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CLINICAL INVESTIGATION **Head and Neck**

POSTOPERATIVE RADIOTHERAPY FOR MAXILLARY SINUS CANCER: LONG-TERM OUTCOMES AND TOXICITIES OF TREATMENT

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Purpose: To determine the effects of three changes in radiotherapy technique on the outcomes for patients irradiated postoperatively for maxillary sinus cancer.
Methods and Materials: The data of 146 patients treated between 1969 and 2002 were reviewed. The patients were separated into two groups according to the date of treatment. Group 1 included 90 patients treated before 1991 and Group 2 included 56 patients treated after 1991, when the three changes were implemented. The outcomes were compared between the two groups.
Results: No differences were found in the 5-year overall survival, recurrence-free survival, local control, nodal control, or distant metastasis rates between the two groups (51% vs. 62%, 51% vs. 57%, 76% vs. 70%, 82% vs. 83%, and 28% vs. 17% for Groups 1 and 2, respectively). The three changes were to increase the portals to cover the base of the skull in patients with perineural invasion, reducing their risk of local recurrence; the addition of elective neck irradiation in patients with squamous or undifferentiated histologic features, improving the nodal control, distant metastasis, and recurrence-free survival rates (64% vs. 93%, 20% vs. 3%, and 45% vs. 67%, respectively; $p < 0.05$ for all comparisons); and improving the dose distributions within the target volume, reducing the late Grade 3–4 complication rates (34% in Group 1 vs. 8% in Group 2, $p = 0.014$). Multivariate analysis revealed advancing age, the need for enucleation, and positive margins as independent predictors of worse overall survival. The need for enucleation also predicted for worse local control.
Conclusion: The three changes in radiotherapy technique improved the outcomes for select patients as predicted. Despite these changes, little demonstrable overall improvement occurred in local control or survival for these patients and additional work must be done. **© 2007 Elsevier Inc.**

Maxillary sinus cancer, Paranasal sinus cancer, Postoperative radiotherapy, Sinus carcinoma.

INTRODUCTION

Malignant neoplasms of the nasal cavity or paranasal sinuses are uncommon in the United States, constituting <1% of all cancers and only 3% of head-and-neck cancers (1, 2). The yearly incidence of paranasal sinus cancers is 0.75 cases/100,000 individuals (3), with carcinomas of the maxillary sinus comprising nearly 80% of all cases (4). Consequently, our understanding of these tumors' clinical behavior, response to treatment, and prognosis has been derived from retrospective studies (5–22).

We previously analyzed the results of 73 patients treated with surgery and postoperative radiotherapy (PORT) for maxillary sinus cancer at our institution (21). The findings were that the local recurrence rate was significantly greater in patients with perineural invasion than in patients without it (36% vs. 10%); the nodal relapse rate without elective lymphatic irradiation was >30% in patients with squamous cell and undifferentiated carcinoma; and major complications occurred when large, wedge-pair portals were used, radiation doses of >2 Gy/fraction were administered, or significant dose heterogeneity existed within the target volume.

On the basis of these observations, three modifications in technique were introduced: *(1)* design radiation portals to encompass the base of the skull, including the trigeminal ganglion, more generously in patients with evidence of perineural invasion; *(2)* deliver elective RT to the ipsilateral upper neck nodes in patients with Stage T2–T4 squamous cell or undifferentiated carcinoma; and *(3)* use measures to

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improve dose distribution within the target volume, such as the exclusive use of ≥6-MV photons and the use of water-filled balloons to fill large resection cavities.

This report has updated the long-term outcomes for patients treated in accordance with these modifications and compared their outcomes with those of patients treated before the changes were implemented. The influence of these changes and other disease and treatment variables on overall survival (OS), recurrence-free survival (RFS), local control, nodal control, distant metastasis, and complication rates are presented.

METHODS AND MATERIALS

Study design

A retrospective chart review was performed for all patients with maxillary sinus cancer treated at The University of Texas M.D. Anderson Cancer Center between 1969 and 2002. The institutional review board approved this study and provided a waiver of consent. The patients included had primary maxillary sinus cancer treated for cure with surgery and PORT. Patients with lymphoma, melanoma, or sarcoma were excluded. The data of 146 patients were analyzed. These patients were separated into two groups according to the date of treatment. Group 1 included 90 patients treated before 1991 when the updated radiotherapy technique was implemented; and Group 2 included 56 patients treated after those changes had been implemented.

Staging

The disease stage of each patient was restaged clinically using data from the medical record according to the 6th edition of the American Joint Committee on Cancer TNM classification. The workup included a complete history and physical examination, plain X-rays, and tomograms of the sinuses; after 1975, computed tomography (CT) was added to the routine assessment of patients. After 1987, magnetic resonance imaging was occasionally used to better assess base-of-skull and perineural invasion. Staging in 43 cases was determined from X-rays only, in 72 cases from X-rays and CT, and in 31 cases from X-rays, CT, and magnetic resonance imaging.

Surgery

Of the 146 patients, 134 underwent primary surgery at the M.D. Anderson Cancer Center and 12 had undergone surgery elsewhere. The procedures used were modifications of partial or radical maxillectomy, depending on the disease stage. Ipsilateral orbital exenteration was performed in 54 patients (36 in Group 1 and 18 in Group 2) because of evidence of tumor extension to the orbital wall or cavity.

The pathologic specimens were coded in terms of margin status (negative, <5 mm, microscopically positive, or macroscopically positive) and the presence or absence of perineural invasion according to the pathology report. Margin status could not be assessed in 2 patients in Group 1 because of incomplete reports. Perineural invasion could not be determined in 4 patients because of insufficient pathologic material (1 in Group 1 and 3 in Group 2).

Radiotherapy

All patients underwent PORT at the M.D. Anderson Cancer Center. Of the 146 patients, 122 began PORT within 6 weeks of surgery. Of the 90 patients in Group 1, 88 underwent RT with a ^{60}Co unit, 11 of whom also received a boost dose with electrons ($n = 4$) or photons ($n = 7$). The remaining 2 patients were treated with 6-MV photons. Of the 56 patients in Group 2, 52 were treated with ≥6-MV photons and 4 were treated with ^{60}Co.

The portal design consisted of a three-field technique (one anterior and two lateral wedged fields) in 108 patients and a wedged pair in 25 patients, as previously described (25). Of the remaining 13 patients, 9 underwent RT using slightly modified techniques, such as the combination of a three-field technique with a wedged pair, and 4 patients were treated with intensity-modulated RT (IMRT).

During the earlier treatment period, the isodose lines were generated using external contours. The dose was prescribed to the isodose line best covering the intended treatment volume. With the introduction of CT-simulation in the late 1990s, 19 of the 56 patients in Group 2 underwent CT simulation with three-dimensional planning and treatment with heterogeneity correction and 4 patients underwent IMRT.

Patients with negative or close (<5 mm) resection margins received a median dose of 60 Gy in both groups with dose ranges of 44–67 Gy (Group 1) and 54–70 Gy (Group 2). Patients with positive margins received a median dose of 60 Gy (range, 50–68 Gy) in Group 1 and 66 Gy (range, 60–70 Gy) in Group 2.

Neck treatment

Of the 146 patients, 20 presented with palpable lymphadenopathy: 9 in Group 1 and 11 in Group 2. Of these 20 patients, 19 had squamous cell or undifferentiated histologic features and 1 had adenocarcinoma. Neck treatment consisted of ipsilateral neck dissection and PORT in 11 patients, RT alone in 7 patients, and RT followed by neck dissection in 2 patients. Of the patients treated with PORT, 4 received bilateral neck irradiation to 50 Gy, with a 16–22-Gy boost to the areas of initial nodal involvement; and 7 received treatment to the entire ipsilateral neck with 50–56 Gy, followed by a 4–10-Gy boost to the areas of initial nodal involvement. In those treated with RT alone, 5 underwent bilateral neck RT to 42–50 Gy, with a boost of 6–20 Gy to the areas of nodal involvement; and 2 received ipsilateral neck irradiation to 50 Gy, with a 16-Gy boost to involved nodal regions. The 2 patients treated with RT followed by surgery received 50 Gy to the entire ipsilateral neck; 1 also received a 10-Gy boost.

Of the 81 patients with node-negative disease in Group 1, 19 received elective neck RT (18 with squamous cell histologic features and 1 with adenoid cystic histologic features) at a dose of 50 Gy in 25 fractions. Of the 19 patients, 7 received treatment to the entire neck bilaterally, 5 received treatment to the upper neck bilaterally through Level II alone, 4 received treatment to the entire ipsilateral neck, and 3 received treatment to the upper ipsilateral neck through Level II alone.

In accordance with the changes described previously, 32 of the 45 node-negative patients in Group 2 received elective neck RT of 50 Gy in 25 fractions. Twenty-six patients received treatment to the ipsilateral upper neck through Level II alone; five received treatment to the entire ipsilateral neck; and one received treatment to the entire neck bilaterally.

Chemotherapy

Twenty-four patients with advanced disease (4 in Group 1 and 20 in Group 2) received neoadjuvant chemotherapy, 15 of whom received both intra-arterial and intravenous chemotherapy. One received intra-arterial chemotherapy alone. Eight patients received intravenous chemotherapy alone.

Of the 16 patients receiving intra-arterial chemotherapy, 2 had disease progression, 2 had stable disease, 8 experienced a partial response, and 4 experienced a complete response by repeat examination and radiography. Of the 8 patients treated with intravenous chemotherapy, 2 progressed, 2 had stable disease, 4 had a partial response, and 1 experienced a complete response. Of the many different regimens used, no specific chemotherapy regimen correlated with the response rates. Neoadjuvant chemotherapy did not have significant effect on the outcome parameters.

Statistical analysis

The study endpoints were OS, RFS, local control, nodal control, and distant metastasis rates. The complication rates were compared between the two groups. Late toxicity to the ocular and auditory systems was graded according to the Common Terminology Criteria for Adverse Events, version 3.0, guidelines (23). All other late toxicity was graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring schema (24). Differences in categorical variables were compared using chi-square analysis. Differences in mean values were assessed by analysis of variance. The Kaplan-Meier method was used to estimate the local and regional control, distant metastasis, RFS, OS, and complication rates. Multivariate Cox regression analysis was used to determine which disease and treatment variables were independent predictors of outcome.

RESULTS

Patient, tumor, and treatment characteristics

Table 1 outlines the patient, tumor, and treatment characteristics and compares these characteristics between the two groups. Both groups contained a majority of patients with advanced T-stage, but node-negative, disease. The patients were also similar in age, gender, surgical margin status, and the need for ipsilateral enucleation at initial surgery. Squamous cell carcinoma made up most of the histopathologic subtypes in both groups but comprised a statistically greater proportion of patients in Group 2 than in Group 1 (73% vs. 53%). Patients in Group 1 had greater rates of perineural invasion identified than did patients in Group 2 (55% vs. 20%, respectively). This finding is consistent with the known predilection for perineural invasion in adenoid cystic carcinoma, which occurred in a greater proportion of patients in Group 1 than in Group 2.

In accordance with the treatment modifications previously described, patients in Group 2 were more likely to receive treatment with ≥6-MV photons than were patients in Group 1 (93% vs. 2%, respectively) and were more likely to undergo elective neck RT than were patients in Group 1 (57% vs. 21%, respectively).

OS and RFS

Figure 1 shows the actuarial OS and RFS curves for Groups 1 and 2. The estimated 5-year OS rate was 51% and 62% for Groups 1 and 2, respectively ($p = 0.81$). The estimated 5-year RFS rate was 51% and 57% for Groups 1 and 2, respectively ($p = 0.93$). At a median follow-up of 54 months, 43 recurrences were observed in the 90 Group 1 patients. At a median follow-up of 39 months, 26 recurrences were observed in the 56 Group 2 patients.

Figure 2 shows the actuarial OS curves for patients stratified by T and N stage. At 5 years, patients with Stage T1–T2, T3, or T4 disease had an estimated OS rate of 66%, 57%, and 50%, respectively ($p = 0.25$). Patients presenting with node-negative vs. node-positive disease had an estimated 5-year OS rate of 56% vs. 44%, respectively ($p = 0.06$).

Table 2 summarizes the influence of the disease and treatment variables on the estimated survival rates. Age, analyzed as a continuous variable by Cox regression analysis, was the strongest predictor of survival (risk ratio [RR], 1.032/y; $p < 0.001$). On univariate analysis, the only other significant predictors of OS were histopathologic subtype and whether a patient required ipsilateral enucleation at the initial surgery. Patients with squamous cell or undifferentiated disease had significantly worse 5-year OS than did patients with other histopathologic subtypes. However, this finding was confounded because, on average, patients presenting with squamous cell or undifferentiated carcinomas were significantly older than patients with other histolopathologic subtypes (mean 60 years vs. 53 years, respectively; $p = 0.004$).

Patients requiring enucleation had a significantly worse 5-year OS rate than those whose eyes were intact (41% vs. 63%, respectively; $p = 0.003$), as well as a worse 5-year RFS rate (44% in patients requiring enucleation vs. 57% in patients with the eye intact; $p = 0.044$). Age and the need for ipsilateral enucleation were significant predictors of survival on multivariate analysis as shown in Table 3. Although not observed on univariate analysis, negative margin status was associated with improved survival on multivariate analysis, with a trend toward improved survival in female patients. Other factors included in the model, but that did not reach statistical significance, were radiation dose, T stage, N stage, histopathologic features, elective neck treatment, and perineural invasion.

Local control

Table 4 summarizes the failure patterns. Primary disease control was achieved in 76% of patients in Group 1 and 70% of patients in Group 2 ($p = 0.16$). The sites of failure in these 39 patients were the remaining maxillary sinus ($n = 18$), orbit ($n = 6$), ethmoid sinus ($n = 4$), pterygomaxillary space ($n = 4$), nasal cavity ($n = 3$), middle cranial fossa ($n = 2$), cavernous sinus ($n = 2$), hard palate ($n = 1$), soft palate ($n = 1$), alveolar ridge ($n = 1$), nasopharynx ($n = 1$), and soft tissue of the cheek ($n = 1$). Five patients had relapses at two sites. Recurrence developed inside the radiation field in 24 patients, at the field margin in 13 patients, and in both places in 2 patients.

Table 2 summarizes the 5-year local control rates by disease and treatment variables. Although perineural invasion was not a significant predictor of local failure overall, analysis by treatment era revealed that patients in Group 1 were at the greatest risk of local recurrence if perineural

Table 1. Patient, tumor, and treatment characteristics

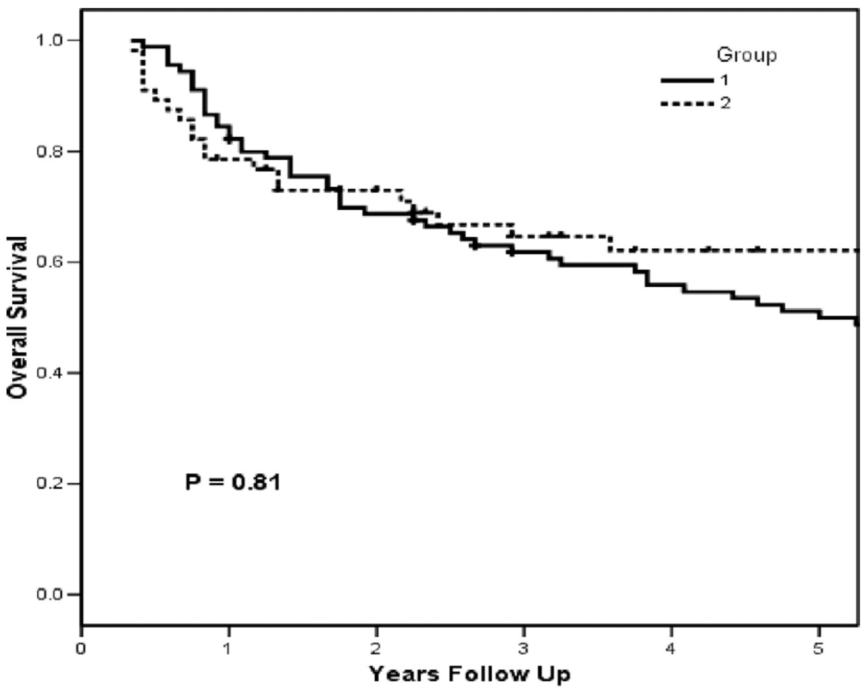
Characteristic	Group 1 (n = 90)	Group 2 (n = 56)	Total (n = 146)	p
Patient				
Follow-up (mo)				0.003
Median	54	39	46	
Range	5–357	4–172	4–357	
Age (y)				0.07
Median	58	62	59	
Range	27–90	26–90	26–90	
Gender (n)				0.08
Male	48 (53)	38 (68)	86 (59)	
Female	42 (47)	18 (32)	60 (41)	
Tumor (n)				
T stage				0.88
T1–T2	14 (16)	8 (14)	22 (15)	
T3	30 (33)	17 (30)	47 (32)	
T4	46 (51)	31 (56)	77 (53)	
N stage				0.10
N0	81 (90)	45 (80)	126 (86)	
N+	9 (10)	11 (20)	20 (14)	
Histologic features (n)				0.008
Squamous cell	48 (53)	41 (73)	89 (61)	
Adenoid cystic	25 (28)	8 (14)	33 (22)	
Undifferentiated	9 (10)	2 (4)	11 (8)	
Adenocarcinoma	6 (7)	0 (0)	6 (4)	
Other	2 (2)	5 (9)	7 (5)	
Treatment				
Neoadjuvant chemotherapy (n)	4 (4)	20 (36)	24 (16)	<0.001
Margin status (n)				0.45
Negative	58 (65)	37 (66)	95 (65)	
<5 mm	6 (7)	6 (10)	12 (8)	
Microscopic	21 (23)	12 (21)	33 (23)	
Macroscopic	3 (3)	1 (2)	4 (3)	
Unknown	2 (2)	0 (0)	2 (1)	
Perineural invasion (n)				<0.001
Yes	49 (55)	11 (20)	60 (41)	
No	40 (44)	42 (75)	82 (56)	
Unknown	1 (1)	3 (5)	4 (3)	
Enucleation (n)	36 (40)	18 (32)	53 (36)	0.30
RT technique (n)				<0.001
^{60}Co	88 (98)	4 (7)	92 (63)	
≥6-MV photons	2 (2)	52 (93)	54 (37)	
RT dose (Gy)				<0.001
Mean	59	62	60	
Median	60	60	60	
Range	44–68	54–70	44–70	
Elective neck RT (n)	19 (21)	32 (57)	51 (35)	<0.001

Abbreviation: RT = radiotherapy.

Data presented as numbers of patients, with percentages in parentheses, unless otherwise specified.

invasion had been identified pathologically. The actuarial 5-year local control rate for patients in Group 1 with and without perineural invasion was 64% and 93%, respectively (p = 0.001). Of the patients in Group 1 with local recurrence, 77% also had perineural invasion. In an attempt to improve local control, the radiation portals were increased to cover the base of skull for Group 2 patients with evidence of perineural invasion. After this treatment change, the association between local recurrence and the presence of perineural invasion was no longer significant; only 18% of the local recurrences in Group 2 were associated with perineural invasion.

The strongest predictor of local control for the entire series on univariate analysis was whether a patient underwent enucleation (62% local control in patients requiring enucleation vs. 80% in patients with eyes left intact; p = 0.009). Patients with squamous cell histologic features tended to have greater local failure rates than did patients with other histopathologic subtypes, but this was not statistically significant (p = 0.064). The only variable predicting



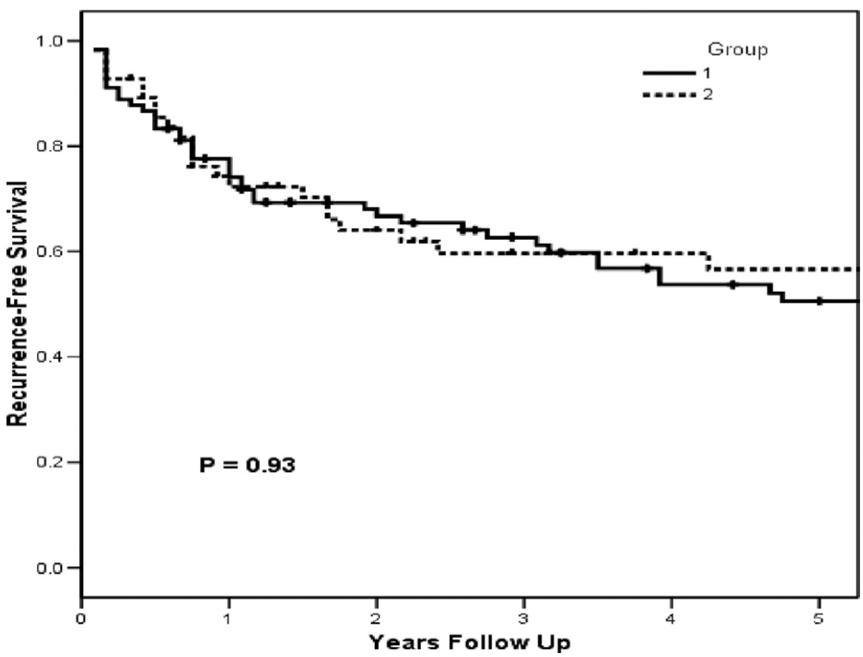


Fig. 1. Overall and recurrence-free survival for patients in Group 1 ($n = 90$) vs. Group 2 ($n = 56$).

for local control that remained significant on multivariate analysis was the need for enucleation (RR, 0.450 for the eyes left intact; 95% confidence interval [CI], 0.238–0.853; $p = 0.014$).

Nodal control

Of the 20 patients presenting with palpable lymph nodes, 3 developed a recurrence in the neck; all were salvaged with surgery and PORT. Of the 126 node-negative patients, 19 had recurrences in the neck: 14 in Group 1 (17%) and 5 in Group 2 (9%). Sixteen of these patients had either squamous cell or undifferentiated histologic features (one clear cell carcinoma, one adenocarcinoma, and one adenoid cystic carcinoma).

Figure 3 shows the effect of elective neck RT on nodal control for node-negative patients with squamous cell or undifferentiated carcinoma. Of the 36 patients in whom the ipsilateral neck was left untreated, 13 (36%) developed nodal recurrence vs. only 3 (7%) of the 45 patients in whom elective neck irradiation was administered ($p < 0.001$). The use of elective neck treatment in these patients translated into a significant reduction in distant metastases (3% in

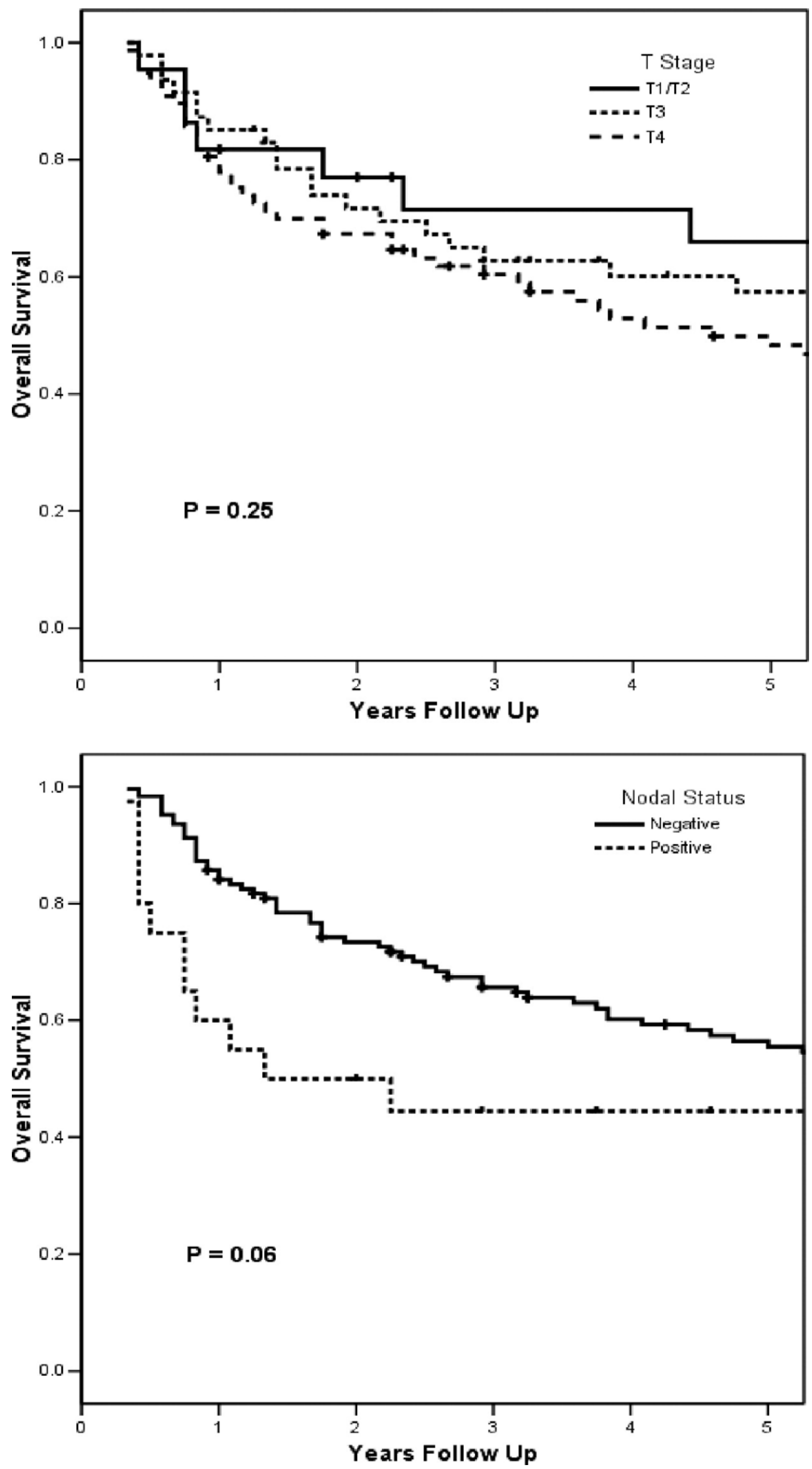


Fig. 2. Overall survival in patients stratified by presenting T stage and nodal status.

treated vs. 20% in untreated at 5 years; $p = 0.045$) and an increase in RFS (67% in treated vs. 45% in untreated at 5 years; $p = 0.025$).

Of the 13 patients who developed nodal recurrence without elective neck treatment, 7 had recurrence in the ipsilateral Level II neck, 4 had recurrence in the ipsilateral Level Ib neck, 1 had recurrence in the bilateral Level II neck, and 1 had recurrence in the contralateral Level II neck. Five of these patients also had recurrence at the primary site. All 3 of the patients with recurrence in the neck (Level II) after elective treatment also had simultaneous failure at the primary site.

Distant metastasis

The 5-year actuarial distant metastasis rate was 28% for patients in Group 1 and 17% for patients in Group 2 ($p =$

Table 2. Outcomes by disease and treatment variables

Variable	Patients (n)	5-y OS (%)	5-y RFS (%)	5-y LC (%)	5-y NC (%)	5-y DM (%)
Group						
1	90	51	51	76	82	28
2	56	62	57	70	83	17
Gender						
Male	86	51	50	71	83	22
Female	60	58	56	77	83	26
T stage						
T1–T2	22	66	53	73	76	32
T3	47	57	60	84	82	16
T4	77	50	48	68	84	27
N stage						
N0	126	56	54	73	83	23
N+	20	44	46	79	75	28
Histologic features						
Squamous cell	89	49††	53	68	80	11*
Adenoid cystic	33	69	54	85	96	37
Undifferentiated	11	36	62	91	73	40
Adenocarcinoma	6	60	42	80	75	37
Other	7	71	57	64	80	33
Neoadjuvant chemotherapy						
Yes	24	61	58	83	81	28
No	122	62	52	72	83	24
Margin status†						
Negative/close	107	59	58	74	84	21
Positive	37	41	37	73	77	31
Elective neck treatment						
Yes	51	47	67	69	93††	5††
No	95	57	47	76	77	32
Perineural invasion‡						
Yes	60	45	35††	66	82	38††
No	82	61	63	81	83	16
Enucleation						
Yes	54	41††	44††	62††	77	24
No	92	63	57	80	85	24

Abbreviations: OS = overall survival; RFS = recurrence-free survival; LC = local control; NC = nodal control; DM = distant metastasis.

* Significant at $p < 0.05$.

† Excluding 2 patients with unknown status.

‡ Excluding 4 patients with unknown status.

0.2). The most common site of metastatic disease was the lung ($n = 23$).

The strongest predictor of distant metastasis was the histopathologic subtype (Table 2). Only 11% of the patients with squamous cell histologic features developed metastatic disease at 5 years vs. 33–40% of patients with other histopathologic subtypes ($p = 0.002$). Although the addition of elective neck RT significantly decreased the distant metastasis rates for the entire series on univariate analysis, this finding was confounded because most patients treated with elective neck RT also had squamous cell cancer. As such, elective neck treatment did not remain a significant predictor of distant failure on multivariate analysis.

Table 3. Multivariate analysis of potential predictors of overall survival

Factor	Relative risk	95% CI	p	Comparison group
Age	1.033	1.017–1.050	<0.001	Continuous variable
Eye intact	0.606	0.407–0.904	0.014	Eye removed
Negative margins	0.636	0.407–0.994	0.047	Positive margins
Female	0.674	0.450–1.010	0.056	Male

Abbreviation: CI = confidence interval.

Table 4. Pattern of failure after initial treatment

Group	L	R	DM	L+R	L+DM	R+DM	L+R+DM
1 (n = 90)	13	5	11	4	4	5	1
2 (n = 56)	13	3	4	2	0	1	2

Abbreviations: L = local; R = regional; DM = distant metastasis.

Data presented as number of patients.

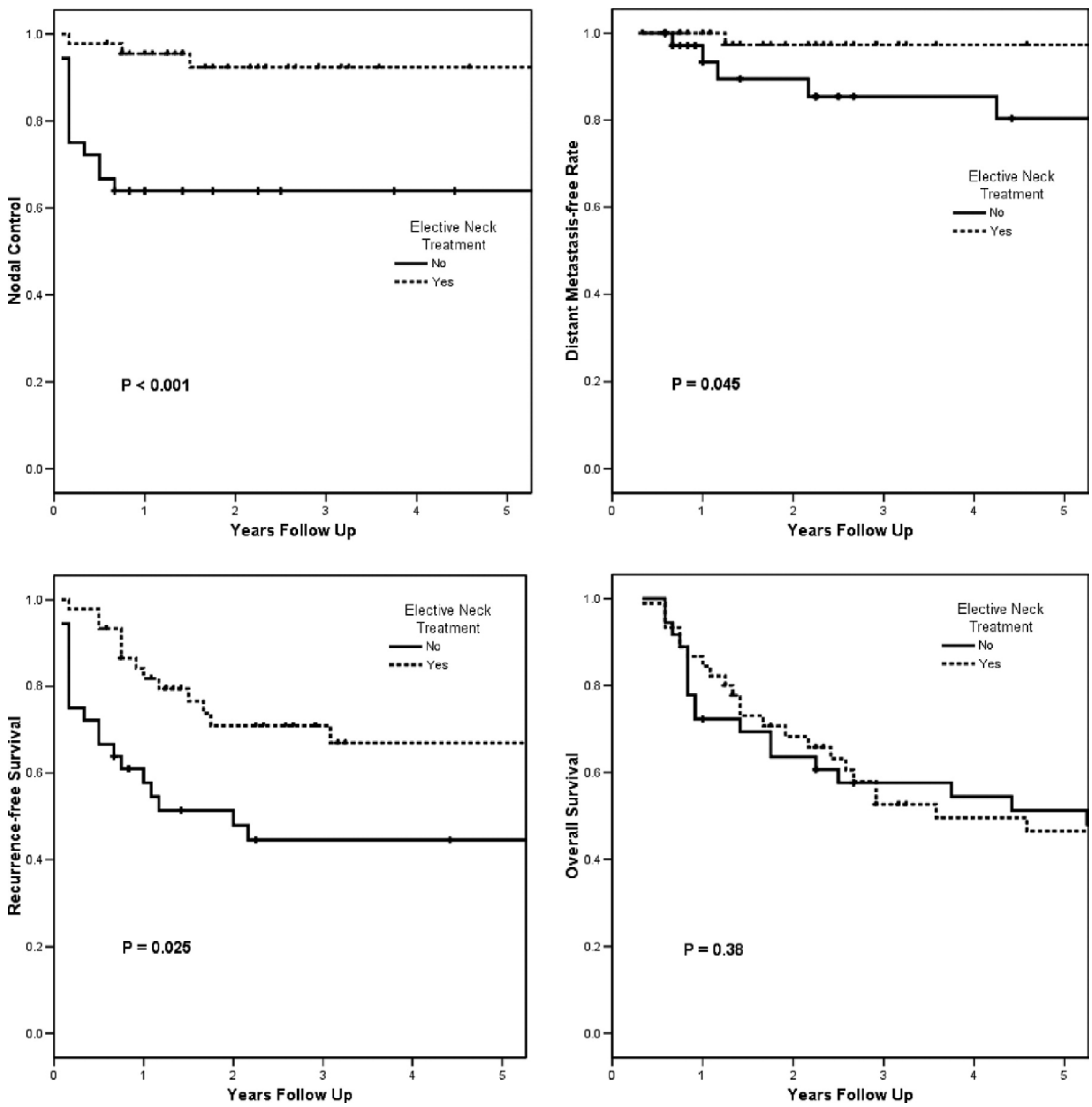


Fig. 3. Nodal control, distant metastasis-free survival, recurrence-free survival, and overall survival rates for patients with squamous cell or undifferentiated carcinoma treated with (n = 45) or without (n = 36) elective neck irradiation.

The presence of perineural invasion was associated with a greater 5-year distant metastasis rate on univariate analysis (38% vs. 16% without perineural invasion; $p = 0.05$), but this finding was not confirmed on multivariate analysis. The two significant predictors of distant metastasis on multivariate analysis were squamous cell histologic features (RR, 0.184; 95% CI, 0.070–0.484; $p = 0.001$) or presentation with nodal disease (RR, 4.293; 95% CI, 1.419–12.982; $p = 0.01$).

Complications

Table 5 lists the complications in Groups 1 and 2. At last follow-up, 17 Grade 3 and 36 Grade 4 complications had occurred in 34 patients in Group 1 vs. only 12 Grade 3 and no Grade 4 complications in 10 patients in Group 2. Of the 36 Grade 4 complications in Group 1, 22 were ocular and resulted in blindness. Figure 4 shows the actuarial Grade 3–4 late complication-free rates (>6 months after RT) for patients in Group 1 vs. Group 2. At 5 years, the patients in Group 1 had an estimated Grade 3–4 late complication-free rate of 66% vs. 92% for patients in Group 2 ($p = 0.01$). Multivariate analysis of the disease and treatment variables on the late Grade 3–4 complication rates confirmed the significance of treatment group and the radiation type administered. Patients who were treated primarily with ^{60}Co were at a much greater risk of developing late Grade 3–4 complications than were patients treated with ≥6-MV photons (RR, 2.755 for ^{60}Co; 95% CI, 1.046–7.261; $p = 0.04$).

The eye was left intact in 54 (60%) of the 90 patients in Group 1 and 38 (68%) of the 56 patients in Group 2 ($p = 0.30$). Of these 54 patients in Group 1 and 38 patients in Group 2, 3 had Grade 3 and 19 had Grade 4 ocular com-

Table 5. Complications observed for all patients

	Group 1 (n = 90)				Group 2 (n = 56)			
Complication	G1	G2	G3	G4	G1	G2	G3	G4
Ocular	1	3	3	22	1	6	7	0
Auditory	7	11	4	1	2	8	0	0
Bone	0	11	0	4	0	3	1	0
Brain	0	0	0	6	0	1	0	0
Subcutaneous tissue	2	5	6	2	0	3	4	0
Skin	1	3	0	1	0	0	0	0
Endocrine	0	1	4	0	0	2	0	0
Infection	2	0	0	0	5	0	0	0
Total	13	34	17	36	8	23	12	0

Data presented as number of patients with complication by grade.

plications and 7 had Grade 3 and none had Grade 4 ocular complications in Groups 1 and 2, respectively. The most common Grade 4 ocular complication was keratitis, which led to functional blindness (vision 20/200 or worse) in 10 patients. The other Grade 4 ocular complications included retinopathy (n = 4), optic atrophy (n = 1), optic chiasmatic injury (n = 1), scleral necrosis (n = 1), and other nonspecified causes (n = 2). Chiasmatic injury occurred in 1 patient and contralateral optic neuropathy in 2 patients who had undergone initial enucleation. All 3 of these patients were in Group 1, and all 3 developed complete blindness. The most common Grade 3 ocular toxicity was eyelid dysfunction, occurring in 8 patients. Another common complication experienced by patients in both groups was Grade 2 epiphora resulting from nasolacrimal duct stenosis that in most cases required intermittent dilation.

The potential predictors of late Grade 3–4 ocular complications in the patients whose ipsilateral eye was left intact were the radiation type administered, technique used, and the use of eye blocks where appropriate. Patients treated with ^{60}Co were at an increased risk of developing major ocular complications vs. patients treated with ≥6-MV photons (p = 0.041). Patients treated with a wedged-pair technique or modifications of the wedged pair were at a greater risk of developing major ocular complications than were patients treated with a three-field technique (p = 0.024). The use of eye blocks decreased the risk of Grade 3–4 late ocular complications (p < 0.001).

The radiation dose analyzed as a continuous variable did not have a statistically significant effect on the risk of developing a late complication.

DISCUSSION

This study compared two cohorts of patients with maxillary sinus cancer treated with surgery and RT to determine the impact of three changes in radiation technique on outcomes. First, more generous coverage of the base of skull in the presence of perineural invasion was associated with fewer recurrences at the base of skull. Treating the ipsilat-

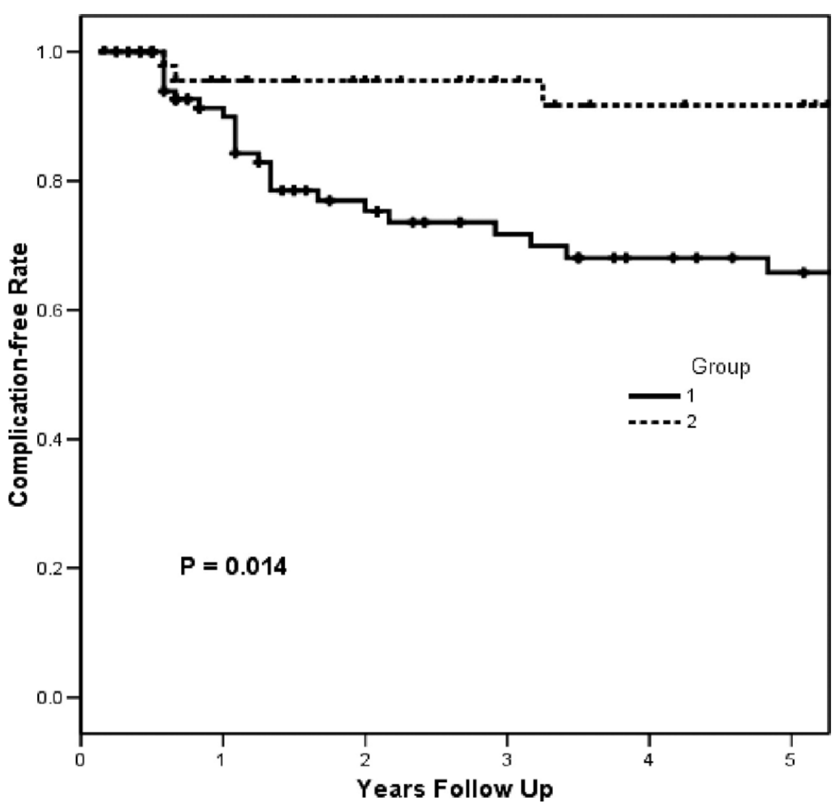


Fig. 4. Late Grade 3–4 toxicity rates for patients in Group 1 (n = 90) vs. Group 2 (n = 56).

eral upper neck in patients suspected of harboring microscopic nodal disease was associated with a significant reduction in regional recurrences, which may have translated into a reduction in distant recurrence, as well. Although the more modern cohort did not have a significant gain in survival, severe late toxicity was significantly less in this group, reflecting an improvement in the therapeutic window.

Regarding the changes that were implemented after our analysis in 1991 (21), although several other studies have also confirmed the negative impact of nerve invasion on local control and survival in patients with paranasal sinus malignancies (26–28), by increasing the portal size to cover the base of skull in patients with perineural invasion, the negative impact of nerve invasion on local control was effectively reduced. As such, we recommend coverage of the base of skull for patients with perineural invasion identified pathologically.

The use of elective neck RT in patients with squamous cell and undifferentiated histologic features was associated with a significant reduction in nodal recurrence rates. Several investigators have discussed the potential utility of adding elective neck treatment to patients with squamous cell carcinoma of the maxillary sinus (29–32). Cantu *et al.* (29) analyzed 153 patients with squamous cell cancer of the maxillary sinus and reported a nodal relapse rate of 17% for patients with Stage T2 disease, 9% with T3 disease, and 12% with Stage T4 disease. In 75% of the patients who experienced a nodal relapse, primary recurrence also occurred contemporaneously. They concluded that because nodal recurrence was rarely the cause of death, prophylactic lymph node excision in N0 patients was not indicated. Kondo *et al.* (31) also concluded that because cervical relapse frequently accompanied uncontrollable primary recurrence or distant spread, prophylactic RT to the neck should not be recommended. In contrast, a review by Jeremic *et al.* (32) concluded that elective nodal RT for locally advanced squamous cell carcinoma of the maxillary sinus was justified and that a dose of 50 Gy at 2-Gy fractions achieved nodal control in 95% of cases with little toxicity.

Our data support the latter conclusions. The addition of elective neck RT to patients with squamous cell and undifferentiated histologic features reduced the nodal recurrence rate from 36% to 7% at 5 years. Also, 46% of the nodal recurrences were isolated and only 38% were associated with simultaneous local recurrence. Moreover, the addition of elective neck RT was associated with a significant reduction in the rate of distant metastasis at 5 years (20% vs. 3%). We believe this justifies the use of elective neck RT in these patients and supports the notion that untreated microscopic disease in the neck increases the risk of subsequent distant failure. Nonetheless, although adding elective neck coverage in these patients was associated with decreases in nodal recurrence and distant metastasis rates and an improvement in RFS, no difference was found in OS. Why no difference in OS was observed remains unclear but could have been a consequence of other unknown prognostic factors differing between the two groups.

Regarding which elective nodal regions to cover, 85% of the recurrences observed in the patients who did not receive elective neck treatment occurred in the ipsilateral Level Ib and Level II neck. This justifies coverage of the ipsilateral upper neck alone.

This review also addressed the impact of RT technique on the complication rates. By using measures to improve target homogeneity and limit the dose to critical structures, patients treated after 1991 (Group 2) were less likely to develop major late complications. Multivariate analysis confirmed the importance of using $\geq$6-MV photons instead of ^{60}Co to reduce the complication rates without compromising disease control. Of the patients who did not undergo enucleation, the improved RT technique significantly reduced complications without compromising control. The use of high-energy photons, a three-field vs. a wedged-pair technique, and the use of eye shielding, when possible, all independently improved the complication rates.

Although the numbers of patients treated with IMRT in this series was small, we have now adopted the use of IMRT for all patients presenting with this disease. With IMRT, we are able to improve target coverage and decrease the dose to normal neighboring structures. Several studies have confirmed the theoretical advantage of using three-dimensional conformal planning techniques compared with conventional two-dimensional planning or using IMRT compared with three-dimensional conformal techniques to improve target coverage with better normal tissue sparing (33–36). It will be interesting to see whether this theoretical advantage translates into real clinical outcomes as our data for patients treated with IMRT matures.

Additionally, the increased cohort size and longer follow-up provided additional insight into the prognostic factors influencing the outcomes of patients with maxillary sinus cancer treated with surgery and PORT. The 5-year OS estimate for patients treated before 1990 (Group 1) and after 1990 (Group 2) was 51% and 63%, respectively, in accordance with other series incorporating a combination of surgery and RT that showed 5-year survival rates of 34–63% (5, 7, 9, 10, 13, 16, 37–40). The strongest predictors of OS in this series were age, followed by enucleation status. Other studies have also found orbital invasion to be a negative predictor of survival (6, 41). Patients who underwent enucleation in this series were also at the greatest risk of local recurrence. These findings imply a locally aggressive phenotype for disease that extends to involve the orbit. Despite enucleation and a median PORT dose of 60 Gy, these patients still had high local recurrence rates and poor survival. Given that 67% of local failures occurred within the radiation field, a greater dose could be considered to help improve the local control rates and, possibly, survival rates for these patients.

Finally, more patients in Group 2 received induction chemotherapy than did patients in Group 1. In theory, this could confound the patterns of failure between the two groups, although the number of patients receiving this treatment was small, and we found no significant association between induction chemotherapy and any of the outcome parameters.

CONCLUSION

Surgery and PORT provided primary disease control in 70–76% of patients with maxillary sinus cancer. Disease that extends to involve the orbit is associated with high local recurrence rates and poor survival. Extending the radiation volume to include the base of skull in patients with perineural invasion reduced the negative impact of this disease variable on local control. Adding elective neck RT to the treatment of patients with squamous cell or undifferentiated histologic features decreased the nodal recurrence rates and might decrease distant failure. Modern RT technique improved toxicity without compromising local control.

Despite the many technical improvements within the past 35 years, the local control and survival rates for this disease remain almost unchanged. Newer strategies must be tested, including dose escalation using more conformal techniques such as IMRT and protons, and systemic therapies must be integrated, particularly chemoradiotherapy (42), to improve the outcomes of patients with this disease.

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