Intra-arterial Cisplatin and Concomitant Radiation Therapy Followed by Surgery for Advanced Paranasal Sinus Cancer

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Objective: To report the long-term efficacy of a combined regimen of intra-arterial high-dose cisplatin chemotherapy and concomitant radiation therapy followed by organ-sparing surgery when possible in the treatment of advanced paranasal sinus cancer.

Design: Review of prospectively collected data.

Setting: Academic referral center.

Patients: Nineteen patients with advanced paranasal sinus malignancies with a minimum follow-up of 2 years. Malignancies included 14 squamous cell carcinomas (74%), 2 adenocarcinomas (10%), 2 adenoid cystic carcinomas (10%), and 1 undifferentiated carcinoma (5%). Sixteen patients (84%) had T4 disease.

Intervention: Treatment consisted of preoperative radiation therapy (2.0 Gy/fraction per day; total dose, 50 Gy in 5 weeks) given concomitantly with 3 to 4 weekly infusions of intra-arterial cisplatin (150 mg/m² per week) and systemic sodium thiosulfate neutralization. The regimen included planned surgery performed approximately 8 weeks after completion of radiation therapy. Ten patients underwent a transcranial anterior craniofacial resection; 1, a medial maxillectomy; and 1, an endoscopic restaging only.

Results: After a median follow-up of 53 months, actual overall survival at 2 and 5 years was 68% and 53%, respectively. One patient died of myocardial infarction during treatment. No other treatment-limiting toxic effect was noted. Although 3 patients had persistence of disease, delayed local failure occurred only in 2 and distant metastasis in 3. Except for cataract in 2 patients, no visual loss developed.

Conclusion: Despite the advanced stage and unfavorable nature of cancer in this cohort, our results indicate that this regimen holds promise and merits further study.

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A variety of cancers arise in the nasal cavity and paranasal sinuses. Squamous cell carcinoma forms the majority (approximately 60%), followed by undifferentiated carcinoma, adenocarcinoma, and salivary neoplasms such as adenoid cystic and mucoepidermoid carcinoma. Esthesioneuroblastoma, neuroendocrine carcinoma, mucosal melanoma, lymphoma, and various sarcomas are a few of the other malignancies that are encountered in this region. Inclusion of multiple histological types in most reports on paranasal sinus tumors poses a considerable challenge for comparison of treatment results.

For most epithelial malignancies, a combination of radical surgery and preoperative or postoperative radiation therapy constitutes standard treatment. Total maxillectomy, with or without orbital exenteration, is the most commonly performed surgical operation for maxillary sinus cancers, whereas transfacial medial maxillectomy or craniofacial resection is used when disease involves the ethmoid sinuses. Despite such aggressive therapy, the outcome is poor, with fewer than half of the patients surviving at 5 years. For advanced disease (T3 or T4), survival is further reduced (6.7%-29% for T4 cancers).

Treatment failure at the primary site is the greatest stumbling block in successful management of these cancers, ranging from 33% to 57% in various series. In addition, distant metastasis remains the second most common reason for failure of treatment, occurring in 15% to 34% of the patients.

At the University of Tennessee Health Science Center, Memphis, patients with advanced paranasal sinus cancer have been treated since 1994 with a combination of preoperative radiation therapy and con-
comitant intra-arterial cisplatin chemotherapy, followed by conservative skull base resection aimed at preserving midface structures such as the eye and the palate to the extent possible. In this report, we present the results of this approach in the first 19 patients treated in this manner after a median follow-up of 53 months.

**METHODS**

Only patients with a minimum follow-up of 2 years, who had been treated between July 1, 1995, and July 31, 2000, were included for this analysis. There were 19 such patients, with a minimum follow-up of 24 months and a median follow-up of 33 months.

All patients underwent detailed assessment of tumor extent with computed tomography and/or magnetic resonance imaging. Tumor staging was performed using the 1997 edition of the American Joint Committee on Cancer classification\(^1\); patients treated earlier underwent retrospective restaging for this report. Staging was based on clinical and radiologic findings.

Chemotherapy was administered intra-arterially. The patients received up to 4 weekly infusions of cisplatin (150 mg/m\(^2\)) via selective transmural catheterization of the internal maxillary artery. On occasion, part of the dose was delivered through other branches of the external carotid artery, such as the ascending pharyngeal artery in case of nasopharyngeal involvement and the middle meningeal artery in case of parasellar invasion. A significantly higher dose of cisplatin could be delivered into the tumor owing to the simultaneous intravenous administration of sodium thiosulfate, a neutralizing agent that covalently binds to cisplatin as it reaches the systemic circulation; in this regard, our protocol differs from all previous attempts at intra-arterial chemotherapy.

Simultaneously with intra-arterial cisplatin, the patients received external beam radiation therapy in standard fashion (2 Gy/fraction) delivered through an anterior and 1 or 2 wedged lateral fields, to a total dose of 50 Gy only. The reason for abbreviating the course of radiation was to minimize ophthalmic complications.

The treatment also incorporated a planned surgical resection performed 6 to 8 weeks after the completion of chemoradiation therapy.

The surgical approach to these tumors at our center consisted of a conservative, sometimes piecemeal, resection of the affected sinuses while avoiding removal of uninvolved bone or soft tissues. Craniofacial resection was performed via a transcranial approach (through a frontal craniotomy), and the contents of the frontal, ethmoid, sphenoid, and maxillary sinuses; the nasal cavity; and the nasopharynx were cleared in a piecemeal fashion with microscopic dissection in a single operation. The medial wall of the orbit was examined for involvement of the lamina papyracea or the orbital periosteum by tumor. All of the lamina and considerable portions of the periosteum could be removed and reconstructed, if necessary, with a pericranial patch. The floor of the anterior cranial fossa was reconstructed with a pericranial flap, taking meticulous care to avoid any cerebrospinal fluid or air leakage. Most patients were able to go home in about 1 week. A sublabial approach to the maxillary sinus was required only in cases with extensive involvement through the anterior, lateral, or inferior walls of this sinus. Here, too, a sublabial-only or a degloving approach was usually sufficient for complete surgical resection of disease; facial incisions were seldom necessary.

For this report, we retrospectively reviewed information on clinical findings, radiologic investigations, toxic effects of treatment, operative findings, and histopathologic features, which were collected on a prospective basis. Survival was calculated by the Kaplan-Meier method using date of diagnosis as the starting point.

**RESULTS**

Malignancies included 14 squamous cell carcinomas (74%), 2 adenocarcinomas (10%), 2 adenoid cystic carcinomas (10%), and 1 undifferentiated carcinoma (5%) (Table). Sixteen patients (84%) had T4 disease, whereas 3 (16%) had T3 tumors. The primary tumor involved maxillary and ethmoid sinuses in 10 patients; in 5 other patients, tumor location was mainly superior—in the ethmoid sinuses—without any maxillary sinus involvement, whereas in 4 the tumor was primarily inferior, in the maxillary sinus, with no extension into the ethmoids. In addition, there was extension of cancer into the orbit in 4 patients, into the middle cranial fossa and the infratemporal fossa in 6 patients each, and into the anterior cranial fossa in 4 patients (Figures 1, 2, and 3).

Fifteen patients received a radiation dose near 50 Gy. The patient who died of a myocardial infarction midway through treatment had received only 30 Gy. Three patients, treated earlier in the course of the study period, received close to 70 Gy.

Twelve of the 19 patients underwent surgery, including a craniofacial resection in 10, lateral rhinotomy in 1 (this was earlier in the study period), and endoscopic biopsy of the maxillary sinus for restaging in 1. Among the 7 patients who had no surgery, distant metastasis was detected in 2 before the time of restaging, 2 refused surgery, 1 died of myocardial infarction, 1 had inoperable persistent disease, and 1 had only a computed tomography-guided biopsy of a questionable radiologic abnormality remaining after chemoradiation therapy.

Of the 10 patients undergoing craniofacial resection, none required a total maxillectomy and no facial

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**TABLE**

Patient and Treatment Characteristics and Survival*

<table>
<thead>
<tr>
<th>No. of patients</th>
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<td>Minimum</td>
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<td>Histology</td>
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<td>Overall at 5 y</td>
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<tr>
<td>Disease free at 5 y</td>
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*Unless otherwise indicated, data are expressed as number of patients.
incisions were necessary. Only 1 patient underwent an orbital exenteration, although 4 had radiologic evidence of orbital invasion at presentation.

**COMPLICATIONS**

Grade 3 mucosal toxic effects developed in 10 patients, whereas 3 patients experienced grade 3 hematologic toxic effects. Confusion developed in 1 patient, which lasted 2 weeks, without sustained neurologic sequelae. None of these toxic effects were treatment limiting. One patient died of a myocardial infarction during therapy.

Of the 10 patients undergoing craniofacial resection, only 1 (10%) had a complication. A brain abscess developed in the postoperative period and required reexploration. The patient recovered well subsequently without any sequelae.

A delayed complication in the form of necrosis of a portion of the frontal lobe secondary to radiation developed in 1 patient and was detected in the third year of follow-up. This patient had extensive invasion of squamous cell carcinoma (5 × 5 × 4 cm) into the anterior cranial fossa with edema of the neighboring frontal lobe (Figure 3A-C) and had received radiation treatment to this area. The necrotic area required excision via an anterior craniotomy. The patient recovered well from the procedure and remains well without any clinically noticeable neurologic impairment to this day. No patient developed any visual loss from retinal, optic nerve, or chiasm injury, except for 1 patient who underwent an orbital exenteration as part of his craniofacial resection. A cataract developed in the ipsilateral eye in 2 patients.

Most patients undergoing craniofacial resection had a common nasal-paranasal sinus cavity that required endoscopic clearance in the office, more frequently in the first year of follow-up and less often or never thereafter.

**ONCOLOGIC OUTCOME**

The overall and disease-free survival rates were 68% and 63%, respectively, at 2 years, and both were 53% at 5 years. Three patients had persistent progressive disease; all of these had massive skull base invasion at the outset. Distant metastasis that was detected before the time of restaging developed in 2 patients, and delayed pulmonary metastasis developed in 1. In those 13 patients in whom disease was controlled by the time of completion of treatment (after chemoradiation therapy and surgery), local failure developed in only 2 (15%).

Figure 1. A, Squamous cell carcinoma invading the middle cranial fossa before chemoradiation. B, After chemoradiation. C, After craniofacial resection using a transcranial approach only, coronal view. No facial incisions were necessary. D, After craniofacial resection, sagittal view.
Seven of the 12 patients undergoing histological assessment of response to chemoradiation therapy (by means of surgery or biopsy) had a complete response. All 7 are alive after a median of 4.5 years after the diagnosis, although pulmonary metastasis of adenoid cystic carcinoma developed in 1 patient after 3 years. This patient is alive 6 years after the diagnosis. Local failure of squamous cell carcinoma of the sphenoid sinus developed in another patient after a little more than 4 years, but this patient is still alive (and working) 6 years after the diagnosis—although with evidence of disease at the skull base—after further therapy with the gamma knife, external beam radiation, and intravenous chemotherapy. Of the 5 patients who were partial responders, 3 are alive and free of disease 2, 3, and 6 years after their diagnosis; one had progression of disease shortly after completion of therapy; and local failure developed in another 4 years into follow-up (Figure 4).

COMMENT

Treatment of paranasal sinus malignancies is primarily surgical because of the drawbacks of radiation treatment of these cancers. Centers where radiation treat-
ment has been used as the primary modality report poorer outcomes compared with surgical treatment and a prohibitively high rate of complications related to the optic structures. Parsons et al\textsuperscript{13} reported their experience of treating 48 patients with nasal cavity, ethmoid, and sphenoid cancers of varying histological types at the University of Florida, Gainesville. The 10-year actuarial survival was 52\% for the entire group, although substantially lower (22\% were disease free for 10 years) for stage III disease. The 10-year local control rates for stages II and III disease were 53\% and 30\%, respectively. Isaacs et al\textsuperscript{14} subsequently reported the results in 37 patients with squamous cell carcinoma of the maxillary sinus from the same center, 25 of whom were treated primarily with irradiation, whereas the other 12 were treated with surgery with or without radiation. Of those treated with radiation alone,
0 of 6 with T3 cancers and 1 of 14 with T4 disease were surviving at 5 years.

At the University of Toronto, Toronto, Ontario, patients with paranasal sinus cancers have received primary radiation treatment. In a series of 29 patients with carcinoma of the ethmoid complex who received primary radiation therapy and who were described by Waldron et al,13 overall survival at 5 years was 39%; local progression was documented in 15 (52%) of the 29 and distant metastasis in 5 (17%). In another report from the same center, Waldron et al16 found the 5-year cause-specific survival in a group of 110 patients with maxillary sinus carcinoma, 83 of whom had been treated with primary radiation therapy and 27 with surgery with or without radiation therapy, to be 43%. Local control at 5 years was only achieved in 42% of the patients.

Drawbacks of radiation treatment of paranasal sinus cancers are not limited to lack of efficacy. Higher doses of radiation pose a significant risk for injury to optic structures, such as the retina, optic nerves, and chiasm. Unilateral blindness developed in 16 (33%) of 48 patients in the series on nasal cavity and ethmoidal cancer reported by Parsons et al17 from the University of Florida, whereas bilateral blindness developed in 4 (8%). In the 4 patients with bilateral blindness, neither orbit was definitively involved by the tumor. Even in the patients treated for maxillary sinus cancer, ipsilateral blindness developed in one third.18 Similarly, of the 29 patients with ethmoid sinus cancer treated at the University of Toronto, complications relating to the visual apparatus developed in 19 (66%). One patient became blind in both eyes, 11 had ipsilateral blindness, and 7 others had impairment of vision.

Parsons et al17 studied the risk of radiation-induced optic neuropathy according to the total radiotherapy dose and fraction size and found that the complication did not develop in any of the 106 optic nerves receiving a dose of 59 Gy or less. For the nerves receiving a radiation dose of 60 Gy or greater, the 15-year actuarial risk of optic neuropathy was 11% for a fraction size of less than 1.9 Gy and 47% for a fraction size of 1.9 Gy or greater.17 The same group later reported that radiation retinopathy occurred at the rate of 50% in retinnae exposed to radiation doses ranging from 45 to 54.99 Gy and 100% in those exposed to a dose above 65 Gy.18 Radiation retinopathy was not observed in the 33 eyes that received doses of less than 45 Gy.

Despite the drastic increase in the use of chemotherapy for management of head and neck cancers in the past 15 years, information on its role in treating paranasal sinus cancers is remarkably scanty. Few reports in the published literature have sufficiently large numbers of patients with cancers of this location who have received a combination of chemotherapy and radiation therapy as an alternative to or in association with surgical treatment. A single report from University of Chicago, Chicago, Ill, included only 12 patients treated with neoadjuvant chemotherapy followed by radical surgery and radiotherapy, among whom very high survival was found. Eleven of 12 patients were cured (92% survival after a median follow-up of 55 months; range, 13-105 months) after treatment with multimodality therapy composed of cisplatin- and fluorouracil-based neoadjuvant chemotherapy followed by standard surgery and postoperative radiation therapy with or without concomitant hydroxyurea and fluorouracil chemotherapy.23 Eleven of the 12 patients had T4 disease. Surgery consisted of maxillectomy in 8 patients and a craniofacial resection in 3; 5 patients underwent orbital exenteration. Pathological complete response to chemotherapy was 25% (3 of 12 patients), and the overall response rate was 83% (10 of 12 patients). Although the report must be interpreted with sufficient caution because of its preliminary nature and small number of patients treated, it points toward a possible role of chemoradiation as an important modality in the management of paranasal sinus cancers. No study with larger numbers and longer follow-up is yet available from the same center.

In several centers in Japan and Rotterdam, the Netherlands, alternative methods of chemotherapy application, such as intra-arterial or topical application of chemotherapeutic agents (commonly cisplatin and fluorouracil), have been used for treating these cancers.20-24 Common to these treatment regimens is the use of all 3 modalities of cancer therapy. In addition to chemotherapy as described, varying doses of radiation have been used along with surgical excision that has ranged from repeated sublabial clearance to more traditional, radical operations such as maxillectomies. The results reported from these centers appear to be similar (5-year survival ranging from 45%-76%), if not superior, to those obtained with standard therapy, ie, radical surgery and adjuvant radiation therapy. Particularly notable are the results of thorough microscopic clearance of disease via a sublabial approach when combined with topical and regional chemotherapy and radiation therapy.22-24 It is possible, however, that an inherent difference in the biological characteristics of disease accounts for a more favorable result, as paranasal sinus cancer constitutes approximately 23% of head and neck malignancies in Japan compared with only about 3% in western countries.21 However, these results suggest that the combination of regionally directed chemotherapy, radiation therapy, and conservative surgery must be evaluated further.

In the United States, the only recently published experience with regional chemotherapy is the one from the University of Texas M. D. Anderson Cancer Center, Hous-
ton, reported by Lee et al. Twenty-four patients with advanced paranasal sinus cancer of varying histological types, including 21 with previously untreated disease, were treated with intra-arterial chemotherapy followed by surgery and/or radiotherapy. Most patients had cisplatin (100 mg/m²) and bleomycin sulfate (30 U) infused via the maxillary artery, after which they received fluorouracil intravenously for the next 5 days (total dose, 5000 mg/m²). Patients with osteosarcoma or olfactory neuroblastoma received intravenous cisplatin and intravenous doxorubicin hydrochloride (total dose, 90 mg/m²) instead. The entire procedure was repeated every 3 to 4 weeks, and the patients underwent evaluation for tumor response after 2 or 3 courses. The overall response rate was 91%, with 48% having a complete response. Seven patients with complete response and 1 of the patients with a partial but near-complete response underwent radiotherapy without surgical intervention and remained free of disease until the time of reporting. Another report from the same center, published only in abstract form, recently reported preliminary results with the use of intra-arterial cisplatin with systemic paclitaxel and ifosfamide followed by definitve therapy (surgery or radiation) in 19 patients with locally advanced paranasal sinus cancer. Eye preservation was possible in 74% of the cases, and 63% were rendered disease free at the end of all therapy. No long-term survival results are available.

The rationale and results of high-dose intra-arterial cisplatin therapy with sodium thiosulfate rescue and concomitant radiation therapy for head and neck carcinoma have been reported previously. For paranasal sinus cancers, this regimen was modified by reducing the dose of radiation to 50 Gy to minimize injury to visual structures and by adding planned surgery, which is performed 6 to 8 weeks after completion of chemoradiation therapy. The goal of surgery was to achieve meticulous, albeit piecemeal, clearance of the contents of affected sinuses, immediately adjacent bony walls, and any involved neighboring soft tissues and not a radical ablation of portions of midface skeleton such as in a total maxillectomy. Conceptually, this may be thought of as an “inside-out” approach to resection, where the extent of tumor removal is similar to that of the more traditional maxillectomy or craniofacial operations, except that uninvolved portions of the maxillary alveolus, hard palate, lateral orbital floor, malar bone, frontal process of the maxilla, or piriform aperture margin are not removed (Figure 1C-D). None of our patients experienced the functional and cosmetic morbidity of a maxillectomy defect. We were able to save the eye in 3 of the 4 patients presenting with radiologic evidence of orbital invasion.

Limiting the amount of radiation to 50 Gy was successful in avoiding delayed ophthalmic complications. Any augmentation of radiation effect by concomitant targeted cisplatin therapy was not translated into increased toxic effects to critical visual structures. Also, the incidence of complications of anterior craniofacial resection noted in this study (10%) compares favorably with that recorded in the literature (30%). Hence, anterior skull base surgery may be performed safely after the chemoradiation regimen described herein.

Despite the conservative approach to surgery, local failure rate (15%) was considerably improved compared with that reported in literature for advanced disease (>50%). Similarly, the survival rate (53% overall and disease-free survival at 5 years) appears to be an improvement compared with that noted for subsets of patients with comparably staged disease in other series. These results may be viewed as long term with regard to oncologic outcome and the complication rates, as the minimum duration of follow-up was 2 years and the median follow-up was 53 months. However, some caution must be exercised in interpreting the outcome of this study because the sample size (n=19) is not sufficiently large (given the single-institution setting and relatively uncommon nature of this disease), and the number of patients eligible for long-term follow-up is smaller still (n=13).

In conclusion, intra-arterial high-dose cisplatin with concomitant radiation therapy followed by conservative surgery in the manner described herein holds promise in the treatment of paranasal sinus malignancies. Newer methods of conformal radiation delivery, such as intensity-modulated radiation therapy, may result in further optimization of such combined therapy by allowing higher doses of radiation to be administered to the tumor while avoiding exposure to the adjacent critical structures.

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