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Treatment of Clinically Positive Cervical Lymph Nodes by Limited Local Node Excision and Adjuvant Radiotherapy in Melanoma Patients with Major Comorbidities

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ABSTRACT

Introduction. When cervical lymph nodes are clinically positive for metastatic melanoma, surgeons may be hesitant to recommend a therapeutic complete lymph node dissection if the patient is elderly or has major comorbidities. A limited local node excision of the clinically positive nodes only, followed by adjuvant radiotherapy to the entire node field, may be an effective alternative in such patients.

Methods. All patients who had presented with a primary head and neck melanoma or an unknown primary site and had subsequently undergone limited local node excision and adjuvant radiotherapy for macroscopically involved cervical nodes between 1993 and 2010 at a tertiary referral center were selected for study.

Results. Twenty-eight patients were identified, with a median age of 78 years and a median of 2 major comorbidities. The 5-year regional control, disease-free survival, and overall survival rates were 69%, 44%, and 50%, respectively. At the time of data analysis, seven patients were alive without evidence of disease. Twenty-one patients had died: 11 of melanoma (4 with neck recurrence) and 10 of other causes (2 with neck recurrence).

Conclusions. Excision of clinically positive metastatic cervical lymph nodes followed by radiotherapy provides satisfactory regional disease control without risking serious morbidity or mortality in melanoma patients whose general

condition is considered a contraindication for therapeutic complete lymph node dissection.

For patients with clinically positive (palpable) metastatic melanoma in cervical lymph nodes, a therapeutic complete lymph node dissection (TCLND) of the cervical nodes is currently the standard treatment.[1–3] Despite the morbidity of surgery, and even though TCLND has not been shown to improve survival, a TCLND is normally recommended in patients with good general health, because regional disease control can be achieved in up to 81% of patients.[3–5]

Adjuvant radiotherapy (RT) to the node field following a TCLND has been reported to reduce the local recurrence rate in cervical lymph nodes even further, from 19 to 5.6%.[6] A recent multicenter, randomized, controlled trial confirmed that adjuvant RT following TCLND substantially improves long-term regional disease control in patients with a high risk of local recurrence; after 6 years of follow-up, 36% of patients in the control group had recurred locally versus 21% in those who did receive RT.[7]

In elderly patients and/or those with major comorbidities, however, surgeons may be hesitant to recommend a TCLND because of the risk of greater procedure-related morbidity and mortality.[8] Furthermore, elderly patients are less likely to benefit from a TCLND, because increased age is associated with shorter disease-free survival (DFS) and shorter overall survival (OS).[9,10] In view of this, a limited local node excision, involving removal of clinically positive cervical lymph nodes only, may be a suitable treatment option in these patients. Although in one study the results of this approach, when it was used in younger patients and those with few comorbidities, were somewhat

disappointing, others have suggested that adjuvant RT following limited local node excision may be effective in improving regional disease control.[11–13] We therefore analyzed our results for limited local node excision followed by adjuvant RT in elderly patients and those with major comorbidities. We hypothesized that this combined treatment would be effective in these patients and could be more appropriate than TCLND because of the much lower risk of treatment-related morbidity and mortality.

PATIENTS AND METHODS

Patients considered for inclusion in this retrospective study had a limited local node excision of clinically positive metastatic cervical lymph nodes after previous resection of a head and neck melanoma or those with clinically positive metastatic cervical lymph nodes with an unknown primary, followed by adjuvant RT. The study was approved under existing ethical approval from the Royal Prince Alfred Hospital for retrospective research studies, utilising the Melanoma Institute Australia research database. To identify eligible patients, two overlapping search strategies were used. First, the Royal Prince Alfred Hospital Radiation Oncology database was interrogated to identify patients who received RT to the cervical region for node metastases of cutaneous melanoma between 1993 and 2010. This identified 243 patients. Next, each patient file was reviewed, and those who also had undergone a limited local node excision were selected. Patients who had undergone a formal radical or modified radical cervical node dissection, as well as those who had not undergone any cervical node surgery, were excluded. There remained 23 patients who were eligible for inclusion in the study. Second, the database of Melanoma Institute Australia was interrogated to identify patients with histologically positive cervical nodes, and the files of 840 patients identified were reviewed. Using the criteria described above, 21 eligible patients were identified. After eliminating duplicates between the two databases, 28 patients fulfilled the study criteria and constituted the final study cohort of patients with clinically positive cervical melanoma lymph node metastases treated by limited local node excision followed by adjuvant RT. All patients were discussed in a multidisciplinary team meeting during which limited local node dissection and adjuvant RT was discussed if they were considered not suitable candidates for standard treatment.

The surgical and pathology reports and RT records of these patients were then reviewed. Data collected included age, gender, comorbidities, primary melanoma characteristics (site, Breslow thickness, ulceration, number of mitoses, presence of local recurrence), time from diagnosis of primary melanoma to clinically positive metastatic cervical lymph nodes, preoperative imaging, number of involved cervical nodes removed at surgery, RT dose and fractionation, regional toxicity grade, time to local disease-recurrence or distant metastases following limited local node excision, and time and cause of death.

Possible differences between the variables were tested for statistical significance using the Chi-squared test for comparison of frequency distributions, and the Mann–Whitney U test for the nonparametric variables.[14] Regional disease control, DFS, and OS were estimated using the Kaplan–Meier method.[15] The influence of the different characteristics on regional disease control, DFS, and OS were analyzed using the log-rank test. A significant difference was assumed for a probability value of < 0.05. Statistical analyses were performed using SPSS 21.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

Patient and Tumor Characteristics

The patient and tumor characteristics are listed in Table 1. Of the 28 patients, 21 were male (75%), and their median age was 78 (range 55–91) years. Although the youngest patient was 55 years of age, this patient had three major comorbidities (ischemic heart disease, occlusive peripheral arterial disease, and dementia) and therefore was considered unsuitable for general anesthesia and standard surgical treatment. The patients had a median of two major comorbidities (range 1–5). These comorbidities included ischemic heart disease, dementia, atrial fibrillation, diabetes mellitus, occlusive peripheral arterial disease, and advanced cerebrovascular disease. One patient had only one major comorbidity (dementia); she was a widowed 91-year-old lady who was living in a nursing home and barely able to walk. After discussion with the patient and her family, treatment by limited local node dissection and RT was offered.

The most frequently involved sites of the previously resected primary melanoma were the scalp or the cheek (both $n = 6$) and the neck or forehead (both $n = 5$). Two patients had cervical node metastases from an unknown primary melanoma. The median Breslow thickness of the primary melanomas was 2.1 (range 0.4–8.0) mm, and the median Clark level of invasion was IV. All patients had either a CT scan of the chest and abdomen ($n = 19$) or a PET/CT scan ($n = 9$) preoperatively to rule out distant metastatic disease.

TABLE 1 Patient characteristics

Characteristic	No. of patients (%)
Sex	
Male	21 (75)
Female	7 (25)
Age (years)	
≤ 80	16 (57)
> 80	12 (43)
Median (range)	*78 (55–91)*
Number of major comorbidities	
≤ 2	17 (60)
> 2	11 (30)
Median (range)	*2 (1–5)*
Site[a]	
Scalp	6 (21)
Neck	5 (18)
Cheek	6 (21)
Forehead	5 (18)
Shoulder	1 (4)
Ear	3 (10)
Unknown	2 (7)
Breslow thickness[a]	
≤ 2 mm	12 (43)
> 2 mm	12 (43)
Unknown	4 (14)
Median	*2.6 (0.4–8.0)*
Ulceration[a]	
Yes	11 (39)
No	11 (39)
Unknown	6 (21)
Mitotic rate (mitosis/mm^2)[a]	
< 1	7 (25)
≥ 1	15 (54)
Unknown	6 (21)
Number of positive nodes excised	
≤ 3	25 (90)
> 3	3 (10)
Median (range)	*2 (1–5)*
Diameter of positive nodes (cm)	
Median (range)	*2.3 (0.8–5.6)*

[a]Primary melanoma

Treatment Characteristics

Eighteen patients had a biopsy preoperatively of the cervical nodes that showed metastatic melanoma on histopathology. Ten patients underwent cervical limited local node excision based on convincing physical examination of metastatic melanoma to the cervical nodes only.

The limited local node excision involved removal of a median of two lymph nodes (range 1–5) with a median diameter of 2.3 cm (range 0.8–5.6 cm). The surgery was performed as an outpatient procedure using local anesthesia only in 11 patients and as a day-stay procedure in 14 patients using local anesthesia and IV sedation ($n = 10$) or general anesthesia ($n = 4$). In three patients, the type of anesthesia was not documented. All patients were discharged on the day of surgery with low-dose oral analgesia. In all but 3 of the 28 patients, all resected nodes were found to contain metastatic melanoma. In the other three patients, one of the resected nodes showed no metastatic melanoma (2 of these patients had 3 nodes resected and 1 had 4 nodes resected). Extranodal tumor spread was reported in 19 patients (68%). Different RT dose/fractionation schedules regimes were used: 20 patients received 48 Gy in 20 daily fractions over 4 weeks; 6 received 33 Gy in 6 fractions over 3 weeks; and 2 received 54 Gy in 27 daily fractions over 5.5 weeks.

There were few complications following limited local node excision. Four patients (14%) experienced a postoperative complication: two (both on long-term anticoagulation) had minor postoperative bleeding from the surgical site, and two developed a low-grade wound infection. All of these complications were successfully managed conservatively. No nerve damage or other adverse surgical events occurred. During RT, 15 patients developed erythema or moderate edema (grade 2 acute radiation morbidity), and 3 patients developed moist skin desquamation or pitting edema (grade 3).[16] There was no statistically significant relationship between RT dose and the development of local toxicity. Despite the skin toxicity, all but two patients completed their planned RT course without difficulty, and the side-effects resolved rapidly after completion of the RT without lasting symptoms. The two patients (7%) who experienced grade 3 toxicity were not able to complete their RT course because of the side-effects: both these patients missed three treatment sessions. Thus, the combined complication rate of the surgical procedure and RT was 21% ($n = 6$). No significant long-term morbidity occurred, and all patients recovered fully.

Regional Disease Control, Disease-Free Survival, and Overall Survival

Median follow-up was 22 (range 1–70) months. One patient was lost to follow-up after 36 months but was disease-free at that time. Three patients had a follow-up of less than 6 months due to disease progression: two refused additional treatment and further follow-up, and one did not complete the planned course of RT after limited local node excision because of grade 3 toxicity. This patient was seen

in the outpatient clinic 1 month after RT and died 3 months later from widespread metastatic disease.

Regional disease control was achieved in 69% of the patients after 5 years (Fig. 1), and 5-year DFS was 44% (Fig. 2). The 5-year OS was 50% (Fig. 3). At the time of analysis, seven patients were alive. The 21 patients who died during the follow-up period of the study had a median survival of 16 months following limited local node excision (range 3–42 months).

Distant metastases subsequently developed in 11 patients (39%) and became evident after a median time of 5 (range 1–18) months following the limited local node excision. All 11 patients who developed distant metastases died from melanoma. These 11 patients were younger than those (n = 10) who died of other causes (73 vs. 83 years) and had a shorter survival time following limited local node excision (median 11 vs. 21 months), although this difference was not statistically significant. None of the 7 patients who were alive at the time of data collection had any evidence of locally recurrent or distant disease.

Analysis of patient, tumor, and treatment characteristics showed that a thicker primary melanoma (Breslow thickness; $p = 0.010$), ulceration of the primary tumor ($p = 0.017$), and extranodal tumor spread ($p = 0.023$) were statistically significant factors predicting OS. Recurrent metastatic disease in the cervical nodes after limited local node excision did not reach significance for OS ($p = 0.08$). None of the other tumor and patient characteristics, including age, number of major comorbidities, and size of positive nodes significantly influenced regional disease control, DFS, or OS (Table 2).
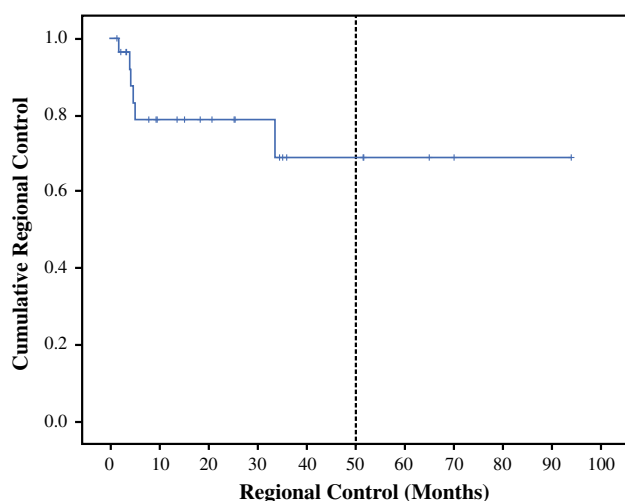

FIG. 1 Regional disease control of melanoma patients with clinically-positive cervical lymph node metastases treated with limited local node excision followed by radiotherapy (n = 28)
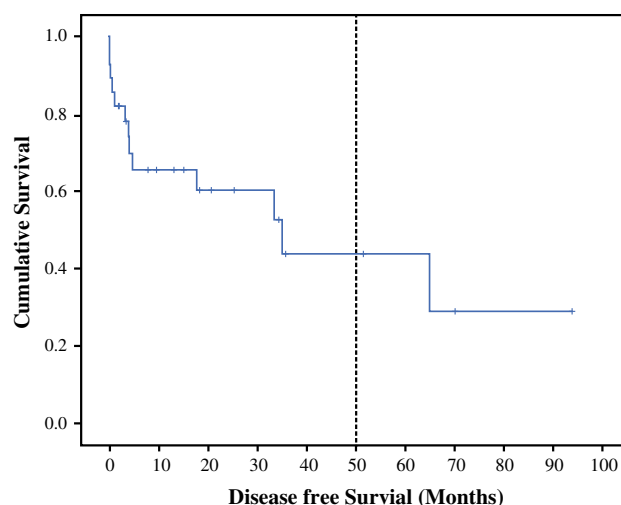

FIG. 2 Disease-free survival of melanoma patients with clinically-positive cervical lymph node metastases treated with limited local node excision followed by radiotherapy (n = 28)
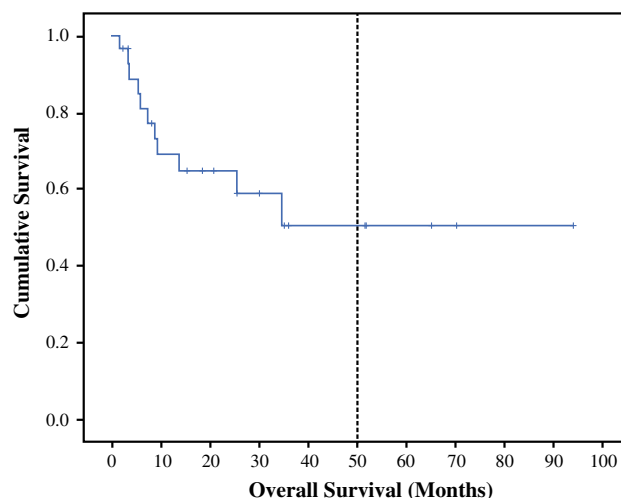

FIG. 3 Overall survival of melanoma patients with clinically-positive cervical lymph node metastases treated with limited local node excision followed by radiotherapy (n = 28)

DISCUSSION

The standard therapy for patients with AJCC Stage III melanoma who have clinically positive cervical lymph nodes is a TCLND.[3] Postoperatively, adjuvant RT often is recommended in patients with parotid node involvement, two or more involved cervical lymph nodes, an involved node more than 3 cm in diameter or when there is extranodal spread.[5,17] A recently published, multicenter, randomized, controlled trial investigating the role of adjuvant RT after TCLND reported a significant reduction in the rate of regional recurrence (21% vs. 36%; $p = 0.023$) and thus confirmed the improved node field control of RT following TCLND.[7] However, TCLND is a major, invasive

TABLE 2 Results of log-rank test of patient and tumor characteristics on regional disease control, disease-free survival and overall survival

Characteristic	Regional disease control	Disease-free survival	Overall survival (p values)
Age	n.s.	n.s.	n.s.
Sex	n.s.	n.s.	n.s.
No. of major comorbidities	n.s.	n.s.	n.s.
Site[a]	n.s.	n.s.	n.s.
Breslow thickness[a]	n.s.	n.s.	0.010
Ulceration[a]	n.s.	n.s.	0.017
Mitotic rate[a]	n.s.	n.s.	n.s.
No. of positive nodes excised	n.s.	n.s.	n.s.
Diameter of positive nodes	n.s.	n.s.	n.s.
Extranodal tumor spread	n.s.	n.s.	0.023
Recurrent local disease after limited local node excision	N.A.	N.A.	0.08

n.s. Not statistically significantly different, *N.A.* not applicable

[a]Of primary melanoma

surgical procedure with reported complication rates of approximately 20% but with late surgical morbidity rates as high as 72%.[7,18,19] In view of this, elderly patients and/ or those with multiple major comorbidities often are considered unsuitable for this procedure.[8] Limited local node excision may be a more suitable treatment option for these patients, because it is a minor procedure that can be performed under local anesthesia or with a brief general anesthetic, as shown in the current study. Limited local node excision alone, however, has previously led to unsatisfactory regional disease control, whereas limited local node excision in combination with adjuvant RT resulted in regional disease control of 77–93% in melanoma patients with cervical metastases.[11–13,20] Therefore, in the current study, we analyzed our results following this combined treatment approach in elderly patients and those with multiple comorbidities. Because of their age and physical frailty, some of the patients found attendance at the outpatient clinic for follow-up difficult. When we were unable to collect the follow-up information directly from the patient, we were able to collect follow-up data in all cases by contacting their family physician. We were able to confidently ascertain that regional disease control was achieved in 69% of the patients after 5 years, and that 5-year DFS and OS were 44 and 50% respectively.

After TCLND in melanoma patients with metastatic melanoma in cervical lymph nodes, O'Brien et al. reported regional disease control in 77% of patients without (n = 75) and 93% in patients who had adjuvant RT to the node field (n = 27). This difference, however, did not reach statistical significance.[12] Ballo et al.[20] reported a 5-year regional disease control rate of 93% in 36 patients, with a DFS of 59% and OS of 69%, following a treatment regimen of limited local node excision and postoperative

radiotherapy comparable to the treatment used in the present study, and Hamming-Vrieze et al.[13] reported similar results. A possible explanation for the better results of these studies compared with our study may be patient selection; the median patient ages in these studies were 50 and 53 years respectively, compared with 78 years in our study, bearing in mind that increased age is associated with a worse regional disease control rate and shorter DFS and OS rates.[9,10] Furthermore, our patients had multiple comorbidities and therefore a substantially higher competing risk of death from other causes. Finally, patients in the series reported by Ballo et al. were all staged with a PET/CT scan before surgery to exclude those with distant metastases, whereas we did not perform a PET/CT scan in all cases because PET/CT was not readily available in our institution until 2004. In view of these differences in patient selection, the results of the current study can be considered satisfactory.

Consistent with the previous studies, locoregional treatment had no effect on OS.[11–13] The average expected 5-year OS for patients with stage IIIb melanoma is 83% but decreases to 32% for those with stage IIId disease when more lymph nodes are involved.[1] OS is further reduced when stage IV disease becomes apparent, the 5-year survival then being 7–19%. As expected, a reduction in OS was observed in the patients in our study who developed distant metastases. Analysis of patient, tumor, and treatment characteristics showed that a thicker primary melanoma (Breslow thickness; p = 0.010) and ulceration (p = 0.017) were statistically significant factors predicting OS. This is in accordance with the AJCC staging system for melanoma.[1] None of the other tumor and patient characteristics showed significant effects on regional

disease control, DFS, or OS. However, no firm conclusions in relation to OS can be drawn because of our limited patient numbers.

The combined treatment approach of limited local node excision and adjuvant RT was well tolerated by our patients without any treatment-related deaths and with an overall combined (surgery and RT) complication rate of 21% ($n = 6$). This included four minor surgical complications (14%), all able to be managed conservatively, and all but two patients (7%) completed the planned course of RT to the neck. Although the majority of patients ($n = 18$) developed slight-to-moderate acute skin side-effects during RT, all but the two mentioned above completed their RT course, and the side-effects resolved rapidly after completion of the RT. No significant long-term morbidity occurred, and all patients recovered fully from both the surgery and the RT. The low complication rate following limited local node excision and adjuvant RT was similar to that reported in previous studies and, as mentioned earlier, was much lower than the complication rate reported following TCLND. This supports the proposal that this approach can be successful in minimizing procedure-related morbidity and mortality, especially in elderly patients and those with multiple comorbidities.[12,13,18–20]

Alternative management options to limited local node excision followed by RT for patients with Stage III melanoma with clinically positive cervical lymph node metastasis also may be considered. Therapeutic RT alone without surgery, for example, may be an option for patients who are thought to be unfit even for limited local node excision using local anesthesia. However, no results of definitive RT alone for clinically positive lymph nodes have been published, and a high total radiation dose would be required to sterilize adequately the macroscopic nodal disease.[17] Furthermore, in this era of effective systemic therapies, the responses and survival of patients with distant metastatic melanoma (Stage IV) have improved substantially using immunotherapy and targeted therapies, with generally low toxicity rates.[21–25] Although some have suggested the use of these systemic therapies to treat patients with Stage III disease, they have to date been assessed only as adjuvant therapies following surgical resection, and their potential toxicities cannot be ignored.[7,12,13,20,22,23] Whereas in the current study the objective was to minimize treatment complexity and morbidity, drawbacks of the new systemic therapies include potential side-effects and the need for frequent follow-up visits, as well as cost. All of these are particularly important considerations in elderly patients and those with serious medical comorbidities.[23,26,27] It seems that for now there may be a limited role for these drugs in the treatment of frail or elderly melanoma patients with clinically positive cervical lymph node metastases.

Some limitations of the current study have to be addressed. As mentioned, this study was conducted in a retrospective fashion in only a small number of patients. In the future, data collected from a larger patient cohort, preferably randomized trial data, will be required to determine the efficacy of the combined treatment of limited local node excision followed by RT in melanoma patients with clinically positive cervical lymph node metastases who suffer from major comorbidities. Furthermore, due to the wide range in location and the number of involved cervical lymph nodes, the range of comorbidities the patients were suffering from, the desire of some patients for limited treatment, and the time span of 18 years of the current study, there was a wide variety in the treatment these patients underwent, mainly in preoperative imaging and the RT dose and scheme.

CONCLUSIONS

The present study demonstrates that satisfactory regional disease control can be achieved in most patients with melanoma metastases in cervical nodes who are treated with limited local excision of the affected nodes followed by adjuvant RT to the entire node field. This treatment approach may be considered as a satisfactory pragmatic option in selected patients who are elderly and who have major comorbidities that make them poor candidates for TCLND. In the future, a study with prospectively collected data will be necessary to define the place of this combined treatment modality in this patient category.

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