8.5 (1.5)	10.3 (1.6)
N+	2	NE	NE	12	36.4 (8.5)	36.4 (8.5)

Abbreviations: AJCC-UICC, American Joint Committee on Cancer–International Union Against Cancer TNM classification[6]; NE, not estimated.

tant metastases whose incidence rate was around 4% and did not significantly differ between the 2 groups ($P=.78$).

Lymph node recurrences (66 overall) were mostly observed in the maxillary sinus group, with a cumulative incidence significantly higher (12.5%) than for the ethmoid sinus group (4.3%) ($P=.001$).

In the maxillary sinus group, among the 31 patients who developed isolated LN recurrences as a first event, only 1 presented with unresectable nodes. Thirty patients underwent neck dissection (selective, radical or modified radical, or monolateral or bilateral) with or without postoperative radiotherapy according to histologic findings; 1 of these patients developed an unresectable recurrence in the field of the dissected neck. Only 2 of 31 patients died from nodal-only metastases.

According to a number of disease characteristics, **Table 3** shows the number of LN recurrences and the corresponding crude cumulative incidence estimates. In the ethmoid sinus group, the incidence of LN recurrences showed, in general, little variation between distinct subgroups, possibly with the exception of patients with undifferentiated carcinoma (25.5%); that number, however, was too low for us to draw firm conclusions. Considering the maxillary sinus group, a relatively high incidence of LN recurrence was observed in those with N+ tumors (36.4%), T2 tumors (18.0%), ADE (22.2%), and SCC (20.7%). The latter finding is of particular interest, considering the prevalence of this type of histologic characteristic among maxillary sinus tumors. **Figure 2** shows crude cumulative incidence curves of LN recurrence for patients with SCC or other histotypes. The corresponding 5-year estimates were 20.7% and 7.2%, respectively ($P<.001$). The incidence rate was even higher among the 77 patients with T2 stage SCC (26.0%).

Table 4 and **Table 5** provide information on the number of deaths and overall survival estimates according to

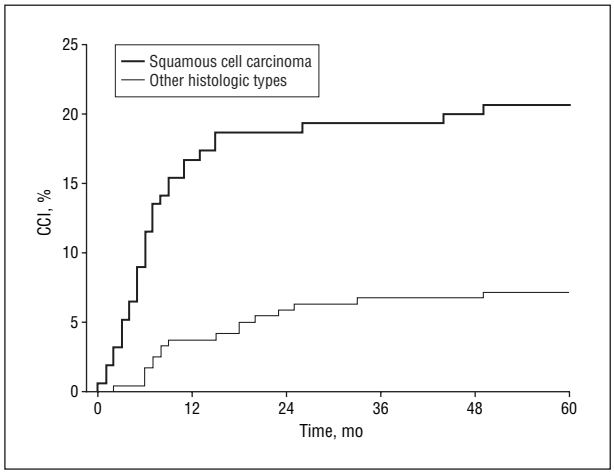

Figure 2. Crude cumulative incidence (CCI) estimates of lymph node recurrence (occurring alone or with concurrent local recurrence and/or distant metastasis) for squamous cell carcinoma and other histologic types for patients in the maxillary sinus group.

tumor site and other disease characteristics. Survival did not significantly differ between the ethmoid sinus and maxillary sinus groups (**Figure 3**; $P=.83$), even though deaths unrelated to the paranasal sinus carcinoma were unevenly distributed among the maxillary sinus and ethmoid sinus groups (Table 4). Most of the latter were treated after 1987, when we began to perform anterior craniofacial resections, and consequently they had a shorter follow-up (a median duration of 75 months, compared with 141 months for the maxillary sinus group), as well as fewer deaths unrelated to carcinoma. All the 45 deaths unrelated to tumors occurred more than 5 years after the initial treatment or retreatment because of local and/or regional recurrence. The exact causes could not be established in 15 cases, whereas in the remaining 30 cases, deaths were

Table 4. Survival Probability Estimates According to Tumor Site

Event	Ethmoid Sinus			Maxillary Sinus		
		Survival Estimate (SE), %			Survival Estimate (SE), %	
	No.	2-Year	5-Year	No.	2-Year	5-Year
All deaths	165	67.3 (2.8)	44.6 (3.2)	266	68.5 (2.3)	47.8 (2.6)
Death due to specific malignant neoplasms	148	NR	NR	160	NR	NR
Death due to other malignant neoplasms	3	NR	NR	51	NR	NR
Other causes	14	NR	NR	31	NR	NR

Abbreviation: NR, not reported.

Table 5. Overall Survival (OS) Probability Estimates According to Tumor Site and Other Disease Characteristics

Characteristic	Ethmoid Sinus			Maxillary Sinus		
		OS Estimate (SE)			OS Estimate (SE)	
	No.	2-Year	5-Year	No.	2-Year	5-Year
Tumor histologic characteristic						
Adenocarcinoma	85	69.6 (3.9)	43.6 (4.5)	10	77.8 (9.8)	53.8 (12.1)
Esthesioneuroblastoma	5	96.3 (3.6)	81.7 (8.4)			
Adenoid cystic carcinoma	13	78.3 (8.6)	64.1 (10.3)	61	83.4 (3.9)	53.1 (5.5)
Melanoma	9	13.3 (12.1)	0	0	NA	NA
Sarcoma	1	NE	NE	32	74.2 (5.7)	48.7 (6.7)
Squamous cell carcinoma	22	45.7 (9.3)	18.7 (8.1)	111	55.9 (4.0)	45.2 (4.0)
Undifferentiated carcinoma	12	20.1 (11.6)	0	17	45.8 (10.3)	30.5 (10.0)
Mucoepidermoid carcinoma	1	NE	NE	14	88.9 (6.1)	61.9 (9.5)
Other	17	66.7 (9.6)	32.1 (9.7)	21	72.7 (9.5)	35.8 (10.3)
AJCC-UICC 2002 classification						
T1	11	81.2 (7.6)	53.2 (10.7)	0	NA	NA
T2	18	86.6 (5.1)	60.3 (8.2)	92	78.8 (3.3)	61.7 (3.9)
T3	48	72.1 (5.0)	48.2 (5.7)	22	70.2 (7.5)	50.5 (8.3)
T4A/B	88	55.1 (4.4)	35.4 (4.6)	152	60.2 (3.5)	35.9 (3.5)
Nodal status at baseline						
N–	161	67.9 (2.8)	45.3 (3.2)	238	70.3 (2.4)	50.6 (2.7)
N+	4	26.7 (22.6)	0	28	48.5 (8.7)	16.8 (6.7)

Abbreviations: AJCC-UICC, American Joint Committee on Cancer–International Union Against Cancer TNM classification[6]; NA, not applicable; NE, not estimated.

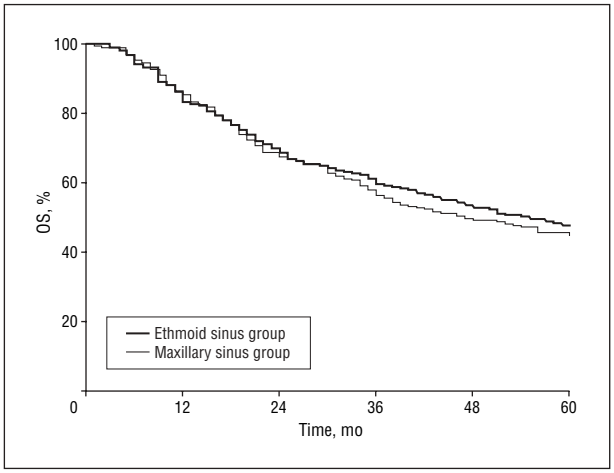

Figure 3. Overall survival (OS) curves for patients in the ethmoid sinus and maxillary sinus groups.

related to patient aging (age ≥75 years). As shown in Table 5, overall survival tended to decrease in patients with N+ tumors and with increasing T stage, regardless of tumor site. Regarding histologic traits, a clear picture cannot be obtained because of the large number of categories and the small patient or event number in most of them. In the maxillary sinus group, the prognosis for survival for patients with SCC was less favorable than that of patients with other histotypes (**Figure 4**), but the difference failed to reach statistical significance (P=.12).

COMMENT

Malignant tumors of the paranasal sinuses represent a difficult undertaking for both the surgeon and the radiotherapist. Because these tumors are asymptomatic for a long time, the disease often presents in an advanced stage involving important surrounding structures (orbit and skull base).

The first maxillectomy was performed in the 1820s; however, it was little more than a piecemeal resection. For many years, anterior skull base and/or infratemporal fossa involvement have been considered a contraindication to surgery. In 1963, Ketcham et al[9] published

their outstanding article on resection of tumors involving the anterior cranial base. In 1956, Conley[10] described his surgical approach to the pterygoid area, and in 1969, Terz et al[11] demonstrated the possible resection of tumors involving the infratemporal fossa with a lateral craniofacial resection. From then on, many advances in surgical techniques for resection and reconstruction have enabled skilled surgeons to safely resect nearly all types of malignant tumors invading the skull base that would have been considered inoperable in the past.[12] Oncologic contraindications to surgical resection of the primary tumor are not universally accepted, but almost all agree that large intracranial extension with brain invasion, bilateral cavernous sinus, and bilateral optic nerve or chiasma involvement are contraindications.

The initial presence or later development of neck metastases is generally considered to be an unfavorable prognostic factor.[1,4,5,13-19] Fortunately, the incidence of neck metastases at presentation is low. Dulguerov et al,[1] in their meta-analysis, reported a 12% rate, although the incidence of nodal metastases during the follow-up was around 13%.

Obviously, all authors agree about indication of surgery and/or radiotherapy on the neck for patients with clinically positive nodes. Much more controversial is the strategy to be adopted for patients with an N0 neck. On the one hand, in addition to the statements reported at the beginning of this article,[4,5] other authors[13-15,20] stressed the indication for prophylactic neck treatment. On the other hand, some authors,[16,21-24] reporting similar or lower rates of neck metastases (about 10%-15%), drew the opposite conclusion: that it is useless to treat the N0 neck. It is important to emphasize that some of these articles deal with very small series. Moreover, the series are often heterogeneous for histologic characteristics, tumor extension, and treatment.

Le et al[4] present 97 cases of maxillary sinus carcinoma treated with surgery or radiotherapy, of which 58 presented with SCC, 4 with ADE, 16 with UC, and 19 with ACC. The authors[4] conclude that the rates of neck metastases of their patients (14% for SCC, 25% for ADE, and 7% for both UC and ACC) are high, and therefore, there is the indication for prophylactic radiotherapy on the neck. The same conclusion is drawn by Jeremic et al[20] from their series of 44 patients with T3 or T4 tumors, and by Paulino et al[5] (42 cases). Stern et al[13] present a series of 85 patients with SCC of the maxillary sinus and conclude that there is the indication for

> systematic elective irradiation of the cervical lymph nodes during the course of postoperative radiotherapy for all patients with squamous cell carcinoma, except for those who have T1 or T2 staged neoplasms.[13(p968)]

However, some authors[1,16,21] conclude that prophylactic irradiation of the N0 neck is not indicated because cervical recurrences alone are rare and frequently salvaged by neck dissection.

Regarding nasal cavity and ethmoid sinus carcinoma, there is a consensus about the usefulness of prophylactic neck irradiation, except for patients with poorly differentiated tumors and for those involving areas rich in capillary lymphatics, such as the nasopharynx.[2]

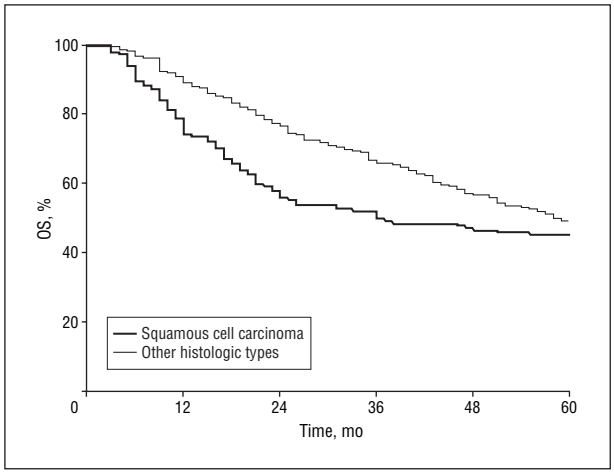

Figure 4. Overall survival curves for squamous cell carcinoma and other histologic types for patients in the maxillary sinus group.

The analysis of our large series of patients allows us to draw some conclusions. Nodal metastases from malignant tumors of the ethmoid sinus are very rare, either at presentation (1.6%) or during follow-up (4.3%). Moreover, most subsequent neck metastases appeared together with a recurrence of the primary tumor. Therefore, in our opinion, there is no indication for prophylactic treatment of the neck. Only patients with UC had a high rate of regional recurrence (25%). Probably, these tumors have a biological behavior similar to nasopharyngeal UC, and we agree with Katz et al[2] about the indication for prophylactic irradiation of the neck for these cases, in particular when the primary tumor is treated with radiotherapy.

The problem is more intricate for maxillary sinus malignant tumors. Regarding nonsquamous cell carcinomas, the rate of neck metastases in this series was very low at presentation (6%). In addition, subsequent nodal metastases were rare, except for UC (13%) and ADE (22.2%). These data are in agreement with the results of Le et al.[4] Actually, ADE of the maxillary sinus is a tumor originating in minor salivary glands, it acts like ADE of major salivary glands, and it is very different from ITAC of the ethmoid sinus, for which the rate of regional metastases is very low.

The rate of neck metastases at presentation for SCC was 10.3%. The percentage of cervical metastases is much higher in T2 tumors than in T3 or T4 tumors. Actually, a T2 tumor is a tumor involving the floor of maxillary sinus (with possible invasion of the mucosa of the hard palate and upper gum), and/or the inferior nasal cavity; these structures have a lymphatic network more expanded than the mucosa of paranasal sinuses. Therefore, regarding LN metastases, such tumors have a behavior more similar to that of oral cancers than to that of paranasal cancers. This fact was recognized as far back as 1937 by del Regato[25] and was later confirmed by other authors.[1,3,16,21,22] Shibuya et al[26] were even able to demonstrate a higher rate of cervical metastases from SCCs originating from the mucosa of the upper jaw and hard palate with secondary maxillary sinus involvement, in comparison with carcinomas originating in the maxillary sinus with involvement of the upper jaw. Other au-

thors[4,13,14] did not agree with this statement and reported a higher rate of neck metastases in T3 and T4 tumors, even if in these series of patients there were few T2 lesions.

Paulino et al,[5] for example, had only 1 T1 and 4 T2 tumors among their 38 patients with N0 tumors. Despite a very high rate of late neck recurrence for these patients with T1 and T2 tumors (4 of 5) in comparison to those with T3 tumors (5 of 15) and T4 tumors (3 of 18), the authors conclude with contradictory sentences: "Invasion to areas known to be rich in lymphatics such as nasopharynx and oral cavity/oropharynx was not found to influence the rate of neck recurrence"[5p287] and "Only the tumor stage was found to be statistically significant, with T1 and T2 patients faring worse compared to T3 and T4 lesions."[5(p287)]

Jeremic et al wrote:

> The probability of lymph node spread increases with extension outside the maxillary sinus, especially with extension to the oral cavity or nasopharynx. The risk of lymph node involvement is, therefore, higher in T3 and T4 tumors by virtue of their local invasiveness.[27(pp235-236)]

Once again, it is important to state that extension to the oral cavity causes the tumor to be staged as T2 rather than as T3 or T4.

From these misunderstandings and from small and unbalanced series, many authors[4,13,14,20,28,29] arrived at the decision to treat the neck with prophylactic irradiation only in patients with advanced tumors.

In this large series of patients with SCC of the maxillary sinus, there were no T1 tumors but many T2 tumors. The rate of neck metastases either at presentation or after treatment was much higher in patients with T2 tumors than in those with T3, T4a, or T4b tumors, thus confirming the statement by del Regato.[25] Therefore, because a tumor involving the oral and/or nasal cavity without any other extension is staged as T2, carcinoma of the maxillary sinus turns out to be different from any other cancer of the head and neck. Actually, in all head and neck sites, the rates of regional metastases normally grow according to increasing stage.

This series confirms that the presence or development of neck metastases is an important factor that worsens the prognosis for those with ethmoid tumors as well as for those with maxillary sinus tumors. In the ethmoid sinus group, 2-year survival rates were 67.9% in patients with N0 tumors vs 26.7% in those with N+ tumors. Corresponding 5-year survival rates were 45.3% vs 0% (Table 5). In the maxillary sinus group, 2-year survival rates were 70.3% vs 48.5%, and 5-year survival rates were 50.6% vs 16.8%. Actually, no patients in the ethmoid sinus group with nodal metastases at presentation or during follow-up survived. In the maxillary sinus group, the situation was similar, even if less dramatic. However, among 31 patients who developed node metastases during follow-up, only 1 presented with unresectable nodes, whereas 30 underwent neck dissection with or without radiotherapy. In summary, only 2 of these patients died from nodal metastases per se.

Le et al[4] made a correlation between elective radiation of the N0 neck and the avoidance of disyant metastases. They wrote[4(p541)]:

> None of the patients presenting with SCC histology and N0 necks had nodal relapse after elective neck irradiation. Patients who had nodal relapse had a higher risk of distant metastases and poorer survival. Therefore, our present policy is to consider elective neck irradiation in patients with T3-T4 SCC of the maxillary sinus.

We do not agree with this statement for several reasons. First, in accordance with the findings of many other authors,[1,3,16,21,22,25] our experience demonstrates that the rate of clinically detected neck metastases, either at presentation or during follow-up, is higher in T2 than in T3 and T4 tumors; therefore, it is logical that microscopic nodal involvement also follows the same rule. Second, almost all authors agree that for advanced tumors, the prognosis is more related to the recurrence of the primary tumor than to nodal spread. Finally, prophylactic irradiation of the neck cannot prevent nodal metastases; at the most, it may cure microscopic nodal metastases before they can be clinically detected. It is hard to believe that, without neck irradiation, during the time between the presence of microscopic nodal involvement and its clinical evidence, some neoplastic cells may spread to distant sites from nodal localization of the tumor. It is more logical that the presence of subclinical or clinical nodal metastases in these tumors that rarely have a regional spread is the effect of an intrinsic biological aggressiveness not the cause of distant metastases. If this is the case, we believe that preventive neck irradiation cannot prevent distant spread.

CONCLUSIONS

From this investigation, we may draw the following conclusions:

- The rate of LN metastases in malignant ethmoid sinus tumors is very low (1.6%), whereas the risk of neck recurrence during follow-up is relatively high in undifferentiated carcinomas (25.5%).
- The rate of LN metastases from a malignant maxillary sinus tumor is quite low at presentation (8.3% overall, and 10.3% for SCC). Tumors staged as T2 have a higher rate than T3 and T4 tumors.
- Early or late LN metastasis is an unfavorable prognostic factor but only rarely directly affects survival (only 1 patient in our series died from nodal metastases per se).
- Patients with neck metastasis at presentation must undergo a neck dissection. A prophylactic neck treatment is not indicated in patients with T3 and T4N0 tumors.
- Regarding T2N0 SCC, the treatment of the neck may be questionable.

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