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Original Article

Hypofractionated or Conventionally Fractionated Adjuvant Radiotherapy After Regional Lymph Node Dissection for High-Risk Stage III Melanoma

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Abstract

Aims: Adjuvant radiotherapy can be beneficial after regional lymph node dissection for high-risk stage III melanoma, as it has been shown to reduce the risk of recurrence in the node field. However, the optimal fractionation schedule is unknown and both hypofractionated and conventionally fractionated adjuvant radiotherapy are used. The present study examined the oncological outcomes of these two approaches in patients treated in an era before effective systemic immunotherapy became available.

Materials and methods: This retrospective cohort study involved 335 patients with stage III melanoma who received adjuvant radiotherapy after therapeutic regional lymph node dissection for metastatic melanoma between 1990 and 2011. Information on tumour characteristics, radiotherapy doses and fractionation schedules and patient outcomes was retrieved from the institution's database and patients' medical records.

Results: Hypofractionated radiotherapy (median dose 33 Gy in six fractions over 3 weeks) was given to 95 patients (28%) and conventionally fractionated radiotherapy (median dose 48 Gy in 20 fractions over 4 weeks) to 240 patients (72%). Five-year lymph node field control rates were 86.0% (95% confidence interval 78.4–94.4%) for the hypofractionated group and 85.5% (95% confidence interval 80.5–90.7%) for the conventional fractionation group ($P = 0.87$). There were no significant differences in recurrence-free survival (RFS) (41.7%, 95% confidence interval 32.5–53.5 versus 31.9%, 95% confidence interval 26.1–38.9; $P = 0.18$) or overall survival (41.2%, 95% confidence interval 32.1–52.8 versus 45.0%, 95% confidence interval 38.7–52.4; $P = 0.77$). On multivariate analysis, extranodal spread was associated with decreased RFS ($P = 0.04$) and the number of resected lymph nodes containing metastatic melanoma was associated with decreased RFS ($P = 0.0006$) and overall survival ($P = 0.01$).

Conclusion: Lymph node field control rates, RFS and overall survival were similar after hypofractionated and conventionally fractionated adjuvant radiotherapy. The presence of extranodal spread and an increasing number of positive lymph nodes were predictive of an unfavourable outcome.

Key words: Adjuvant radiotherapy; dose fractionation; lymph node dissection; melanoma; recurrence; survival

Introduction

The role of adjuvant radiotherapy following regional lymph node dissection for high-risk stage III melanoma was defined by a large randomised trial (ANZMTG 01.02/TROG 02.01) that showed significant improvement in lymph node field control, although there was no impact on overall survival [1]. Based on this trial, consideration of adjuvant radiotherapy was recommended for patients in this clinical situation. However, its role is once again the subject of discussion, now that effective adjuvant systemic treatments are available [2].

Another debate concerns the optimal fractionation schedule of adjuvant radiotherapy, if given. This has not been determined. Radiobiology studies show a large

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'shoulder' on the *in vitro* melanoma cell survival curve [3–5]. This indicates a great ability of some melanoma cells to accumulate sublethal damage, suggesting that hypofractionation may be more effective and that conventional fractionation might have been a reason for the poor results that were originally reported [4,5]. In other words, rather than the total dose, larger fraction doses may be the key to achieving adequate responses to radiotherapy [6,7]. This concept led to the practice of using hypofractionation [8], which is often given as 30–33 Gy in five to six fractions, whereas the only randomised trial of adjuvant radiotherapy for resected stage III melanoma used the fractionation of 2.4 Gy per fraction to a total dose of 48 Gy [1]. A prospective randomised trial of palliative radiotherapy in 126 patients with unresectable melanoma metastases comparing 32 Gy in four fractions and 50 Gy in 20 fractions showed no difference in the response rates [9]. Currently, there is no consensus and it has been suggested that the evidence for hypofractionation was potentially biased by small numbers, a wide range of tumour sizes and total doses, and short follow-up [10].

The aim of the present study was to compare the oncological outcomes of hypofractionated and conventionally fractionated adjuvant radiotherapy following regional lymph node dissection for high-risk melanoma metastases in patients treated in an era before effective systemic therapy. The primary end point was node field recurrence (as a first recurrence). Secondary end points were recurrence-free survival (RFS) and overall survival. Risk factors associated with lymph node field recurrence (as a first recurrence), RFS and overall survival were also assessed.

Patients, Materials and Methods

Study Population and Treatment

Data for patients who had undergone regional lymph node dissection for a first lymph node metastasis followed by adjuvant radiotherapy between 1990 and 2011 were retrieved from our institution's database, which contains comprehensive prospectively collected data. Patients with recurrent nodal disease after previous node surgery or with distant metastasis at the time of radiotherapy and patients without adequate follow-up were excluded. All patients had given informed consent for their data to be collected and used for research purposes. The research protocol was approved by our institution's Research Committee.

The choice of fractionation schedule was at the discretion of each patient's treating radiation oncologist. Patients received either conventionally fractionated radiotherapy (usually 48–50.4 Gy in 20 fractions of 1.8–2.5 Gy, five times per week) or hypofractionated radiotherapy (33 Gy in six fractions of 5–6 Gy twice a week). Due to the wide geographical distribution of patients referred to the Melanoma Institute Australia (MIA), some patients in the study chose to receive radiotherapy at a local facility closer to their place of residence.

Recurrence at any site was defined by the detection of any clinical, histological or radiographic evidence of tumour. Node field recurrence was defined as soft-tissue or lymph node recurrence within the anatomical lymph node field.

Statistical Analysis

Patients' characteristics were summarised using standard descriptive statistics. Continuous variables were described by their median (range) and categorical variables by their frequency (proportion). The primary end point was lymph node field recurrence (as a first recurrence). This end point was consistent with the ANZMTG 01.02/TROG 02.01 trial end point. Secondary end points were RFS and overall survival. Survival times were calculated from the first date of radiotherapy to the date of node field recurrence, recurrence (local, regional or distant), death due to melanoma or death from any cause. Patients without recurrence were censored at either their date of death or the last date known alive. Survival outcomes were described graphically using the Kaplan–Meier method and stratified by fractionation schedule (conventional versus hypofractionated). Univariate Cox regression was carried out to assess the risk factors associated with node field recurrence, RFS and overall survival. The investigated risk factors included fractionation schedule, known or unknown primary melanoma, RT treatment facility, presence or absence of extranodal spread, number of positive lymph nodes, size of largest positive lymph node and site of node field. Multivariate models were developed using stepwise backward selection on the initial models that included fractionation schedule and variables with a P-value $< 20\%$ from the univariate analysis. Ulceration was not included in the multivariate models because this parameter was missing in 30% of cases, attributed to the large number of unknown primaries. P-value was based on Wald statistics to test the global effect of the covariate; $P < 0.05$ was considered significant. Acute skin toxicity data were scored using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) or Radiation Therapy Oncology Group (RTOG) toxicity criteria. Statistical analyses were carried out using SPSS version 26.0 (IBM Corporation, Armonk, NY, USA), SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.6.1 (R Core Team, Vienna, Austria).

Results

The inclusion criteria for the study were met by 335 patients (Table 1). The indications for lymph node dissection were palpable metastatic disease in 304 patients (91%) positive sentinel nodes in 28 patients (8%) and an elective lymph node dissection with positive nodes in three patients (1%). Of the 137 patients with axillary nodal disease, 131 underwent level I–III axillary node dissection. Six patients had both a level I–III axillary dissection and various levels of cervical node dissection. The extent of the lymph node

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Table 1
Baseline characteristics

Characteristics	Hypofractionated radiotherapy ($n = 95$)	Conventionally fractionated radiotherapy ($n = 240$)	*P*-value
Age at nodal disease diagnosis			
Median (range)	59.0 (23.0–90.0)	58.0 (19.0–88.0)	0.6296
Gender			
Female	18/95 (19%)	63/240 (26%)	0.1594
Male	77/95 (81%)	177/240 (74%)	
Breslow thickness			
Median (range)	2.3 (0.2–21.0)	2.1 (0.0–23.0)	0.2994
Location of the primary			
Head and neck	35/95 (37%)	57/240 (24%)	0.0748
Trunk	23/95 (24%)	72/240 (30%)	
Upper limb	4/95 (4%)	19/240 (8%)	
Lower limb	14/95 (15%)	52/240 (22%)	
Unknown primary	19/95 (20%)	40/240 (17%)	
Mitotic rate (59 unknown primary, 35 missing data)			
Absent	8/69 (12%)	16/172 (9%)	0.591
Present	61/69 (88%)	156/172 (91%)	
Ulceration (59 unknown primary, 41 missing data)			
No	42/66 (64%)	96/169 (57%)	0.339
Yes	24/66 (36%)	73/169 (43%)	
Type of surgery			
Therapeutic lymph node dissection	85/95 (89%)	219/240 (91%)	0.334
Completion lymph node dissection	8/95 (8%)	20/240 (8%)	
Elective lymph node dissection	2/95 (2%)	1/240 (0.4%)	
Node field			
Neck	45/95 (47%)	70/240 (29%)	0.005
Axilla	34/95 (36%)	103/240 (43%)	
Groin	16/95 (17%)	67/240 (28%)	
Number of nodes identified in specimen			
Total median (range)	24 (5–83)	24 (4–74)	0.171
Neck	36 (9–69)	34 (12–74)	
Axilla	24 (5–83)	24 (7–61)	
Groin	11 (8–25)	17 (4–38)	
Number of positive nodes			
Total median (range)	3 (1–83)	3 (1–51)	0.086
Neck	2 (1–44)	2 (1–26)	
Axilla	4 (1–83)	3 (1–51)	
Groin	3 (1–16)	4 (1–22)	
Presence of extranodal spread (five missing data)			
No	30/92 (33%)	106/238 (45%)	0.048
Yes	62/92 (67%)	132/238 (55%)	
Size of largest nodal deposit (mm)			
Median (range)	28.5 (5–120)	30 (5–120)	0.557
Radiotherapy treatment centre			
Melanoma Institute Australia	90/95 (95%)	136/240 (57%)	<0.001
Other	5/95 (5%)	104/240 (43%)	

dissection varied in the 115 patients who had a cervical node dissection. In 28 patients, this was a level I–V+parotid (P) dissection, 19 patients had level II–V, 18 had level II–V+P, 17 had level I–V, 11 had level I–III+P, seven had level I–IV+P, three had level III–V and two had level I–III dissections. In solitary cases, the following levels were dissected: level I–IV+ axillary I–III, level I–V, level II–III+P, level II–IV, level II–IV+P, level V, level V + P and P+suprahyoid region. In two patients the extent of the cervical dissection was not recorded. Of the 83 patients with inguinal node disease, 34 had an inguinal dissection and 49 had ilio-obturator-inguinal dissection.

Hypofractionated radiotherapy (median dose 33 Gy in six fractions over 3 weeks) was given to 95 patients (28%) and conventionally fractionated radiotherapy (median dose 48 Gy in 20 fractions over 4 weeks) to 240 patients (72%). Most of the baseline characteristics and burdens of nodal disease were well balanced between the two radiotherapy groups, except for node field site, presence of extranodal spread and radiotherapy treatment centre (Table 1). The

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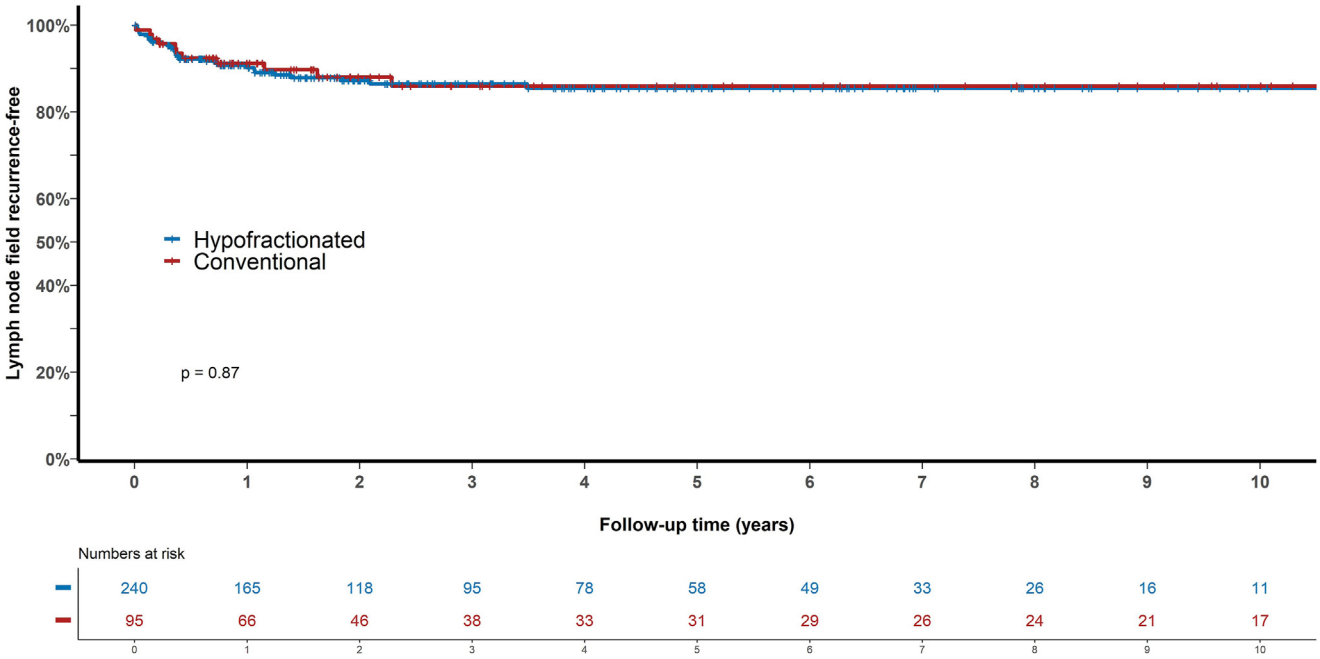

Fig 1. Lymph node field control: percentage of patients without lymph node field recurrence (as a first recurrence).

median follow-up was 26 months (range 1 month–21 years) and there was no difference between the hypofractionation group (25 months, range 2 months–21 years) and the conventional fractionation group (26 months, range 1 month–16 years). Patients treated at MIA had a slightly longer duration of follow-up than patients treated at other radiotherapy treatment centres (median 27 months versus 24 months).

In total, 226 patients (68%) received radiotherapy at MIA and the remaining 109 patients (33%) had their radiotherapy at other facilities. Of the patients treated at MIA, 58% received conventional fractionation, whereas 95% of those treated at other facilities did so. The median interval between surgery and the start of radiotherapy was 6 weeks (range 0–22 weeks). In five patients, radiotherapy treatment was ceased early; in four this was due to disease progression and one patient decided not to complete the treatment.

Adjuvant systemic treatment was given to 52 patients (16%); 39 of them received a vaccine or participated in an adjuvant vaccine therapy trial and 13 received interferon-α [11–16]. None of the patients in this series received modern adjuvant therapy with an immune checkpoint inhibitor or a BRAF/MEK inhibitor.

In the hypofractionation group, 12 of the 95 patients (13%) developed a first recurrence in or adjacent to the irradiated field and in the conventional fractionation group this occurred in 29 of the 240 patients (12%; $P = 0.87$) (Figure 1). Five-year lymph node field control rates were almost equal, being 86% (95% confidence interval 78.4–94.4%) in the hypofractionated group and 85.5% (95% confidence interval 80.5–90.7%) in the conventional fractionation group. Neither univariate analysis nor multivariate analysis revealed any factors predictive of node field recurrence (Table 2).

Most recurrences arose within the first 3 years (Figure 2). Five-year RFS rates were 41.7% (95% confidence interval 32.5–53.5) in the hypofractionation group and 31.9% (95% confidence interval 26.1–38.9) in the conventional fractionation group ($P = 0.18$). Multivariate analysis showed that the presence of extranodal extension ($P = 0.04$) and an increasing number of positive lymph nodes ($P = 0.0006$) were predictive of reduced RFS.

There was no significant difference in overall survival between the two groups ($P = 0.77$) (Figure 3). The 5-year overall survival rates were 41.2% (95% confidence interval 32.1–52.8) in the hypofractionation group and 45.0% (95% confidence interval 38.7–52.4) in the conventional fractionation group. An increasing number of positive lymph nodes was predictive of death on multivariate analysis ($P = 0.01$) (Table 2).

Acute skin toxicity data could be quantified into an NCI CTCAE or RTOG score in 233 of the 335 patients (70%). Grade 2 acute skin toxicity was documented in 24 patients (44%) in the hypofractionated group and in 108 patients (60%) in the conventional fractionation group. Grade 3 acute skin toxicity was documented in zero (0%) and 12 patients (7%) and grade 4 acute skin toxicity in five (9%) and 13 patients (7%), respectively. The following late toxicity data could be extracted from the patient files: atrophy, fibrosis and/or induration were noted in 28 patients (29%) in the hypofractionation group and in 51 patients (21%) in the conventional fractionation group. Lymphoedema was documented in 32 patients (34%) and 106 patients (44%), respectively. The relationship to either lymph node dissection or radiotherapy treatment could not be

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Table 2
Univariate/multivariate Cox regression analysis

Variables	*n*	Lymph node field recurrence				Recurrence-free survival			
		Univariate		Multivariate		Univariate		Multivariate	
		HR (95% CI)	*P*-value*	HR (95% CI)	*P*-value*	HR (95% CI)	*P*-value*	HR (95% CI)	*P*-value*
Radiotherapy type									
Hypofractionated radiotherapy	95	1		1		1		1	
Conventional radiotherapy	240	1.06 (0.53–2.12)	0.87	1.27 (0.45–3.54)	0.64	1.24 (0.91–1.69)	0.18	0.77 (0.56–1.06)	0.11
Unknown primary									
No	277	1				1			
Yes	58	0.34 (0.11–1.11)	0.07			0.80 (0.55–1.16)	0.24		
Institution									
Other institution	109	1		1		1			
Melanoma Institute Australia	226	0.57 (0.31–1.07)	0.08	1.69 (0.79–3.64)	0.18	0.90 (0.67–1.21)	0.48		
Presence of extranodal spread									
No	136	1				1		1	
Yes	194	1.30 (0.69–2.45)	0.42			1.38 (1.04–1.83)	0.03	1.35 (1.01–1.80)	0.04
Number of positive lymph nodes									
0–1	99	1				1		1	
2–3	116	1.70 (0.72–4.02)	0.18			1.36 (0.94–1.95)	0.0002	1.39 (0.96–2.01)	0.0006
>	120	2.20 (0.95–5.08)				2.05 (1.44–2.90)		2.00 (1.39–2.82)	
Node field									
Axilla	131	1		1		1			
Groin	83	0.94 (0.43–2.09)	0.97	0.94 (0.39–2.14)	0.77	1.29 (0.92–1.80)	0.05		
Neck	121	0.91 (0.45–1.85)		0.74 (0.30–1.82)		0.84 (0.61–1.16)			

Variables	*n*	Overall survival			
		Univariate		Multivariate	
		HR (95% CI)	*P*-value*	HR (95% CI)	*P*-value*
Radiotherapy type					
Hypofractionated radiotherapy	95	1		1	
Conventional radiotherapy	240	0.94 (0.69–1.29)	0.70	1.04 (0.75–1.45)	0.80
Unknown primary					
No	277	1			
Yes	58	0.79 (0.53–1.17)	0.23		
Institution					
Other institution	109	1			
Melanoma Institute Australia	226	1.12 (0.81–1.54)	0.49		
Presence of extranodal spread					
No	136	1		1	
Yes	194	1.42 (1.05–1.92)	0.02	1.35 (0.99–1.83)	0.06
Number of positive lymph nodes					
0–1	99	1		1	
2–3	116	1.38 (0.94–2.02)	0.0007	1.35 (0.91–2.00)	0.01
>	120	2.02 (1.40–2.91)		1.80 (1.22–2.67)	
Node field					
Axilla	131	1		1	
Groin	83	1.10 (0.77–1.57)	0.07	1.00 (0.69–1.42)	0.38
Neck	121	0.73 (0.52–1.02)		0.79 (0.55–1.12)	

CI, confidence interval; HR hazard ratio.
* Based on Wald statistics to test the global effect of the covariate.

distinguished. Long-term wound issues were documented in four patients (4%) and six patients (3%), respectively. Osteoradionecrosis occurred in one patient who was treated with conventional fractionation.

Discussion

In the only completed randomised trial of adjuvant radiotherapy following regional node dissection for

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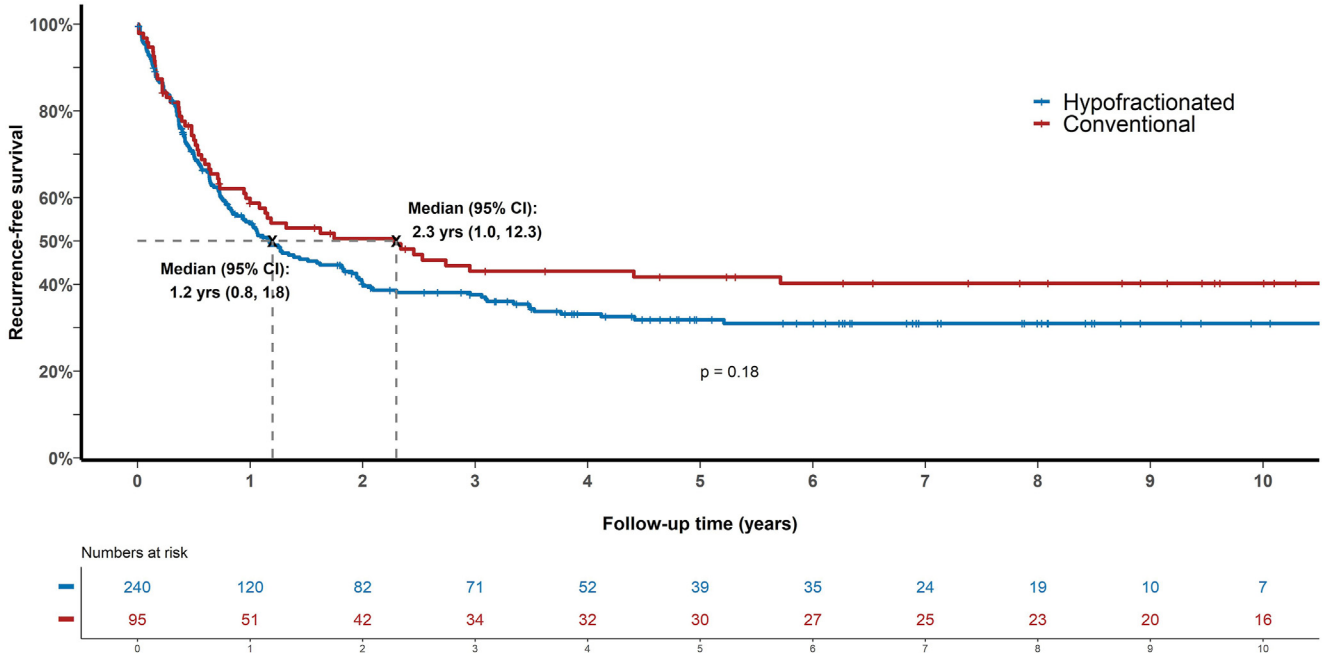

Fig 2. Recurrence-free survival.

high-risk stage III melanoma, 48 Gy in 20 fractions was shown to significantly improve node field control after regional lymph node dissection, but there was no overall survival benefit [1]. The present study showed that the risk of node field recurrence, RFS and overall survival with hypofractionated and conventionally fractionated adjuvant radiotherapy were similar. There was no indication of increased toxicity in the hypofractionation group. With the availability of effective adjuvant systemic therapy, the role of adjuvant radiotherapy for resected high-risk stage III melanoma needs to be re-evaluated. Adjuvant radiotherapy is less frequently recommended, whereas adjuvant systemic therapies with immune checkpoint inhibitors or targeted therapy have become standard. Recent studies suggest an immunogenic effect when combining radiotherapy with concurrent checkpoint inhibition, especially with the use of hypofractionated radiotherapy [17–19]. This development warrants further investigation of radiotherapy fractionation in patients with melanoma. In addition to the potential immunogenic effect, a hypofractionated schedule would also mean six treatment visits instead of 20, which would be easier for patients and reduce demand on healthcare resources. During the recent COVID-19 pandemic, the use of hypofractionation in cancer patients has been successfully expanded to minimise treatment time [20].

Finally, adjuvant radiotherapy remains an important option for patients who are not eligible for adjuvant systemic therapy (such as those patients with a history of significant autoimmune disease or transplantation).

Our results correspond with those of three previous studies that have compared hypofractionated and conventionally fractionated radiotherapy in patients with melanoma. In the only prospective study, the RTOG 83-05 trial directly compared 4 × 8 Gy in 62 patients with 20 × 2.5 Gy in 64 patients [9]. However, the radiotherapy was not used as adjuvant therapy, but its purpose was palliation for macroscopic disease. There was no difference in the measurable response rate between the two arms, but toxicity was slightly higher in the hypofractionation group. Chang *et al.* [21] retrospectively assessed locoregional control in patients treated with nodal radiotherapy with curative intent. They compared 5 × 6 Gy in 41 patients with 30 × 2 Gy in 14 patients and found no difference in node field control, melanoma-specific survival or overall survival. In the combined group, 5-year node field control was 87%, melanoma-specific survival 57% and overall survival 46%, after a median follow-up of 4.4 years. The authors reported minimal toxicity in the hypofractionation group. Patient selection, however, was different from selection for our study, as 52% of patients were treated after recurrence of disease, whereas our cohort comprised solely patients with first nodal disease presentation. Also, 87% of their patients had undergone a cervical lymph node dissection, which was the case in only 48% of our patients. In the most recently reported study, Mendenhall *et al.* [22] compared 42 patients treated with hypofractionated radiotherapy and 40 patients who underwent conventionally fractionated radiotherapy in the adjuvant setting because they were considered to be at high risk of locoregional recurrence. In 78% of patients, the nodal disease was located in the head and neck region. Most (62%) patients were treated for recurrent disease after initial surgery; the others were clinically disease-free after initial surgery. In the latter group, four patients (5%) did not have sentinel lymph node biopsy or lymph node dissection, so their nodal status at the time of radiotherapy was

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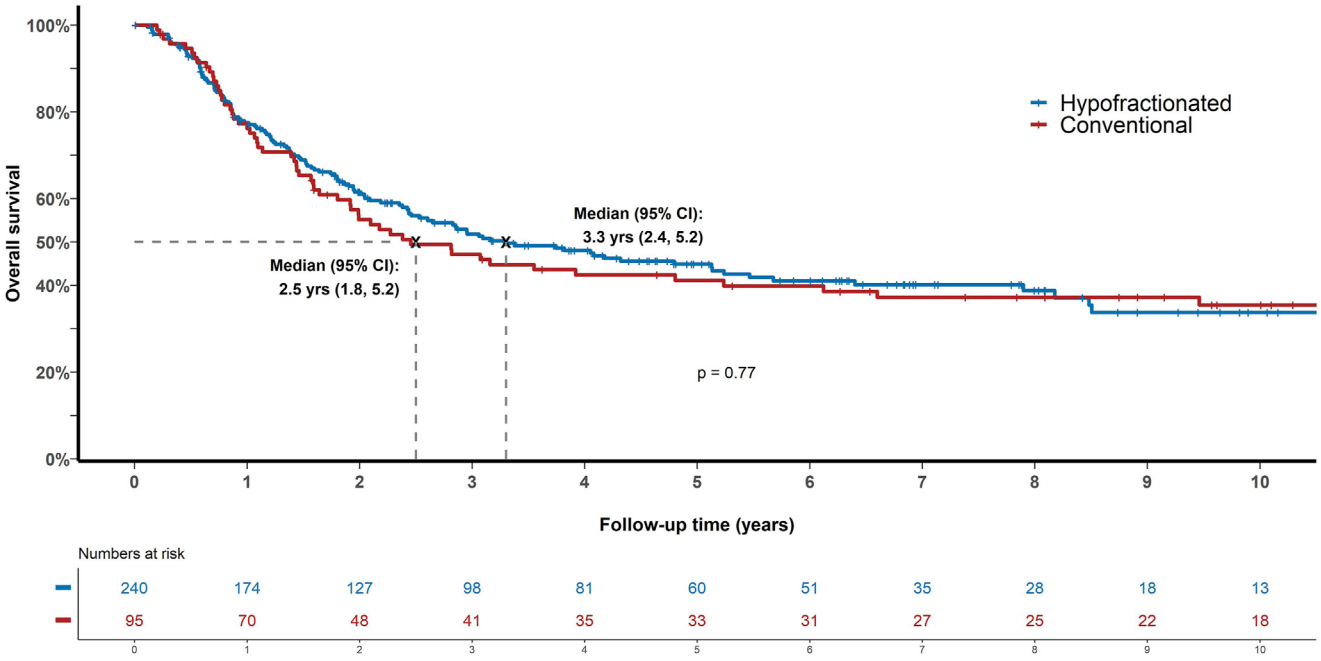

Fig 3. Overall survival.

unknown. There was no significant difference in 5-year node field control when comparing the fractionation schedules. In the combined group of 82 patients, node field control was 82%, melanoma-specific survival 56% and overall survival 43% after a median follow-up of 3 years. Toxicity was modest in the combined group.

We assessed the risk factors associated with node field recurrence, RFS and overall survival. Extranodal spread was associated with worse RFS. An increasing number of positive lymph nodes was associated with worse RFS and overall survival. This is in line with the findings from other studies [23–28].

The main strength of the present study was the size of the cohort, to our knowledge the largest comparing fractionation schedules in a strictly adjuvant setting after regional lymph node dissection for metastatic melanoma. One of the risk factors we had planned to assess was the size of the metastatic lymph nodes, but incompleteness of the available data prevented a meaningful analysis. As 91% of patients had undergone an initial therapeutic lymph node dissection for palpable disease, the sizes of positive lymph nodes were unlikely to have been documented by pathologists as thoroughly as in patients undergoing sentinel lymph node biopsy. Follow-up was somewhat shorter in the group of patients receiving radiotherapy at other institutions, which may have influenced the assessment of outcomes for this subgroup.

The retrospective nature of our study limited reliable assessment of acute and late toxicity; therefore, our toxicity data should be interpreted with caution. Hypofractionated radiotherapy is potentially associated with more late toxicity, such as fibrosis and lymphoedema. However, this suggestion is based on the results of older retrospective studies using outdated radiotherapy techniques, and hypofractionation has not been prospectively compared with conventional fractionation in the adjuvant setting in patients with melanoma [8,27,29]. In another adjuvant radiotherapy setting, whole-breast irradiation after breast-conserving surgery has been studied prospectively and long-term follow-up data have shown no difference in late toxicity effects between hypofractionated and conventionally fractionated radiotherapy schedules [30]. Furthermore, advances in radiotherapy treatment planning and the use of image guidance and motion management allow for better sparing of normal structures and, hence, toxicity is probably reduced. We emphasise the importance of prospectively collected toxicity data to further determine the role of hypofractionated radiotherapy.

Conclusions

This study confirms that adjuvant hypofractionated radiotherapy to the node field is an option after lymph node dissection in patients with high-risk nodal melanoma metastases, with outcomes similar to those achieved by conventionally fractionated radiotherapy. There were no significant differences in the risk of node field recurrence ($P = 0.87$), RFS ($P = 0.2$) or overall survival ($P = 0.77$). In both groups, on multivariate analysis, extranodal spread was associated with decreased RFS ($P = 0.04$) and the number of metastatic lymph nodes was associated with decreased RFS and overall survival ($P = 0.0006$, $P = 0.01$, respectively). Future studies should investigate the benefit of radiotherapy in patients with high-risk nodal disease receiving contemporary adjuvant systemic therapy.

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Conflicts of Interest

J.F. Thompson reports a relationship with BMS Australia that includes: board membership and consulting or advisory. J.F. Thompson reports a relationship with MSD Australia that includes: board membership and consulting or advisory. J.F. Thompson reports a relationship with GSK that includes: board membership, consulting or advisory, and travel reimbursement. J.F. Thompson reports a relationship with Provectus Inc. that includes: board membership, consulting or advisory, and travel reimbursement. J.F. Thompson reports a relationship with Novartis that includes: speaking and lecture fees. A. Hong reports a relationship with QBiotics Group Limited that includes: board membership and consulting or advisory. A. Hong reports a relationship with Bayer that includes: board membership and consulting or advisory.

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Author Contributions

LHJH is the guarantor of integrity of the entire study. LHJH, ON and AH were responsible for study concepts and design. LHJH and AH were responsible for literature research. LHJH and AH carried out experimental studies/data analysis.

MD, SL and LHJH carried out the statistical analysis. LHJH prepared the manuscript. AH, SL, ON, JFT and LHJH were responsible for editing the manuscript.

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