The Role of Radiation Therapy in Melanoma

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KEYWORDS

• Melanoma • Radiation therapy • Locoregional recurrence • Nodal metastases • Lymphedema

KEY POINTS

- Adjuvant radiation therapy can reduce local recurrence for certain high-risk primary melanomas, including lentigo maligna, desmoplastic/neurotropic features, and mucosal melanomas (head and neck and anorectal).
- There are retrospective and limited prospective data to support adjuvant radiation following lymphadenectomy for nodal metastatic disease at high risk for regional recurrence.
- Radiation therapy is associated with increased potential toxicity, such as lower extremity lymphedema, and may negatively interact with concurrent adjuvant interferon therapy.

INTRODUCTION

Radiation therapy (RT) is a locoregional treatment that can be very effective at reducing the risk of recurrence for many cancers. Given that radiation is not tumor specific, there can also be significant toxicity to adjacent anatomic structures. Historically, melanoma was thought to be radiation "resistant." This assumption led to either its exclusion as an adjuvant therapy or very hypofractionated dosing regimens. More recent data would suggest that melanoma is radiation sensitive, including to standard fractionation treatment plans. This review examines high-risk situations for locoregional recurrence following melanoma surgical therapy, the available literature supporting the role of both adjuvant and definitive RT, and treatment-related complications. The use of RT for situations whereby melanoma is not typically treated surgically (uveal melanoma, brain metastases, palliation, and so forth) are not addressed.

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RADIATION FOR LOCAL CONTROL

Lentigo Maligna

Although it is only melanoma in situ, complete surgical excision of a lentigo maligna (LM) can be difficult secondary to the large size, poorly visualized margins, and cosmetically important locations such as the face. In addition, 16% to 50% of cases can have an associated invasive melanoma component (lentigo maligna melanoma [LMM]).[1–3] Local recurrence rates following conventional surgical resection can be as high as 20%.[4] However, even negative margin staged excisions or Mohs micrographic surgery with a low risk for local recurrence often produces a very morbid cutaneous defect.

In light of these issues, RT has been used as definitive therapy for LM. A small series by Harwood[5] reported on conventional fractionated RT for 17 patients with LM and 23 with LMM. The clinical response following RT took up to 24 months. Although the follow-up was variable, only 2 of the LM patients recurred, both of whom were salvaged by either surgery or additional radiation. Local control was obtained in 91% of the LMM patients. The 2 recurrences were both salvaged by surgical excision.

Grenz rays, or "soft" x-rays, are produced at low kilovoltages, being completely absorbed within the first 2 mm of the skin. Schmid-Wendtner and colleagues[6] examined 42 patients with LM and 22 with LMM treated with fractionated radiation (100 Gy). In contrast to the Harwood study, the nodular melanoma portion of the LMM lesion was excised before radiation. At a median follow-up of 15 months, local control was 100% in the LM group and 91% in the LMM patients (all recurrences were salvaged with surgery). Another study of Grenz rays/soft x-rays for definitive therapy involved patients with LM alone (n = 93), LMM (n = 54), or both components (n = 3).[7] The patients were older (mean age 70 years) and 90% of tumors were on the face. For patients with 2 years or more of follow-up, the local recurrence rate was only 5%. Eighty percent of recurrences were at the edge of the radiation field; all were salvaged with surgery or additional radiation. Only 2 patients developed nodal disease, both of whom died of distant metastases. The largest series of Grenz rays/soft x-rays for LM is 593 patients: definitive therapy in 350, partial excision/radiation in 71, and adjuvant therapy after surgery in 172.[8] The total radiation dose was 100 to 160 Gy (given as twice-weekly fractions over 3 weeks). Only 3.6% of patients with residual LM did not have a complete response, and the overall recurrence rate was only 9.8%. In most of the aforementioned studies, it was considered that the cosmetic outcome was very good, with only occasional radiation-field skin hypopigmentation or hyperpigmentation.

High-Risk Cutaneous Melanoma

Several primary tumor features, such as thickness, ulceration, anatomic location, and satellitosis, predict an increased risk for local recurrence. Reported local recurrence rates for melanomas greater than 4 mm are 12% to 13.2%.[9,10] Even melanomas 3 to 4 mm thick may recur up to 11.7%.[11] In 2 randomized, prospective trials of wide excision margins, ulceration was associated with a rate of local recurrence of 6.6% to 16.2%.[11,12] Local recurrence rates based on high-risk primary tumor site include 9.4% for head and neck, 11.1% for hands, and 11.6% for feet.[10,12] Many of these high-risk features are additive; the recurrence rate for ulcerated melanomas of the distal extremity or head and neck was the highest, at 16.2%.[12] Typically associated with thicker tumors, primary melanomas with histopathologic microsatellites have been shown to recur locally up to 14%.[13]

In 1983, Johanson and colleagues[14] reported on a very hypofractionated RT regimen (800 rad fractions $\times$ 3) for high-risk melanoma. There were 3 cohorts: 22