ROLE OF POSTOPERATIVE IRRADIATION FOR PATIENTS WITH BILATERAL CERVICAL NODAL METASTASES FROM CUTANEOUS MELANOMA: A CRITICAL ASSESSMENT

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Abstract: Background. The aim of this study was to evaluate the role of regional nodal radiation therapy (RT) for patients with bilateral cervical nodal metastases from melanoma.

Methods. Between 1998 and 2008, 16 patients with bilateral cervical metastases without distant metastases were treated with postoperative RT (30 Gy in 5 fractions delivered twice weekly).

Results. Median follow-up was 5 months (range, 1–34 months). Median survival was 9 months (95% confidence interval [CI], 0–23 months). Overall survival was 68%, 50%, and 27% at 6, 12, and 24 months, respectively. Regional nodal control was 74% and 64% at 6 and 12 months, respectively. Rates of development of distant metastases were 60%, 70%, and 90% at 6, 12, and 18 months, respectively. The actuarial rate of RT-related complications was 49% at 12 months.

Conclusion. The limited life expectancy of patients observed with this disease combined with the high rate of RT-related complications argue against the routine use of adjuvant irradiation therapy for high-risk nodal metastases from melanoma. Until such data are available, management decisions continue to be guided by reports on current clinical practice. Some non-randomized and retrospective data have suggested that regional nodal control outcomes are improved with adjuvant irradiation therapy, compared with surgical series for similar high-risk nodal presentations. Furthermore, RT is increasingly being used in clinical practice as an adjuvant therapy for high-risk regional involvement with malignant melanoma.

Some patients with midline scalp or facial primary tumors can present with bilateral nodal disease.
cervical lymph node metastases, and it has been reported that up to 15% of lateralized scalp and facial primary tumors show sentinel nodal drainage patterns that include the contralateral cervical nodal basins. In recent years, the authors of this report noted an increase in referrals for adjuvant irradiation for patients with bilateral cervical nodal metastases from cutaneous melanoma. It had been our experience that even in the absence of clinically apparent distant metastases at the time of referral, patients with bilateral cervical nodal metastases experienced poor survival outcomes. There are currently no reported data in the literature on outcomes for patients with this presentation of melanoma. We undertook a review of our clinical experience with patients referred for adjuvant radiation therapy who were observed with simultaneous bilateral cervical metastases but without distant metastases. Our goal was to offer a critical assessment of the role of radiation therapy with respect to regional control, distant metastatic relapse, survival, and treatment-related complication outcomes.

PATIENTS AND METHODS
Patients were identified through a search of The University of Texas M. D. Anderson Cancer Center, Department of Radiation Oncology databases. Data collection commenced after approval from our institution's institutional review board approved review of records for this analysis. Between 1998 and 2008, 16 patients were identified who had been diagnosed with simultaneous bilateral cervical metastases from melanoma treated with lymphadenectomy and adjuvant RT. Patients were referred for RT to the regional lymphatics for high-risk disease, which was generally defined as having extranodal extension of disease, lymph node (LN) size ≥2 cm, involved LNs, or recurrent disease after previous LN dissection alone for pathologically confirmed disease. Patients with known distant metastases at the time of RT were excluded from this analysis. Patients with mucosal melanoma were also excluded. A waiver of informed consent was obtained from our institution's institutional review board prior to review and analysis of patient data.

Patient, Tumor, and Treatment Characteristics. Patients' ages at the time of presentation ranged from 19 to 85 years (median, 66 years). Patients included 12 men and 4 women. All patients underwent a complete history, physical examination, and appropriate radiological examination to assess for the presence of distant metastases. The primary site was the scalp in 8 patients (7 vertex/midline, 1 right scalp), the face in 6 patients (2 nose, 1 chin, 1 forehead, 1 lip, 1 eyelid), the midline posterior neck in 1 patient, and the midline upper back in 1 patient. All patients underwent negative-margin, wide excision of their primary tumor. The median Breslow thickness was 4.5 mm (range, 0.55–18 mm), and the Clark level was III in 1 patient, IV in 8 patients, V in 4 patients, and unknown in 3 patients. Ulceration was present in 5 patients, and no patient had satellitosis associated with the primary tumor.

Two patients presented having previously undergone unilateral lymphadenectomy for prior presentation of unilateral cervical nodal metastases. For the current presentation of disease, the definitive surgical procedure was bilateral full-neck dissections in 11 patients and bilateral selective neck dissections in 5 patients. The median number of LNs removed was 54 (range, 28–95), and the median number of LNs involved with melanoma was 4 (range, 2–41). All 16 patients had extension of disease beyond the lymph node capsule (extracapsular extension [ECE]).

Median interval between surgery and beginning of RT was 1.1 months (maximum, 2.5 months). All patients were treated with 30 Gy in 5 fractions of 6 Gy per fraction delivered twice weekly over 2.5 weeks (Monday/Thursday or Tuesday/Friday scheduling). Thirteen patients received bilateral cervical irradiation, and 3 patients underwent unilateral cervical irradiation because of the determination that only 1 side of the neck met criteria for being considered high risk for regional nodal recurrence after bilaterally therapeutic lymphadenectomy. The RT technique used was as follows: 10 patients received RT through matched electron and photon fields; 3 patients were treated with appositional electron fields only; 2 patients were treated with opposed photon fields; and 1 patient was treated with intensity-modulated radiation therapy (IMRT). Tissue equivalent bolus was used in appropriate cases to draw dose off of neurologic or laryngeal structures to minimize toxicity to these tissues. In 11 of the 16 patients, efforts were undertaken to shield the midline structures, either by placing a
midline block or by using appositional electron fields. Radiation fields included the primary tumor site with the cervical lymphatics in 5 patients. Six patients received adjuvant chemotherapy, and 5 of these patients received immunotherapy as part of their adjuvant systemic therapy management.

Follow-up and Statistical Analysis. The median follow-up time of patients alive at last contact was 5 months (range, 1–34 months). The completion of RT was used as time 0. Disease relapse was scored if there was any clinical or radiographic evidence of tumor at any site. Regional relapse was scored if there was any evidence of nodal, dermal, subcutaneous, or soft tissue tumor regrowth within or around the dissected nodal basin. Actuarial data for local regional control, disease-free survival (DFS), distant metastasis–free, complication-free, and overall survival (OS) curves were calculated using the Kaplan–Meier method, and tests of significance were based on the log-rank statistic. Differences between proportions for categorical variables were analyzed using the chi-square statistic or Fisher’s exact test as appropriate. Surgical and radiation-related surgical complications were scored as follows: mild (self-limited and requiring no treatment); moderate (requiring conservative medical management); and severe (requiring surgical intervention or hospitalization).

RESULTS

Survival. The median survival time was 9 months (95% confidence interval [CI], 0–23 months). The actuarial OS for these patients is shown in Figure 1. The OS survival rates at 6, 12, and 24 months were 68%, 50%, and 27%, respectively. DFS rates were 41%, 31%, and 10% at 6, 12, and 18 months, respectively. Of the 16 patients, 12 (75%) experienced disease relapse. Of those 12, no patients were salvaged and median survival after relapse of disease was 5.5 months (range, 0.1–24 months).

Locoregional Control. No patient experienced local recurrence at the site of the primary tumor. Five patients (31%) experienced nodal relapse in the cervical region. Four of these patients had recurrences in the irradiated field, and 1 patient had recurrence at the RT field margin with a nodal recurrence in an area abutting the radiotherapy field. The actuarial rates of regional nodal control were 74% at 6 months and 64% at 12 months and beyond. The actuarial curve for regional control is depicted in Figure 1. Regional nodal control was significantly inferior in patients who had >4 LN positive compared with those with ≤4 LN (30% vs 89% at 2 years, respectively; p = .04). There was no significant difference in regional nodal control with respect to whether explicit efforts at midline shielding had been undertaken in configuring the radiotherapy fields (68% vs 60%, respectively; p = .55).

Distant Metastases. Twelve patients (75%) experienced distant metastatic relapse (distant metastasis). The median time to development of distant metastasis was 3.5 months (range, 0–7.3 months). Actuarial rates of development of distant metastasis were 60%, 70%, and 90% at 6, 12, and 18 months, respectively. Figure 1 shows distant metastasis-free survival. The sites of distant metastases included lung, liver, brain, bone, spleen, peritoneum, subcutaneous tissues, and distant LN. Univariate analyses revealed that the presence of >4 LNs involved with tumor was significantly prognostic of higher likelihood of developing distant metastasis, with 100% of those with >4 LN-positive having distant metastasis versus 49% for those with ≤4 LNs involved (p = .01) at 1 year after RT.

Complications. Nine patients (56%) experienced RT-related complications. The complications were as follows: dysphagia (2 patients), mucositis (2 patients); hearing loss (2 patients); delayed wound healing (1 patient); edema (1

FIGURE 1. Overall and distant metastasis–free survival.
patient); xerostomia (1 patient). The actuarial rates of development of any RT-related complication were 49% and 83% at 1 and 2 years, respectively (see Figure 2). The median time to development of an RT-related complication was 12 months (range, 0–21 months). Seven of these patients (44% of the 16) experienced complications that were clinically significant (scored as moderate or severe). The actuarial rates of development of clinically significant complications were 42% and 61% at 1 and 2 years, respectively. There was no significant difference in rates of development of RT-related complications with respect to whether the RT fields were unilateral or bilateral \( (p = .21) \) nor whether explicit attempts were made to shield the midline structures \( (p = .31) \). One patient experienced a surgical complication of severe chronic pain, requiring medical management and nerve block procedure.

**DISCUSSION**

Although the use of adjuvant irradiation for cervical nodal metastases in patients with cutaneous melanoma of the head and neck is controversial and data on its use are limited to the nonrandomized experience of a few centers worldwide, there is evidence that RT is increasingly being used for management of high-risk disease in the lymph node basins.\(^{10-12,16-20}\) All published data to this point address management for unilateral cervical metastases.\(^{1,2,4,5}\) Our investigation is the first to report specifically on outcomes for patients with simultaneous bilateral cervical nodal metastases. In this small series, we observed poor survival outcomes and high rates of development of distant metastases within a few months of management of their regional nodal metastases. Almost all patients experienced relapse of their disease by 18 months. Median survival time was \(<1\) year, and 3 of 4 patients had died at 2 years. Furthermore, rates of clinically significant RT-related complications were high in this series in which the majority of patients were treated with bilateral neck irradiation.

The rationale for postoperative irradiation for cervical nodal metastases from melanoma arose from the observation that surgical series reported nodal recurrence rates of 30% to 50% after neck dissection alone for high-risk clinicopathologic features such as multiple positive lymph nodes, extranodal extension of disease, or large lymph node size.\(^{6-9}\) Also, some investigators have demonstrated that cervical location of nodal disease was itself an adverse prognostic factor, with associated rates of recurrence in the neck of 30% to 40%.\(^{6,9,21}\) These data were compared with data reporting regional recurrence rates of approximately 10% when analyzing series of patients with these high-risk features who were treated with surgery followed by postoperative RT.\(^{4,5}\) In our series of patients with simultaneous bilateral cervical metastases, the regional nodal control was only 64% at 1 year. This outcome is no better than series reporting on management with surgery alone and notably less than the regional control percentage observed in the other series reporting high regional control rates with the use of postoperative RT for patients with unilateral cervical metastases.

Radiation-related complication rates in this series were higher than those seen in series for patients with unilateral cervical metastases treated with postoperative RT. Although the optimal dose and fractionation for RT in melanoma remains a matter of debate,\(^{4,11,13}\) it is our practice to use a hypofractionated regimen (30 Gy in 5 fractions delivered twice weekly) for melanoma. Ballo and colleagues reported extensively on the use of the same hypofractionated regimen used in this series for treatment to the unilateral neck and showed complication rates of only 8% to 10%. It is possible that the use of this hypofractionated regimen itself may have conferred an unacceptably high potential for toxicity when administered simultaneously to the bilateral cervical regions.
fractionation for radiation therapy for melanoma remains a matter of debate, and randomized trials have not shown a clear benefit to larger fraction sizes.24,25 This raises the question of whether a more standard fractionation scheme might be appropriate in cases where aggressive regional disease is present. However, it is difficult to speculate that a more conventional fractionation schedule appropriate for melanoma (e.g., 60 Gy in 30 fractions over 6 weeks) would offer significantly fewer side effects,26 nor would 1.5 months of radiotherapy be desirable in a patient population whose median time to development of distant metastases is 3.5 months. In cases in which regional nodal disease presents with clinicopathologic features that are particularly ominous for risk of rapid regional recurrence, it may be reasonable to consider other standard regimens, such as 3 Gy × 15 fractions over 3 weeks. This might offer an acceptable alternative to the large fraction regimen, especially in cases in which aggressive palliation of regional disease is desired.

CONCLUSIONS

In conclusion, patients diagnosed with simultaneous bilateral cervical metastases from cutaneous melanoma of the head and neck have a dismal prognosis. The majority of patients in our series with this presentation of melanoma developed distant metastases within months of diagnosis of bilateral cervical disease. Although this makes regional nodal control a secondary concern in the overall outcome for these patients, even so it is notable that little benefit was seen in that regard in our cohort. This analysis is very limited by the small number of patients and the retrospective nature of the investigation. Furthermore, the occurrence of bilateral cervical nodal disease is rare. However, the incidence of melanoma is increasing, and the use of RT for melanoma also appears to be on the rise.27,28 We feel it is appropriate at this time to offer a report on the outcomes for patients diagnosed with bilateral nodal disease because no other literature exists on this matter. The role of RT for regional nodal melanoma continues to evolve, and forthcoming randomized data may show it to be nonbeneficial. However, even if the results of the ANZMTG/TROG 02.01 randomized trial demonstrate a regional nodal control benefit when RT is used as an adjuvant to surgery for unilateral high-risk nodal metastases, we feel that survival and distant relapse outcomes observed here are so poor as to preclude consideration of its use in patients diagnosed with simultaneous bilateral cervical metastases from melanoma. Furthermore, rates of radiation-induced complications were unacceptably high in a patient cohort with such a limited survival horizon. It is our clinical practice to no longer recommend adjuvant nodal basin irradiation for patients diagnosed with bilateral cervical nodal metastases from cutaneous melanoma of the head and neck.

REFERENCES