Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial

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Summary

Background The use of elective regional node dissection in patients with cutaneous melanoma without any clinical evidence of metastatic spread is still debated. Our aim was to evaluate the efficacy of immediate node dissection in patients with melanoma of the trunk and without clinical evidence of regional node and distant metastases.

Methods An international multicentre randomised trial was carried out by the WHO Melanoma Programme from 1982 to 1989. The trial included only patients with a trunk melanoma 1·5 mm or more in thickness. After wide excision of primary melanoma, patients were randomised to either immediate regiona node dissection or a regional node dissection delayed until appearance of regional-node metastases.

Findings Of the 252 patients entered, 240 (95%) were eligible and evaluable for analysis. 122 of these were randomised to immediate node dissection. 5-year survival observed in patients who had delayed node dissection was 51·3% (95% CI 41·7–60·1) compared with 61·7% (52·0–70·1) of patients who had immediate node dissection (p=0·09). 5-year survival rate in patients with occult regional node metastases was 48·2% (28·0–65·8) and 26·6% (13·4–41·8, p=0·04) in patients in whom the regional node dissection was delayed until the time of appearance of regional node metastases. Multivariate analysis showed that routine use of immediate node dissection had no impact on survival (hazard ratio 0·72, 95% CI 0·5–1·02), whilst the status of regional nodes affected survival significantly (p=0·007). The patients with regional nodes that became clinically and histologically positive during follow-up had the poorest prognosis.

Interpretation Node dissection offers increased survival in patients with node metastases only. Sentinel node biopsy may become a tool to identify patients with occult node metastases, who could then undergo node dissection.

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Introduction

Elective node dissection in patients with cutaneous melanoma with no clinically detectable node metastases has been long debated. Until the report of the Melanoma Intergroup Committee randomised trial,[1] the benefit from elective node dissection in these patients had not been shown.[2–5] The Intergroup trial showed that a subgroup of patients aged 60 or younger, with a primary melanoma of maximum thickness between 1 and 4 mm, benefited from elective regional node dissection even though the same evaluation on the whole series treated was negative. These results confirm that not all stage I and stage II patients benefit from elective node dissection.[6] We report a randomised clinical trial (WHO Clinical Trial #14) that was designed to evaluate the efficacy of elective dissection of regional nodes in patients with a primary melanoma on the trunk at a tumour thickness of 1·5 mm or greater.

Patient and methods

Eligible patients were aged 65 or younger, with a primary melanoma on the trunk with no evidence of regional node or distant metastases, and Breslow thickness of 1·5 mm or greater. The patients had to be either previously treated or have had a biopsy within 6 weeks of final surgical treatment. Patients with a history of previous cancer (excluding basal cell carcinoma of the skin and non-invasive cancer of the uterine cervix) were excluded, as were patients with clinically positive nodes. The basin of first drainage was selected according to the localisation in figure 1, which was defined previously by the group. Patients with a primary cancer in the area C were at first excluded. The protocol was approved by the ethical committee of the collaborating centres. When lymphoscintigraphy became available, it was used to identify the first drainage basin, irrespective of the site of origin. Oral informed consent was obtained from most patients; only three did not give oral consent and they were excluded.

Patients were randomised to receive, after wide excision, either immediate node dissection or node dissection delayed until clinical diagnosis of regional node metastases (figure 2). Patients were stratified by sex, tumour thickness (1·5–4·0 and >4 mm), and centre.

Randomisation was done by telephone after eligibility criteria had been checked. The code randomisation was kept at the secretariat of the WHO Melanoma Programme in Milano by the data manager, and was broken when the last patient entered the trial. Primary melanoma was excised with a 3 cm margin from the visible border of the tumour or from the biopsy scar down to the muscular fascia, which was not excised. The three axillary levels, including resection of the pectoralis minor muscle and inguino-iliac node dissection, were completely dissected. The technique of regional node dissection was agreed during a workshop among all participating surgeons. Histological diagnosis was done by local pathologists and confirmed on representative slides selected for each patient by a panel of five pathologists of the WHO Melanoma Group who also verified Breslow thickness. All patients were followed up quarterly

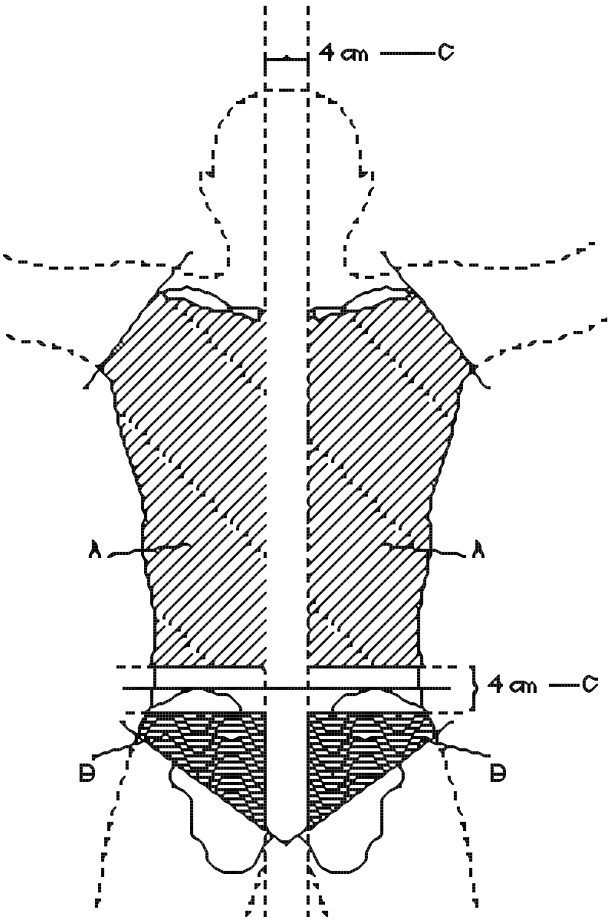

Figure 1: **Site of origin of primary melanoma and lympatic basins to be dissected**
A=area of trunk draining to homolateral axilla; B=area of trunk draining to homolateral groin; and C=area draining to multiple lymphatic basins.

during the first 2 years, every 6 months up to the fifth year, and once a year thereafter. Regional node status in patients who had had wide excision as primary treatment was clinically assessed. In symptom-free patients, chest radiography and liver scan were done every 6 months during the first 2 years and then once a year

The study was designed to detect at α=0·05 a difference of 20% with a power of 90%. We used *t* tests to compare continuous variables between the treated and control arms. The χ^2 test with Yates' correction was used to compare the frequencies of important prognostic factors, such as sex and nodal status. The null hypothesis was that there is no difference between immediate and delayed dissection. The two arms of the study were balanced for major factors that might worsen the prognosis. The proportions of patients surviving in subgroups were analysed by the Kaplan-Meier method with the logrank test. Cox's proportional hazards model was used to analyse major prognostic factors. The proportionality of factors entering the prognostic model was assessed by the plot of the logarithm of minus the logarithm of survival function versus time in each subgroup identified by the covariants sex, age 60 years or more, and Breslow thickness. The significance of covariates was assessed by the likelihood ratio test and the role of each covariate entering the model was assessed by the Wald statistic. The program used was Stata 5·0 for Windows 95.

Results

252 patients entered the study between 1982 and 1989; 240 (95%) were evaluable. The mean follow-up was 132

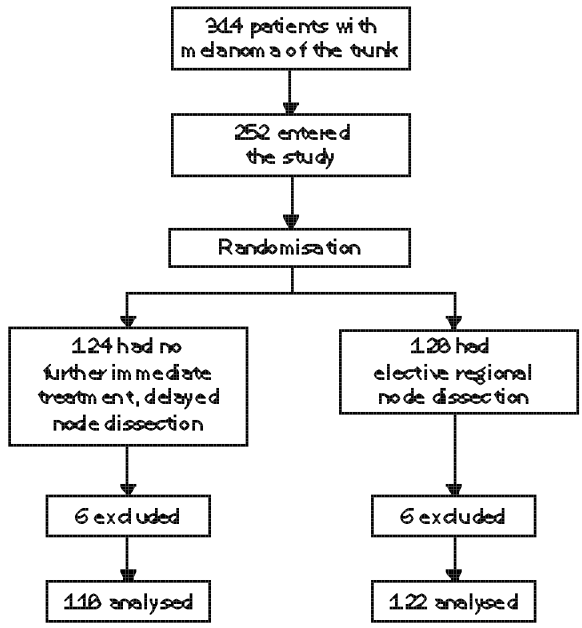

Figure 2: **Trial profile**

months. 12 patients were excluded from analysis, six in each arm. Reasons for exclusion were: treatment not in accordance with randomisation (seven patients), diagnosis of melanoma not confirmed by the pathologists' panel (three), site of origin outside the trunk (one), and lack of pathological documentation (one). 62 additional patients did not enter into the study: 59 because primary melanoma was located in the C area (figure 1), and three because consent was not obtained.

Of the 240 evaluable patients, 122 were randomised to receive wide excision and immediate node dissection and 118 were randomised to receive wide excision and dissection delayed until the time of appearance of clinically detectable node metastases. The two treatment arms were balanced for sex, tumour thickness, and age of patients. In the "delayed" patients, there were 77 (65%) men and 41 (35%) women, with a median age of 51·5 years (interquartile interval [IQI] 18 years) and a median thickness of 3·2 mm (IQI 3). In the "immediate" group, there were 83 (68%) men and 39 (32%) women, with a median age of 50 years (IQI 16) and a median Breslow thickness of 3·4 mm (IQI 2·5). Node metastases as the first evidence of dissemination were found in 63 (26%)

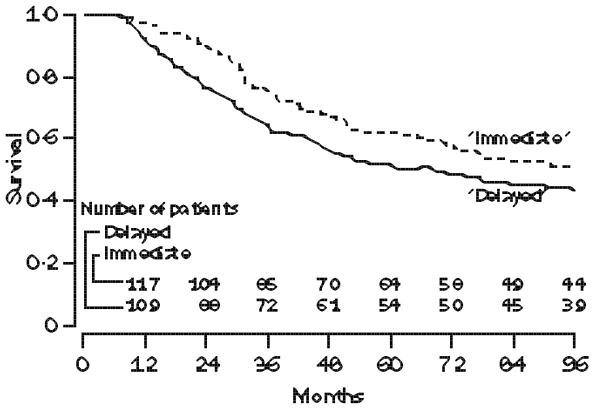

Figure 3: **Survival of patients with primary melanoma of trunk (1·5 mm or thicker) according to time of node dissection**
Intermediate=wide excision and elective node dissection (n=122). Delayed=wide excision and node dissection delayed until time of clinically detectable node metastases (n=118).

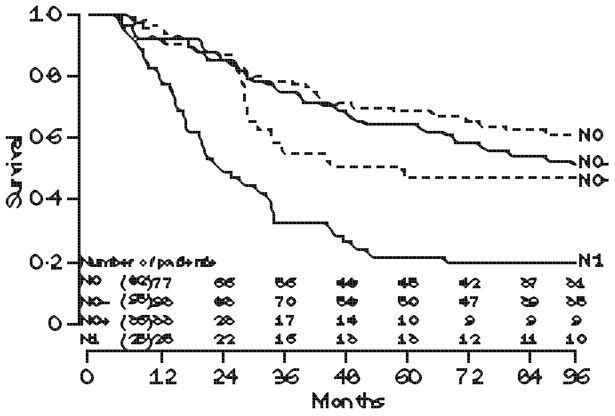

Figure 4: **Survival according to status of regional nodes**
N0=patients who never developed node metastases after wide excision of primary. N0−=patients with clinically and histologically negative nodes at elective node dissection. N0+=patients with clinically negative and histologically positive nodes at elective node dissection. N1=patients who developed node metastases during follow-up and underwent delayed regional node dissection.

patients. 27 (22%) of the 122 patients who had immediate node dissection were found to have occult node metastases (N0+) and 36 (30·5%) of 118 patients who received wide excision only as primary treatment developed regional node metastases as first recurrence of the disease (N1+) during follow-up. The median lag between excision of primary tumour and the clinical diagnosis of regional node metastases was 8·3 months (interquartile range 3·7–16·2). The minimum delay was 0·43 months and maximum 55·0 months. The site of first regional node metastases was in the expected drainage site for all patients who underwent "delayed" node dissection. Eight additional patients (7%) out of these 118 developed node metastases synchronous with distant metastases. These patients did not undergo node dissection and in the survival analysis were considered as patients who developed distant metastases as first evidence of recurrence.

Survival of the 240 patients by treatment arm is shown in figure 3. "Delayed" patients had a survival rate at 5 years of 51·3% (95% CI 41·7–60·1). 5-year survival in "immediate" patients was 61·7% (52·0–70·1). The difference was not statistically significant (p=0·09).

Figure 4 shows survival by nodal status evaluated from the time of primary treatment. Survival of patients who never developed node metastases (N0) when primary

Criterion	Cox's model			Likelihood-ratio test (p)
	Hazard ratio	p	95% CI	
Sex				
Male	1	. .	. .	
Female	0·49	0·001	0·32–0·75	0·0004
Thickness (mm)*	1·11	0·02	1·01–1·20	0·03
Age (years)				
≤60	1	. .	. .	
>60	0·92	0·73	0·56–1·50	0·71
Treatment				
Wide excision ("delayed" group)	1	. .	. .	
Wide excision + elective dissection ("immediate" group)	0·72	0·07	0·49–1·04	0·04

*As continuous variable.

Table 1: **Multivariate analysis of survival of 240 evaluable patients**

Criterion	Cox's model			Likelihood-ratio test (p)
	Hazard ratio	p	95% CI	
Sex				
Male	1	. .	. .	
Female	0·52	0·003	0·34–0·80	0·002
Thickness (mm)*	1·08	0·08	0·99–1·18	0·09
Age (years)				
≤60	1	. .	. .	
>60	0·97	0·91	0·59–1·59	0·87
Nodes†				
N0	1	. .	. .	
N0−	0·85	0·49	0·54–1·34	
N0+	1·25	0·47	0·67–2·34	0·007
N1	2·11	0·005	1·25–3·57	

*As continuous variable. †See figure 4 for explanation,

Table 2: **Multivariate analysis of survival**

treatment was wide-excision only and that of patients who were found to have no metastatic deposits in the electively dissected regional nodes (N0−) were similar (p=0·63). Survival of patients who were found to have occult node metastases at elective node dissection (N0+) and that of patients who developed regional node metastases during follow-up and who had delayed dissection (N1) are also shown in figure 4. The differences between these two groups were statistically significant (p=0·04).

Table 1 shows the results of multivariate analysis of survival taking into consideration sex, Breslow thickness as a continuous variable, age of patients, and type of treatment. Age had no impact on survival, sex and Breslow thickness were relevant for prognosis, and the timing of node dissection did not significantly influence survival. Table 2 shows multivariate analysis of survival when the status of regional nodes was taken into consideration instead of the timing of regional node dissection. Sex maintained its importance, relevance of the Breslow thickness became borderline, and the status of regional nodes had a significant impact on survival (p=0·007).

Discussion

Our results from this randomised trial confirm the inefficacy of elective regional node dissection as routine treatment in all melanoma patients with a primary melanoma of the trunk thicker than 1·5 mm (p=0·09). Comparison with the Intergroup results[1] is not possible because the length of follow-up was longer in our patients, patients in our study had on average thicker melanomas, and we dealt with trunk melanoma only. In addition, our sample size did not allow subgroup analysis.

The secondary outcome of our study was that N0+ patients had a better prognosis than N1+ patients, although the number of patients with surgically treated positive nodes in our series was small. However, this result seems consistent because the treatment is not biased by surgeon's choice and because survival was evaluated from the date of primary treatment. Furthermore, if minor differences in surgical technique of node dissections had a role, this would have been balanced between the two groups of patients being stratified by centre.

Our data indicate that the dissection of clinically undetectable node metastases leads to higher long-term survival (p=0·04). The results lend support to the introduction of clinical procedures aimed at early

detection of metastatic deposits in regional lymph-nodes. In this context Morton and co-workers,[7] and others,[8–10] developed a minimally invasive intraoperative lymphatic mapping technique that allows identification of the sentinel node that is defined as the first node in the regional nodal basin into which the primary site drains. With this procedure, one may select patients with clinically occult nodal disease who benefit from regional node dissection, thus introducing the concept of selective lymph-node dissection in melanoma patients. The use of prognostic variables of the host and primary melanoma does not seem to be as adequate as sentinel node biopsy to select patients for "radical" node dissection for two reasons. First, selection on the basis of prognostic variables still induces surgeons to perform node dissections in patients with no histologically proven node metastases. Second, the relevance of the most important prognostic criterion (Breslow thickness) for primary melanoma is less important when adjusted by status of regional nodes, as shown in our study (table 2) and by others.[11–13]

Until the results of the ongoing international randomised study assessing the efficacy of selective lymphadenectomy are available,[11] our results could have important implications for regional node management in patients with cutaneous melanoma, finally settling the debate between advocates and opponents of elective lymphadenectomy. The problem is to define the minimum requirement for identification of sentinel node(s) and the standard of their pathological examination. New methods of detection and pathological evaluation of micrometastases are now under investigation and the WHO Melanoma Programme has already planned a clinicopathological study designed to answer this question.

Contributors

N Cascinell, A Morabito, M Santinami, R M MacKie, and F Belli planned the study, did the statistical analysis, and wrote the manuscript.

Acknowledgments

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References

1 Balch CM, Soong S-J, Bartolucci AA, et al. Efficacy of an elective regional lymph node dissection of 1 to 4 mm thick melanomas for patients 60 years of age and younger. *Ann Surg* 1996; **224:** 255–66.
2 Veronesi U. Efficacy of immediate node dissection of stage I melanoma. *N Engl J Med* 1977; **2:** 627–30.
3 Veronesi U, Adamus J, Bandiera DC, et al. Delayed regional lymph node dissection in stage I melanoma of the skin of the lower extremities. *Cancer* 1982; **49:** 2420–30.
4 Sim FH, Taylor WF, Ivins JC, et al. A prospective randomized study of the efficacy of routine elective lymphadenectomy in management of malignant melanoma. *Cancer* 1978; **41:** 948–56.
5 Cascinelli N. The role of clinical trials in assessing optimal treatment of cutaneous melanoma not extending beyond the regional nodes. *Eur J Surg Oncol* 1996; **22:** 123–33.
6 Balch CM, Milton GW, Cascinelli N, et al. Elective lymph node dissection: pros and cons. In: Balch CM, Houghton A, Milton GW, et al (eds). Cutaneous melanoma. 2nd edn. Philadelphia: Lippincott, 1992: 345–66.
7 Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992; **127:** 392–99.
8 Reintgen D, Cruse CW, Wells K, et al. The orderly progression of melanoma nodal metastases. *Ann Surg* 1994; **220:** 756–67.
9 Thompson JF, McCarthy WH, Bosch CM, et al. Sentinel lymph node status as an indicator of the presence of metastatic melanoma in regional lymph nodes. *Melanoma Res* 1995; **5:** 255–60.
10 Kapteijn BAE, Nieweg OE, Liem IH, et al. Localizing the sentinel node in cutaneous melanoma: gamma probe detection versus blue dye. *Ann Surg Oncol* 1997; **4:** 156–60.
11 Ross MI. Surgical management of stage I and II melanoma patients: approach to the regional lymph node basin. *Semin Surg Oncol* 1996; **12:** 394–401.
12 Gershenwald J, Thompson W, Mansfield P, et al. Patterns of failure in melanoma patients after successful lymphatic mapping and negative sentinel node biopsy. In: abstract book of 48th annual cancer symposium of the Society of Surgical Oncology, March 21–24, 1996, Atlanta. Arlington Heights: Society of Surgical Oncology, 1996: 20 abstr.
13 MacKie RM, Byrno D, Lingam HR, et al. Prognostic evaluation of sentinel node biopsy. *Melanoma Res* 1997; **7** (suppl 1): S102.