Published in final edited form as:

Melanoma Res. 2016 December ; 26(6): 595–603. doi:10.1097/CMR.0000000000000292.

The influence of postoperative lymph node radiation therapy on overall survival of patients with stage III melanoma, a National Cancer Database analysis

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Abstract

Recently, TROG 02.01 results showed that in stage III melanoma patients with nodal metastasis, adjuvant radiation to lymph node basin after nodal dissection improves lymph node field relapse without an overall survival (OS) benefit. However, this trial was neither designed nor powered to detect an OS difference. In the present study, we analyzed patients in the National Cancer Database (NCDB) with stage III melanoma with pathologically involved nodes and compared survival outcomes of adjuvant radiation and no-radiation cohorts. Inclusion criteria were as follows: age at least 18 years; diagnosed 2003–2011; surgery to regional lymph nodes; pathologically involved lymph nodes; and American Joint Committee on Cancer stage (IIIA–C). We used propensity score matching analysis to compare the OS of patients with similar baseline demographic, clinical, and pathologic characteristics who received adjuvant radiation and no adjuvant radiation. Overall, 912 patients were analyzed with an average age at diagnosis of 54.4 years and a median follow-up time of 5.5 years. In this cohort, the 5-year OS was 69.0, 51.1, and 30.6% for stage IIIA, IIIB, and IIIC, respectively. On propensity score-adjusted multivariate analysis, we found that adjuvant radiation had no statistically significant impact on OS (hazard ratio: 1.09, 95% confidence interval: 0.75–1.58, $P=0.640$). Furthermore, age older than 60 years, number of nodes, increasing pathologic stage, and absence of immunotherapy correlated with worse OS. In this NCDB analysis, we found that the adjuvant radiotherapy for node-positive, stage

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Conflicts of interest

There are no conflicts of interest.

III melanoma patients did not improve OS. This is consistent with TROG 02.01; however, there may be patient selection bias not accounted for by the NCDB.

Keywords

adjuvant radiation; melanoma; National Cancer Database; radiotherapy; stage III

Introduction

A common site of disease spread for cutaneous melanoma is regional nodal basins. Patients with regional nodal involvement are managed initially with wide local excision of the primary tumor and lymph node dissection. Retrospective analysis from Roswell Park Cancer Institute has shown a significant risk of nodal basin failure in patients with cervical involvement, extranodal disease, more than three positive lymph nodes, clinically involved nodes, or any node of more than 3 cm [1]. For patients with high-risk nodal metastases, the role of adjuvant radiation in improving locoregional control has been controversial [2–5]. Radiation may help patients to avoid or delay locoregional recurrence and the subsequent morbidity of salvage surgery and/or chemotherapy, while also potentially improving quality of life by decreasing the risk of pain, bleeding, infection, or loss of limb function [6]. However, adverse effects of radiation can include pain, fibrosis, and lymphedema [7–9]. Thus, the risks and benefits of adjuvant regional radiotherapy (RT) should be evaluated carefully on an individual basis.

Until recently, most modern reports of the effectiveness and toxicities of adjuvant radiation have been retrospective. These studies have shown that radiation reduces in field relapses after surgery and may improve disease-specific survival [10,11]. The Australia and New Zealand Melanoma Trials Group (ANZMTG) and the Trans-Tasman Radiation Oncology Group (TROG) have published a 6-year follow-up of their international, multiinstitutional, randomized phase 3 trial ANZMTG/TROG 02.01 [9]. In this trial, node-positive patients at high risk for relapse (1 parotid node, 2 cervical or axillary, 3 inguinal nodes, size 3 cm for cervical and 4 cm for axillary/inguinal nodes, extranodal extension) were randomized to observation or 48 Gy to the nodal basin. The 5-year incidence of lymph node field relapse, as a site of first relapse, was 18% for the adjuvant radiation group and 33% for the observation group [difference 15%, 95% confidence interval (CI) 3.5–27, $P = 0.011$]. There was no difference in overall survival (OS) nor relapse-free survival; however, the study was powered only to assess lymph node field relapse, not OS.

The aim of the current study was to investigate the impact of adjuvant radiation on OS for stage III cutaneous melanoma patients with pathologically positive nodes. We analyzed patients in the National Cancer Database (NCDB) and used propensity score matching analysis to compare the outcomes of patients with similar baseline demographic, clinical, and pathologic characteristics who received adjuvant radiation and no adjuvant radiation.

Methods

Patient selection

We analyzed patients in the NCDB cancer registry. The NCDB is sponsored by the American College of Surgeons and the American Cancer Society, and is sourced from hospital registry data that are collected in more than 1500 Commission on Cancer accredited facilities in the USA. This database represents about 70% of newly diagnosed cancer cases nationwide [12].

We obtained a deidentified, Health Insurance Portability and Accountability Act (HIPAA)-compliant Participant Use Data File with 541 250 cases of melanoma. Inclusion criteria for our study were as follows: age of at least 18 years; year of diagnosis 2003–2011; American Joint Committee on Cancer (AJCC) pathologic stage III; surgery to regional lymph nodes; pathologically confirmed involved regional lymph nodes; and first malignancy or only lifetime malignancy. Exclusion criteria were as follows: in-situ histology, metastatic disease, unknown number of pathologically involved regional lymph nodes, more than $1.5 \times$ times the upper limit of normal serum lactate dehydrogenase; nonwhite race or hispanic ethnicity; and facility of initial diagnosis differing from the facility of any treatment received. For patients who received adjuvant regional radiation, we excluded unknown radiation treatment volumes, radionuclide treatment, radiosurgery, and brachytherapy.

Covariates included clinical, pathologic, and demographic information: age, sex, education, income, insurance, facility type, year of diagnosis, Charlson–Deyo score, primary site location, histology, ulceration, Breslow thickness, lymph vascular invasion, grade, primary mitotic count rate, surgical margins, clinical lymph node status, number of pathologic lymph nodes positive, primary tumor size, pathologic N stage, pathologic T stage, pathologic stage group, immunotherapy, and chemotherapy. The Charlson–Deyo comorbidity index predicts mortality for a patient who may have a range of comorbid conditions mapped from as many as 10 reported ICD-9-CM secondary diagnosis codes [13]. Each condition is assigned a score of 1, 2, 3, or 6 depending on the risk of mortality. Scores are summed to provide a total score.

Statistical analysis

The primary endpoint was OS, defined as time from the date of diagnosis to the date of death or last follow-up. Patients who were lost to follow-up were censored.

Descriptive statistics, such as frequencies and percentages, were generated for categorical variables, and means and SDs were generated for numeric variables. Patient characteristics were compared across treatment groups (no radiation versus adjuvant radiation) using χ^2 -tests for categorical characteristics and analysis of variance (ANOVA) for numerical characteristics. OS was estimated using the Kaplan–Meier method and was compared across pathologic stage using log-rank tests. Univariate Cox proportional hazards models were fit for each characteristic. A multivariable (MV) Cox proportional hazards model was fit to assess the impact of treatment group on OS while controlling for key patient characteristics. Covariates in the MV model included year of diagnosis, pathologic group stage, number of

pathologically involved regional lymph nodes, age at diagnosis, sex, histology, facility type, Charlson–Deyo Score, chemotherapy, immunotherapy, and primary site location.

In addition, we carried out a propensity score matching analysis using a matching algorithm for OS. Patients with radiation were matched 1 : 1 to those without radiation using a greedy matching approach [14,15]. Variables included in the propensity score matching analysis were the same as those fit in the standard MV Cox model and standardized differences were calculated between treatment groups for each variable. Variables with standardized differences less than 0.1 are generally considered well balanced. Kaplan–Meier curves for OS were plotted by matched treatment groups from the propensity score matching analysis. Proportional hazards assumptions were checked and the analysis was carried out using SAS 9.3 (SAS Institute, Cary, North Carolina, USA). Significance was assessed at the 0.05 level.

Results

A total of 912 patients who fulfilled the inclusion and exclusion criteria were analyzed. Average age at diagnosis was 54.4 ($\pm$ 15.5) years and the median follow-up duration was 5.5 years. A total of 118 cases (12.9%) received adjuvant radiation, 578 (63.4%) were aged 60 years or younger, 623 (68.3%) were men, 58 (6.4%) received chemotherapy, 183 (20.2%) received immunotherapy, and 527 (57.8%) were treated at an academic medical center. Table 1 shows patient clinical, pathological, and demographic information stratified by radiation versus no radiation.

Patients who received radiation were more likely to have a more recent year of diagnosis ($P = 0.017$), men ($P = 0.046$), primary site in the head and neck ($P < 0.001$), macroscopic clinical lymph nodes ($P < 0.001$), malignant melanoma, not otherwise specified or nodular melanoma histology ($P = 0.001$), increasing Breslow thickness ($P < 0.001$), positive surgical margins ($P < 0.001$), higher number of pathologically involved nodes ($P < 0.001$), higher AJCC pathologic stage group ($P < 0.001$), higher AJCC pathologic N stage ($P < 0.001$), and higher AJCC pathologic T stage ($P < 0.001$).

Figure 1 shows Kaplan–Meier OS analysis stratified by pathologic stage for all patients. 30.9% patients were pathologic stage III with a median OS of 72.1 months, 29.6% pathologic stage IIIA with a median OS of 122.2 months, 20.4% pathologic stage IIIB with a median OS of 60.3 months, and 19.1% pathologic stage IIIC with a median OS of 27.7 months ($P < 0.0001$). Incidence by stage was stage IIIA ($n = 270$, 43%), IIIB ($n = 186$, 30%), and IIIC ($n = 174$, 28%). 5-year OS for stage IIIA, IIIB, and IIIC were 69.0, 51.1, and 30.6%, respectively.

On univariate analysis for OS age older than 60 years at diagnosis, Charlson–Deyo Score 2, primary site in head and neck compared with all other sites, macroscopic clinical lymph node status, ulceration, increasing Breslow thickness, positive surgical margins, higher number of pathologically involved lymph nodes, increasing AJCC pathologic N stage, increasing AJCC pathologic T stage, AJCC pathologic stage group IIIB compared with IIIA, AJCC pathologic stage group IIIC compared with IIIB, no immunotherapy, and median income of less than \$30 000 correlated with worse OS (Table 2). When we analyzed only the

adjuvant radiation cohort, univariate analysis showed that no immunotherapy [hazard ratio (HR) 1.86, 95% CI 0.99–3.50, $P = 0.053$] trended toward worse OS and increasing AJCC pathologic N stage was significant for worse OS (HR trend 1.44, 95% CI 1.06–1.98, $P = 0.021$).

On multivariable analysis for OS age older than 60 years at diagnosis, Charlson–Deyo Score 2, AJCC pathologic stage group IIIB compared with IIIA, AJCC pathologic stage group IIIC compared with IIIB, higher number of pathologically involved lymph nodes, and no immunotherapy correlated with worse OS (Table 2).

Because of significant baseline differences in demographic and clinical/pathologic factors, we carried out a propensity score matching analysis and generated a cohort of 113 no adjuvant radiation and 113 adjuvant radiation patients with no significant differences in standardized baseline characteristics (Table 3). Figure 2 shows Kaplan–Meier OS analysis for the propensity score-matched cohorts. Patients who received adjuvant radiation had a median OS of 30.7 months versus no adjuvant radiation 39.8 months ($P = 0.6317$). Five-year survival for the no-radiation group was 34.4 versus 41.1% for those who received adjuvant radiation. On propensity score-adjusted multivariate analysis, the HR for adjuvant radiation compared with no radiation was 1.09 (95% CI 0.75–1.58, $P = 0.640$).

Discussion

We examined the impact of adjuvant radiation on OS by using propensity score matching analysis to create two cohorts with similar baseline clinical and pathological factors, and found that adjuvant radiation had no statistically significant influence on OS. In the unmatched overall cohort, 5-year OS was 69.0, 51.1, and 30.6% for stage IIIA ($n = 270$, 43%), IIIB ($n = 186$, 30%), and IIIC ($n = 174$, 28%), respectively. These OS and incidence rates are consistent with previous reports from the AJCC [16]. Patients with more recent years of diagnosis, male sex, head and neck primary, increasing number of pathologically involved lymph nodes, increasing Breslow thickness, increasing AJCC pathologic stage, and positive surgical margins were more likely to receive adjuvant radiation therapy. Finally, on multivariable analysis, age older than 60 years, increasing pathologic nodal involvement, increasing AJCC pathologic stage, and absence of immunotherapy significantly predicted for worse OS.

There are two modern prospective trials assessing the impact of adjuvant, postoperative lymph node radiation therapy. In 2006, the phase II study, TROG 96.06, reported results of 254 high-risk, node-positive, melanoma patients treated with 48 Gy to the nodal basin after lymphadenectomy [17]. Of these, 6.8% (16/234) had regional infield relapses. Five-year OS was 36% and log-rank analysis showed that more than two involved lymph nodes predicted worse OS. Most recently, the 6-year follow-up results of the phase III trial, TROG 02.01, were published. Patients at high risk for relapse after lymphadenectomy were randomized to observation or 48 Gy to the nodal basin. Radiation therapy reduced lymph node field relapse as the first site of relapse by 15% (95% CI 3.5–27, $P = 0.011$) [9]. Five-year OS was 40% for the adjuvant RT arm and this was not significantly different from the observation group, although this trial was not powered for OS end point. On multivariable analysis, patients

with extranodal disease, male sex, and increasing number of positive nodes had worse OS. Mild long-term radiation toxicities including pain and fibrosis were common and 22% of patients developed grade 3–4 toxicities. Patients who received radiation to inguinal nodes showed a 15% increase in the mean volume ratio of lower limb versus 7.7% in the observation group (difference 7.3%, 95% CI 1.5–13.1, $P=0.014$). In the present analysis, we also found increasing nodal burden to correlate with worse OS in multivariable analysis. In addition, patients who received radiation treatment had a 5-year OS of 41.1%, which is similar to these prospective studies. However, we did not observe any benefit related to OS with the use of RT.

Ballo *et al.* [10] retrospectively reviewed their cohort of 466 node-positive, nonmetastatic melanoma patients treated between 1983 and 2003 at the MD Anderson Cancer Center with lymphadenectomy, followed by radiation, with or without systemic therapy. Five-year in-basin control rate for all patients was 89% and disease-specific survival was 49%. On multivariable analysis, more than three nodes involved and ulceration of primary were associated with worse survival. This NCDB analysis showed survival similar to that reported by the MD Anderson Cancer Center cohort, and confirmed the poor prognostic significance of increasing numbers of involved nodes on survival.

In univariate analysis, we also found that the primary site in the head in neck had worse OS compared with all other sites. Two retrospective studies have shown worse regional recurrence rates with cervical nodal involvement, but none showed an impact on OS [1,2,18]. In addition, the absence of immunotherapy was also a poor prognostic factor for OS. This cohort of patients was treated in the era before targeted therapies and immune check point inhibitors. Before 2011, they likely received interleukin 2 and/or interferon, which has been shown to improve both disease-free and OS [19]. Recently, adjuvant ipilimumab was approved by the Food and Drug Administration for high-risk stage III melanoma patients. The development of targeted molecular treatments and immunotherapies has resulted in improved disease-free survival [20–22]. As systemic treatments improve distant disease control, local control may also become more important as in other disease sites [23]. It will be important to monitor patients who receive modern systemic agents for patterns of relapse in the coming years. Furthermore, radiation may also interact synergistically with these emerging therapies as it can increase antigen presentation, CTLA 4 expression, and PD1/PDL-1 expression in radiated tissue [24–27]. Thus, the use of radiation therapy for the management of melanoma may potentially increase in the future. Clinical trials are ongoing to explore how radiation can be better combined with emerging immunotherapy agents to improve the outcomes of melanoma patients. There are some promising results from small, early phase trials with IL-2 and stereotactic body RT with complete response/partial response rates of 66% [28] as well as local RT and granulocyte-macrophage colony-stimulating factor with an abscopal response of 26.8% [29]. There are also several clinical studies [30–32] as well as ongoing trials with CTLA4 and PD1 in combination with RT (NCT01497808, NCT02303990, NCT02407171, NCT02107755, NCT02406183, NCT0211 5139, and NCT01565837).

Our analysis had several notable limitations that are inherent to any retrospective analysis of a centralized database. Like any registry, the NCDB may be subject to errors in data entry or

coding. The NCDB registry for melanoma did not include complete radiation data including dose, fractionation, and technique on a sufficient sample of patients to carry out an analysis on these covariates. In addition, there is no coding for local or distant recurrence in the NCDB database; therefore, relapse patterns could not be analyzed. The RT group may be more unfavorable than the group that did not receive RT as patients who receive RT are typically referred in the community for adverse risk factors. Although propensity score matching analysis was carried out to compare patients with similar characteristics, not all factors could be controlled for including extranodal extension and nodal size as the NCDB database does not contain this information. It is noteworthy that although the mitotic rate is reported by NCDB, ~ 83% of patients did not have this variable reported. However, on the basis of our own referral pattern experiences, patients with more adverse risk factors are offered RT compared with those with more favorable characteristics. Thus, it is plausible that these additional factors, not accounted for by the NCDB, may also explain the lack of OS benefit observed with the use of RT.

However, our NCDB analysis also has several strengths. There was detailed information on clinical pathological factors including staging information, pathology of primary and nodes, and adjuvant treatments. This detail of data allowed us to gain insights into clinical and pathological factors that significantly impact OS of patients. The cohort analyzed was developed from a national sample representing diversity among treatment center type, location, and geographical region. We accounted for significant baseline differences through propensity score matching analysis. The size of our matched cohorts ($n = 226$) and total sample ($N=912$) is similar to the TROG 02.01 and comparable with previous retrospective series, respectively.

Conclusion

In the absence of a prospective trial designed to determine the survival benefit of adjuvant radiation in node-positive stage III melanoma patients, our large retrospective study shows that adjuvant radiation to the nodal basin did not have any influence on OS. Our results are in agreement with the prospective TROG 02.01 study. Furthermore, we validated the variables that portend a worse prognosis, namely, larger burden of pathological nodal disease, absence of immunotherapy, higher stage, older age, and Charlson–Deyo score 2. As shown by prospective trials, radiation therapy adds benefit in terms of improved local control. However, radiation has not been shown to improve OS. In the future, the potential benefit from RT may further increase, especially with the use of modern immunotherapy as part of a combination multimodality therapy approach in melanoma. Both prospective and large retrospective studies may contribute toward our continued understanding of optimal treatment for different stages of melanoma and how best to improve outcomes for this tumor.

Acknowledgments

Research reported in this publication was supported in part by the Biostatistics and Bioinformatics Shared Resource of Winship Cancer Institute of Emory University and NIH/NCI under award number P30CA138292. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Fig. 1.
Overall survival stratified by pathologic stage, all patients. AJCC, American Joint Committee on Cancer.

Fig. 2.
Overall survival of matched adjuvant radiation and observation cohorts.

Table 1

Baseline demographic, clinical, and pathologic characteristics of patients (unmatched)

Covariates	Adjuvant treatment [n (%)]		P-value ^a
	No-radiation group (N=794)	Radiation group (N=118)	
Year of diagnosis			
2003–2006	377 (47.48)	40 (33.9)	0.017
2007–2009	246 (30.98)	43 (36.44)	
2010–2011	171 (21.54)	35 (29.66)	
Age at diagnosis			
60	507 (63.85)	71 (60.17)	0.438
> 60	287 (36.15)	47 (39.83)	
Sex			
Male	533 (67.13)	90 (76.27)	0.046
Female	261 (32.87)	28 (23.73)	
Charlson–Deyo score			
0	684 (86.15)	96 (81.36)	0.123
1	93 (11.71)	21 (17.8)	
2	17 (2.14)	1 (0.85)	
Primary site			
Head and neck	241 (30.35)	59 (50)	< 0.001
Trunk	249 (31.36)	19 (16.1)	
Upper extremities	114 (14.36)	10 (8.47)	
Lower extremities	157 (19.77)	10 (8.47)	
Other	33 (4.16)	20 (16.95)	
Ulceration			
None	383 (62.18)	41 (51.9)	0.078
Present	233 (37.82)	38 (48.1)	
Clinical lymph node status			
None	22 (3.42)	3 (2.88)	< 0.001
Microscopic lymph node	472 (73.41)	50 (48.08)	
Macroscopic lymph node	134 (20.84)	45 (43.27)	
Transit metastases	15 (2.33)	6 (5.77)	
Histology			
Malignant melanoma NOS	388 (49.18)	70 (59.32)	0.001
Nodular melanoma	177 (22.43)	31 (26.27)	
Superficial spreading melanoma	187 (23.7)	9 (7.63)	
Other	37 (4.69)	8 (6.78)	
Grade			
Well differentiated	1 (10)	0 (0)	0.806
Moderately differentiated	1 (10)	0 (0)	
Poorly differentiated	4 (40)	1 (33.33)	
Undifferentiated	4 (40)	2 (66.67)	

Covariates	Adjuvant treatment [n (%)]		P-value ^a
	No-radiation group (N=794)	Radiation group (N=118)	
Primary tumor mitotic count rate (mitosis/mm ²)			
< 1	17 (12.32)	0 (0)	0.105
1 +	121 (87.68)	19 (100)	
Breslow thickness (mm)			
No mass found	15 (2.29)	12 (13.64)	< 0.001
<1	129 (19.66)	7 (7.95)	
1–2	173 (26.37)	11 (12.5)	
2–4	202 (30.79)	26 (29.55)	
> 4	137 (20.88)	32 (36.36)	
Surgical margins status			
Negative	690 (93.5)	77 (82.8)	< 0.001
Positive	48 (6.5)	16 (17.2)	
Lymph vascular invasion			
Not present	102 (82.26)	20 (86.96)	0.582
Present	22 (1 7.74)	3 (13.04)	
Tumor size pathologic (cm)			
< 2	230 (57.21)	36 (61.02)	0.581
2	172 (42.79)	23 (38.98)	
Regional lymph nodes pathologically positive			
1	482 (60.86)	37 (31.36)	< 0.001
2	172 (21.72)	15 (12.71)	
3	60 (7.58)	17 (14.41)	
4–10	63 (7.95)	38 (32.2)	
11	15 (1.89)	11 (9.32)	
AJCC pathologic N			
1, 1A, 1B	478 (60.66)	31 (26.5)	< 0.001
2, 2A, 2B, 2C	187 (23.73)	31 (26.5)	
3	123 (15.61)	55 (47.01)	
AJCC pathologic T			
0	12 (1.72)	11 (11.7)	< 0.001
1, 1A, 1B, IS	34 (4.89)	1 (1.06)	
2, 2A, 2B	196 (28.16)	10 (10.64)	
3, 3A, 3B	252 (36.21)	29 (30.85)	
4, 4A, 4B	202 (29.02)	43 (45.74)	
AJCC pathologic stage group			
3	245 (30.86)	37 (31.36)	< 0.001
IIIA	263 (33.12)	7 (5.93)	
IIIB	167 (21.03)	19 (16.1)	
IIIC	119 (14.99)	55 (46.61)	
Chemotherapy			

Covariates	Adjuvant treatment [n (%)]		P-value ^a
	No-radiation group (N=794)	Radiation group (N=118)	
No	742 (93.81)	108 (92.31)	0.536
Yes	49 (6.19)	9 (7.69)	
Immunotherapy			0.128
No	636 (80.61)	88 (74.58)	
Yes	153 (19.39)	30 (25.42)	
No high school degree quartiles (%)			0.393
> 29	85 (11.17)	17 (15.32)	
20–28.9	183 (24.05)	25 (22.52)	
14–19.9	178 (23.39)	30 (27.03)	
<14	315 (41.39)	39 (35.14)	
Median income quartiles (\$)			0.023
< 30 000	68 (8.94)	16 (14.41)	
30–35 999	134 (17.61)	15 (13.51)	
36–45 999	209 (27.46)	41 (36.94)	
> 46 000	350 (45.99)	39 (35.14)	
Primary payor			0.356
Not insured	32 (4.1)	8 (6.84)	
Private	507 (65)	69 (58.97)	
Medicaid	41 (5.26)	7 (5.98)	
Medicare	192 (24.62)	30 (25.64)	
Other	8 (1.03)	3 (2.56)	
Facility types			0.935
Community cancer program	36 (4.53)	5 (4.24)	
Comprehensive community cancer program	301 (37.91)	43 (36.44)	
Academic	457 (57.56)	70 (59.32)	

AJCC, American Joint Committee on Cancer; NOS, not otherwise specified.

^aThe parametric *P*-value is calculated using the χ^2 -test.

Significant *P* values of < 0.05 shown in bold.

Table 2

Summary of univariate and multivariable analyses

Covariate	Hazard ratio	95% CI	P value
Univariate analysis			
Age > 60 at diagnosis	1.68	1.38–2.05	< 0.001
Charlson–Deyo score 2	2.54	1.42–4.52	0.002
Primary site in head and neck compared with all other sites	1.39	1.14–1.70	0.001
Macroscopic clinical lymph node status	1.78	1.40–2.26	<0.001
Ulceration	2.02	1.60–2.56	<0.001
Increasing Breslow thickness trend	1.30	1.17–1.44	<0.001
Positive surgical margins	2.00	1.43–2.79	<0.001
Higher number of pathologically involved lymph nodes trend	1.42	1.31–1.53	<0.001
Increasing AJCC pathologic N stage trend	1.66	1.47–1.87	<0.001
Increasing AJCC pathologic T stage trend	1.40	1.24–1.58	<0.001
AJCC pathologic stage group IIIB compared with IIIA	1.98	1.46–2.69	<0.001
AJCC pathologic stage group IIIC compared with IIIB	3.61	2.69–4.85	<0.001
No immunotherapy	1.40	1.08–1.82	0.010
Median income < \$30 000	1.47	1.04–2.07	0.029
Multivariable analysis			
Age > 60 at diagnosis	1.52	1.24–1.88	<0.001
Charlson–Deyo score 2	2.03	1.11–3.69	0.021
AJCC pathologic stage group IIIB compared with IIIA	1.66	1.21–2.29	0.002
AJCC pathologic stage group IIIC compared with IIIB	2.13	1.47–3.07	<0.001
Higher number of pathologically involved lymph nodes trend	1.27	1.15–1.41	<0.001
No immunotherapy	1.40	1.07–1.84	0.014

AJCC, American Joint Committee on Cancer; CI, confidence interval.

Table 3

Baseline demographic, clinical, and pathologic characteristics of patients (matched cohorts)

Covariates	Levels	Regional treatment modality [n (%)]		P-value ^d	Standardized difference ^b
		No-radiation group (N=113)	Radiation group (N=113)		
Year of diagnosis	2003–2006	28 (24.78)	39 (34.51)	0.262	0.214
	2007–2009	46 (40.71)	42 (37.17)		0.073
	2010–2011	39 (34.51)	32 (28.32)		0.134
Age at diagnosis	60	71 (62.83)	69 (61.06)	0.784	0.036
	> 60	42 (37.17)	44 (38.94)		0.036
Sex	Male	84 (74.34)	85 (75.22)	0.878	0.020
	Female	29 (25.66)	28 (24.78)		0.020
Charlson–Deyo score	0	92 (81.42)	93 (82.3)	0.985	0.023
	1	20 (17.7)	19 (16.81)		0.023
	2	1 (0.88)	1 (0.88)		0.000
Primary site	Head and neck	56 (49.56)	56 (49.56)	0.974	0.000
	Trunk	18 (15.93)	19 (16.81)		0.024
	Upper extremities	13 (11.5)	10 (8.85)		0.088
	Lower extremities	9 (7.96)	10 (8.85)		0.032
	Other	17 (15.04)	18 (15.93)		0.024
Histology	Malignant melanoma, NOS	61 (53.98)	67 (59.29)	0.841	0.107
	Nodular melanoma	31 (27.43)	29 (25.66)		0.040
	Superficial spreading melanoma	12 (10.62)	9 (7.96)		0.092
	Other	9 (7.96)	8 (7.08)		0.034
AJCC pathologic stage group	3	45 (39.82)	37 (32.74)	0.727	0.148
	IIIA	7 (6.19)	7 (6.19)		0.000
	IIIB	15 (13.27)	18 (15.93)		0.075
	IIIC	46 (40.71)	51 (45.13)		0.089
Regional lymph nodes pathologically positive	1	38 (33.63)	37 (32.74)	0.985	0.019
	2	16 (14.16)	15 (13.27)		0.026
	3	18 (15.93)	17 (15.04)		0.024
	4–10	31 (27.43)	35 (30.97)		0.078

Covariates	Levels	Regional treatment modality [n (%)]		P-value ^a	Standardized difference ^b
		No-radiation group (N=113)	Radiation group (N=113)		
Chemotherapy	11	10 (8.85)	9 (7.96)		0.032
	No	103 (91.15)	104 (92.04)	0.811	0.032
	Yes	10 (8.85)	9 (7.96)		0.032
Immunotherapy	No	85 (75.22)	84 (74.34)	0.878	0.020
	Yes	28 (24.78)	29 (25.66)		0.020
Facility types	Community cancer program	7 (6.19)	4 (3.54)	0.621	0.124
	Comprehensive community cancer program	43 (38.05)	42 (37.17)		0.018
	Academic	63 (55.75)	67 (59.29)		0.072

AJCC, American Joint Committee on Cancer; ANOVA, analysis of variance; NOS, not otherwise specified.

^aThe parametric P value is calculated by ANOVA for numerical covariates and the χ^2 -test for categorical covariates.

^b A standardized difference <0.1 is considered well-balanced, values >1 are shown in bold.