Adjuvant Radiation for Malignant Melanoma: The KUMC Experience

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Abstract

Background. The role of external beam radiation in the treatment of melanoma remains controversial. While melanoma is no longer considered radio-resistant, the indications and outcomes for adjuvant radiation therapy in melanoma patients are still evolving.

Methods. A retrospective review was conducted of patients diagnosed with malignant melanoma and treated with postoperative radiation therapy at the University of Kansas Medical Center.

Results. Forty-five patients (27 male; 18 female) with a diagnosis of malignant melanoma were treated with external beam radiation therapy for curative intent between 1985 and 2005. Local control at the treatment site was achieved in 42 of 45 patients and was maintained in 35 patients (78%) at a median follow-up of 14 months. The median time for freedom from any disease progression was 12 months.

Conclusions. Radiation therapy is an effective option for management of patients with malignant melanoma with local control being achieved and maintained in the majority of patients. *KJM 2008; 2(1):1-7.*

Introduction

The role of radiation in the treatment of malignant melanoma often is palliative to relieve the symptoms of widespread metastatic disease. However, there is a possible role of radiation in the curative setting. While surgical resection remains the standard primary treatment, a significant number of completely excised lesions will recur, especially in patients with high-risk features.

Some of the adverse prognostic factors for overall survival include tumor thickness and ulceration[1], while extra-capsular extension, cervical lymph node involvement, and excised lymph nodes larger than 3 cm are prognostic factors for lymph node failure.[2] Patients who test positive for these factors can have local failure rates after surgery alone as high as 50%.[3] These high local failure rates have prompted the search for ways to achieve better local control. Although interferon initially looked promising[4], further studies have not shown this modality to be as beneficial as first thought.[5]

Radiation therapy is another option in the adjuvant treatment of malignant melanoma. Several studies have examined the role of radiation in the non-palliative setting. The results of these studies indicated that adjuvant radiotherapy may be beneficial for patients with high risk features, both for reducing failure at the primary site[6,7] and failure in the lymph node basins[7-13].

This report will examine the results of and possible indications for post-operative radiation therapy in the management of patients with malignant melanoma.

Methods

A retrospective review of the malignant melanoma patients receiving radiation therapy at the University of Kansas Medical Center (KUMC) between 1985 and 2005 was conducted. Approval for this study was granted by the KUMC Institutional Review Board.

The KUMC tumor registry identified all patients with a diagnosis of melanoma who received radiation as a component of their treatments. Patients who were treated for palliation and those who received radiation by means other than external beam (such as brachytherapy) were excluded from this review. After exclusion, 45 patients and a total of 47 treatments were available for analysis. One individual received three separate treatments over a time span of 19.2 months; only the first treatment is considered.

Statistical analysis was performed with SPSS for Windows (Release 16.0, SPSS Inc, Chicago, IL). Categorical variables were summarized by frequencies and percentages, and quantitative variables were summarized by medians and ranges. The duration of follow-up was calculated from the time of completion of radiation treatment until the date of event or last known follow-up. Time to event (overall survival, freedom from disease progression, and freedom from local recurrence) was analyzed by Kaplan-Meier survival plots and univariate analysis by the log-rank test.

For univariate analysis, categorical variables were compared by the log-rank test and/or continuous variables by Cox proportional hazards analysis. Multivariate analysis by Cox regression analysis was then performed. Probability values of $p<0.05$ were considered to be statistically significant. No corrections for multiple comparisons were made.

Results

The study population consisted of 27 males and 18 females with a median age of 60.3 years (range 14 to 85 years). All patients had surgery as the initial component of their therapy. The primary tumor sites were head and neck (16 patients, 36%), upper extremity (6, 13%), lower extremity (15, 33%), and trunk (6, 13%); with two patients (4%) having an unknown site. The tumor stage and nodal status at diagnosis is provided in Table 1**.**

All patients had surgery as the initial component of their therapy prior to radiotherapy. Thirty-three of the radiation treatments (73%) were to the site of resected primary disease; of which 12 (27%) were at the time of original presentation and 21 (47%) were at the time of recurrence. Lymph node regions were included in the treatments of 26 patients (57%), 9 (20%) at the time of original presentation and 17 (38%) at the time of recurrence. Fifteen patients (33%) received radiation treatment to both the primary site and the lymph nodes. One patient (2%) was treated later to another site other than lymph nodes.

Table 1. Tumor stage and nodal status at diagnosis.

Tumor Stage	Nodal Status				
	0	**1**	**2**	**3**	**Total**
Tx*	4**	2	1		7
T1	7				7
T2	5	2	1		8
T3	6	1			7
T4	6	4	3	3	16
Total	28	9	5	3	45

*Tx denotes a primary tumor that could not be assessed.

**One patient was M1a.

External beam radiation varied in terms of both dose per fraction and fractions per week. The majority of patients (28, 60%) were treated on a daily basis, Monday through Friday, for five fractions per week. Other fractionation schemes included three times per week (9 patients, 20%), twice per week (7 patients, 16%), and one patient was treated twice daily (10 times per week). Dose also was variable with 33 treatments at four gray (Gy) per fraction, seven treatments at six Gy per fraction, and five treatments at 2-3 Gy per fraction. Total dose ranged from 24 to 66 Gy, but was centered at 32 Gy. Twenty-three (51%) of the patients were treated with eight fractions of four Gy. Moreover, these eight fractions were delivered over an interval that included one weekend, for a total treatment time of nine days. Four others were treated over one additional weekend for a total treatment time of 11 days.

Systemic therapies included interferon and chemotherapy. Eight (18%) patients received interferon as an initial aspect of treatment and five (11%) received interferon after recurrence or progression. Chemotherapy was used initially in two (4%) patients and as secondary treatment in six (13%) patients.

The median follow-up from completion of radiation treatment for all patients analyzed was 23 months with a range of 2.4 to 136 months. At last follow-up, 24 patients were alive with a median follow-up of 32 months (range 13 to 136 months). For the 21 patients who had died, the median follow-up was 13 months with a range of 2.4 to 44 months. Of the 24 patients alive, 11 (24%) had evidence of disease and 13 (29%) had no evidence of disease. Two expired patients and one patient still alive never achieved disease-free status after completion of treatment.

The median disease free survival (DFS) for all patients was 12 months (Figure 1). For 26 patients (including the three with persistent disease) that had evidence of malignancy, the median time to progression was six months. Of the three patients that had residual local disease after treatment, one had persistent stable disease but experienced distant failure and died at seven months; two patients had progressive local disease but no distant failure (one dead at seven months and one alive at 13 months). An additional seven patients had a subsequent recurrence within the radiation field; all but one also had distant failure concurrent with the local failure. For the seven local failures, the median time to disease recurrence was 12 months. Overall, local control was achieved and maintained in 35 patients (78%), with a median time to recurrence not being reached (Figure 1).

A total of 26 patients had a recurrence outside the radiation field with a median time to distant failure of seven months. Of the 26 distant failures, six patients (as described above) had concurrent local failures leaving 21 patients with isolated distant failures. The median time for failure for these 21 patients was nine months. The most common site of distant failure was the central nervous system with 13 patients or half of all distant failures.

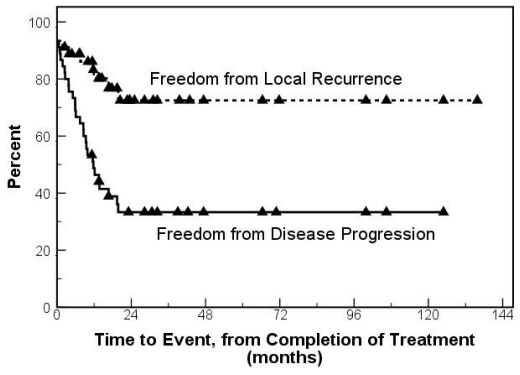

Figure 1. Comparison between Freedom from Local Recurrence (dashed line) and Freedom from Disease Progression (solid line). The triangles indicate times at which patients were censored.

Table 2. Analysis of factors associated with outcome.

Factor		**Number of Patients**	**Freedom from Disease Progression**		**Freedom from Local Recurrence***
			Median, months	**p value**	**p value**
Gender	Male	27	17	**0.010**	0.078
	Female	18	6		
Prior treatment	Primary radiotherapy	16	12	0.90	0.77
	Secondary radiotherapy	29	12		
Lymph nodes at time of treatment	Positive	25	9	0.19	0.39
	Negative	20	14		
Age	< 60 years	19	9	0.79	0.45
	> 60 years	26	12		
Total dose	< 32 Gy	11	6	0.090[a]	0.26[a]
	32 Gy	23	20	**0.010****	**0.001****
	> 32 Gy	11	7	**0.002**[b]	**0.010**[b]
Depth (initial)	Tis-T2 (0-2 mm)	22	10	0.77	1.0
	T3-T4 (> 2 mm)	23	10		
Lymph nodes at initial diagnosis	Positive	17	14	0.96	0.64
	Negative	28	12		
Treatment time	≤ 12 days	24	14	0.042	**0.001**
	> 12 days	21	9		

*Median times for Freedom from Local Recurrence were not reached except for the sub-groups of Total dose > 32 Gy and Treatment time > 12 days, both of which were 12 months.

**Global analysis for difference: [a]Comparison between <32 Gy and 32 Gy; [b]Comparison between 32 Gy and >32 Gy.

Multiple factors were examined for a possible effect on freedom from disease progression (Table 2). The only factors that were statistically significant predictors by univariate analysis were gender (p=0.010), with males doing better, and total dose (p=0.010 overall), with better outcome being exhibited when the dose was exactly 32 Gy, compared to doses <32 Gy (p=0.090) or >32 Gy (p=0.002). There were no statistically significant differences in clinical presentation (age, T-stage, nodal status, histology, etc.) between the three dose groups (<32 Gy, 32 Gy, >32 Gy). There was a marginal influence of total treatment time, with patients treated in 12 days or less exhibiting better outcome than patients whose treatment required longer than 12 days (p=0.042). By multivariate Cox regression analysis, both total dose (p=0.006) and gender (p=0.019) were retained as independent predictors of freedom from disease progression.

Similarly, factors influencing freedom from local recurrence were examined (Table 2). As with freedom from disease progression, total dose influenced the outcome (p=0.001 overall), with patients that received >32 Gy exhibiting a poorer outcome (6/11 patients recurring, 55%) than

patients that received exactly 32 Gy (4/23 patients, 17%), which was statistically significantly different (p=0.010). However, patients that received <32 Gy actually exhibited a better outcome (none of the 11 patients recurred) than patients who received 32 Gy, although the difference was not statistically significant (p=0.26). Only for the >32 Gy group was a median time to event reached (12 months). Also, overall treatment time was a factor (p=0.010) with patients treated in less than 12 days doing better than patients whose treatment required >12 days. Again, only for the latter group was median time to event reached (12 months). By multivariate Cox regression analysis, the overall treatment time was retained (p<0.001) and gender (p=0.050) was added as independent predictors of freedom from local recurrence. However, if overall treatment time was not included, then only total dose was identified as a predictor (p=0.001).

Discussion

As with any retrospective review, these data need to be interpreted with caution. There is an inherent bias in patients that are referred for adjuvant radiation treatment and also patients who elect to undergo radiotherapy. Despite these limitations, outcomes data such as these are valuable in estimating the possible benefit to patients in terms for local control and overall-survival.

Our outcomes, with a median time for freedom from disease progression and DFS of 12 months and a local control rate of 78%, were consistent with some of the ranges reported in the literature. Stevens et al.[6] found a local recurrence rate of 11% and median disease free survival of 25 months in 174 high-risk patients. Ang et al.[7] reported a 5-year 88% local control rate and survival rate of 47%, with a hypofractionated treatment regiment for high-risk head and neck melanoma. Ballo et al.[8] reported on treatment of 89 consecutive patients with axillary radiation, finding a 13% failure rate in the treated axilla and in a separate report of 160 patients with cervical radiation, a 9% local failure rate at 10 years.[9] Cooper et al.[10] had a five-year actuarial failure rate of 16% in a review of 40 patients treated with elective post-operative radiation. Corry et al.[11] described a 74% treatment failure rate at five years in their treatment of high-risk nodal areas. One explanation for the wide range of results for adjuvant radiation was the different institutional indications for treatment, thus different patient populations.

We analyzed the data to see if certain patient subsets had better outcomes. For freedom from disease progression, gender was a significant factor, with males having a more favorable prognosis. This finding was contrary to other authors who have found male gender to be an adverse prognostic factor.[1] This result may reflect a type I statistical error due to the small number of patients in our study. In addition, the total dose delivered had a significant impact on outcome, with those patients receiving 32 Gy in eight fractions of four Gy each (51% of all patients) exhibiting superior outcomes compared to patients that received total doses less than or greater than 32 Gy.

For freedom from local recurrence, similar findings were obtained, with a better prognosis for those patients treated with 32 Gy than for those patients that received >32 Gy total dose. These analyses are confounded by the fact that a large proportion (51%) of patients were treated with the same regimen, eight fractions of four Gy for a total dose of 32 Gy. Of the ten additional patients treated with four Gy fractions, two received a total dose <32 Gy and eight received a total dose >32 Gy. Likewise, of the 23 patients that received a total dose of 32 Gy, all but four required a total treatment time of 12 days or less. Thus, there were close correlations between

total dose, dose per fraction, and treatment time, with the consequent potential for one variable to confound the impact of another variable in the analysis. None-the-less, the results suggested that overall the KUMC "standard" regimen of 8 x 4 Gy in less than two weeks was effective for achieving and maintaining local control.

Many institutions have reported results using a hypofractionated (giving the same total dose of radiation over fewer fractions) radiation scheme, typically 30 Gy in five twice-weekly fractions[6-10] although this has not been proven to be superior to more conventional fractionation schemes. Chang et al.[15] retrospectively compared hypo-fractionation and conventional fractionation in 56 cutaneous melanoma patients and did not find any difference in the two regimens. While a larger series may reveal a patient subset that benefits from higher overall treatment dose, caution should be used in higher fraction doses since this will predispose patients to a greater degree of radiation side effects, especially lymphedema.

Post-operative radiation therapy appears to provide good local control but it may not affect survival since the majority of patients have distant failures despite good local control. In this series of patients, there were no isolated local failures. The implications for future treatment directions should thus focus on more systemic therapies. While it is possible that more aggressive use of radiation for the initial primary tumors and lymph node basins could destroy microscopic disease before it has a chance to spread distantly, it is possible that such treatment would only provide improved local control and that patients would eventually succumb to distant failures.

While a randomized trial would give the best level of evidence for the usefulness of postoperative radiation, our data indicated that adjuvant radiation in a post-operative setting appears to reduce local recurrence and should be considered for patients with malignant melanoma at high risk for local failure.

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