Received: 29 August 2022 | Accepted: 7 March 2023

DOI: 10.1002/jso.27245

RESEARCH ARTICLE

Journal of SURGICAL ONCOLOGY WILEY

Adjuvant radiotherapy after salvage surgery for melanoma recurrence in a node field following a previous lymph node dissection

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Funding information
Groningen Melanoma and Sarcoma Foundation; Australian National Health and Medical Research Council, Grant/Award Number: APP1093017; Vreedefonds; Melanoma Institute Australia

Abstract

Background and Objectives: Adjuvant radiotherapy (RT) can be given to melanoma patients following salvage surgery for node field recurrence after a previous regional node dissection, but the value of this treatment strategy is poorly documented. This study evaluated long-term node field control and survival of patients treated in this way in an era before effective adjuvant systemic therapy became available.

Methods: Data for 76 patients treated between 1990 and 2011 were extracted from an institutional database. Baseline patient characteristics, treatment details and oncological outcomes were analysed.

Results: Adjuvant RT with conventional fractionation (median dose 48 Gy in 20 fractions) was given to 43 patients (57%) and hypofractionated RT (median dose 33 Gy in 6 fractions) to 33 patients (43%). The 5-year node field control rate was 70%, 5-year recurrence-free survival 17%, 5-year melanoma-specific survival 26% and 5-year overall survival 25%.

Conclusions: Salvage surgery with adjuvant RT achieved node field control in 70% of melanoma patients with node field recurrence following a prior node dissection. However, disease progression at distant sites was common and survival outcomes

Abbreviations: ANZMTG, Australia and New Zealand Melanoma Trials Group; CI, confidence interval; MIA, Melanoma Institute Australia; MSS, melanoma-specific survival; OS, overall survival; RFS, relapse-free survival; RT, radiotherapy; TROG, Trans-Tasman Radiation Oncology Group.

were poor. Prospective data will be required to assess outcomes for contemporary combinations of surgery, adjuvant RT and systemic therapy.

KEYWORDS
adjuvant radiotherapy, lymph node metastasis, melanoma

1 | INTRODUCTION

The optimal combination and sequencing of surgery, radiotherapy (RT) and systemic therapy in melanoma patients with lymph node metastases are the subjects of ongoing investigation. RT is a long-established adjuvant treatment option after lymph node dissection for patients with high-risk stage III melanoma.[1–6] Published regional control rates after therapeutic lymph node dissection range from 40% to 85%, whereas control rates of 81%–95% have been reported with the addition of RT.[7] Despite this improvement in node field control, adjuvant RT does not provide a melanoma-specific survival (MSS) benefit or an overall survival (OS) benefit because of the high incidence of distant metastases in this cohort of patients.[6] Effective adjuvant systemic therapy is now available and is increasingly given in lieu of adjuvant RT.[8,9] Based on a subgroup analysis of their landmark randomized trial, undertaken in an era when potentially effective adjuvant systemic therapy was not available, Henderson et al. suggested that adjuvant RT after salvage surgery for recurrence after lymph node dissection might also be of benefit in these high-risk patients, but this has not been adequately studied.[10] Nor has the combined effect of both adjuvant RT and systemic therapy in this clinical situation been assessed.

The present study examined the outcome of further (salvage) surgery followed by adjuvant RT in patients who developed isolated node field recurrence after a previous lymph node dissection for stage III melanoma, but who did not receive adjuvant systemic therapy with a checkpoint inhibitor or with agents targeting the MAP kinase pathway. The primary study aim was to assess the frequency of further node field recurrence, and secondary aims were to determine relapse-free survival (RFS), MSS and OS. Our hypothesis was that adjuvant RT in this setting would result in node field control comparable to that achieved by immediate adjuvant RT after an initial therapeutic node dissection. A further objective of the study was to provide baseline data that would allow the efficacy of adjuvant systemic therapy in this setting to be assessed.

2 | PATIENTS AND METHODS

2.1 | Patients

Patients were eligible for the study if they had developed node field recurrence after a previous lymph node dissection for microscopic or macroscopic (clinically apparent) metastatic melanoma, had no evidence of disease at any other site and had undergone further surgery followed by adjuvant RT. Patients treated between 1990 and 2011 were identified from the Melanoma Institute Australia (MIA) database, which contains comprehensive prospectively collected data. The study cohort included longer follow-up of 29 patients treated between 1990 and 1998, some of whom have been reported previously.[1] Patients with an initial negative elective lymph node dissection, those with distant metastasis (beyond the regional node field) at the time of their further surgery and those without complete follow-up data were excluded. All patients had given informed consent for their data to be collected and used for research purposes. The study protocol was approved by the MIA Research Committee, and ethics approval was obtained from the Sydney Local Health District Ethics Office (protocols X15-031 and 2019/ETH06854).

2.2 | RT

The RT fractionation schedule for each patient was at the discretion of the treating radiation oncologist. Conventionally fractionated RT was defined as 1.8–2.5 Gy per fraction, usually a total dose of 48 Gy in 20 fractions, 5 fractions per week over 4 weeks. Hypofractionated RT was defined as 5–6 Gy per fraction, usually a total dose of 33 Gy in six fractions, two fractions per week over 3 weeks. Due to the wide geographic distribution of patients who had surgery at MIA, some chose to receive RT at a local facility closer to their place of residence.

2.3 | Follow-up

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

2.4 | Statistical analysis

Patient characteristics were summarized using standard non-parametric descriptive statistics, given the moderate cohort sample size. Continuous variables were described by their median (range) and categorical variables by their frequency (proportion). The study endpoints were node field recurrence (as a first recurrence), RFS, MSS and OS. Survival times were calculated from the first date of RT to the date of node field recurrence, local, regional or distant

TABLE 1 Baseline patient characteristics and treatment details.

Patient characteristics (total number = 76)	
Median age at the time of RT (years)	60 (range 31–89)
Gender	
Male	47 (62%)
Female	29 (38%)
Primary site	
Head and neck	16 (21%)
Trunk	33 (43%)
Upper limb	9 (12%)
Lower limb	15 (20%)
Unknown primary	3 (4%)
Median Breslow thickness of the primary (range)	2.2 mm (0.5–13.0 mm)
Ulceration	
Yes	20 (26%)
No	45 (59%)
Unknown	11 (15%)
Patients with multiple primaries	9 (12%)
Indication for the initial node dissection	
Therapeutic lymph node dissection	46 (61%)
Completion of lymph node dissection	26 (34%)
Elective lymph node dissection	4 (5%)
Node field	
Axilla	37 (49%)
Groin	20 (26%)
Neck	19 (25%)
Initial node dissection	
Median number of excised/positive nodes (range)	20 (5–86)/2 (1–31)
Axilla	19 (5–51)/1 (1–13)
Neck	35 (11–86)/1 (1–31)
Groin	15 (5–27)/2 (1–11)
Involved surgical margin	1 (1%)
Extracapsular extension	24 (32%)
Surgery for the node field recurrence	
Median number of excised/positive nodes (range)[a]	0 (0–42)/0 (0–12)
Axilla	0 (0–42)/0 (0–10)
Neck	1 (0–16)/0 (0–6)
Groin (inguinal and pelvic)	0 (0–22)/0 (0–12)
Involved surgical margin	19 (25%)
Extracapsular extension	18 (24%)

Abbreviation: RT, radiotherapy.

[a]Some patients had surgical excision of soft tissue recurrence, therefore no nodes were excised.

recurrence, death due to melanoma or death from any cause, respectively. Patients without recurrence were censored at either their date of death or the last date that they were known to be alive. Survival outcomes were described graphically using the Kaplan–Meier method. Statistical analyses were performed using SPSS version 26.0 (IBM Corporation) and R version 3.6.1 (R Core Team). A two-sided *p*-value of <0.05 was considered statistically significant.

3 | RESULTS

A total of 76 patients with a median age of 60 years received RT after resection of one or more melanoma recurrences in a previously dissected lymph node field (see Table 1). The indications for the initial lymph node dissection were macroscopic nodal metastatic disease in 46 patients (61%), completion lymph node dissection after a positive sentinel lymph node biopsy in 26 patients (34%) and elective lymph node dissection, with involved nodes identified, in the remaining 4 patients (5%).

The extent of the initial node dissection and disease burden is documented in the Table. The initial operation was a full level I–III axillary dissection in 32 of the 37 patients (87%) with axillary nodal disease. An inguinal dissection was performed in 9 of the 20 patients (45%) with groin node disease, and iliac–obturator–inguinal dissection in the other 11 (55%). The extent of the operation varied in the 19 patients with disease in cervical nodes. Seven patients (37%) had a level II–V dissection, five patients (21%) had a level I–V dissection, three patients (16%) had a level I–V plus parotid dissection and the remaining patients had various extents of neck dissection.

3.1 | Salvage surgery

The median time to diagnosis of node field recurrence after initial node dissection was 8 months (range 23 days to 17 years). Twenty-nine patients (38%) had a nodal recurrence and 47 patients (62%) had an apparently nonnodal soft tissue recurrence within the anatomical node field. The salvage surgery in all these patients was

performed with the objective of obtaining complete macroscopic clearance of the recurrent disease in the node field. It involved local excision of the scar and/or soft tissue recurrence ($n = 40$), local excision of an involved node ($n = 10$) or a full redo lymph node dissection ($n = 26$), as considered appropriate for the individual patient to achieve macroscopic clearance. However, involved surgical margins were reported in 25% of patients, and there was extranodal spread in 14 of the 29 patients with nodal recurrence (48%). The median time between salvage surgery and the commencement of RT was 40 days (range 9–113 days). Thirteen patients (17%) underwent more than one surgical procedure to remove node field recurrences before receiving adjuvant RT to the node field. The median time between surgical procedures when there was more than one procedure was 3 months (range 1–13 months).

3.2 | RT dosage and fractionation

Conventional fractionated RT (median dose 48 Gy over 4 weeks) was given to 43 patients (57%) and hypofractionated RT (median dose 33 Gy over 3 weeks) to 33 patients (43%). In total, 66 patients (87%) received their RT at MIA, and the remaining 10 patients (13%) at other facilities. Equal numbers of the patients treated at MIA received hypofractionated RT and conventionally fractionated RT. Patients treated at other facilities all received conventional RT fractionation. No patient failed to complete their planned course of RT due to toxicity.

3.3 | Other adjuvant treatments

No patients in this series received adjuvant systemic therapy with an immune checkpoint inhibitor or a BRAF/MEK inhibitor. However, other forms of adjuvant systemic treatment were provided to 34 patients (45%). Adjuvant interferon-α was given to 4 patients, while 32 patients received either adjuvant vaccine therapy or participated in the treatment arm of an adjuvant vaccine therapy trial.[11–16]

3.4 | Treatment outcome

The primary endpoint was node field recurrence (as a first recurrence). During RT, 13 of the 76 patients (17%) developed a melanoma recurrence (three in-transit metastasis, nine further node field recurrence and one distant metastasis). RT was terminated early in two patients (one with node field recurrence and one with distant metastasis). After RT, another nine patients developed a node field recurrence, three of whom also had concurrent local recurrence or distant metastasis). This resulted in a total of 18 patients (24%) with node field recurrence as a first recurrence at the time of the last follow-up (Figure 1). Node field recurrence as a first recurrence occurred in 15.6% of the patients treated with hypofractionated RT and in 29.5% of those treated with conventional RT ($p = 0.16$). The node field recurrences were in the irradiated field in 12 patients (67%) and just outside the irradiated field but within the anatomical node field in 6 patients (33%). Overall the 5-year node field control

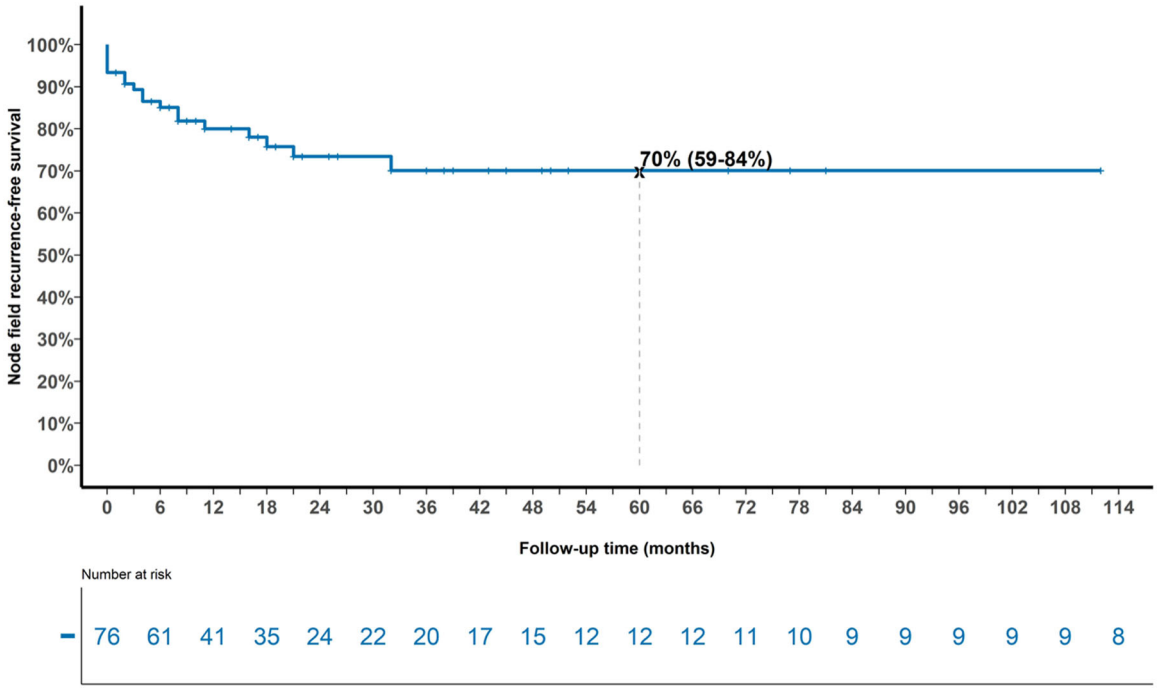

FIGURE 1 Kaplan–Meier curves for adjuvant radiotherapy after surgical treatment of node field recurrence following a prior node dissection for stage III melanoma ($n = 76$). Node field control.

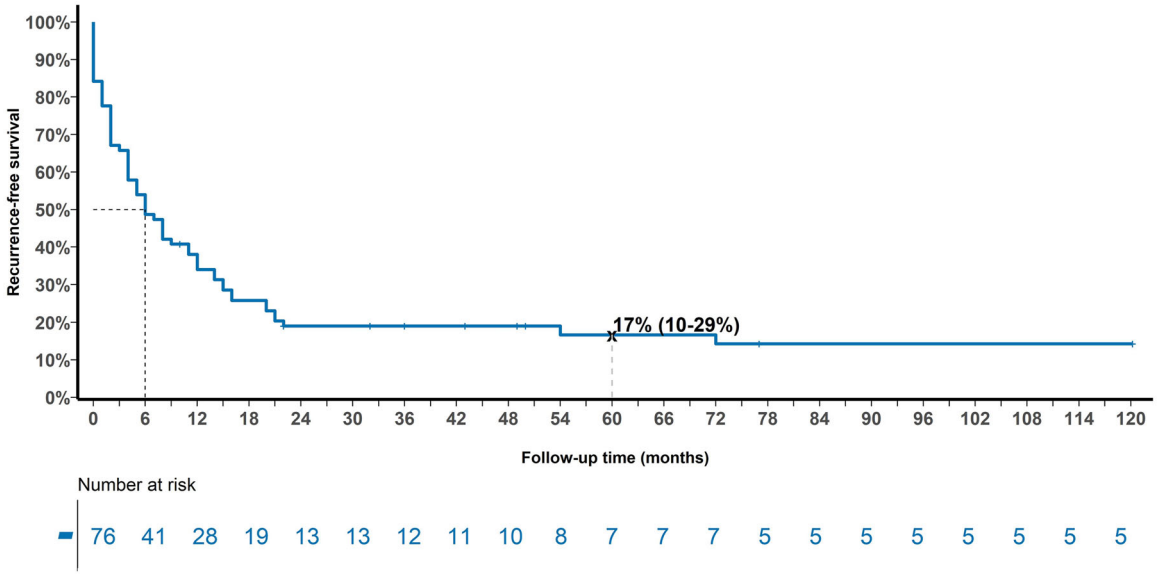

FIGURE 2 Kaplan–Meier curves for adjuvant radiotherapy after surgical treatment of node field recurrence following a prior node dissection for stage III melanoma ($n = 76$). Recurrence-free survival.

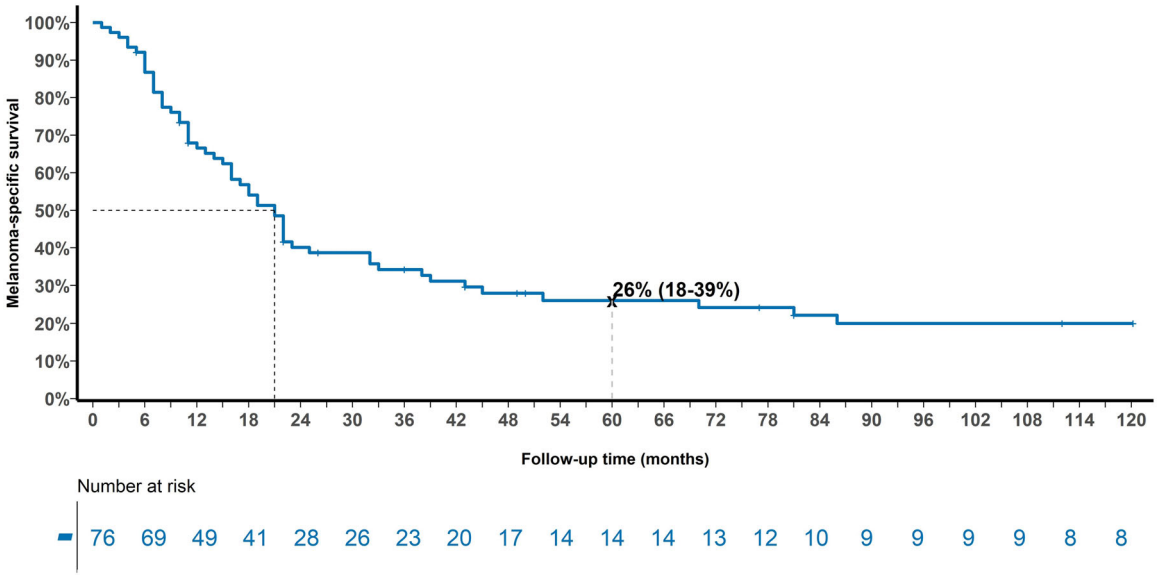

FIGURE 3 Kaplan–Meier curves for adjuvant radiotherapy after surgical treatment of node field recurrence following a prior node dissection for stage III melanoma ($n = 76$). Melanoma-specific survival.

rate was 70% (95% confidence interval [CI]: 59%–84%). At the time of the last follow-up, 13 patients (17%) remained disease-free, and 60 of the 76 patients (79%) had developed distant metastatic disease (Figure 2). The 5-year RFS was 17% (95% CI: 10%–29%). The 5-year MSS was 26% (95% CI: 18%–39%). At the last follow-up, 58 patients had died (37 of the 40 patients who had local excision of the recurrence, 7 of the 10 patients who had excision of involved nodes and 14 of the 26 patients who had a full redo node dissection). Most of the death occurred during the first 24 months. The 5-year OS was 25% (95% CI: 17%–38%, Figures 3 and 4). The median follow-up duration for the entire group was 19 months (range 1–246 months) in the total group. The median follow-up duration for the group that remained disease-free was 50 months (range 10–246 months).

4 | DISCUSSION

The efficacy of adjuvant nodal RT for recurrent melanoma after a previous therapeutic regional lymph node dissection has not been extensively described. Despite the recurrence and the presence of high-risk features such as a positive margin in 25% of patients and extranodal spread in almost half of the patients with nodal

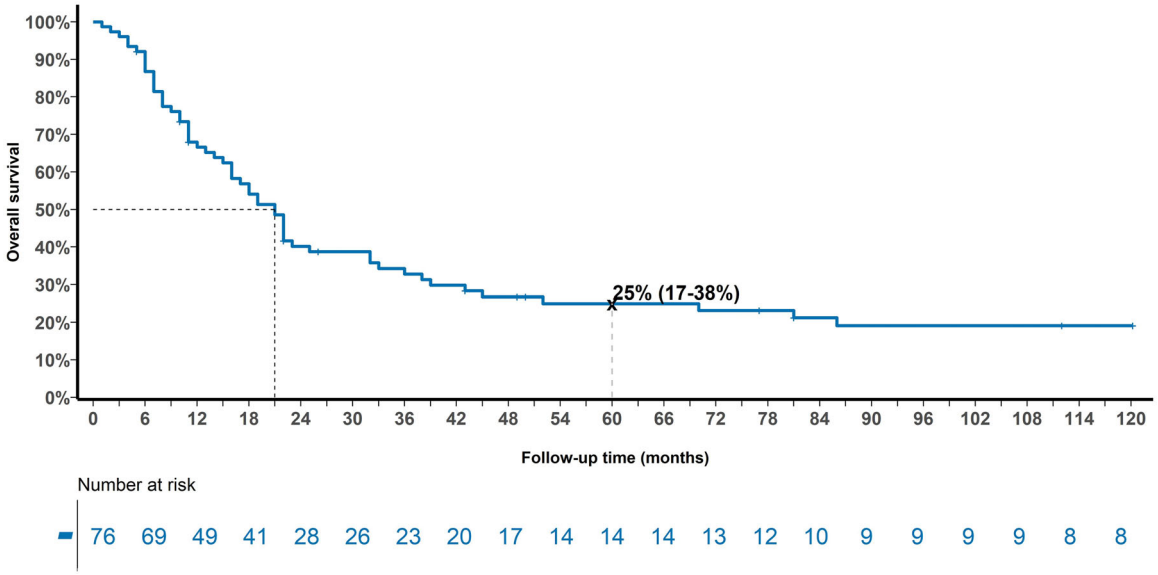

FIGURE 4 Kaplan–Meier curves for adjuvant radiotherapy after surgical treatment of node field recurrence following a prior node dissection for stage III melanoma ($n = 76$). Overall survival.

recurrence, the 5-year node field control rate in the present study was 70% after further surgery and adjuvant RT. However, the 5-year OS was poor (25%).

The only prospectively collected data examining this question have been from a small subgroup of patients in the Australia and New Zealand Melanoma Trials Group (ANZMTG 01.02)/Trans-Tasman Radiation Oncology Group (TROG 02.01) randomized trial comparing immediate RT with observation after nodal dissection.[10] In the observation group of this trial, 26 patients developed an isolated node field recurrence, with a median time to recurrence of 7 months (interquartile range: 4–12). Twenty of them (77%) were treated with further surgery and RT. The other six patients received either surgery alone, RT alone or no treatment. Overall long-term node field control was achieved in 23 of them (88%).[10] The 5-year OS of this cohort was 34%, but the CIs were wide (95% CI: 18%–63%) due to the small patient numbers. Several retrospective studies of adjuvant RT have included patients with recurrence in a previously dissected lymph node field and reported node field control rates in this group of patients ranging from 85% to 96%.[1,4,17] However, the numbers of patients in these analyses were again small, which limits the reliability of the reported outcomes. In an earlier MIA study by Stevens et al., 35 patients received hypofractionated RT after resection of recurrent disease in a previously dissected lymph node field, while 107 patients received hypofractionated RT after initial surgery for metastatic lymph node disease.[1] The node field control rate for the two groups combined was 89% (median follow-up 30 months) and the MSS (38%) did not significantly differ between the two groups. Conill et al. reported a cohort of 77 patients treated mainly with hypofractionated RT.[17] For the 27 patients with recurrent nodal disease, the node field control rate was 96.3%; however, median follow-up was not stated. Beadle et al. presented results for 200 melanoma patients receiving hypofractionated RT after axillary lymph node dissection (median follow-up 59 months).[4] For the 37 patients with recurrent nodal disease, the node field control rate was 85%. The choice between conventionally fractionated RT and hypofractionated RT in the present study was at the discretion of the treating radiation oncologists based on institutional preference and patient choice. We have recently published an analysis of the effects of adjuvant RT fractionation on outcomes in 335 patients after resection of high-risk stage 3 melanoma.[18] There were no significant differences in node field control, RFS or OS between hypofractionated and conventionally fractionated adjuvant RT.

The best way to assess the efficacy of adjuvant RT in patients with recurrent nodal disease would be to compare their results with those of patients who underwent salvage surgery but who did not have RT. Based on the currently available literature no valid comparison can be made since node field control rates in patients who recurred and had further surgery but did not receive adjuvant RT have not been reported. We sought to address this question by analysing data from our own institution but could identify only eight patients who did not receive adjuvant RT after a second surgical procedure for node field recurrence, too few for meaningful analysis.

An important finding in our study was that 33% of the subsequent recurrences after RT occurred in areas of anatomical lymph node fields as defined in the ANZMTG 01.02/TROG 02.01 trial protocol that had not been actually irradiated. This suggests that even better control rates might have been achieved if RT planning had ensured that the entire anatomical field was treated in every patient. In the ANZMTG 01.02/TROG 02.01 trial, the anatomical boundaries of the cervical, axillary and inguinal lymph node fields were very precisely specified and coverage of the entire anatomical field was mandated in the trial protocol.[10] The importance of quality control in RT in achieving optimal outcomes is well documented. In a

large head and neck cancer trial, an independent central review of the quality of the RT showed that a noncompliant RT plan was associated with significantly worse 2-year OS, with more patients developing locoregional failure.[19] Similarly, in a randomized trial of preoperative RT for retroperitoneal sarcoma, a noncompliant RT plan was associated with worse abdominal RFS and a trend towards worse OS.[20]

The poor overall RFS of 17% in our study points to the need for effective systemic treatment. Today, checkpoint inhibitors and targeted therapies are available as adjuvant treatments, and these agents have been shown to improve the RFS of patients with resected nodal melanoma recurrences.[8,9,21] Patients with a first presentation of stage III disease are increasingly being treated with neoadjuvant systemic therapy, which has been reported to produce a complete pathological response in 40% of them.[22] Those with a complete pathological response to neoadjuvant systemic therapy had an excellent 2-year RFS of 89% and an OS of 95%. Given the high risk of disease relapse in patients with node field recurrence after a previous node dissection, there is thus a likely benefit of neoadjuvant systemic therapy as well.[22–24] Therefore, most melanoma clinicians would currently recommend neoadjuvant and/or adjuvant systemic therapy and consider RT for patients with high-risk disease, those who develop isolated node field recurrence despite systemic therapy or those with a poor pathological response to neoadjuvant therapy. This is consistent with the recommendation for RT in the most recent National Comprehensive Cancer Network guidelines.[25] In the setting of isolated node field recurrence after adjuvant immunotherapy, preliminary data reported in an abstract indicate that adjuvant RT after further surgery substantially reduced the risk of further nodal recurrence (from 36% to 8%).[26] Our results from the era before modern systemic therapy became available can serve as a baseline to assess the efficacy of systemic therapy in this setting.

There is increasing preclinical as well as clinical evidence that combining RT with checkpoint inhibitors may increase the immune response and further improve long-term control of metastatic disease.[27] It is, therefore, likely that node field control will be improved further by the combined use of both RT and checkpoint inhibition as adjuvant therapies. This could be a particularly useful strategy for those patients who have had a poor pathological response to neoadjuvant systemic therapy.

In addition to its retrospective nature, the present study has several limitations. The follow-up of some patients was incomplete, mainly for those who had their RT at other facilities. A possible confounder was the administration of other adjuvant treatments; however, the efficacy of the systemic agents that were used (interferon-α, vaccinia melanoma cell lysate, CancerVax and dendritic cell vaccines) is likely to have been negligible, based on reported results.[11–16] Comparing our node field control rate after salvage surgery and adjuvant RT with a cohort treated with salvage surgery without RT was not feasible using our institutional database because the number of patients who had salvage surgery without RT was too small to draw any reliable conclusions. Detailed toxicity data were also not available.

5 | CONCLUSIONS

Salvage surgery with adjuvant RT achieved node field control in 70% of patients with node field recurrence following prior node dissection for stage III melanoma. When further recurrence did occur, it was in a nonirradiated area of the anatomically defined node field in 33% of cases, explaining the importance of RT quality control. The overall prognosis was poor due to the subsequent development of distant metastatic disease.

Prospective studies examining the role of adjuvant RT in the setting of adjuvant systemic therapy with checkpoint inhibitors or targeted therapy and sequencing options with surgery will be required to determine the value of each modality in these patients. The results from this study serve as a baseline to assess the efficacy of modern systemic therapies. Until then, adjuvant RT remains a valid option after salvage surgery for an isolated node field recurrence after a previous lymph node dissection for stage III melanoma.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge support from Melanoma Institute Australia and Cancer Institute New South Wales, and the contributions and assistance of colleagues at the Royal Prince Alfred Hospital, the Mater Hospital, St Vincent's Hospital and the Royal North Shore Hospital, Sydney. Lodewijka H. J. Holtkamp received a research grant from the Groningen Melanoma and Sarcoma Foundation and was funded by Het Vreedefonds and Melanoma Institute Australia. John F. Thompson was the recipient of a Program Grant from the Australian National Health and Medical Research Council.

CONFLICTS OF INTEREST STATEMENT

John F. Thompson has received honoraria for advisory board participation from BMS Australia, MSD Australia, GSK and Provectus Inc., and travel and conference support from GSK, Provectus Inc. and Novartis. Robyn P. M. Saw has received honoraria for advisory board participation from MSD, Novartis and Qbiotics and speaking honoraria from BMS and Novartis. Angela M. Hong has received honoraria for advisory board participation from QBiotics Group Limited, Bayer and Oncobeta. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Holtkamp LHJ, Lo SN, Thompson JF, et al. Adjuvant radiotherapy after salvage surgery for melanoma recurrence in a node field following a previous lymph node dissection. *J Surg Oncol*. 2023;1-8. doi:10.1002/jso.27245