The Role of Postoperative Adjuvant Radiation Therapy in the Treatment of Mucosal Melanomas of the Head and Neck Region

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Background: Mucosal melanoma of the head and neck is uncommon, and has a poor prognosis due to locoregional and distant failure. The optimal treatment paradigm for patients with this disease has yet to be determined.

Objective: To compare the outcomes of patients treated with various commonly used protocols for mucosal melanoma of the head and neck.

Design: Retrospective study.

Setting: Academic tertiary referral center.

Patients: The medical records of 48 consecutive patients treated at a single institution from January 1, 1985, to December 31, 1998, were reviewed.

Interventions: Patients were treated with surgery alone, surgery and adjuvant radiotherapy, or surgery and biochemotherapy, with or without adjuvant radiotherapy.

Main Outcome Measures: The outcomes of disease recurrence and survival were correlated with the treatment received.

Results: Twenty patients received surgical treatment alone; in 9 patients (45%), this treatment failed locoregionally, and 10 (50%) of the patients developed distant metastases. The 5-year survival rate was 45% (9 of 20 patients). Twenty-four patients received postoperative adjuvant radiotherapy; in 4 patients (17%), this treatment failed locally, and 11 (46%) of the patients developed distant metastases. The 5-year survival rate was 29% (7 of 24 patients).

Conclusion: The addition of radiotherapy tended to decrease the rate of local failure ($P = .13$), but did not significantly improve survival ($P = .73$), because of the high rate of distant metastatic disease.

The patient database of the MDACC was used to identify patients treated for malignant melanoma of the head and neck from January 1, 1985, to December 31, 1998. Among these patients, those whose lesions were in cutaneous sites were omitted from consideration, leaving 54 patients with mucosal malignant melanoma of the head and neck. Patient data were obtained by review of the MDACC medical record and available correspondence from patient families and referring physicians. Data were collected in August 2000.

Of the initial group of 54 candidates, 48 were included in the data analysis. Six patients were excluded from the study because of inadequate follow-up. Four patients received treatment other than surgery or surgery and radiation; these patients were, however, included in the demographic data. Otherwise, all patients treated during the stated period were included in the analysis. The 48 patients included 39 males and 9 females. The ethnic distribution was as follows: 39 white patients, 1 black patient, 5 Latin American patients, and 3 Asian patients. The average age was 55.5 years (range at diagnosis, 3 months to 88 years). The available information for these patients was examined, and the outcomes of local, regional, and/or systemic recurrence and overall and disease-specific survival were correlated with the treatment received and the tumor site using a statistical software application (Statistica; StatSoft, Inc., Tulsa, Okla).

RESULTS

Among the 48 patients who were included in this series, 32 were seen at MDACC following biopsy as their only prior treatment; 10 had undergone surgery before referral.

Thirty-seven tumors (77%) were located in the oral cavity or in oropharyngeal locations, and 11 (23%) were in sinonasal sites. Among oral lesions, the 2 most common sites were the lower lip and the hard palate. The most frequent sinonasal site was the maxillary antrum. One lesion of the base of the tongue was seen.

Most patients presented with no symptoms. Of 44 patients, 6 (14%) reported significant nasal obstruction and 11 (25%) complained of bleeding at the site of the lesion. Less common presenting symptoms included pain, deformity, dysphagia, and diplopia.

Of the 48 patients, 44 were included in the data analysis. Twenty patients (45%) were treated with surgery as the sole therapy for their primary tumor (group 1). Twenty-four patients (55%) underwent surgery followed by radiotherapy postoperatively (group 2). Six patients underwent neck dissections at initial treatment. Surgery performed at MDACC included comprehensive resection to obtain wide margins negative for disease, when possible. Some sinonasal tumors presenting technical difficulty were not completely resected en bloc, but in a piecemeal fashion with narrow margins. All patients who underwent surgery before referral underwent reexcision, and had margins negative for disease.

Twelve patients—5 in group 1 and 7 in group 2—received systemic biochemotherapy as salvage treatment following local or systemic failure.

Radiation therapy was generally used as adjuvant therapy for patients with more extensive disease, while adjuvant therapy was not elected in those with more localized tumors. The patients with sinonasal tumors receiving radiation received 6000 rad (60 Gy) in 30 fractions, while those with oral lesions received 3000 rad (30 Gy) in 5 fractions.

Biochemotherapy was used almost exclusively in patients who had clinical evidence of recurrence of disease, mostly those with distant metastases. The protocols used included cisplatin (20 mg/m2 per dose), vinblastine sulfate (2 mg/m2 per dose), and dacarbazine (800 mg/m2 per dose), with or without the addition of the immunologic agents interferon alfa-2b (5 × 106 IU/m2 per dose) and interleukin 2 (9 × 106 IU/m2 per dose). The chemotherapeutic agents are administered at 3-week intervals, while the immunotherapeutic agents are administered 3 times during the treatment protocol.

Among the patients in treatment group 1, 9 (45%) experienced local or regional recurrence of disease. Failure occurred in 5 of these patients within 24 months of initial treatment; recurrence occurred in a sixth patient 147 months after surgery (range, 4-147 months; median, 14 months). Ten (50%) of the group 1 patients developed documented distant metastases; the average duration from surgery to the development of metastases in these patients was 30.3 months (range, 3-107 months; median, 20 months). The overall survival rates at 3 and 5 years were 65% (13 of 20 patients) and 45% (9 of 20 patients), respectively. Two patients in group 1 have survived for 117 and 155 months; the latter patient developed recurrent local disease at 147 months.

Four (17%) of the patients in group 2 experienced local or regional recurrence; the average time to treatment failure was 34.7 months (range, 21-40 months). Eleven patients (46%) in this group developed documented distant metastases an average of 17.5 months following initial therapy. The overall survival rates at 3 and 5 years were 58% (14 of 24 patients) and 29% (7 of 24 patients), respectively. When compared with group 1, the addition of radiotherapy to surgery tended to decrease the rate of local failure (Figure 1) (P = .13), but did not significantly improve the rates of distant metastases (Figure 2) (P = .83) or survival (Figure 3) (P = .73).

Biochemotherapy regimens were used for patients experiencing recurrent and metastatic disease. For pa-
patients in group 1 treated with such a regimen, no significant improvement in survival was noted (P = .34). Group 2 patients receiving salvage biochemotherapy also did not exhibit any significant difference in survival (P = .37).

With regard to primary site, 37 patients had oral or oropharyngeal lesions, and 11 had sinonasal tumors. Three (27%) of the patients with sinonasal tumors had local recurrence of disease, while failure occurred locally in 9 (24%) of those with oropharyngeal lesions. The average interval to failure in patients with sinonasal tumors was 14.3 months (range, 3-36 months; median, 13 months); for patients with oral or oropharyngeal lesions, it was 31.6 months (range, 3-147 months; median, 14 months). All 3 patients with recurrent sinonasal disease died, while 2 of those with oropharyngeal recurrence survived. For patients with sinonasal disease, the overall survival rates at 3 and 5 years were 50% (5/10) and 33% (3/9), respectively. The overall survival rates for those with oropharyngeal lesions were 53% (17/32) at 3 years and 37% (11/30) at 5 years.

**Mucosal melanoma of the head and neck accounts for 6% to 8% of the cases of head and neck melanoma.**

These tumors tend to affect males more commonly (58%), with 73% to 78% of the patients being older than 50 years. A handful of cases in pediatric patients as young as 8 months have been presented, but these cases are extremely rare. The youngest patient in this series was aged 3 months. Differences in incidence between certain ethnic groups have been noted, such as in Japan and Uganda, where mucosal melanomas compose up to 10% of nasal malignancies.

The etiology of mucosal melanoma is unclear. An environmental carcinogen associated with these lesions has not been identified. Melanocytes are present in the oral and nasal respiratory epithelium of black and white people. It has been presumed that these melanocytes are biologically identical to those residing in cutaneous sites, because all are neural, are crest derived, and migrate to their final location, presumably during late gestation.

Patients with sinonasal melanoma generally present with symptoms of nasal obstruction, epistaxis, or both. Less common symptoms include pain, facial deformity, and visual disturbances. Oral lesions may cause dysphagia, but present as asymptomatic masses much more regularly. These indolent symptoms and lack of pain commonly result in delay of presentation to physicians. While many of the patients in this series were asymptomatic, the symptoms that were reported were consistent with those in previous reports.

The histopathologic diagnosis of mucosal melanoma is confounded not only by the rarity of the tumor but also because the lesion is often amelanotic. Fontana staining may be helpful in identifying more tumors, but immunohistochemical techniques are more successful in identifying lesions. Antibodies to S100 and HMB-45 react positively with these tumors; anti–cytokeratin antibodies generally do not react, although an exception has been documented.

The generally poor prognosis and low incidence of mucosal melanoma have made identification of prognostic indicators difficult. The histopathologic subtype does not seem to affect survival. Some series have suggested that thinner lesions are associated with improved survival. It has also been suggested that surgical margins do not influence recurrence or survival. An association between site and prognosis has been documented. Their meta-analysis revealed the 5-year survival for nasal cavity lesions to be 30.9%, while that for sinus disease was 0%. The 5-year survival for oral cavity melanoma was 12.3%. Our data suggest that these differences may not be quite this dramatic, because the difference between the 3- and 5-year survival rates for the oral and sinonasal subgroups in this series was not statistically significant. Our reported survival rates for sinonasal disease are consistent with a recent report.

Local tumor control has been associated with improved survival in one series, and was reinforced by a meta-analysis that reported a 73.1% rate of distant metastasis among patients with local failure; those with local control developed distant metastases at a rate of 52.1%. A recent series reports a 76% rate of distant metastases in patients with locally controlled disease.

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The treatment strategy that offers the greatest likelihood of achieving local tumor control has not been unequivocally demonstrated. Lee et al\textsuperscript{10} reported that radical surgery is more likely to effect local control than local resection or radiotherapy alone. Gilligan and Selvin\textsuperscript{25} reported local control in 17 (61%) of 28 patients treated with radiotherapy alone; however, many patients with local control died of early metastatic disease. Nandapan et al\textsuperscript{24} demonstrated no difference in survival between cohorts treated by radiotherapy. Although the addition of radiotherapy to surgery improves local control, these reports have demonstrated no difference in survival between cohorts treated with surgery alone vs those treated with surgery and radiation.\textsuperscript{4,26} In contrast to these studies, Kingdom and Kaplan\textsuperscript{27} demonstrated an improvement in survival among patients treated with surgery and radiotherapy vs those treated with surgery alone.

In the previous analysis of mucosal melanoma at MDACC, Stern and Guillamondegui\textsuperscript{4} noted similar survival outcomes as those presented herein, with 5-year survival rates of 48%. Only 8 patients in the previous series received adjuvant or salvage radiation, and no outcome analysis was performed; most patients were treated with surgery alone. Local recurrence rates for patients treated with surgery alone are similar between the 2 series. Stern and Guillamondegui recommended adjuvant radiation therapy for patients with gross residual disease following surgical excision.

The results of our series suggest that the addition of radiotherapy to surgical treatment of mucosal melanoma led to an improvement in locoregional tumor control. However, this finding was not statistically significant. Furthermore, treatment with postoperative adjuvant radiation therapy did not significantly improve the overall survival of these patients vs those treated with surgery alone. Despite the lack of impact on overall survival, the improvements in local control rates afforded by adjuvant radiation treatment suggest that its use be considered in selected cases. The biochemotherapy protocols used as salvage therapy for clinical recurrence had little effect on the course of disease in these patients. These results may be somewhat skewed by the selection bias inherent to the retrospective design of this and the previously mentioned studies, because patients with more extensive disease were treated more aggressively. Thus, the inability of a retrospective study to prove that the addition of adjuvant radiotherapy improves survival does not necessarily suggest that its addition is not beneficial to the patient.

We, therefore, recommend the use of postoperative adjuvant radiotherapy for mucosal melanoma, especially in those patients with extensive disease in whom wide margins may not be attainable. Other selection criteria for the use of adjuvant radiation are less clear, given that few histologic prognostic indicators are available. It is our contention that the morbidity of radiation therapy is acceptable when compared with the nearly uniform poor survival in those who experience local, regional, or distant disease failure. Hypofractionated radiotherapy protocols are used most commonly at MDACC. These protocols include a dose of 3000 rad (30 Gy) in 5 fractions over 15 days. This protocol is appropriate as an adjuvant postoperative therapy for all patients with mucosal melanoma, except those in whom critical structures, such as the orbit or central nervous system, are at risk of radiation-related injury. In these patients, conventional treatment schedules are used.

The failure of biochemotherapy to improve the survival of patients with metastatic disease is consistent with the known natural history of metastatic mucosal melanoma, because patients developing distant metastases tend to die soon after the development of distant disease. The nearly equivalent survival seen in this subset of patients compared with the other groups justifies the use of biochemotherapy given the dismal prognosis in this group. The role of biochemotherapy in the management of advanced cutaneous melanoma has been reported.\textsuperscript{27,28} Response rates of 40% to 60% and complete remission in approximately 10% of patients with metastatic disease have been reported.\textsuperscript{27} Specifically, the response in patients treated with cytokines is superior to that noted in patients receiving chemotherapy alone.\textsuperscript{28} The correlation between the response of metastatic cutaneous vs mucosal melanomas and these agents has not been determined. Furthermore, our data do not suggest that no role exists for biochemotherapy as a potential adjuvant therapy in the initial treatment of mucosal melanoma, because regimens may contribute to local control of disease.

To make a meaningful impact on the natural history of this disease and improve survival, aggressive and effective prospective clinical treatment protocols for metastatic melanoma are necessary in addition to aggressive treatment of locoregional disease.

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