The British Association of Plastic Surgeons (2003) **56**, 534–539

BJPS
An International Journal of Surgical Reconstruction
www.bjps.com

Nodal staging in localized melanoma. The experience of the Brescia Melanoma Unit

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Received 12 December 2002; accepted 30 May 2003

KEYWORDS
Sentinel lymph node biopsy; Melanoma; Lymphatic metastasis

Summary *Background and objectives*: We report our experience with patients affected by cutaneous melanoma undergoing sentinel node (SN) biopsy.

Methods: From November 1997 to October 2000 we performed 128 selective lymphadenectomies (SN biopsy) on 127 patients with cutaneous melanoma with Breslow thickness $>$ 1 mm or regression or ulceration. Age, sex, tumour location ad histology were recorded.

Results: Two hundred and thirty eight SNs were identified by lymphoscintigraphy in 167 lymphatic stations, 236 of them were identified intraoperatively using a gamma probe and patent blue V injection. Twenty-one patients had SNs with melanoma metastases (15.8%), 12 patients in the groin, eight patients in the axilla and one patient in the neck. After therapeutic lymphadenectomy eight more lymph nodes with metastases of melanoma were found in the specimens of three patients. After a follow-up ranging from 10 to 56 months the results are that 111 patients are free of disease. Ten patients died. Three patients have visceral metastases and are alive. One patient has developed two more melanomas. One patient was lost to follow-up.

Conclusions: Our data confirm the clinical reliability of the SN technique in melanoma; for optimisation of the therapeutic strategy, this technique might be considered the standard method of nodal staging in the evaluation of melanoma patients.

Melanoma is mostly a local disease with no clinical evidence of lymph node metastases. Nevertheless, tumours with intermediate or high thickness (Breslow $>$ 1 mm) may have microscopic lymph node involvement and such cases have a worse prognosis. The authors illustrate their experience with 127 patients with skin melanoma, admitted for

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S0007-1226/03/$ - see front matter
doi:10.1016/S0007-1226(03)00208-X

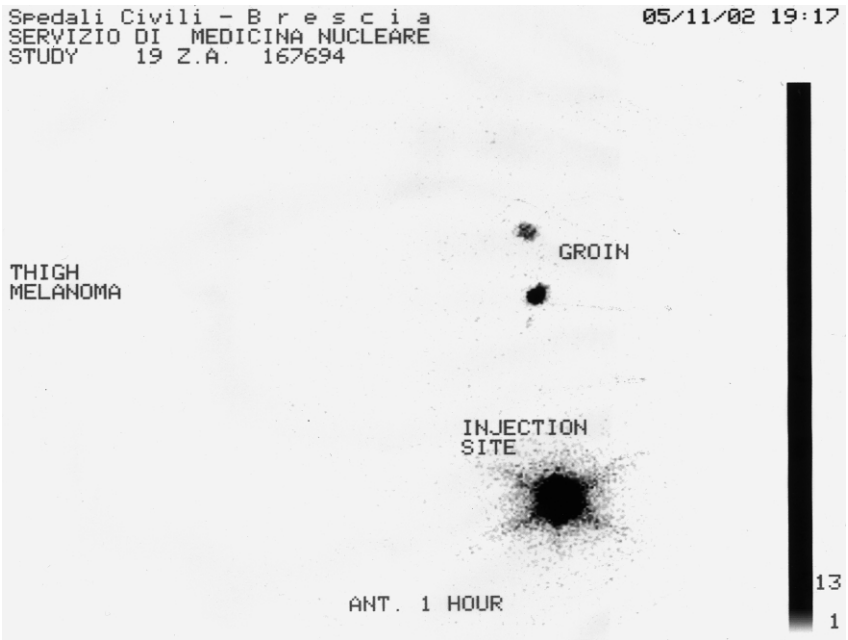

Fig. 1 Lymphoscintigraphy with ^{99m}Tc-colloid: detection of two sentinel nodes in the groin.

selective lymphadenectomy. They outline indication, techniques and the results achieved.

Patients and methods

From November 1997 to October 2000, we performed 128 consecutive selective lymphadenectomies on 127 patients (47 females and 80 males, age range 15–80 years) affected by localized melanoma with Breslow $>$ 1 mm or regression or ulceration, without palpable nodes, and clear diagnostic ultrasound of the abdomen, and lymphatic basins or total body computer tomogram.

In one patient with multiple melanomas of the trunk we did a double lymphoscintigram and sentinel node (SN) biopsy. In seven patients the melanoma was localized on the head and neck, in 56 patients (one of them had two tumours) the melanoma was localized on the trunk and in 64 patients the tumour was on the extremities.

Sentinel node detection was performed by lymphoscintigraphy with ^{99m}Tc-colloid (20–30 MBq). Two to four peritumoral intradermal injections were given. Images of the lymphatic drainage were registered after 5–10 min and 1 and 2 h (Figs. 1 and 2). A surgical marker was positioned at the site of the SN.

The following day the patients underwent selective lymphadenectomy and in most cases also the excision of the primary tumour. The SN was identified by using both patent blue V injection intradermally at the periphery of the scar (1–2 ml) and a portable gamma probe (Scintiprobe MR 100 by pol.hi.tech. Carsoli (AQ) Italy).

All excised lymph nodes were cut in half and embedded in paraffin. Several sections were evaluated by standard haematoxylin-eosin staining and by immunostaining with S-100 and HMB45 (Fig. 3).

Statistical analysis: results are presented for the continuous variables as mean (SD) and as proportions for the categorical ones. The distribution of the Breslow index in the two groups (SN $-$ and SN $+$) was analysed by the Fisher test. *T*-test was performed to evaluate possible difference in age between the two groups. The logrank test was applied to analyse the survival in the two groups.

Results

Two hundred and thirty eight SN were identified by lymphoscintigraphy in 167 lymphatic stations (88% in the groin and axilla). Two hundred and thirty five of them were identified intraoperative using a gamma probe and patent blue V injection, and excised (98.7%).

Twenty-one patients (15.6%) had SN with metastases (one of them was included in the positive (SN $+$) group after retrospective analysis of the SN performed when he developed a lymph nodal metastasis in the groin 22 months after SN biopsy), 12 patients in the groin, eight patients in the axilla and in one patient in the neck. The patient with two melanomas of the trunk for which a double SN biopsy was performed had negative SN for one

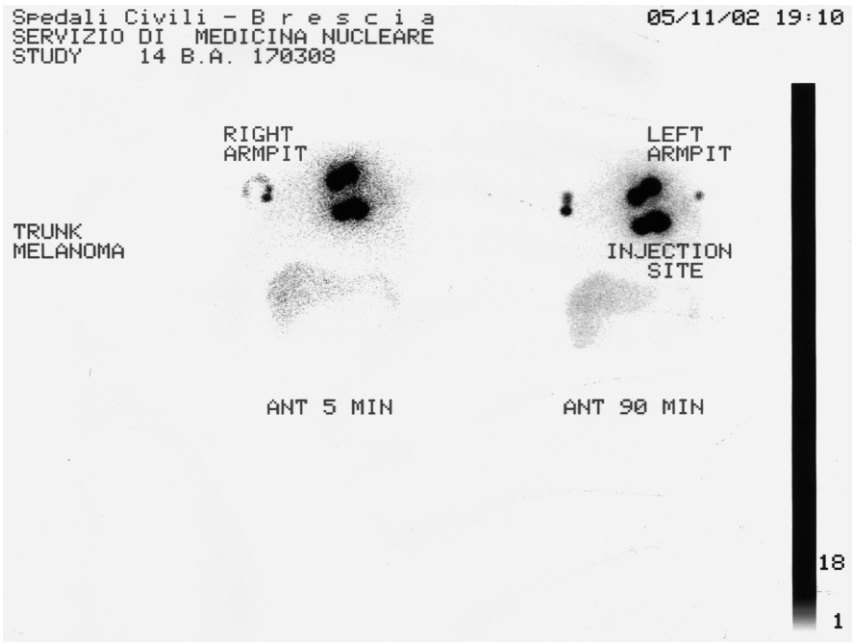

Fig. 2 Lymphoscintigraphy with ^{99m}Tc-colloid: detection of sentinel nodes in both right and left axilla.

tumour while the SN for the other one was positive. This patient was included in the positive SN group.

Seventeen of the 21 patients with positive SN underwent a radical lymphadenectomy after SN biopsy.

The relatives of one patient refused the operation, one patient was in poor general conditions and one patient went to another institution. The fourth patient did not undergo a radical node dissection until he developed a lymph nodal metastasis in the groin after 22 months.

After therapeutic lymphadenectomy eight more lymph nodes with metastases of melanoma were found in the specimens of three patients (17.6%): one in the axilla of one patient, one in the groin of one patient, six in the groin of one patient.

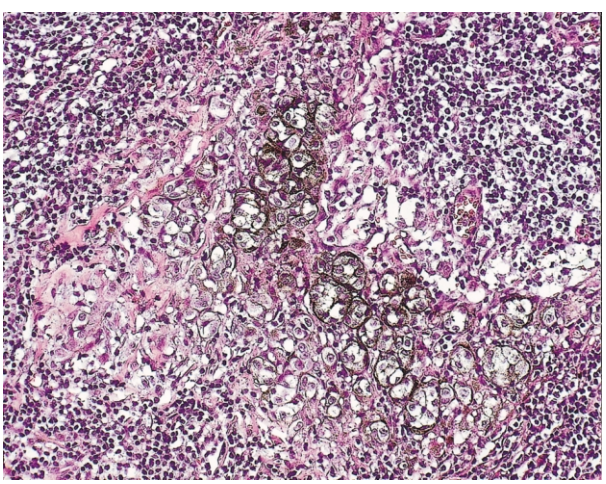

Fig. 3 Metastatic deposit of melanoma. Immunoperoxidase for HMB45, (original magnification $\times 200$).

Therefore, the SN was the only positive lymph node in 14 of the 17 patients who underwent a radical lymphadenectomy (82.4%).

The Breslow index and the SN biopsy shows a statistical significant association ($p < 0.001$) (Table 1).

The follow-up ranged from 10 to 56 months, median 33 months. Among the 106 patients with negative SN one patient with negative SN in the neck (scalp melanoma with Breslow 6.2 mm) developed bilateral cervical metastatic nodes one year after the excision of the tumour and died after six months of visceral metastases. Four more patients with negative SN developed lymph node metastases in the axilla or groin, and two of them died after developing distant metastases. Two patients are still alive (the characteristics of the tumours are shown in Table 2). One patient with negative SN in the neck (neck melanoma with Breslow 2 mm) developed a parietal bone metastasis nine months

Table 1 The number of patients with SN + increases with the thickness of the tumour (0% of those with Breslow <1 mm, almost 50% of those with Breslow >4 mm)

Row	1	2	3	4	Total
1	0	7	6	7	20
2	38	38	24	8	108
Total	38	45	30	15	128

Fisher's exact = 0.000.

Table 2 Patients with false SN −

Sex	M	M	F	M	M
Age	80	60	45	53	51
Localisation of T	Leg	Shoulder	Foot	Scalp	Trunk
Breslow (mm)	4	2.1	1.6	6.2	1.7
Ulceration	Absent	Absent	Present	Present	Absent
Sentinel node	-	-	-	-	-
Metastasis	Groin	Axilla, lung	Groin	Neck, brain	Axilla, lung, brain
Present status	Dead	Remission	Free of disease	Dead	Dead
Interval free of disease (months)	29	23	43	9	37
Overall survival (months)	44	23	43	15	45

Table 3 Diseased patients (SN +)

Sex	F	M	M	M	M
Age	77	77	80	71	20
Localisation of T	Leg	Trunk	Trunk	Trunk	Leg
Breslow (mm)	3	12	12.1	3.4	1.43
Ulceration	Present	Present	Present	Present	Absent
Metastasis	Brain	Brain	Brain	Liver	Groin, lung, brain
Interval free of disease (months)	10	1	2	19	22
Survival after T excision (months)	12	3	8	18	48

after the excision of the tumour. The patient underwent radical excision of the secondary lesion and high dose INF therapy. Four months after the excision of the parietal bone metastasis the patient developed two brain metastases. He then underwent radiotherapy of the brain and is now undergoing chemotherapy.

One patient who underwent the excision of a melanoma of the trunk in 1999, developed two new melanomas of the trunk. Ninety seven patients are still disease free.

Among the 21 patients with positive SN one was lost to follow-up, five died after 3, 8, 12, 18 and 48 months, respectively, (Table 3), one recurred with lung metastases, 14 are free of disease.

The patients with positive SN or false negative SN (FN) were 26 (19 males and seven females, with no significant difference with the other group ($p = 0.23$)), had an age range between 16 and 80 years (median 58 years). Nine patients had the primary tumour on the trunk, 15 on the extremities and two on the head and neck. The tumour thickness ranged between 1.38 and 12.1 mm (median 2.98 mm).

The patients with negative SN were 101 (61 males and 40 females), had an age range between 15 and 74 years (median 53). Forty-eight patients had the primary tumour on the trunk, 49 on the extremities and five on the head and neck. The tumour thickness ranged between 0 and 7 mm (median 1.24 mm) (Table 4).

Discussion

The association of lymphoscintigraphy and intraoperative SN detection by portable probe and patent blue V injection is successful in a high percentage of patients, 98.7% in our experience according with previous reports.[1-3] Lymphoscintigraphy is particularly useful in trunk melanoma, especially if located near the median line.[3-8] In some cases more than one drainage district is identified. In a previous article, we reported that 10% of our patients with trunk melanoma drained in an unsuspected region and in 40% of cases colloid particle migration was observed in more than one district.[8]

The rate of metastases was 15.8% according to the literature[9-11] and in 82.4% of the cases the SN was the only metastatic site.

Table 4 Principal characteristics of the two groups of patients compared

	Patients	Age (median)	M	F	Trunk	Extremities	Head and neck	Breslow (median)
SN −	101	15-74 (53)	61	40	48	49	5	0-7 mm (1.24 mm)
SN + FN	26	16-80 (58)	19	7	9	15	2	1.38-12.1 mm (2.98 mm)

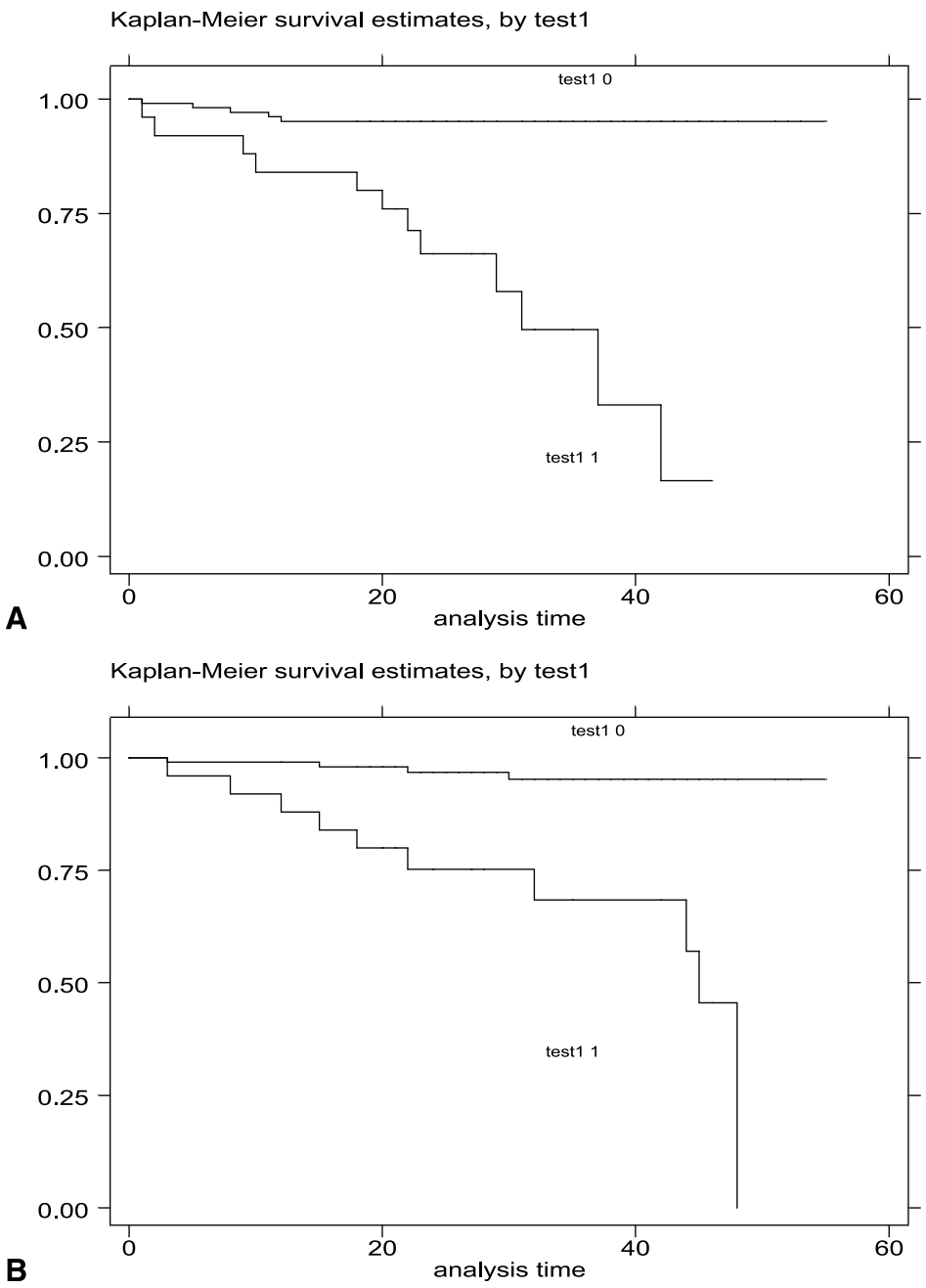

Fig. 4 Difference in event free survival time (A) and overall survival time (B) between the two groups of patients.

We started observing positive SN in patients with Breslow $>$ 1 mm. The percentage of positivity increased with melanoma thickness. We observed six cases of recurrence with lymph node involvement in patients who had negative SN (false negative rate 4.7%). Retrospective analysis of the SN of these patients was performed. In one patient the SN was positive for micrometastasis. So the real false negative rate is 3.9%.

The prognosis is significantly worse in patients with positive SN or false negative SN than in patients with negative SN. The statistical analysis has demonstrated a significant difference in both event free survival time and overall survival time between the two groups of patients ($p < 0.001$ in both cases) (Figs. 4(A) and (B)).

Conclusions

Sentinel node biopsy is a minimally invasive, highly accurate staging procedure that is associated with few complications and is performed at the time of

wide local excision of the primary melanoma. The nodal staging information is invaluable for:

1. Defining prognosis for patients: Gershenwald et al. reported that SN status was the most important independent prognostic factor in respect to recurrence and disease-specific survival.[12]
2. Determining the need for therapeutic lymph node dissection. Results of the WHO melanoma program 14 trial showed that among patients with nodal micrometastases, immediate nodal dissection conferred a significant survival benefit compared to delaying dissection until patients developed nodal metastases (48% versus 27% survival at five years, $p = 0.04$).[13]
3. Identifying patients for adjuvant therapy with interferon alfa-2b. The benefit of adjuvant interferon alfa-2b therapy was first demonstrated in the ECOG trial EST 1684.[14] The magnitude of the impact of overall survival remains in question. It may be that the population that benefits most is the group of patients with low tumour burden—those with early nodal metastasis detected by SN biopsy.[15]
4. Stratifying homogeneous patient populations for entry into clinical trials of new adjuvant therapies. To study very heterogeneous patient populations confounds interpretation of the results. One of the major goals of SN biopsy is to identify homogeneously staged patient populations for entry into clinical trials.[16]

Our data confirms the clinical reliability of the SN technique in melanoma; for optimisation of the therapeutic strategy, we believe this technique should be considered the standard method of nodal staging in the evaluation of melanoma patients.

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