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Adjuvant radiotherapy for melanoma metastatic to axillary and inguinal nodes: Regional tumor control and late effects

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Abstract

Background: Adjuvant radiotherapy reduces nodal recurrence in metastatic melanoma. The purpose of this study was to examine the effects of adjuvant radiotherapy on in-field nodal control of melanoma metastatic to axillary and inguinal lymph nodes. *Methods:* The medical records of patients who received adjuvant radiotherapy from January 1, 2003, through December 31, 2011, at Mayo Clinic were reviewed. *Results:* In the 20 patients identified, the rates of 2-year overall survival, nodal control, and freedom from distant metastases were 53%, 54%, and 44%, respectively. Intensity-modulated radiotherapy was used in 15 patients (75%) and 3-dimensional conformal radiotherapy in 5 (25%). Disease progression was documented in 13 patients, with a total of 10 distant metastases and 6 in-field nodal recurrences. Treatment complications occurred in 14 patients: lymphedema, 9; lymphedema and fibrosis, 1; lymphedema and wound dehiscence, 1; wound dehiscence, 1; lymphedema and seroma, 1; and lymphedema, seroma, and fibrosis, 1. *Conclusion:* Patients with axillary and inguinal nodal metastases from melanoma have poor overall survival. Surgery and adjuvant radiotherapy provided a 54% nodal control rate. No plexopathy or grade 3 lymphedema complications were seen; however, 20% developed wound dehiscence.

Keywords: adjuvant radiotherapy; axillary; inguinal; lymph node; melanoma; metastasis

Introduction

Surgery has been the standard treatment for melanoma metastatic to lymph nodes [1-4]; however, recent data suggest adjuvant radiotherapy reduces regional nodal recurrence [5]. Regional lymph node recurrence rates range from 5% to 20% after adjuvant radiotherapy compared with 20% to 50% after surgery alone [1-4, 6-11].

Radiotherapy is often not administered because of a belief that melanoma is radioresistant [12]. Studies have suggested high-dose-per-fraction radiotherapy may render melanoma radioresponsive [13]. However, this has not been confirmed by prospective clinical trials [14]. The long-term sequelae of high-dose-per-fraction radiotherapy, especially intensity-modulated radiotherapy (IMRT), in patients with melanoma metastatic to axillary or inguinal lymph nodes have not been thoroughly characterized [7, 12, 14]. The aim of this study was to examine the effects of adjuvant radiotherapy on in-field nodal control (NC) of melanoma metastatic to axillary and inguinal lymph nodes and to document treatment-related complications.

Materials and methods

After approval from the Mayo Clinic Institutional Review Board, patients who received postoperative radiotherapy for melanoma metastatic to axillary or inguinal lymph nodes were identified through a search of the Department of Radiation Oncology tumor registry at Mayo Clinic, Rochester, Minnesota. We started using IMRT in 2003, and the study period spanned January 1, 2003, through December 31, 2011. All patients whose data were used in

this study granted permission for their data to be used for research purposes.

Relapse was defined as any clinical or radiographic evidence of tumor recurrence. In-field NC was defined as non-recurrence of lymph node disease within the radiotherapy treatment volume. Out-of-field marginal recurrence was defined as recurrence of lymph node disease outside but adjacent to the radiotherapy treatment volume. Treatment-related lymphedema was retrospectively characterized according to the Common Terminology Criteria for Adverse Events version 4.0. Grade characterization required inference based on documented pertinent positive and negative physical examination findings.

Overall survival, freedom from relapse, freedom from distant metastasis, freedom from out-of-field marginal recurrence, and in-field NC were estimated using the Kaplan-Meier method and compared between subgroups using the log-rank test in univariate analysis. Because of small sample size, multivariate analysis was not performed.

Data were analyzed using JMP statistical software (version 9; SAS Institute Inc, Cary, North Carolina). Chi-squared tests were used to examine associations between categorical variables. A *P* value of less than 0.05 was considered significant. The start of radiotherapy was used as time 0.

Results

Patient characteristics

Twenty-four patients received radiotherapy after axillary or inguinal lymph node surgery for metastatic melanoma. Excluded were 4 patients treated palliatively for gross residual disease. A total of 20 patients (11 with axillary lymph node metastases, 9 with inguinal lymph node metastases) were studied. Patient and tumor characteristics at the time of initial melanoma diagnosis are listed in Table 1.

Treatment

Sixteen patients (80%) underwent axillary or inguinal lymph node surgery at the time of the initial diagnosis and surgery for the primary tumor and were found to be lymph node positive. The remaining 4 patients (20%) were observed and subsequently developed lymph node metastases. The time to delayed lymph node metastasis was 9 months, 17 months, 22 months, and 31 months. For the 17 patients in whom the size of the largest involved lymph node was documented, the median was 6.0 cm (range, 0.4-8.8 cm). The median number of lymph nodes involved was 2 (range, 1-19). Table 2 lists the nodal characteristics. Nodal staging according to the American Joint Committee on Cancer staging system (seventh edition) [15] was categorized at the time of surgery that preceded radiotherapy. None of the patients had local recurrence at the time of their delayed nodal recurrence.

Table 1 Patient and tumor characteristics at initial melanoma diagnosis (N=20)[a]

Characteristic		Value
All patients		20 (100)
Age (years)		
	Median	53
	Range	28-72
Sex		
	Male	14 (70)
	Female	6 (30)
Site of primary melanoma		
	Occult primary	6 (30)
	Upper extremity	4 (20)
	Lower extremity	4 (20)
	Back	3 (15)
	Chest	2 (10)
	Conjunctiva	1 (5)
Breslow thickness, mm		
	Median	1.6
	Range	0.4-17
	≤1.00	3 (15)
	1.01-2.00	2 (10)
	2.01-4.00	5 (25)
	>4.00	4 (20)
	Unknown primary	6 (30)
Clark level		
	I	0 (0)
	II	0 (0)
	III	1 (5)
	IV	7 (35)
	V	2 (10)
	Not documented	4 (20)
	Unknown primary	6 (30)
Ulceration		
	Yes	7 (35)
	No	7 (35)
	Unknown primary	6 (30)

Abbreviations: [a] = All values are number (percentage) unless indicated otherwise.

The surgical procedure performed was lymphadenectomy or lymph node dissection in 17 patients (85%) and local lymph node excision in 3 patients (15%). Immunotherapy agents were prescribed to 14 patients, and cytoxic chemotherapy was prescribed to 2 patients. Table 2 lists the radiotherapy dose administered. The median time interval from surgery to the start of postoperative radiotherapy was 5.1 weeks (range, 3.0-10.5 weeks).

Table 2 Lymph node characteristics at time of surgery preceding postoperative radiotherapy (N=20)[a]

Characteristic	Axillary	Inguinal
Total	11 (55)	9 (45)
Status of node disease		
Primary	8 (73)	8 (89)
Delayed	3 (27)	1 (11)
Size of largest node, cm		
< 3	1 (9)	5 (56)
≤ 3	8 (73)	3 (33)
Unknown	2 (18)	1 (11)
No. of positive nodes		
≤2	6 (55)	6 (67)
>2	5 (45)	3 (33)
Extracapsular extension		
No	7 (64)	5 (56)
Yes	4 (36)	4 (44)
Nodal staging[b]		
1a	0 (0)	1 (11)
1b	4 (36)	4 (44)
2a	1 (9)	0 (0)
2b	3 (27)	2 (22)
3	3 (27)	2 (22)
RT dose, Gy/fractions		
30/5	9 (82)	3 (33)
35/5	1 (9)	0 (0)
36/6	1 (9)	1 (11)
48/20	0 (0)	5 (56)

Abbreviations: [a] = Values are number (percentage); [b] = American Joint Committee on Cancer [15].

The median dose was 30 Gy in 5 fractions over 14 days (ranges, 30-48 Gy; 5-20 fractions; 12-29 days). One patient received 35 Gy in 5 fractions (over 14 days) and 2 patients received 36 Gy in 6 fractions (over 14 days) because of suspected microscopic residual disease based on our review of the operative notes, pathology reports, imaging studies, and clinical notes. Treatment of patients who received 30 Gy in 5 fractions or 48 Gy in 20 fractions was considered truly adjuvant.

IMRT was used in 15 patients (75%), and 3-dimensional conformal radiotherapy was used in 5 patients (25%). Thirteen patients (65%) received radiotherapy immediately after initial lymph node surgery, whereas 7 patients (35%) received radiotherapy after surgery for lymph node recurrence or progression after initial lymph node surgery or after initial systemic therapy. Four of 7 patients received radiotherapy on the first nodal recurrence or progression after lymph node surgery or systemic therapy, whereas 1 patient received

radiotherapy on the second documented lymph node recurrence after initial lymph node surgery, and 1 patient received radiotherapy on the third documented lymph node recurrence. One patient received systemic therapy for the initial lymph node metastasis and then received surgery and radiotherapy on lymph node progression. Patient nodal characteristics, treatment course, outcomes, and complications are summarized in Table 3.

Survival outcomes

At the time of analysis, 10 patients were alive, with a median follow-up time of 15 months (range, 6-33 months). The 2-year overall survival, freedom from any relapse, and in-field NC rates were 53% (95% confidence interval [CI], 32%-87%), 27% (95% CI, 12%-60%), and 54% (95% CI, 31%-95%), respectively (Figure 1). The 2-year freedom from distant metastases was 44% (95% CI, 25%-77%) and freedom from out-of-field marginal recurrence was 89% (95% CI, 77%-100%) (Figure 1). The 2-year NC rate was 54% and 67% (at 19 months) for patients with axillary metastases and inguinal metastases, respectively (P=.99).
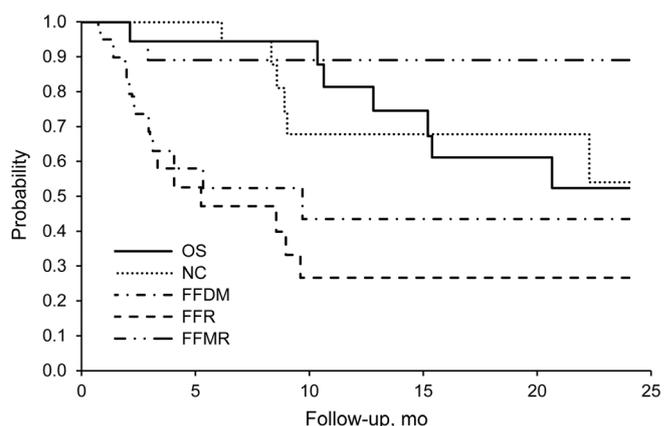
Figure 1 Survival outcomes. Two-year overall survival (OS), nodal control (NC), freedom from relapse (FFR), freedom from distant metastases (FFDM), and freedom from marginal failure (FFMR) (n=20).

Univariate analysis of several patient and treatment characteristics was performed (Table 4). IMRT was associated with a higher 2-year freedom-from-recurrence rate of 38% compared with 0% for 3-dimensional conformal radiotherapy (P=.01). Factors typically considered prognostic (eg., thickness, node size and number, extracapsular extension) were not significant in our study, likely due to small numbers.

Recurrence

With a median follow-up of 15 months in surviving patients, 13 patients (65%) had experienced disease progression (Table 5). Distant metastases developed in 8 patients (40%), in-field nodal recurrence in 2 (10%), out-of-field marginal recurrence in 1 (5%), in-field nodal recurrence and distant metastasis in 1 (5%), and out-of-field marginal recurrence and distant metastasis in 1 (5%). In 3 patients who initially experienced distant metastases, in-field nodal recurrences developed eventually, for a total

Table 3 Patient nodal characteristics, treatment course, outcomes, and complications (N=20).

Patient	LN site	LN diagnosis	Surgery type	No. of positive LNs	Largest LN, cm	ECE	AJCC nodal staging	Time to postoperative RT, wk	RT type	RT dose, Gy/fx	Days of RT	Surgery and postoperative RT timing	Recurrence	Survival	Complications
1	A	P	Lymphadenectomy	11	3	No	3b	5.0	3-D	30/5	14	First line	D	Dead	None
2	A	R	Excisional biopsy	1	8.3	No	1b	3.3	3-D	30/5	12	First line	D	Dead	L
3	A	P	Lymphadenectomy	5	7.2	Yes	3b	3.0	IMRT	30/5	14	First line	N+D	Dead	None
4	A	P	Dissection	1	0.4	Yes	1b	5.1	3-D	30/5	14	First line	D	Dead	None
5	A	P	Lymphadenectomy	3	8	Yes	2b	5.6	IMRT	30/5	14	First line	D	Dead	WD
6	A	P	Dissection	15	No information	Yes	3b	10.4	IMRT	36/6	14	First line	D	Dead	L
7	A	R	Lymphadenectomy	1	6.2	No	1b	6.7	IMRT	30/5	15	First line	None	Alive	None
8	A	P	Dissection	2	6	No	2b	6.4	IMRT	35/5	14	First line	None	Alive	None
9	A	P	Lymphadenectomy	3	No information	No	2a	6.1	IMRT	30/5	14	First line	N	Alive	None
10	A	R	Dissection	2	6.5	No	2b	4.6	IMRT	30/5	14	First line	None	Alive	L
11	A	P	Dissection	1	6	No	1b	5.0	IMRT	30/5	14	Recurrence	None	Alive	L
12	I	P	Dissection	1	5	No	1a	3.7	IMRT	48/20	24	First line	None	Alive	L
13	I	P	Lymphadenectomy	1	7.4	No	1b	10.5	3-D	48/20	29	Recurrence	M+D	Dead	L
14	I	P	Lymphadenectomy	3	8.8	No	2b	4.8	IMRT	48/20	24	Recurrence	D	Alive	L, fibrosis
15	I	R	Excision	1	2	Yes	1b	6.0	IMRT	30/5	14	Recurrence	None	Alive	L
16	I	P	Lymphadenectomy	2	3.5	Yes	2b	5.3	IMRT	30/5	14	First line	D	Dead	L
17	I	P	Dissection	19	2.8	No	3b	4.8	IMRT	48/20	25	Recurrence	M	Dead	L
18	I	P	Dissection	5	0.9	Yes	3b	4.0	IMRT	48/20	25	Recurrence	None	Alive	L, seroma
19	I	P	Dissection	1	2.7	Yes	1b	5.0	IMRT	30/5	14	First line	D	Alive	L, WD
20	I	P	Wide excision	1	No information	No	1b	6.7	3-D	36/6	14	Recurrence	N	Dead	L, seroma, fibrosis

Abbreviations: A = axillary lymph node; AJCC = American Joint Committee on Cancer seventh edition; D = distant failure; ECE = extracapsular extension; fx = fractions; I = inguinal; IMRT = intensity-modulated radiotherapy; L = lymphedema; LN = lymph node; M = marginal failure; M+D = marginal and distant failure; N = nodal failure; N+D = nodal and distant failure; P = primary diagnosis; R = diagnosis at time of recurrence; RT = radiotherapy; 3-D = 3-dimensional conformal radiotherapy; WD = wound dehiscence.

Table 4 Univariate analyses for several characteristics (N=20).

Characteristic		OS, %	P Value	FFR, %	P Value	NC, %	P Value	FFDM, %	P Value
All patients		53		27		54		44	
Sex									
	Male	46	0.72	27	0.54	80	0.04[a]	49	0.22
	Female	60		33		21		33	
Primary tumor site									
	Known	52	0.86	32	0.40	44	0.95	61	0.09
	Unknown	50		17		67		17	
Thickness									
	≤ 4 mm	80	0.1	49	0.03[a]	36	0.82	65	0.44
	> 4 mm	25		0 (at 8 mo)		50		50 (at 20 mo)	
Systemic therapy									
	No	38	0.28	27	0.97	67	0.77	80	0.36
	Yes	56		27		51		37	
Node size									
	< 3 cm	53	0.99	25 (at 12 mo)	0.88	100	0.14	44 (at 12 mo)	0.57
	≥ 3 cm	56		40		43		40	
Positive nodes									
	≤ 2 nodes	63	0.13	44	0.08	67	0.06	55	0.24
	> 2 nodes	34		0 (at 9 mo)		35		0 (at 9 mo)	
ECE									
	No	55	0.89	33	0.49	33	0.15	64	0.12
	Yes	51		17 (at 12 mo)		88		17 (at 12 mo)	
RT technique									
	3-D conformal	40	0.58	0 (at 8 mo)	0.01[a]	25	0.27	20 (at 20 mo)	0.08
	IMRT	62		38		74		51	
RT dose									
	< 48 Gy	53	0.46	25	0.99	56	0.64	40	0.67
	≥ 48 Gy	50 (at 21 mo)		40 (at 19 mo)		50 (at 19 mo)		60 (at 19 mo)	
Timing of S+RT									
	Immediate	64	0.20	28	0.99	65	0.16	35	0.33
	Delayed	30 (at 21 mo)		25 (at 12 mo)		33 (at 12 mo)		67 (at 20 mo)	
Eligible for TROG trial									
	Yes	62	0.23	26	0.74	56	0.62	37	0.45
	No	0 (at 20 mo)		33 (at 12 mo)		50 (at 12 mo)		67 (at 20 mo)	

Abbreviations: ECE = extracapsular extension; FFDM = freedom from distant metastases; FFR = freedom from recurrence; IMRT = intensity-modulated radiotherapy; NC = nodal control; OS = overall survival; RT = radiotherapy; S = surgery; TROG = Trans-Tasman Radiation Oncology Group; [a] = Statistically significant.

of 6 in-field nodal recurrences. The median time to in-field nodal recurrence for the 6 patients was 8.7 months (range, 2.0-22 months). The first site of distant metastasis was lungs, 4; bone, 6; pancreas, 1; liver, 1; subcutaneous nodules, 2; supraclavicular nodule, 1; and jugular vein, 1.

Table 5 Site of disease progression after radiotherapy (N=20)[a]

Site of disease progression	3-D conformal (n=5)	IMRT (n=15)	Immediate RT administration (First Line) (n=13)	Delayed RT administration (Recurrence) (n=7)
Local	0 (0)	0 (0)	0 (0)	0 (0)
Distant	3 (60)	5 (33)	7 (54)	1 (14)
Nodal	1 (20)	1 (7)	1 (8)	1 (14)
Nodal+distant	0 (0)	1 (7)	1 (8)	0 (0)
Marginal	0 (0)	1 (7)	0 (0)	1 (14)
Marginal+distant	1 (20)	0 (0)	0 (0)	1 (14)
No disease progression	0 (0)	7 (47)	4 (31)	3 (43)

Abbreviations: IMRT = intensity-modulated radiotherapy; RT = radiotherapy; 3-D = 3-dimensional; [a] = Values are number (percentage).

In 1 of the 2 patients with marginal recurrences, the treatment failure occurred inferior to the target volume, which extended generously beyond the operative bed. In the other patient, the recurrence was inside the operative bed, which was not covered by the target volume.

Treatment-related complications

Treatment-related complications were documented in 14 patients (70%) (Table 6). Nine patients experienced only lymphedema. Of these, 5 patients had grade 1 lymphedema. Two patients had grade 1 lymphedema before the start of radiation without subsequent progression of symptoms. One patient initially had grade 1 lymphedema, which progressed to elbow contracture with a second course of radiotherapy. Another patient had an initial diagnosis of grade 1 lymphedema, which progressed to a "recalcitrant" state. One patient had grade 1 lymphedema before the start of radiation, but fibrosis developed. All patients experiencing lymphedema were treated with a compression garment.

Table 6 Treatment-related complications by nodal site, RT technique, and RT dose (N=20)[a]

Complication	Axillary (n=11)	Inguinal (n=9)	3-D Conformal (n=5)	IMRT (n=15)	<48 Gy (n=15)	≥48 Gy (v=5)
Lymphedema	4 (36)	5 (56)	2 (40)	7 (47)	6 (40)	3 (60)
Lymphedema + fibrosis	0 (0)	1 (11)	0 (0)	1 (6.67)	0 (0)	1 (20)
Wound dehiscence	1 (9)	0 (0)	0 (0)	1 (6.67)	1 (6.67)	0 (0)
Lymphedema + wound dehiscence	0 (0)	1 (11)	0 (0)	1 (10)	1 (6.67)	0 (0)
Lymphedema + seroma	0 (0)	1 (11)	0 (0)	1 (6.67)	0 (0)	1 (20)
Lymphedema + seroma + fibrosis	0 (0)	1 (11)	1 (20)	0 (0)	1 (6.67)	0 (0)
None	6 (55)	0 (0)	2 (40)	4 (27)	6 (40)	0 (0)

Abbreviations: IMRT = intensity-modulated radiotherapy; RT = radiotherapy; 3-D = 3-dimensional; [a] = Values are number (percentage).

One patient had grade 1 lymphedema and an inguinal wound dehiscence. The wound was treated with a free-flap reconstruction (grade 3 complication). One patient had an axillary and shoulder wound dehiscence attributed to radiation recall, initiation of multidrug chemotherapy after radiotherapy, and infection with methicillin-sensitive *Staphylococcus aureus*. The wound was managed with multiple débridements and 2 free-flap closures (grade 3 complication).

One patient had grade 1 lymphedema and a seroma after initial inguinal lymph node surgery and continued to experience these complications through radiotherapy. This patient had a prior lymph node dissection. After radiotherapy, the lymphedema worsened to the point of "limited mobility," and the seroma remained unresolved (grade 3 complication). One patient had grade 2 lymphedema documented as "erythema and induration"; however, it was unclear whether the findings were from the lymphedema or from the lymphedema and concurrent inguinal seroma and recurrent cellulitis. This patient had 3 prior inguinal dissections, and fibrosis also developed in this patient.

Interestingly, 3 patients received a prophylactic lymphedema compression stocking but did not have lymphedema documented. There was no brachial or lumbosacral plexopathy. The median time interval between surgery and the start of postoperative radiotherapy did not differ in patients who did and did not have complications: 5.0 weeks (range, 3.3-10.5 weeks) compared with 5.6 weeks (range, 3.0-6.7 weeks respectively).

Discussion

Although melanoma has traditionally been regarded as a radioresistant disease, a contemporary study has shown NC is significantly improved in selected patients treated with adjuvant radiotherapy [5]. We report a 2-year NC rate of 54% for the entire group, with a rate of 54% for patients with axillary metastases and 67% for patients with inguinal metastases. Though our reported time frame for outcomes is different than 5-year published reports, we still see that our NC rate is less than reported NC rates of 81% to 89% for all nodal metastases, 88% to 91% for axillary metastases, and 69% to 77% for inguinal metastases at 5 years (Table 7) [1, 7, 15]. The intergroup randomized Trans-Tasman Radiation Oncology Group (TROG) trial reported that 20 of 109 patients who received adjuvant radiotherapy experienced a recurrence within the lymph node field compared with 34 of 108 observational patients [5]. The 3-year reported cumulative incidence of lymph node relapse was 19% in the radiotherapy group and 31% in the observational group [5]. The higher risk of lymph node field relapse in the observational group was also similar on analysis for axillary and inguinal nodal sites [5]. Therefore, our NC rate of 54% is also less than that in both arms of the TROG trial. The lower NC rate in our study might be a reflection of our cohort's characteristics. Only 4 of our patients met the eligibility criteria for the TROG study. Three of the patients were treated with adjuvant radiotherapy after 2 or more nodal recurrences. Further, we also reported subsequent nodal recurrences even after distant metastases were documented.

With regard to treatment-related complications, there was no plexopathy. Lymphedema was mainly grade 1 and managed by referral to the lymphedema clinic and use of compression garments. Moreover, none of the lymphedema cases were severe enough to cause skin folds. The 2 patients with the poor inguinal, axillary and shoulder wound healing were successfully treated with reconstructive surgery. There was no difference in the time interval between surgery and the start of postoperative radiotherapy between patients who had no complications and those in whom wound dehiscence developed, suggesting there is no relationship between wound-healing issues and the interval between surgery and the onset of radiotherapy in our study.

Nevertheless, the pattern of lymphedema-prominent treatment-related complications in our study is similar to that previously reported, with the greater part of

Table 7 Studies of melanoma metastatic to axillary and/or inguinal lymph nodes.

Study, Year	No. of patients	Era	Median follow-up, mo	LN field	Radiotherapy	No. of relapses	No. of LN relapses/NC rate, % in all patients (Follow-up)	No. of distant relapses/ DMFS, %	No. of deaths/ OS, %	Common toxic effects
Present study, 2013	20	2003-2011	15	A, I	Generally 30 Gy/5 fx	13	6/54 (2 y)	8/44 (2 y)	10/53 (2 y)	Lymphedema (medically manageable)
TROG [5], 2012	109	2002-2007	40	A, I, H&N	48 Gy/20 fx	69	20-81 (3 y)	54/...	59/...	Seroma, dermatitis
Agrawal et al. [1], 2009	509	1983-2003	60	C, A, I, E	Generally 30 Gy/5 fx	455	52/91 A, 69 I (5 y)	282/55.4	347/44 (5 y) (all patients)	Lymphedema (medically manageable), highest risk for inguinal region
Beadle et al. [15], 2008	200	1984-2005	59	A	Generally 30 Gy/5 fx	111	20/88 (5 y)	.../46 (5 y)	99/51 (5 y)	Lymphedema
Ballo et al. [7], 2005	466	1983-2003	50.3	C, A, I, E	Generally 30 Gy/5 fx	252	42/89 (87 A, 77 I) (5 y)	240/44 (5 y)	221/...	Lymphedema (medically manageable), highest risk for inguinal region

Abbreviations: A = axillary lymph node; C = cervical lymph node; DMFS = distant metastasis-free survival; E = epitrochlear; fx = fractions; H&N = head and neck; I = inguinal; LN = lymph node; NC = nodal control; OS = overall survival.

complications being lymphedema and the vast majority of lymphedema being low grade and manageable medically [1, 2, 6, 7, 16]. In the TROG trial, the most common adverse event related to radiotherapy in the axilla and groin was dermatitis, and the most common adverse events related to surgery were seroma formation and wound infection [5]. This relatively small magnitude of severe radiotherapy-induced lymphedema is most likely a reflection of improved radiotherapy and lymphedema management techniques in the modern era. Interestingly, 3 patients in our study received prophylactic compression stockings, and lymphedema did not develop in these patients, suggesting investigation is warranted into whether prophylactic use of compression stockings reduces the incidence and severity of lymphedema.

Although adjuvant radiotherapy has been shown to improve NC in selected patients in a prospective trial, the optimal technique and schedule remain controversial. This study specifically reports outcomes for IMRT. IMRT is more expensive than 3-dimensional conformal radiotherapy and subsequently may be thought of as placing a greater financial burden on the patient and society. However, IMRT allows for more conformal dose to the tumor volume while sparing critical structures such as the brachial plexus in the axilla and the small bowel, bladder, rectum, external genitalia, and hip when treating the inguinal region. However, the higher charge per treatment can be mitigated by the use of hypofractionation with fewer treatments.

With regard to optimal radiotherapy dose and fractionation, there is no single standard. Hypofractionated regimens have been favored by some on the basis of radiobiological data suggesting melanoma may be more responsive to higher-dose-per-fraction regimens, although this has not been confirmed clinically [12]. The TROG trial used 48 Gy in 20 fractions. Retrospective studies have generally analyzed outcomes for hypofractionated regimens and have documented impressive NC rates [2, 7, 9, 16-18]. A hypofractionated regimen is more convenient for patients and also less costly. Future studies could compare 48 Gy in 20 fractions to a more hypofractionated regimen.

Although surgery and adjuvant radiotherapy may satisfactorily control nodal disease, the risk of distant metastases and melanoma-related death was relatively high in the patients reported in this study. We report a 2-year overall survival rate of 53% and freedom from distant relapse rate of 27%. This is less than the 5-year overall survival and freedom from distant relapse rates of 51% and 46% to 49%, respectively, reported by others [7, 16]. As noted above, our higher rates are probably a reflection of selection bias (our referral pattern and/or patient population). The introduction of ipilimumab into the multidisciplinary management of metastatic melanoma has significantly improved survival outcomes [19]. Nevertheless, distant metastasis remains a high risk in patients with advanced disease requiring

further improvements in systemic therapy and further investigations into outcomes of combined systemic and local therapies.

Conclusion

Our results show outcomes could be improved in patients with melanoma metastatic to axillary or inguinal lymph nodes who receive adjuvant radiotherapy. We recommend evaluating earlier intervention with postoperative adjuvant radiotherapy and hypofractionated treatment protocols. More effective therapeutics that may be safely combined with radiotherapy are also needed. We acknowledge this study has limitations. It was a small cohort with short median follow-up. Additionally, the retrospective nature of this review inherently creates bias and incomplete data. However, this study reports recurrence and treatment-related outcomes specific for hypofractionated IMRT.

Competing interests

The authors declare no conflict of interest.

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