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Radiation Therapy for Cutaneous Melanoma

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Synopsis

Radiation therapy is used infrequently for cutaneous melanoma, despite research suggesting benefit in certain clinical scenarios. This review will present data forming the highest level of evidence supporting the use of radiation therapy in all stages of the disease. In early stages of cutaneous melanoma, radiation therapy has been retrospectively described as a primary treatment modality for lentigo maligna and lentigo maligna melanoma, with variable rates of success. Adjuvant radiotherapy to the site of a resected tumor has been described in a single phase II prospective study which demonstrated a high rate of local control in advanced tumors. An ongoing prospective randomized study is assessing the effect of radiation therapy in neurotropic melanoma because of retrospective data suggesting high rates of local control in tumors with adverse features. Adjuvant radiation therapy to resected regional lymphatics harboring melanoma has been assessed in two prospective randomized controlled trials, each suggesting improvements in regional control. Finally, radiation therapy has demonstrated palliative effects at the site of distant metastases in the brain, bones and other regions. In conclusion, radiation therapy has a role in the optimal care of patients with cutaneous melanoma; awareness of this is incumbent of clinicians caring for patients with this potentially lethal disease.

Keywords

cutaneous melanoma; radiation therapy; lentigo maligna; desmoplastic melanoma; adjuvant; high-risk; nodal recurrence; palliation

Introduction

In 2002, the Collaboration for Cancer Outcomes Research and Evaluation of Australia estimated that over the course of their disease approximately 23% of patients diagnosed with cutaneous melanoma (CM) would be appropriately treated with radiation therapy (RT) based on the best available evidence. Using population registry data, these investigators found that

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RT was part of the treatment of 13% of patients in New South Wales, Australia, and 1-6% of patients in the United States of America (USA)¹. Others have noted the infrequent and dwindling use of RT for CM over time²³. Awareness of the evidence supporting the use of RT for the treatment of CM is vital to delivering the optimal care of patients with this potentially lethal disease.

Several general aspects of RT for melanoma will not be addressed in this review. The myth that melanoma is not responsive to RT has been adequately described and dispelled elsewhere⁴⁵. The curative and organ-preserving potential of RT for *uveal* melanoma has been demonstrated by the Collaborative Ocular Melanoma Study⁶ and is beyond the scope of this review. Likewise, the role of RT in the management of *mucosal* melanoma is beyond the scope of this review. Herein, data providing the highest levels of evidence supporting the use of RT for CM will be presented and discussed, acknowledging a significant dearth of high level evidence in many situations.

Radiation Therapy for the Primary Tumor

While the effective use of RT as definitive local therapy for primary CM has been described⁷⁸⁹¹⁰, the therapeutic modality of choice for resectable CM in the medically operable patient is surgery. At present, pathologic staging by surgery provides the most valuable prognostic information available for early stage CM. However, there are situations in which surgery might preclude acceptable functional or cosmetic outcomes to some patients.

Definitive radiation therapy for lentigo maligna and lentigo maligna melanoma

Most frequently, RT for the primary tumor is considered for lentigo maligna (LM) and lentigo maligna melanoma (LMM). Because patients with LM and LMM are often elderly and present with large, superficial lesions on the face, alternatives to surgery are often considered to optimize cosmetic and functional outcome. Table 1 summarizes the outcome of RT for LM and LMM from the largest updated retrospective series from around the world¹¹¹²¹³¹⁴¹⁵¹⁶¹⁷. Although follow-up has been limited, the pooled results demonstrate that the efficacy of RT compares favorably with other treatment modalities. Of note, relatively high rates of local recurrence have been noted in several series from North America, and may be related to RT technique. Although toxicity generally depends on the technique employed, the outcome of skin RT is generally quite acceptable to elderly patients¹⁸, in whom LM and LMM are most common.

A recent retrospective comparative study of clinical outcomes in the management of CM *in situ* revealed no statistically significant difference in outcome between surgical excision and RT¹⁹. In that study, 15 patients were given RT to primary CM *in situ* in the head and neck region with a 10 kV superficial unit, to a total dose of 120 Gy in 6 fractions, with a “security margin” of 5 mm. Patients treated with RT were older than patients treated with surgical excision (mean 79 vs 59 years). The majority of patients undergoing excision had non-head and neck primary lesions. Among all patients, statistically significant higher rates of local recurrence were noted in patients older than 62 years or with head and neck lesions. While 5-year rates of local recurrence were higher in patients treated with RT compared to surgery

(13.2% vs 6.8%), this difference was not statistically significant. Statistically significant higher rates of 5-year of local recurrence were noted in patients treated with cryotherapy (34.3%, n=22) and laser therapy (42.9%, n=8), compared to surgery (6.8%, n=1041)¹⁹.

Use of RT for LM or LMM varies widely. As noted in Table 1, higher rates of recurrence have been observed in North American centers and may be part of the reason for geographical variations. Even within a single geographic region, there is evidence of disparate opinions about the appropriateness of RT of LM and LMM. For example, guidelines from the United Kingdom (UK) suggesting RT may be an appropriate treatment method²⁰, but a survey of dermatologists in the UK found that few (18%) ever recommended RT for LM or LMM, while 13% considered it the treatment of choice for patients over 70 years²¹.

Adjuvant radiation therapy after resection of primary cutaneous melanoma

Although adjuvant RT to the site of a resected primary tumor at high risk for local recurrence has been advocated, a single phase II study has assessed this prospectively. From 1983 to 1992, 174 patients were enrolled on a single-center study at the M. D. Anderson Cancer Center (MDACC). Patients with CM of the head or neck were eligible if they fulfilled criteria for one of three groups of patients (see Table 2) thought to be at high risk for local (at the site of the excised primary tumor) or regional (in dermal or nodal lymphatics) recurrence. All patients in this study received adjuvant RT (before or after surgery) to the site of the excised primary, unless the primary tumor had been excised more than 1 year prior to nodal recurrence. A dose of 24-30 Gy in 4-5 fractions over 2.5-3 weeks was delivered, using mostly high energy (9-12 MeV) electrons.

Overall, dermal recurrence was noted in 10 patients (5.7%). Among patients in group 1, a large proportion of patients harbored advanced tumors (61% with T2, 27% with T4, by current American Joint Committee on Cancer staging criteria), and 2 (2.5%) experienced any dermal recurrence. Whether dermal recurrence represented tumor recurrence at the site of primary tumor excision site or in-transit dermal lymphatics was not specified by the report. Nevertheless, these favorable local control rates in high-risk patients suggest a benefit of adjuvant RT to the site of the primary tumor. Because of this study, a phase III trial (9302) of adjuvant RT for high-risk CM of the head and neck was initiated by the Radiation Therapy Oncology Group (RTOG) and the Eastern Cooperative Oncology Group (ECOG) in 1994, but subsequently closed due to poor accrual.

Adjuvant radiation therapy after resection of neurotropic cutaneous melanoma

Desmoplastic melanoma is an unusual subtype of CM that frequently occurs in the head and neck where adequate surgical margins can be difficult to obtain. Moreover, desmoplastic melanoma frequently exhibits neurotropism, which may increase the likelihood of local recurrence. For these reasons, many have employed RT to the site of tumor (before, after, or *in lieu* of, resection). The retrospective research presented in Table 3 suggests a benefit of adjuvant RT in patients with neurotropic CM with adverse features (i.e., recurrent tumors, thick tumors, and tumors excised with narrow margins)^{22,23,24}. This topic is controversial, as some suggest that RT may not be necessary to achieve high rates of local tumor control²⁵.

Two recent analyses of the Surveillance, Epidemiology and End Result (SEER) program of the National Cancer Institute found that approximately 8% of patients in the USA with desmoplastic melanoma receive RT. The studies arrived at different conclusions, with one suggesting no survival effect of RT²⁶, and the other finding an association of RT with inferior survival²⁷. The authors attributed the findings to the selection bias of treating physicians, although finding an association of survival and adjuvant RT would seem unlikely, *a priori*. SEER data does not permit assessment of the local tumor control, the proposed benefit of adjuvant RT.

To further assess the effect of adjuvant RT for desmoplastic neurotropic CM, a phase II study (NCT00060333) was initiated by the North Central Cancer Treatment Group in 2003, and results are pending. The Australia and New Zealand Melanoma Trials Group (ANZMTG) and the Trans-Tasman Radiation Oncology Group (TROG) are currently conducting a phase III trial (NCT00975520) of adjuvant RT in patients with neurotropic CM of the head and neck which will provide the high level evidence which is currently lacking.

Radiation Therapy for Regional Lymph Nodes

Regional RT has been studied extensively in retrospective series and well-summarized by Guadagnolo and Zagars²⁸. The topic is controversial, as evidenced by the inability to accrue patients to an intergroup trial of adjuvant RT initiated by the RTOG and ECOG (9302), or in another trial activated by ECOG alone (3697). However, two prospective randomized controlled trials have been performed and form the highest level of evidence available on this topic.

The first trial was conducted at the Mayo Clinic (Rochester, Minnesota)²⁹. Eighty-two patients were enrolled between 1972 and 1977, and 56 were ultimately included in the analysis. Patients with clinically involved and biopsy confirmed nodal metastases from the primary CM of the extremities, trunk or unknown site were eligible after undergoing staging (history, physical examination, liver and bone scan, hematologic and chemical assessment) and lymphadenectomy. Patients were randomly assigned to adjuvant RT or observation. RT was delivered with supervoltage therapy units using parallel-opposed fields, treating one field per day to a dose of 5000 rads (equivalent to cGy) at the midplane over 7-8 weeks, including a 3-4 week break during treatment.

The investigators found a doubling of disease-free survival, from 9 months to 20 months in patients that received RT, a marginally statistically significant finding ($p=0.07$). Median duration of overall survival was extended by 50% patients that received RT, also marginally statistically significant (median survival 33 months, versus 22 months in those undergoing observation, $p=0.09$). Imbalances in the treatment groups, suboptimal RT technique, and small power of the study limit the interpretation, but suggested improved regional control of melanoma in lymph nodes with RT²⁹.

At the American Society for Clinical Oncology³⁰ and American Society for Radiation Oncology³¹ annual meetings in 2009, the ANZMTG and the TROG reported preliminary results of a multi-center phase III trial (TROG 02.01/ANZMTG 01.02) evaluating the effect of adjuvant RT in patients with CM. Based on phase II data³², the group evaluated patients

with palpable recurrent melanoma in regional lymph nodes, who had not experienced prior local, in-transit or metastatic relapse, and were thought to be at significant risk for future lymph node relapse. Risk factors constituting eligibility for the trial are listed in Table 4. Between 2002 and 2007, 250 patients were randomized to adjuvant RT or observation. RT was delivered using standardized fields³², to a dose of 48 Gy in 20 fractions over 4 weeks.

Of the 217 evaluable patients, a statistically significant decrease in lymph node field relapse in patients that underwent adjuvant RT (2-year rate of 5% in patients undergoing RT, 20% in those observed, $p=0.005$). No significant difference in relapse-free or overall survival was noted, with 2-year rates of relapse of 55% and 62% for those undergoing RT and those observed, respectively. Radiation dermatitis was the most common acute grade 3 toxicity and present in 16% and 4% of patients, 2 and 6 weeks after completing RT, respectively. With a median follow-up of 39 months, late radiation-associated grade 3 or 4 toxicity (with the exception of lymphedema, which was not reported yet in this trial) was categorically less than 3%. Final analysis of the trial including quality of life endpoints has been performed and the publication of the report is pending (Angela Hong, personal communication).

RT associated late toxicity was well-characterized by the multi-center phase II study conducted by the TROG³². Two hundred and thirty patients completed RT to a dose of 45-50 Gy in 20-21 fractions. Median follow-up was 58.4 months (range 21.2-158 months). Acute toxicity was not reported. Lymphedema (moderate symptoms requiring treatment) was the most frequently observed moderately severe (grade 3) toxicity, observed in 9% of patients receiving treatment of the axilla and 19% of patients receiving treatment of the ilio-inguinal region; grade 4 lymphedema (incapacitating or causing ulceration in skin creases) was not observed. Grade 1 and 2 skin effects (atrophy, hair loss, telangiectasias) were noted in 46% of patients, with grade 3 and 4 effects in 11%. Grade 1 and 2 subcutaneous effects (induration/fibrosis and loss of subcutaneous fat) were noted in 36% of patients, with grade 3 and 4 effects in 2%. These results indicate that adjuvant RT of regional lymphatics is well-tolerated with few severe side effects observed. While intensity modulation has improved the side effect profile of RT in several randomized trials, confirmation of this benefit in CM is lacking³³.

The phase II study of adjuvant RT for CM of the head and neck conducted by Ang and colleagues at MDACC described above also assessed the effect of adjuvant RT in the cervical lymphatics³⁴. Cervical lymph node recurrence occurred in 6%, 0% and 2% of patients in groups 1, 2, and 3, respectively (see Table 2 for description of groups). Of note, 2 of the 3 cervical lymph node recurrences occurred outside the RT field, indicating the importance of accurate target delineation and the low rate of cervical lymph node recurrence with appropriate field design. Treatment was well tolerated, with acute and transient parotitis being the most common side effect. In less than 5% of patients, moist desquamation and confluent mucositis of short duration were observed. One patient experienced each of the following side effects after RT: surgical site infection, moderate neck fibrosis, mild ipsilateral hearing loss, transient exposure of external auditory canal cartilage³⁴. These data indicate a low rate of nodal recurrence after RT for head and neck CM with high risk features, using a safe and convenient RT regimen that differed from that used in studies conducted by the TROG.

Radiation Therapy for Distant Metastases

RT is most commonly employed for palliative purposes in patients with metastatic melanoma¹. There are a wide variety of situations that RT may be helpful in. However, many of the research studies investigating the efficacy and toxicity of palliative RT have not focused specifically on metastatic melanoma. In many situations, extrapolating findings from other metastatic cancers is necessary. In this section, attention will be paid to studies specifically studying the role of palliative RT in metastatic melanoma.

Radiation therapy for brain metastasis

The most common situation that palliative RT is employed in the care of patients with metastatic melanoma is for the treatment of brain metastasis. In general, the prognosis of patients with brain metastasis from CM is poor. RT strategies typically consist of focal RT (by stereotactic radiosurgery (SRS)³⁵, or other related techniques), whole brain RT (WBRT), or both. The treatment modalities selected depend on a number of factors.

For patients with a single brain metastasis, focal palliative therapy (surgical resection³⁶, SRS, or both) is typically employed. A randomized comparison of surgery and SRS has never been performed adequately; a recent study attempted this, but was discontinued because of poor accrual³⁷. Surgery generally has the advantage of providing tissue for diagnostic and prognostic purposes, relieving mass effect, and being safer for tumors greater than 4 cm. SRS is generally less morbid, with almost no risk of death as a result of the procedure. Retrospective data generally suggest that the oncologic outcomes are comparable. After focal therapy for a single brain metastasis, randomized trials have suggested that WBRT may be used to decrease the risk of brain metastasis recurrence in regions harboring radiographically inapparent disease^{38,39}. However, WBRT is associated with acute fatigue and hair loss, and may cause neurocognitive impairment or delay systemic therapy⁴⁰. The role of WBRT in melanoma specifically is controversial, and a randomized control trial is currently underway to help define the effects⁴¹.

When few (variably defined, but typically less than 4) brain metastases are found, SRS is typically recommended. The ECOG conducted a phase II study (6397) of SRS in 31 eligible patients with 1-3 "radioresistant" brain metastases, including 14 patients with melanoma. After a median follow-up of 32.7 months, median survival was 8.3 months; neurologic cause of death was observed in 38% of patients. About half of patients developed intracranial recurrence, with about 32.2% of these being outside the SRS treatment area, and 32.2% being inside the SRS treatment area. Three grade 3 toxic events were recorded: cytopenia, fatigue and seizure⁴².

When many (variably defined, but typically more than 3) brain metastases are found, WBRT is typically employed. Alternative strategies, including chemotherapy and immunotherapy have been also been used, but no single modality or combination has been proven to be clearly superior to others. A randomized multicenter trial conducted in France showed that patients with at least one unresectable brain metastasis from melanoma treated with WBRT and fotemustine demonstrated statistically significantly longer time to cerebral progression than patients treated with fotemustine alone (49 versus 56 days), although the clinical

significance of this is unclear. In general, patients with brain metastases from melanoma respond to WBRT in a manner similar to patients with multiple brain metastases from other causes⁴³.

Radiation therapy for bone metastasis

RT is generally effective at alleviating pain in patients with metastatic cancer in the bone, with complete pain relief seen in 25% of patients, and at least 50% pain relief in 41% of patients (overall response rate of 66%)⁴⁴. A single arm prospective study has assessed the effect of palliative RT for painful metastases in melanoma. This study found that pain was relieved in 67% of patients with metastatic melanoma, with responders experiencing pain relief for a median of 2.4 months, or 57% of their remaining lifetime⁴⁵. Retrospective studies have suggested that appendicular metastases are more likely to respond than axial metastases^{46,47}. Some retrospective studies have suggested higher response rates with higher doses per RT fraction, or higher total doses, although these are likely biased by patient selection. A randomized trial by the RTOG found no difference in non-bone metastatic tumor response rates using different fractionation regimens⁴⁸.

Radiation therapy for dermal metastasis

RT has been used in the palliative treatment of skin and subcutaneous metastases. Early reports suggested response rates of >90% for patients with skin metastases treated with fractions of 6 Gy and higher, with no responses noted in patients treated with fractions less than 6 Gy⁴⁹. A subsequent prospective randomized controlled trial found no difference in response rate in patients with skin metastases treated with a high total dose of RT in different RT fraction sizes, with a complete response rate of 66% and partial response rate or 33% (overall response rate of 100%) noted⁵⁰. Acute toxicity consisted of grade 2 and 3 erythema and was noted in 47% and 53% of patients, respectively. Late toxicity consisted of moderate fibrosis, although estimates of frequency were not given. A later randomized study of patients with metastatic melanoma in the skin found that complete response rates were doubled when adjuvant hyperthermia was used with palliative high dose RT⁵¹.

Advanced RT techniques for treatment of metastases

Advanced techniques in RT have allowed for the delivery of a single or few high doses to several sites of metastatic melanoma. Gertszen *et al.* reported on the experience at the University of Pittsburgh and found that 96% of patients reported long-term improvement in spine pain, with mean improvement of 7 points on a 10 point pain scale. Treatment with doses of 17.5-25 Gy was found to be safe, with no clinical or radiographic evidence of radiation associated neurologic toxicity⁵². Multicenter phase I/II trials of high dose RT for lung⁵³ and liver⁵⁴ metastases (including, but not exclusively from melanoma) have demonstrated safety and 2-year metastatic tumor control rates of 96% and 92%, respectively. Tumor control probability modeling has suggested that a minimum dose of 48 Gy in 3 fractions is necessary to obtain metastatic tumor control rates over 90% in melanoma⁵⁵.

Conclusion

RT has a role in the management of patients with CM. As new data emerge on the relative efficacy and toxicity of RT, a change in practice patterns may be observed. Further carefully planned studies of RT in CM are necessary to optimize the outcomes of patients with this potentially lethal disease.

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Abbreviations

RT	Radiation therapy
CM	Cutaneous melanoma
USA	United States of America
LM	Lentigo maligna
LMM	Lentigo maligna melanoma
UK	United Kingdom
MDACC	M. D. Anderson Cancer Center
RTOG	Radiation Therapy Oncology Group
ECOG	Eastern Cooperative Oncology Group
SEER	Surveillance, Epidemiology and End Result
ANZMTG	Australia and New Zealand Melanoma Trials Group
TROG	Trans-Tasman Radiation Oncology Group
SRS	Stereotactic radiosurgery
WBRT	Whole brain radiation therapy

Summary of Important Points

- Radiation therapy is infrequently used in the care of patients with cutaneous melanoma despite research suggesting a benefit in certain clinical scenarios
- Definitive radiation therapy may be a viable treatment option for lentigo maligna and lentigo maligna melanoma
- Adjuvant radiation therapy to the site of a resected neurotropic melanoma may improve local control of the tumor
- Adjuvant radiation therapy to the site of resected lymph node metastases from melanoma at high-risk for recurrence may improve regional control of lymphatic metastases
- Palliative radiation therapy is likely to yield a response in patients with distant metastases

Table 1
Outcomes of superficial radiotherapy (RT) for lentigo maligna (LM) and lentigo maligna melanoma (LMM).

<u>Origin of study</u> ^(reference)	<u>Disease</u>	<u>Patients</u>		<u>Local recurrence</u>		<u>Lymphatic recurrence</u>		<u>Distant recurrence</u>		<u>Follow-up</u>
		<u>n=</u>	<u>%</u>	<u>n=</u>	<u>%</u>	<u>n=</u>	<u>%</u>	<u>n=</u>	<u>%</u>	
Netherlands ¹¹	LM	21	1	5%	0	0%	0	0%	0%	median 3 years
Switzerland ¹²	LM	93	5	5%	0	0%	0	0%	0%	not reported (101 patients followed for at least 2 years)
	LMM	54	0	0%	2	4%	0	0%	0%	
Germany ¹³	LM	42	0	0%	0	0%	0	0%	0%	median 1.3 years
	LMM	22	2	9%	0	0%	1	5%	5%	
USA ¹⁴	LM	15	4	27%	1	7%	3	20%	20%	median 2.7 years
	LMM	1	0	0%	0	0%	1	100%	100%	
Canada ¹⁵	LM	36	4	11%	0	0%	0	0%	0%	median 6 years
Canada ¹⁶	LM	31	9	29%						median 3.9 years
Australia ¹⁷	LM	7	0	0%	0	0%	0	0%	0%	median 1.3 years
Pooled estimates	LM	245	23	9%	1	0%	3	1%	1%	
	LMM	77	2	3%	2	3%	2	3%	3%	

Table 2

Treatment groups in phase II adjuvant radiotherapy (RT) study of high-risk cutaneous melanoma of the head and neck.

Group	Patients (n=)	Presentation	Tumor criteria	Nodal criteria	Treatment rendered
1	79	previously untreated	1.5 mm thick or Clark level 4	none palpable	wide local excision of primary tumor (margins 2-4 cm) and RT to tumor bed and 2 echelons of draining lymphatics
2	32	previously untreated	any thickness	palpable	wide local excision with limited neck dissection and RT to the tumor bed and ipsilateral neck to the supraclavicular fossa
3	63	previously excised primary tumors with relapse in nodes only	absent	recurrent, palpable	limited node dissection and RT to the tumor bed and ipsilateral neck

Table 3
Outcomes of adjuvant radiotherapy (RT) for desmoplastic melanoma with or without neurotropism.

Origin of study	reference	Histology	Treatment	Patients n=	Neutrotropic n=	%	Local recurrence n=	%	Comments
USA ²²		Desmoplastic melanoma	Surgery+RT	15			0	0%	All patients treated with RT had locally recurrent tumors
		Desmoplastic melanoma	Surgery alone	29	21 of 44		4	14%	
Australia ²³		Desmoplastic melanoma	Surgery+RT	24	18	75%	2	8%	
Australia ²⁴		Desmoplastic neutrotropic melanoma	Surgery+RT	27	27	100%	2	7%	Patients treated with RT had significantly more adverse features (thick tumors, narrow margins)
			Surgery alone	101	100	100%	6	6%	

Criteria for enrollment on the TROG 02.01/ANZMTG 01.02 trial of adjuvant radiotherapy after lymphadenectomy.

Table 4

Lymph node region	Criteria for inclusion in trial (eligible if any of these were met)		
	Extracapsular extension	Involved lymph nodes (n)	Size of lymph node (cm)
Parotid	yes	1	3
Neck	yes	2	3
Axilla	yes	2	3
Groin	yes	3	4