CARCINOMAS OF THE PARANASAL SINUSES AND NASAL CAVITY TREATED WITH RADIOThERAPY AT A SINGLE INSTITUTION OVER FIVE DECADES: ARE WE MAKING IMPROVEMENT?

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Purpose: To compare clinical outcomes of patients with carcinomas of the paranasal sinuses and nasal cavity according to decade of radiation treatment.

Methods and Materials: Between 1960 and 2005, 127 patients with sinonasal carcinoma underwent radiotherapy with planning and delivery techniques available at the time of treatment. Fifty-nine patients were treated by conventional radiotherapy; 45 patients by three-dimensional conformal radiotherapy; and 23 patients by intensity-modulated radiotherapy. Eighty-two patients (65%) were treated with radiotherapy after gross total tumor resection. Nineteen patients (15%) received chemotherapy. The most common histology was squamous cell carcinoma (83 patients).

Results: The 5-year estimates of overall survival, local control, and disease-free survival for the entire patient population were 52%, 62%, and 54%, respectively. There were no significant differences in any of these endpoints with respect to decade of treatment or radiotherapy technique (p > 0.05, for all). The 5-year overall survival rate for patients treated in the 1960s, 1970s, 1980s, 1990s, and 2000s was 46%, 56%, 51%, 53%, and 49%, respectively (p = 0.23). The observed incidence of severe (Grade 3 or 4) late toxicity was 53%, 45%, 39%, 28%, and 16% among patients treated in the 1960s, 1970s, 1980s, 1990s, and 2000s, respectively (p = 0.01).

Conclusion: Although we did not detect improvements in disease control or overall survival for patients treated over time, the incidence of complications has significantly declined, thereby resulting in an improved therapeutic ratio for patients with carcinomas of the paranasal sinuses and nasal cavity. © 2007 Elsevier Inc.

INTRODUCTION

Carcinomas of the paranasal sinuses and nasal cavity are uncommon, representing approximately 5% of all head and neck cancers and less than 1% of all malignancies (1–3). Because of the locally advanced natures of their presentations and the proximity of these tumors to the critical normal tissues of the anterior skull base, including the brain and optic pathways, the management of these malignancies has and continues to represent a therapeutic dilemma. Although surgery forms the mainstay of initial treatment, a combined-modality approach incorporating radiotherapy (RT), typically in the postoperative setting, has been utilized at the University of California, San Francisco (UCSF) since the early 1960s. Although clinical outcomes for patients treated for carcinomas of the paranasal sinuses and nasal cavity have historically been poor, with long-term series reporting 5-year overall survival rates in the range of 27–54%, we propose that advances in surgical techniques combined with progress in radiation planning and delivery methods have contributed to improvements with respect to both disease control and survival over time (4–6). This hypothesis is supported by a recent meta-analysis of 154 publications demonstrating survival rates of 28%, 36%, 43%, and 51% among patients treated in the 1960s, 1970s, 1980s, and 1990s, respectively (7). The present study was thus undertaken to review a long-term, single-institution
experience with the management of carcinomas of the para-
nasal sinuses and nasal cavity over the course of the last 5
decades.

METHODS AND MATERIALS

Patients
Between April 1960 and December 2005, 127 previously un-
treated, nonmetastatic patients with malignancies of the paranasal
sinuses and nasal cavity underwent RT in the Department of
Radiation Oncology at UCSF. The following patients were ex-
cluded from this analysis: 36 patients with neuroendocrine tumors;
3 patients with lymphoma; 2 patients with melanoma; and 2
patients with sarcoma. An additional 18 patients who underwent
orbital exenteration and 9 patients treated with palliative intent
were also excluded. Table 1 outlines the clinical and disease
characteristics of the remaining 127 patients with histologically
proven carcinoma of the paranasal sinuses and nasal cavity treated
by RT with curative intent according to the decade of diagnosis.
The median age was 61 years (range, 27–92 years). Seventy-six
men (60%) and 51 women (40%) were included.

The primary involved sites were 54 maxillary sinus, 35 nasal
cavity, 26 ethmoid sinus, 8 sphenoid sinus, and 4 frontal sinus.
Histology was squamous cell carcinoma (83 patients), adenoid
cystic carcinoma (28 patients), and adenocarcinoma (16 patients).
Thirty-one patients (24%) underwent magnetic resonance imaging
(MRI) of the head and neck as a component of the initial workup.
Axial imaging with computed tomography (CT) has been a routine
part of patient evaluation since it became available at UCSF in
1974. Metastatic workup was performed at the discretion of the
treating physicians. All patients were retrospectively staged in
accordance with the 2002 American Joint Committee on Cancer
(AJCC) staging classification. Distribution of pathologic T stage
was 4% T1, 9% T2, 25% T3, and 62% T4. The median pathologic
tumor size was 6.0 cm (range, 1.4 –12.1 cm) among the 85 patients
in which this information was available.

Treatment
Eighty-two patients (65%) were treated with RT after gross total
tumor resection. The remaining 44 patients were either treated with
RT alone (20 patients), with radiation postoperatively for macro-
scopic residual disease (16 patients), or with radiation preopera-
tively before definitive surgery (9 patients). The type of surgery
depended on the primary site, extent of disease, cosmetic consid-
erations, and the discretion of the surgeon. Surgical approach
included transfacial resection in 33 patients, transcranial resection
in 19 patients, combined transfacial and transcranial resection in
34 patients, and was unknown in 21 patients. Nineteen patients
(15%) received chemotherapy, 14 concurrently with radiation and
5 subsequent to RT. The most common chemotherapy regimen
used was cisplatin and 5-fluorouracil (11 patients).

<table>
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<tr>
<th>Characteristic</th>
<th>1960s</th>
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<td>2 (11)</td>
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</table>

Abbreviations: RT = radiotherapy; 3D-CRT = three-dimensional conformal radiotherapy; IMRT
= intensity-modulated radiotherapy; ACC = adenoid cystic carcinoma.

Values are number (percentage). N = 127.
Radiation Technique

All patients were treated with external-beam RT using linear accelerators incorporating techniques available at the time of treatment. Fifty-nine patients were treated with conventional RT; 45 patients by three-dimensional conformal RT (3D-CRT); and 23 patients by intensity-modulated RT (IMRT). Radiation was delivered using conventional fractionation with a continuous course of once-daily, 5-days-per-week treatment for all patients. The initial treatment volume was designed to encompass the primary tumor site with 2–3-cm margins, depending on the pathologic findings and the proximity of critical structures. In general, care was taken to delineate the location of the optic apparatus and spinal cord with respect to the primary tumor site for planning purposes. The base of skull was routinely covered for all tumors with perineural invasion or adenoid cystic histology. The median dose to the primary tumor for the entire patient population was 64 Gy (range, 50–74 Gy) and was 63 Gy, 60 Gy, and 66 Gy for patients undergoing postoperative, preoperative, and definitive RT, respectively. Wedges or tissue compensators were used, as appropriate, to maintain dose homogeneity within 10% of the prescribed dose. None of the patients received interstitial RT.

Treatment portals were designed at the discretion of the treating physicians. Conventional radiation techniques were based on plain X-ray films taken at the time of fluoroscopic simulation and included three-field isocentric treatments (34 patients), wedged-pair fields (14 patients), and parallel-opposed lateral fields prescribed to midplane (11 patients). The median tumor dose for patients treated by conventional RT was 63 Gy (range, 50–74 Gy). Three-dimensional CRT based on CT was instituted at UCSF in 1989. Serial CT scan slices, 3-mm thick, from the head down through the clavicles, were obtained for delineation of tumor volumes in these cases. The median dose for patients treated by 3D-CRT was 66 Gy (range, 50–73 Gy). Intensity-modulated RT was instituted at UCSF in 1995, and 23 patients were treated with this technique to a median tumor dose of 70 Gy (range, 66–72 Gy). Our experience with IMRT for head-and-neck cancers has previously been detailed (8, 9).

Eleven patients (9%) presented with palpable neck disease (upper jugular) before surgery and underwent ipsilateral neck dissection followed by postoperative radiation. Elective neck dissection was generally not performed for the clinically negative neck. Forty-five patients (35%) received elective neck irradiation to a median dose of 50 Gy (range, 45–66 Gy) to the clinically N0 neck.

Statistical Analysis

For the purpose of this analysis, patients were grouped into their respective decade of treatment according to the date of surgery or the first day of RT for those treated with preoperative or definitive RT. The endpoints analyzed were overall survival, local control, and disease-free survival. Local control was judged to have been attained if there was no evidence of tumor growth at the primary site on the basis of clinical and radiographic findings at follow-up. Regional failure was recorded separately if there was evidence of an enlarging cervical or supraclavicular mass distinct from the primary site. Acute and late normal tissue effects were graded according to the Radiotherapy Oncology Group/European Organization for the Treatment of Cancer radiation toxicity criteria (10). Patient follow-up was reported to the date last seen in clinic or to the date of expiration. Median follow-up was 49 months (range, 3–151 months) for the entire patient population and 71 months among surviving patients (range, 3–151 months). The median follow-up duration among patients treated with conventional RT, 3D-CRT, and IMRT was 52 months, 59 months, and 44 months, respectively. All events were measured from the date of surgery or the first day of radiation for those treated with preoperative or definitive RT. Actuarial estimates of local control, disease-free survival, and overall survival were calculated using the Kaplan-Meier method, with comparisons among groups performed with two-sided log–rank tests (11). Toxicity was reported as proportional rates rather than actuarial figures because owing to the retrospective nature of this analysis it was difficult to determine the exact onset of complications in most cases. Tests analyzing the difference between the proportions of complications in each treatment group were performed with a chi-square statistic. All tests were two-tailed, with a probability value of <0.05 considered statistically significant.

RESULTS

Overall Survival

Fifty-one patients were alive at the time of this analysis. As illustrated in Fig. 1, the 5-year estimate of overall survival for the entire patient population was 52%. There was no difference in overall survival according to the decade of treatment. The 5-year overall survival rate for patients treated in the 1960s, 1970s, 1980s, 1990s, and 2000s was 46%, 56%, 51%, 53%, and 49%, respectively ($p = 0.23$). None of the other clinical or disease characteristics analyzed, including initial treatment type (surgery vs. radiation), radiation dose, tumor extent at the time of RT (gross vs. presumed microscopic), RT technique, primary disease site, T stage, N stage, tumor size, histology, age at diagnosis, gender, or use of chemotherapy, predicted for overall survival ($p > 0.05$ for all). The 5-year overall survival rate for patients treated by conventional RT, 3D-CRT, and IMRT was 51%, 57%, and 47%, respectively ($p = 0.60$).

Local Control

Forty-eight patients experienced a local recurrence. The median time to local recurrence was 1.2 years (range, 0–6.1
years) with 81% (39 of 48) occurring within 2 years from the date of initial treatment and 94% (45 of 48) recurring within 5 years from date of initial treatment. For the entire patient population, the 5-year estimate of local control was 62%. The only parameter that was identified to be predictive of local control was disease extent at the time of RT. Patients with gross total tumor resection had improved local control compared with those treated with RT for macroscopic disease. The 5-year estimate of local control among the 82 patients treated postoperatively after gross total resection was 65%, compared with 44% for the remaining 45 patients who underwent RT in the presence of macroscopic disease ($p = 0.02$). There was no difference in local control according to the decade of treatment. The 5-year estimate of local control for patients treated in the 1960s, 1970s, 1980s, 1990s, and 2000s was 55%, 62%, 61%, 57%, and 59%, respectively ($p = 0.31$). None of the other clinical or disease characteristics analyzed, including initial treatment type (surgery vs. radiation), radiation dose, RT technique, primary disease site, T stage, N stage, tumor size, histology, age at diagnosis, gender, or use of chemotherapy predicted for local control ($p > 0.05$, for all). With respect to RT technique, 26 of 59 patients treated by conventional RT developed local recurrences, yielding a 5-year local control rate of 59%. In comparison, 15 of 45 patients treated by 3D-CRT developed local recurrences, resulting in a 5-year local control rate of 62%. Among the 23 patients treated by IMRT, 7 experienced local recurrences, leading to a 5-year local control rate of 65%. Figure 2 illustrates local control according to radiation treatment technique.

**Disease-Free Survival**

Sixty patients experienced disease recurrence. The median time to disease recurrence was 1.2 years (range, 0–6.1 years) with 77% (46 of 60) recurring within 2 years from initial treatment and 97% (58 of 60) recurring within 5 years of initial treatment. The initial site of failure was local in 39 patients, distant in 14 patients, and regional in 7 patients. Sites of initial distant metastasis included the lungs (11 patients), bone (2 patients), and liver (1 patient). Among the 51 surviving patients, 46 were disease free at the time of last follow-up. As depicted in Fig. 3, the 5-year estimate of disease-free survival for the entire patient population was 54%. There were no differences in disease-free survival with respect to decade of treatment ($p = 0.65$) or whether patients were treated by conventional RT, 3D-CRT, or IMRT ($p = 0.89$). None of the other clinical or disease variables analyzed predicted for disease-free survival ($p > 0.05$ for all).

**Complications**

Table 2 outlines the rates of severe (Grade 3 or higher) treatment-related late complications according to decade of

<table>
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<tr>
<th>Complication</th>
<th>1960s (n=15)</th>
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<th>1980s (n=33)</th>
<th>1990s (n=40)</th>
<th>2000s (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic–visual</td>
<td>5/15 (33%)</td>
<td>5/20 (25%)</td>
<td>6/33 (18%)</td>
<td>4/40 (10%)</td>
<td>1/19 (5%)</td>
</tr>
<tr>
<td>Neurologic–auditory</td>
<td>3/15 (20%)</td>
<td>3/20 (15%)</td>
<td>5/33 (15%)</td>
<td>3/40 (8%)</td>
<td>1/19 (5%)</td>
</tr>
<tr>
<td>Skin</td>
<td>5/15 (33%)</td>
<td>5/20 (25%)</td>
<td>9/33 (27%)</td>
<td>9/40 (23%)</td>
<td>3/19 (16%)</td>
</tr>
<tr>
<td>Mucous membrane</td>
<td>3/15 (20%)</td>
<td>5/20 (25%)</td>
<td>5/33 (15%)</td>
<td>4/40 (10%)</td>
<td>1/19 (5%)</td>
</tr>
<tr>
<td>Bone</td>
<td>3/15 (20%)</td>
<td>4/20 (20%)</td>
<td>6/33 (18%)</td>
<td>6/40 (15%)</td>
<td>2/19 (11%)</td>
</tr>
<tr>
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<td>8/15 (53%)</td>
<td>9/20 (45%)</td>
<td>13/33 (39%)</td>
<td>11/40 (28%)</td>
<td>3/19 (16%)</td>
</tr>
</tbody>
</table>

Values are number (percentage).
treatment. There were no deaths related to radiation late effects (Grade 5). A significant difference was detected in the incidence of all Grade 3 or 4 toxicity among patients treated in the 1960s, 1970s, 1980s, 1990s, and 2000s. The incidence of any Grade 3 or 4 complication developing was 53%, 45%, 39%, 28%, and 16%, respectively (p = 0.01). Three patients experienced a complete loss of monocular vision as a result of treatment, all of whom were treated in the 1960s or 1970s with conventional RT. Two patients were treated to a dose of 66 Gy for squamous cell carcinoma of the maxillary sinus after gross total resection. The second patient received a dose of 65 Gy for squamous cell carcinoma of the ethmoid sinus after subtotal resection. Table 3 illustrates the rates of toxicity according to RT technique. The incidence of any Grade 3 or 4 complications was 54%, 22%, and 13%, respectively, among those treated with conventional RT, 3D-CRT, and IMRT. The incidence of Grade 3 and 4 late ocular toxicity among patients treated with conventional RT, 3D-CRT, and IMRT was 20%, 9%, and 0, respectively (p = 0.01). With respect to auditory function, the incidence of Grade 3 or greater (clinically significant) radiation-induced complications was 15%, 9%, and 4%, respectively (p = 0.01). Osteoradionecrosis occurred in 12 patients: 7 were treated with conventional RT, and 5 were treated with 3D-CRT. There was no documented case of brain necrosis.

### DISCUSSION

An unexpected observation of this long-term review was that cure rates for carcinomas of the paranasal sinuses and nasal cavity have not appreciably improved among patients treated at our institution since the 1960s. Although on the surface this seems to be a sobering statistic, we contend that this finding is largely due to underlying selection bias related to operative criteria because cases that are referred for definitive treatment have largely become more complex with time, paralleling improvements in surgical and reconstructive techniques. For instance, patients with intracranial involvement who were considered incurable (and unresectable) in the 1960s and 1970s are now operated on routinely, depending on the extent of tumor invasion. Furthermore, indications for orbital exenteration have decreased over time, resulting in the inclusion of many high-risk, locally advanced cases in the latter decades of this series. Thus it is possible that imbalances in potentially important prognostic variables related to tumor extent and disease burden could have obscured any potential improvement in patient outcome over the time span of the present study. The fact that the primary tumor size of those patients included in this series has apparently increased from the 1960s to the present decade, as illustrated in Table 1, strongly supports the notion that cases have become more complex with time. Although general agreement exists that innovations in both operative approaches and reconstruction of surgical defects have revolutionized skull base surgery and have led to the successful resection of tumors of the sinonasal region that were previously considered technically inoperable, these same advances have almost certainly resulted in an increase in the proportion of patients whose disease characteristics place them at an inherently higher risk for disease failure (12–14).

In this respect, one limitation of the present review was that we were unable to determine whether the percentage of patients with features such as intracranial invasion, cranial nerve involvement, dural attachment, positive margins, and orbital infiltration—each of which has been demonstrated by others to be predictive of adverse outcome with respect to both local control and overall survival for those with carcinomas of the paranasal sinuses and nasal cavity—have indeed increased over the time period of this study (15–17). It is of additional interest that the presence of any of the above factors would categorize a tumor as T4 in the current AJCC staging system. Although the overwhelming majority of patients in the present series presented with locally advanced tumors, including 62% with T4 cancers, it should be emphasized that this population represents a heterogeneous group, not only with respect to disease characteristics but also with respect to clinical prognosis. Although the most recent version of the AJCC staging system published in 2002 attempted to address this by dividing cases into T4a (resectable) and T4b (unresectable), it must be recognized that criteria for operability continue to evolve and that a patient considered operable by one surgeon may not be operable by another.

Our finding that patients with gross total tumor resection before RT have more favorable outcomes than those treated for gross tumor is consistent with previous reports (18–20). Despite the obvious selection bias favoring those with complete tumor resections, we nonetheless contend that surgical resection with en bloc removal of all gross tumor should be the goal of treatment for all patients with carcinomas of the paranasal sinuses and nasal cavity who do not have evidence of metastatic disease. In view of advances in perioperative care and emerging data demonstrating acceptably low rates of mortality and morbidity with this aggressive approach, it is likely that significantly more patients with comorbid medical conditions who were previously consid-

<table>
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<th>IMRT</th>
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**Abbreviations:** RT = radiotherapy; 3D-CRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy.

Values are number (percentage).
tered inoperable are now being offered definitive treatment as well (21–23).

As with any retrospective review, several important biases must be considered in the interpretation of these data. Because most cancers from the 1960s and 1970s were clinically staged using radiographic techniques that are no longer used, such as plain films and tomograms, the accuracy of the diagnosis with respect to primary disease site could not be confirmed nor verified. Notably, one concern is that many of the earlier cases treated at our institution could have represented primary tumors arising from the nasopharynx, a disease that is far more commonly seen in our population base and is also considered more radiosensitive. The widespread use of diagnostic CT and MRI for the purposes of both tumor visualization and target delineation in more recent decades also may have influenced outcomes. Similarly, posttreatment surveillance incorporating serial imaging, particularly with MRI, has only been used in the last 2 decades at our institution. It must be recognized that many of the recurrences that were detected among patients more recently treated may not have been discovered had these patients been treated before the implementation of vigorous follow-up regimens. Furthermore, this longitudinal analysis is complicated by potential inconsistencies related to pathologic classification. Because many of the neuroendocrine tumors of the sinonasal region were not recognized until relatively recently, the inadvertent inclusion of these histologic subtypes, particularly esthesioneuroblastoma, which is believed to have a better prognosis than other cancers arising from this site, in the earlier years, may have possibly confounded results (24–26). This is especially relevant given that immunohistochemical staining was not routinely performed at our institution until the latter decades of this study.

Previous studies analyzing temporal trends with respect to clinical outcome have yielded conflicting results. Similar to the findings of the current study, Blanco et al. (4) showed no difference in overall survival among 106 patients treated from 1960 to 1998 at Washington University according to treatment decade. Conversely, a recent meta-analysis published by Dulguerov et al. (7) demonstrated dramatically improved rates of survival with each successive decade among patients treated during this same time span. Despite the investigators’ conclusion that progress has indeed been made over time, these results must be interpreted cautiously, particularly in light of the infrequency of these tumors and their heterogeneity with respect to prognostic factors and pathologic subtypes. Notably, when the results of this meta-analysis were stratified according to T stage, the progressive improvement over time was no longer statistically significant. Last, it is largely unknown how variability in therapeutic techniques may have affected results. For instance, many of the earlier studies used in this meta-analysis included patients treated with radiation delivery methods that are widely considered outdated—by Van der Graaf generators, orthovoltage machines, cobalt units, and using single anterior portal or en face radiation fields—whereas all patients in the present series were treated using modern linear accelerators with more contemporary field designs. In addition, many of the older studies used radiation doses that may have been suboptimal (as low as 40 Gy) and/or included patients treated with palliative intent.

Despite the widespread heralding of the dramatic ability to improve precision and accuracy with 3D-CRT and IMRT for the treatment of cancers of the head and neck, we were unable to discern any difference with respect to disease control or survival among patients treated for carcinomas of the paranasal sinuses and nasal cavity according to radiation technique. This is likely owing to potential imbalances in prognostic variables as discussed previously, because the vast majority of patients treated with 3D-CRT and IMRT were from the 1980s onward. However, the decreased incidence of radiation-induced complications with time is particularly encouraging and can be attributed to advances in technology as well as to improved recognition of the dose limitations and tolerance levels of the surrounding critical structures (27–30). Our findings thus provide important clinical data validating the results of previously published dosimetric exercises demonstrating that sophisticated radiation techniques, such as 3D-CRT and IMRT, can improve tumor dose homogeneity while reducing radiation dose to the brain and optic apparatus for cancers of the head and neck, including those of the paranasal sinuses and nasal cavity (30–33).

Although the results of the present study demonstrate that advances in surgical and radiation technique have apparently increased the number of patients who can be safely treated for carcinomas for the paranasal sinuses and nasal cavity, clinical outcomes with respect to disease control and survival remain disappointing. On the basis of the results of studies suggesting that doses in excess of 65 Gy are required to achieve local tumor control and the ability of conformal techniques to deliver high doses to a precise volume, we currently recommend a dose of 70 Gy for the treatment of carcinomas of the paranasal sinuses and nasal cavity (34, 35). In particular, the pronounced ability of IMRT to achieve a sharp dose fall-off gradient between the target and surrounding normal tissues through optimized nonuniform beam intensities and inverse planning apparently make it the preferred technique for radiation treatment of these tumors. Further improvements in the therapeutic ratio will likely depend on continued advancements in treatment technique along with ongoing developments in chemical and/or biologic modifiers. Sustained investment in these areas should be a priority for future research.
REFERENCES


