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Management of Unresectable Malignant Tumors at the Skull Base Using Concomitant Chemotherapy and Radiotherapy with Accelerated Fractionation

Abstract—Between January 1988 and June 1992, 20 patients with unresectable malignant tumors at the skull base were treated. Eleven had T4 lesions of the paranasal sinus/cavity complex, and 9 had T4 nasopharynx cancer. All patients had stage IV disease by the American Joint Committee on Staging Criteria. The histology was squamous cell cancer in 15 patients and other minor salivary gland histologies in 5. There was brain and/or dural invasion in 11 patients and orbital invasion in 9. All patients received radiation therapy with accelerated fractionation to a total of 70 Gy in 6 weeks. Concomitant cisplatin (100 mg/m²) was given on days 1 and 22 of radiation. Seven patients received mitomycin C (7.5 mg/m²) on days 1 and 22, plus adjuvant chemotherapy with cisplatin and vinblastine. Median follow-up was 11 (range: 1 to 43) months. At 2 years, local progression-free survival was 94%, distant metastases-free survival was 57%, and overall survival was 80%. Complications occurred in 20% and caused the death of 1 patient. Treatment of this group of patients with aggressive chemotherapy and radiation therapy produced excellent local control in our early experience, but longer follow-up is needed. There is a high rate of distant failure. Future strategies are outlined. (*Skull Base Surgery*, 4(3):127–131, 1994)

Radiation therapy alone has yielded suboptimal results for advanced, unresectable head and neck cancers.¹ For this reason, there has been increasing interest in combining radiation therapy with chemotherapy^{2–8} in an effort to improve the outcome. Indeed, a recent prospective randomized trial demonstrated improved survival in patients treated with chemotherapy and radiotherapy com-

bined versus radiotherapy alone⁸ for unresectable squamous cancer of the head and neck.

We have had an ongoing experience with concomitant chemotherapy and irradiation, the preliminary results of which have been reported.⁴ In this report we will present our data on the group of unresectable cancers at the skull base. While improved surgical methods for resect-

able skull base lesions have continued to evolve,^{9,10} advanced and unresectable tumors in this anatomically complex region continue to be a challenge.

MATERIALS AND METHODS

Between January 1988 and June 1992 we prospectively treated 20 consecutive patients with unresectable malignant tumors at the skull base on a combined chemotherapy and radiation therapy protocol. All patients had extensive bone destruction of the skull base, 11 had brain and/or dural invasion, and 9 had eye or orbital invasion. All patients were considered unresectable by a head and neck surgeon at the Memorial Sloan-Kettering Cancer Center. It should be mentioned that no patient with nasopharynx cancer is resected at our center, so none of the patients would be considered "resectable." All of the paranasal sinus/cavity complex (PS/NC) patients had extensive skull base destruction, which is considered unresectable at our institution. No patients had distant metastases prior to therapy, as evidenced by the absence of systemic symptoms, a normal chest x-ray, and normal liver function studies.

There were 13 males and 7 females, with ages ranging from 17 to 75 years (mean = 47). All patients had stage IV disease and all had T4 disease as staged by the American Joint Committee on Cancer.¹¹ Eleven had primary lesions of the PS/NC, and 9 had nasopharynx cancer. All PS/NC patients had T4, N0 stage IV¹¹ lesions. Table 1 shows the stage breakdown for the nasopharynx patients. Only nasopharynx patients with T4 disease¹¹ were included in this protocol because they all had extensive skull base destruction. Table 2 shows the distribution of patients by histologic type. The majority had squamous cell carcinoma. No patients had distant metastasis at the start of therapy.

All patients received radiation therapy with accelerated fractionation to a total of 70 Gy in 6 weeks. The details of this treatment, and the rationale, have been previously reported.⁴ Radiation was given once per day for five days per week for weeks 1 through 4, and twice per day for five days per week for weeks 5 and 6. Dose was 1.8 Gy per fraction for weeks 1 through 4, and for the morning fraction during weeks 5 and 6. Dose was 1.6 Gy for the afternoon fraction (4 to 6 hours after the morning fraction) for weeks 5 and 6. This latter portion of the treatment was a concomitant boost, given only to the area of gross disease. Patients with nasopharynx cancer received treat-

Table 2. Distribution of Patients by Histology

Squamous cell cancer	15
Adenocarcinoma	2
Mucoepidermoid	2
Poorly differentiated cancer	1
Total	20

ment to both the primary site and the neck. Areas involved with disease in the neck received the full 70 Gy. Electively treated areas of the upper neck received 54 Gy in 30 fractions of 1.8 Gy over 6 weeks. The lower neck received 50 Gy in 5 weeks. The spinal cord was shielded at 45 Gy, and supplemental electron beams (6 to 9 MeV) were used to boost the posterior neck to the appropriate dose. Patients with PS/NC tumors received treatments to their primary site alone, as all were N0 on presentation. Elective neck treatment was not given. All patients were treated with photon beams of 6 Mv or 10 Mv. Computed tomography-based treatment plans were created for each patient and varied depending upon the exact anatomical extent of disease. Nasopharynx patients were treated with 6-Mv photons. Technique was either with bilateral opposed portals matched to a low neck field, or with three-dimensional conformal radiation therapy, also matched to neck fields. Paranasal sinus/nasal cavity complex patients were generally treated with wedged pair portals, but more complex beam arrangements were used as needed on an individualized basis.

The chemotherapy protocol consisted of cisplatin 100 mg/m² on days 1 and 22 of irradiation. In addition, the most recent seven patients were on a protocol which called for mitomycin C 7.5 mg/m² on days 1 and 22, plus two cycles of adjuvant chemotherapy with cisplatin and vinblastine beginning 6 to 8 weeks after completing radiation. This consisted of cisplatin 120 mg/m² on adjuvant days 1 and 29, vinblastine 5 mg/m² intravenously on days 1 and 29, and vinblastine 4 mg/m² intravenously on days 8, 15, 22, and 43. The details of cisplatin administration and reconstitution have been previously described.¹² Dose adjustments were made based upon toxicity.

The median follow-up is 11 months, and no patients have been lost to follow-up. Local control, freedom from distant metastasis and overall survival calculations were performed by using the Kaplan-Meier method.¹³ Local control was determined by clinical examination and computed tomography (CT) scan. All patients had CT scan prior to therapy, 6 weeks after therapy, every 3 to 6 months for the first year, and every 6 to 12 months for the second year. Due to the extensive nature of these tumors, the CT scan commonly showed abnormalities in the region of the original lesion that were considered "postradiation" changes. Unless there was progression of these otherwise stable changes on the CT scan, the patient was considered as locally controlled. Distant metastasis was determined by appropriate radiologic assessment.

Table 1. American Joint Committee on Cancer Stage* Distribution, Nasopharynx Group

	N0	N1	N2b	N2c	N3b	Total
T4	2	2	2	2	1	9

*All patients had stage IV disease.

RESULTS

Figure 1 shows the local control. Actuarial local control at 1 year and 2 years is 94%. Figure 2 shows freedom from distant metastasis. It is striking to find that in this group of patients with primary unresectable disease the major cause of treatment failure was distant metastasis. At 1 year, actuarial freedom from distant metastasis was 83%, dropping to 57% by 2 years. Figure 3 shows overall survival, which was 94% at 1 year and 80% at 2 years. The continued decline in overall survival reflects the continued development of distant metastasis with increasing time of follow-up. The data for PS/NC and nasopharynx patients are combined, as there is no difference between the two groups in any of the endpoints analyzed.

All patients were able to complete the course of radiation therapy. However, three required treatment interruption of 1 to 2 weeks due to severe mucositis with sepsis (2 patients) or mitomycin C lung toxicity (1 patient). One patient could not get the day 22 cisplatin due to decreased renal function. Of 7 patients scheduled to get two cycles of adjuvant chemotherapy, 5 actually received both cycles. Two patients could not receive further chemotherapy due to poor performance status after their recently completed chemotherapy and irradiation. Table 3 summarizes our complications, the overall rate of which was 20%. One patient had a fatal complication, caused by a large, unresectable mucoepidermoid carcinoma of the frontal sinus with massive brain invasion. He had a near complete response and underwent resection of residual disease in the frontal sinus. He developed a postoperative cerebrospinal fluid leak and meningitis, and ultimately died. The

Figure 2. Freedom from distant metastasis—all patients. Numbers in parentheses represent the number of patients at risk at given time interval.

overall time course of his death was 9 months after the completion of his therapy.

DISCUSSION

In the surgical literature, skull base tumors are a distinct clinical entity. As such, there are reports of the

Figure 1. Local control—all patients. Numbers in parentheses represent the number of patients at risk at given time interval.

Figure 3. Overall survival—all patients. Numbers in parentheses represent the number of patients at risk at given time interval.

Table 3. Complication

Sepsis and severe mucositis	2
Mitomycin C lung toxicity	1
Mild neuropathy	1
Postoperative cerebrospinal fluid leak and meningitis (fatal)	1
Total	5 (20%)

management of these tumors by primary surgery.^{9,10} Because this category of tumors is receiving increasing multidisciplinary attention, we decided to prepare this report on the management of unresectable skull base tumors to add to the growing surgical literature and to report on the nonsurgical management of these complex entities.

For resectable, nonnasopharyngeal malignancies in this location, craniofacial resection has been the standard primary therapy. Shah⁹ reported local control of 71% and 67% for patients with negative and positive margins, respectively. Five-year survival was 56%. Postoperative radiation therapy usually is given for all tumors with positive margins and for those with negative margins which are large, locally invasive, or high grade. Dural and/or brain invasion has been shown to be an adverse prognostic factor.^{9,14} This is important, as 55% (11/20) of our patients had brain and/or dural invasion by cancer, which was massive in some cases.

All patients in our series had extensive skull base destruction, and their disease was considered unresectable for cure. The expected outcome for these patients is poor. This is true whether their primary disease was nasopharynx cancer or lesions of the PS/NC. Long-term local control using radiotherapy alone for advanced, unresectable head and neck cancer is obtained in no more than 33%, and long-term survival is approximately 15%.¹ Similarly, local control with radiotherapy alone for T4 nasopharynx cancer has ranged from 44 to 50%,¹⁵⁻¹⁷ and long-term survival has been to 29%.^{16,18-20} Therefore, we are dealing with a heterogeneous group of tumors for which optimal therapy has not been defined.

We are encouraged by our 2-year local control of 94%. Longer follow-up is needed to see if this is maintained. Of interest, however, is that the most common pattern of failure has been distant metastasis. For this reason, we are currently adding adjuvant chemotherapy after concomitant chemotherapy and radiotherapy as part of our new protocol. It is too early to know whether this will impact on distant metastasis and overall survival. Other studies have suggested that true adjuvant chemotherapy may improve relapse-free survival.^{7,21} Therefore, this approach appears warranted.

Single-arm studies using concomitant chemotherapy and standard radiation^{2,3,5,6} or delayed hyperfractionation⁴ do suggest that local control and early survival may be superior to conventional radiation alone.¹ Merlano⁸ has recently reported a randomized trial which suggests that alternating chemotherapy and radiotherapy is better than

radiation alone for unresectable disease. Weissberg⁵ reported that mitomycin C during radiation produced improved disease-free survival compared to radiation alone. Clearly, the optimal schedule of combining chemotherapy and radiation has not been determined and continues to be an active area of investigation. Also, which drug combinations are optimal requires further study. However, these reports provide good evidence that combination therapy is better than radiation alone for unresectable disease.

In conclusion, this treatment program appears safe, and it can provide excellent short-term local control. Long-term local control remains to be seen. It is already obvious that distant failure is a major problem, which is surprising in a group of patients with unresectable primary head and neck cancer. Longer follow-up is needed to see whether our current approach of adjuvant chemotherapy can diminish distant failure and improve survival.

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