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Long-term survival after surgery for stage III-IV maxillary sinus carcinoma

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Abstract. *Long-term survival after surgery for stage III-IV maxillary sinus carcinoma. Objectives*: How to optimally treat maxillary sinus carcinoma is subject to debate. This study assessed how clinical features and treatment modalities corresponded with long-term survival.
Methods: Sixty-five patients at our institution were diagnosed with maxillary sinus carcinoma from 1982 to 2003. The median follow-up time was 92.9 months. We evaluated the prognostic value of age, gender, symptoms at presentation, histological classification, tumour stage, and treatment modality with regard to overall survival.
Results: The five-year survival rate was 52%. Age ($p = 0.03$), TNM stage ($p = 0.04$), T classification ($p = 0.04$), nodal involvement ($p = 0.03$), and surgery ($p = 0.04$) were significant prognostic factors for overall survival. There was a significant difference in the overall survival rate and months of survival between patients who underwent surgery and those who had nonsurgical treatment ($p = 0.04$). In patients with T3 disease, patients who received en bloc surgery had a higher overall survival than patients who received piecemeal surgery ($p = 0.045$). Multivariate analysis revealed that T classification was the most powerful prognostic factor for overall survival ($p = 0.026$), followed by nodal involvement ($p = 0.036$). Surgery was a marginally significant prognostic factor ($p = 0.066$).
Conclusions: Although multivariate analysis showed that T classification and nodal involvement corresponded more with survival than did surgery, we conclude that adequate surgical removal should be an integral component of multimodal treatment.

Introduction

Maxillary sinus carcinomas are rare; they account for only 3% of all cancers of the head and neck. However, they account for 80% of all cases of paranasal sinus tumours.[1] Poor outcome has been attributed to complicated anatomic structures and advanced stage at initial presentation,[2] as well as lower tolerance for treatment resulting in a decrease in therapeutic intensity or modification of schedule.[2] Furthermore, there is no consensus regarding the sequence of treatment modalities because randomized controlled trials have included only small numbers of patients.[2-4] Consequently, treatment of maxillary sinus carcinoma remains a difficult clinical challenge.

There are a few specific dilemmas that must be addressed when making decisions regarding treatment. First, because of the introduction over the last two decades of new chemotherapeutic agents and modern radiotherapy techniques, there are new treatment strategies for patients with advanced disease.[5-7] Regimens including surgery and radiotherapy yield local control rates of 49%-59% for all patients of maxillary sinus carcinoma; for patients with T4 tumours, the five-year recurrence-free survival rate is roughly 43%.[8-10] Although en bloc resection is the preferred surgical method of surgery because it leads to maximal tumour control, there are limitations in practice. First, at the time of diagnosis, most late-stage maxillary sinus carcinomas have invaded through the posterior wall into the pterygoid muscles/plates and into the orbital floor. En bloc resection is very difficult to achieve in this situation. Second, surgery entailing wide resection inevitably causes post-operative cosmetic and functional disability.[2] Although Sato and other clinicians have attempted to introduce a combined therapy comprising conservative surgery, radiotherapy, and regional chemotherapy to preserve structures uninvolved in surgery, their efforts have failed to improve functional or oncologic results.[11,12] Third, recurrence at the primary tumour

site is the main issue in treatment, and efforts to improve survival should be directed toward improving local control.[8,13] Although some retrospective studies do not support the use of destructive surgery,[5,6,14] it remains unclear whether the extent of the original surgical treatment correlates with overall survival of patients with advanced disease.

These considerations prompted the present retrospective analysis of 65 consecutive patients with maxillary sinus carcinoma diagnosed between 1982 and 2003 at Chang-Gung Memorial Hospital, Taiwan. We evaluated the extent to which clinical features and treatment modalities such as surgery corresponded with the long-term outcome of patients with maxillary sinus carcinoma.

Patients and methods

Patient characteristics

We conducted a retrospective analysis of the medical records of 65 consecutive patients with previously untreated maxillary sinus carcinoma who were diagnosed at Chang-Gung Memorial Hospital from 1982 to 2003. Their treatments and conditions were tracked until the end of 2007. We analyzed the following possible predictive factors for survival: (1) age and gender, (2) symptoms at presentation, (3) histological classification, (4) tumour stage, (5) modality of therapy, and (6) overall survival rate. The Institutional Review Board of Chang Gung Memorial Hospital approved this study before it was implemented.

We identified 40 male patients and 25 female patients, all of whom were enrolled in this retrospective study (Table 1). Age at diagnosis ranged from 30 to 85 years with a median of 57 years. Common presenting symptoms included facial swelling, nasal obstruction, and painful cheek congestion; one or more of these symptoms were present in 74% of patients. In addition, 30 of 65 patients (46%) had a history of tobacco use or alcohol consumption. Interestingly, only six patients (9%) had a recorded history of chronic paranasal sinusitis.

Tumour characteristics

All of the patients had a histopathological diagnosis (Table 1). The most common histological subtype was squamous cell carcinoma (72%), followed by adenoid cystic

Table 1
Demographic and clinicopathological data for series of 65 patients

Variable	*n* (%)
Gender	
Male	40 (62)
Female	25 (38)
Age (years)	Median, 57 (Range, 30-85)
< 60	37 (57)
> 60	28 (43)
Lifestyle factors	
Tobacco	25 (38)
Alcohol	5 (8)
Betel quid	3 (5)
Chronic paranasal sinusitis history	6 (9)
Initial symptoms	
Facial swelling	18 (28)
Nasal obstruction	17 (26)
Facial pain	13 (20)
Epistaxis	8 (12)
Histology	
Squamous cell carcinoma	47(72)
Adenoid cystic carcinoma	11(16)
Adenocarcinoma	2(3)
Small cell carcinoma	2(3)
Acinic cell carcinoma	1(2)
Poorly differentiated carcinoma	2 (4)
TNM staging	
III	22 (34)
IV	43 (76)
T stage	
T3	22 (34)
T4	43 (76)
Nodal status	
N0	59 (91)
N+	6 (9)
Treatment modality	
Surgery	
Yes	40 (62)
No	25 (38)
Radiotherapy	
Yes	51 (78)
No	14 (22)
Chemotherapy	
Yes	36 (55)
No	29 (45)

carcinoma (17%), adenocarcinoma (3%), small cell carcinoma (3%), poorly differentiated carcinoma (3%), and acinic cell carcinoma (one patient, 2%). Tumours were reclassified retrospectively according to the 2002 American Joint Committee on Cancer Staging System (AJCC) based on physical examination, routine laboratory tests, chest X-ray, and computerized tomography (CT) of the head and neck (Table 1). Using these criteria, none of the patients had T1 or T2 disease. In contrast, 22 patients (34%) had T3 and 43 patients (66%) had T4 disease. Only six patients (9%) showed cervical lymph node involvement at diagnosis, and none of the patients had distant organ metastasis.

Treatment

Of the 65 patients, 40 had undergone surgery; the remaining 25 patients had received chemotherapy, radiotherapy, or both (Table 1). Of the 22 patients with T3 disease and the 43 patients with T4 disease, 20 and 20 patients, respectively, had chosen surgery. Surgical resection was en bloc in 26 patients and piecemeal in 11 patients. We were unable to identify the surgical method in the remaining three patients.

The percentage of all patients receiving radiation therapy was 78%. The total radiation dose ranged from 2,400 cGy to 10,000 cGy. The median dose was 6,600 cGy. The percentage of all patients receiving chemotherapy was 55%. A wide variety of combination chemotherapy protocols were used in neoadjuvant, concurrent chemoradiotherapy, and postoperative adjuvant settings. The most common regimen was cisplatin plus fluouracil (26 patients, 72% of chemotherapy patients). Other chemotherapy regimens were cisplatin alone in two patients; carboplatin alone in one patient; fluouracil alone in one patient; gemcitabine alone in one patient; cisplatin plus methotrexate in two patients; cisplatin plus bleomycin in one patient; carboplatin plus fluouracil in one patient; and cisplatin, etoposide, and bleomycin in one patient.

Statistical analysis

Statistical Program for Social Science version 13.0 software (SPSS, Chicago, IL, USA) was used for all data analysis. Overall survival was calculated from the date of diagnosis to the date of last follow-up or death from any cause and was plotted using the Kaplan-Meier method. Univariate analysis to identify prognostic factors was performed using the log-rank test. Multivariate analysis was performed using Cox's Proportional Hazard Model. Patients who died of other causes were censored on the date of death. Patients lost to follow-up were included in all analyses and were censored on the date of last follow-up. Analyses of differences for demographic factors were performed using the Pearson chi-square test. A p value of less than 0.05 was considered to be a statistically significant difference.

Results

Overall survival

The median follow-up duration was 92.9 months (range: 1.6-207 months). The actuarial survival rate for the 65 patients was 52% at five years. The effect of age at diagnosis on survival is shown in Table 2. Patients who were under 60 years of age had a higher five-year survival rate than patients over 60 years ($p = 0.03$). Five-year survival rates were 73% for T3 disease and 39% for T4 disease. T classification was significantly related to survival ($p = 0.04$, Table 2). Node involvement also affected survival; the actuarial five-year survival rate for the 59 patients with negative nodes was 55%, whereas that of the six patients with positive nodes was 17% ($p = 0.03$, Table 2). In terms of TNM stage, patients with stage III disease had a higher five-year survival rate than those with stage IV disease (73% and 39%, respectively, $p = 0.041$; Table 2). Clinical variables including gender, histologic subtype, and use of chemotherapy or radiotherapy did not correlate with survival (Table 2).

Surgery vs. nonsurgical treatment

We divided our 65 patients into surgery and nonsurgery groups to explore the difference in survival outcome. One group consisted of 40 patients who had undergone surgical resection, and the other group comprised the 25 patients who did not undergo surgery (e.g., refused surgery, had an unresectable tumour, or were medically unfit for surgery) but were scheduled to receive chemotherapy, radiotherapy, or both in the treatment plan.

Of the patients who underwent surgery, 17 patients received surgery as well as radiotherapy and chemotherapy, 14 patients received surgery and radiotherapy, and nine patients received surgery alone. Of the patients who did not receive surgery, 14 patients received combined radiotherapy and chemotherapy, six patients received radiotherapy, and five

Table 2
Prognostic factors resulting from univariate analysis (log-rank test)

Variable	5 year OS (%)	p value
Gender		
Male	52	0.61
Female	51	0.61
Age (years)		
< 60	63	0.03
> 60	35	0.03
Histology		
Squamous cell carcinoma	45	0.36
Non-squamous cell carcinoma	71	0.36
TNM staging		
III	73	0.04
IV	41	0.04
T stage		
T3	73	0.04
T4	39	0.04
Nodal status		
N0	55	0.03
N+	17	0.03
Treatment modality		
Surgery		
Yes	62	0.04
No	36	0.04
Radiotherapy		
Yes	55	0.31
No	44	0.31
Chemotherapy		
Yes	49	0.55
No	55	0.55

OS: overall survival.

patients received chemotherapy. With the exception of TNM stage and T status, clinical information, including age, sex, histology, and laboratory data, were equivalent among the groups (Table 3).

For patients who underwent surgery, the median overall survival was 119.5 months and the five-year overall survival rate was 62%. For patients who did not receive surgery, the median overall survival was 18.3 months and the five-year overall survival rate was 36%. There was a significant difference in terms of overall survival rate and survival months between the two groups (p = 0.04, Figure 1).

Survival benefit for patients with T3 disease following en bloc *resection*

When comparison was limited to patients with T3 disease, patients who received en bloc surgery had a significantly longer median overall survival and a better five-year survival rate than those received piecemeal surgery (180.7 months vs. 29.0 months, p = 0.045; 75% vs. 50%, p = 0.043; Figure 2). However, in patients with T4 disease, those who received en bloc surgery did not have a prolonged median survival or an improved survival rate (p = 0.66).

Patients with T4 disease

For the 43 patients with T4 disease at diagnosis, we compared the median survival and overall survival rates corresponding to different treatment strategies. For the 11 patients who received combined therapy with surgery, chemotherapy, and radiotherapy, the five-year overall survival rate was 60%. For the four patients who received surgery and radiotherapy, the five-year overall survival rate was 50%. In contrast, the five-year overall survival rate decreased to 31% for the 13 patients who received combined chemotherapy and radiotherapy only. We failed to detect a significant difference between patients receiving surgery and radiotherapy with or without chemotherapy and patients receiving only radiotherapy and chemotherapy (p = 0.24); this was likely because of the limited number of patients in our series. For the five patients treated with surgery alone, the five-year overall survival rate was 40%. For the five patients treated with radiotherapy alone, the five-year overall survival rate was 40%. For the 11 patients treated with chemotherapy alone, the five-year overall survival rate was 20%. There were no statistical differences in the survival rates among treatment strategies using only a single modality (p = 0.19).

Multivariate analysis

For multivariate analysis, we used Cox proportional hazards regression to examine those clinical variables – age, TNM stage, T classification, node status, and use of surgery – that were shown to be significant by univariate analysis.

Table 3
Patients classified by surgical or non-surgical treatment

Parameter	Surgery *n* = 40	No surgery *n* = 25	p value
Age (years)			
< 60	26	13	0.30
> 60	14	12	
Gender			
Male	25	15	0.84
Female	15	10	
Histology			
Squamous cell carcinoma	28	19	0.24
Non-squamous cell carcinoma	12	6	
TNM staging			
III	20	2	0.01
IV	20	23	
T stage			0.01
T3	20	2	
T4	20	23	
Nodal status			
N0	38	21	0.22
N+	2	4	
Laboratory examination			
Leukocyte number (1000/μL)			0.35
Median	9.2	8	
Range	3.3-17.7	0.7-126	
Hemoglobin level (g/dL)			0.18
Median	13.1	11.6	
Range	10.4-16	5.7-15.6	
Platelet count (1000/μL)			0.36
Median	253.5	270.5	
Range	131-470	135-488	
Albumin concentration (g/dL)			0.76
Median	4.1	4	
Range	2.8-6.8	2.5-4.6	

p value calculated by chi-square test.

Interestingly, T classification was the most powerful prognostic factor for overall survival (p = 0.026), followed by node involvement (p = 0.036). Surgery became a marginally significant prognostic factor (p = 0.066) with multivariate analysis, while age had no impact on survival outcome.

Discussion

Maxillary sinus carcinoma often presents at diagnosis as locally advanced disease that has invaded near to a number of critical normal structures. Thus, the disease is a considerable therapeutic challenge to physicians. Waldron and colleagues reported a retrospective analysis of 110 cases of maxillary sinus carcinoma treated from 1976 to 1993. Of the 110 patients, 71% presented with T4 disease, 15% had nodal involvement, and the major histologic type was squamous cell carcinoma (86%).[15] Our analysis yielded similar results: 76% of patients had T4 disease, 9% had nodal involvement, and 72% had squamous cell carcinoma. The overall five-year survival rate for our 65 patients was 52%, which is in accordance with previously reported outcomes.[16]

Risk factors for disease include cigarette smoking and occupations such as mining, smelting, and woodworking.[17] Only 38% of the patients in our series had a history of cigarette smoking, while 17% had a history of work in coal mining. These reported risk factors failed to be associated with the incidence rate in the present analysis (chi-square test, p = 0.34 for smoking; p = 0.57 for occupation). Gender was reported to be an independent prognostic factor by Le *et al.*,[1] but we were unable to show a correlation with survival in our series. Consistent with previous reports,[1,4] according to univariate analysis, patients younger than 60 years had a higher survival rate than older patients (Table 2). This could be linked to more-aggressive treatment for younger patients. Nonetheless, the effect of age was diminished in multivariate analysis and failed to be an independent prognostic factor.

Extent of local disease has been shown to correlate with outcome.[1,8,13] This factor reached statistical significance in our series; a higher TNM stage, advanced tumour status, or nodal involvement correlated with a lower survival rate. Multivariate analysis further confirmed that T classification was the most critical prognostic factor for survival in our patient population.

Geneally, the management of maxillary sinus carcinomas requires a multimodal approach involving surgery, radiation therapy, and chemotherapy.[18] There is general agreement that surgery is the appropriate primary treatment for these tumours, and that patients who undergo surgery have better local control of the disease and prolonged

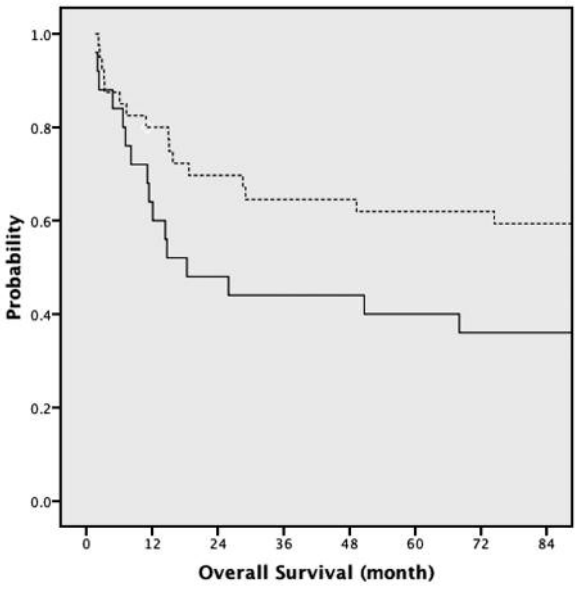

Figure 1
Kaplan-Meier survival curves for overall survival of patients who underwent surgery and those who did not undergo surgery. Dashed line, surgery group; solid line, nonsurgery group.

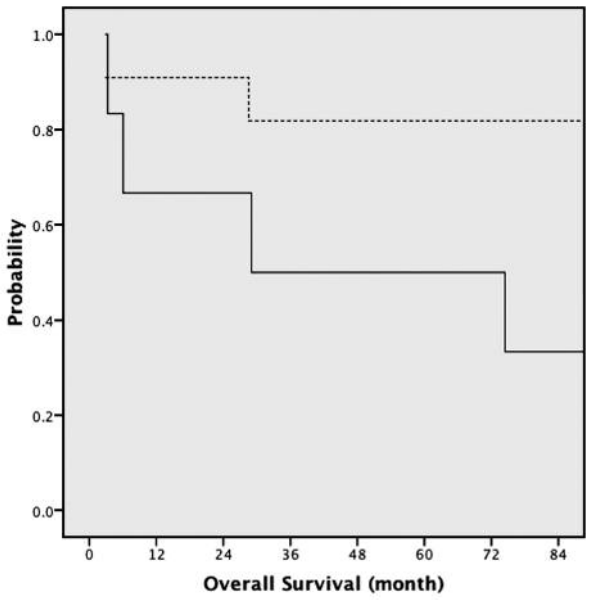

Figure 2
Kaplan-Meier survival curves for overall survival between patients with T3 disease who underwent en bloc resection and those who underwent a piecemeal procedure. Dashed line, en bloc group; solid line, piecemeal group.

survival.[2,9,19,20] The results of the present investigation are consistent with previous retrospective studies and demonstrate that patients treated with surgery have a better five-year survival rate than patients who do not undergo surgery. Bias toward selection of patients with favorable lesions for surgery and non-randomization of treatment modality has been noted previously and is unavoidable in our retrospective study. However, we found that for patients with T4 disease, there was a trend toward higher survival after surgical resection compared with nonsurgical treatment (median overall survival, 93.9 months vs. 14.7 months; five-year survival rate, 53% vs. 30%, p = 0.11). This observation lends further support to the position that surgical resection is an important treatment modality for patients with locally advanced maxillary sinus cancer.

Decisions regarding the particular surgical technique largely depend on patients' general condition, primary tumour size, and relative location to adjacent critical structures.[21-23] Our study found that radical en bloc surgery provides a survival benefit for patients with T3 disease but not for patients with T4 disease. Daele *et al.*[24] suggested that patients with tumour involvement of the skull base, such as in the infratemporal fossa, should be considered for craniofacial resection. In their review, bony erosion of the orbital walls does not constitute an indication for orbital exenteration. Rehabilitation after surgical resection may be accomplished with prosthodontics or reconstructive flaps.[24] In selective cases, minimally invasive endoscopy surgery may be a reliable alternative to an exclusively external approach.[18] Cosmetic and functional loss is caused by radical surgery, whereas conservative surgery is often performed in combination with radiotherapy and chemotherapy. Some series have advocated that the mode of surgery may not be critical if radiotherapy and chemotherapy are included in the treatment plan.[9,25]

In conclusion, multivariate analysis of our data showed that T classification and nodal involvement have a greater correlation with survival than surgery, but adequate surgical removal should still be an integral part of multidisciplinary treatment. Furthermore, previous studies have shown that primary radiotherapy with or without chemotherapy remains the first choice for patients who are unfit for surgery.[11-13] Efforts should also be directed toward minimizing the delay between onset of symptoms and time of diagnosis.

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