Sentinel node biopsy for melanoma: a study of 241 patients

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The aim of this study was to evaluate the sentinel node biopsy (SNB) technique for melanoma using both radiocolloid and blue dye in 241 clinically N0 patients with melanomas >1.0 mm, or thinner lesions exhibiting regression/ulceration. We showed that an increase in injected radioactivity increased both the number of visualized nodes at lymphoscintigraphy and the number of SNs removed surgically. At least one SN was removed in 98% (236) of patients, and all nodes were identified with the probe. Seventy-four per cent of the 194 patients injected with blue dye had stained SNs. In 46% (144) of the lymph node basins, there was a discrepancy between the nodes visualized at lymphoscintigraphy and the nodes removed at surgery. There were 38 unusually located nodes. Only eight of these were removed surgically; none contained metastases. SN metastases were detected in 22% (53) of patients. There were nine haematoxylin and eosin (HE)-negatives, all of which were found by immunohistochemistry. The false negative rate for the SNB procedure was 4% (2/55). The complication rate was 6% after SNB and 29% after complete node dissection. In conclusion, SN status is a strong prognostic factor in melanoma patients, and SNB has made the approach to radical lymphadenectomy more rational. *Melanoma Res* 14:521–526 © 2004 Lippincott Williams & Wilkins.

Melanoma Research 2004, **14**:521–526

Keywords: Gamma-probe, lymphoscintigraphy, melanoma, sentinel node biopsy

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Received 23 August 2003 **Accepted (after revision)** 4 October 2004

Introduction

The incidence of cutaneous melanoma has increased during recent decades [1]: in Denmark, from 5 to 14 per 100 000 men and from 7 to 16 per 100 000 women between 1971 and 1998 [2]. The most powerful predictor of survival for patients with melanoma is the regional lymph node status [3]. Once nodal disease has developed, prognostic factors based on the primary tumour, such as Breslow thickness, Clark level, regression and ulceration, offer little help in predicting recurrence rates and overall survival [3]. For melanoma, the 5-year survival rate is significantly lower for node-positive melanoma than for node-negative melanoma [4,5]. Therefore, early detection of metastatic disease is crucial, and emphasis should be placed on obtaining accurate nodal staging to allow better patient management, in particular to identify patients who may benefit from adjuvant therapy [6]. Melanomas spread primarily via the lymphatic drainage and, in the past, elective lymph node dissection was performed to obtain staging information [7,8], often with long-term complications that affected the patients' quality of life. More importantly, most patients did not directly benefit from this procedure, as they showed no evidence of metastases or subsequent recurrence [9,10]. Sentinel node biopsy (SNB) has been demonstrated to be a minimally invasive and accurate method for the detection of microscopic regional metastases, and thus for the identification of patients likely to benefit from regional lymphadenectomy [6]. The sentinel node (SN) is any lymph node receiving direct lymph from the primary melanoma site, and it is thought that this node(s) is the first involved in regional spread of the disease [11]. Subsequently, there is delayed progression of metastases to other lymph nodes in the region [7]. Although the concept is simple, SN identification is sometimes technically difficult, as lymphatic drainage is clinically very unpredictable [11,12]. Preoperative lymphoscintigraphy should ensure the detection and removal of all SNs for staging purposes.

The purpose of this investigation was to study the distribution of SNs at preoperative lymphoscintigraphy and surgery, the rate of positive nodes, recurrence, complications and the main reasons for failure of SNB using a combination of radiocolloid and blue dye in a consecutive group of melanoma patients over a 4-year period at our hospital in Denmark.

Patients

Two hundred and forty-three consecutive patients undergoing SNB at our hospital between January 1998 and December 2001 were enrolled in this partly retrospective, partly prospective study (melanoma data were

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Table 1 Clinical and pathological data of the 241 melanoma patients

Variable	Data
Sex	
Male	117 (49%)
Female	124 (51%)
Age (years)	
Median with range	55 (18–85)
Primary tumour site	
Head–neck	9 (4%)
Trunk	116 (48%)
Extremity	116 (48%)
Breslow thickness (mm)	
Median with range	1.8 (0.24–15)
≤ 1.0 (T1)[a]	18 (8%)
1.01–2.0 (T2)	103 (43%)
2.01–4.0 (T3)	58 (24%)
>4 (T4)	28 (12%)
Immeasurable[a]	34 (14%)
Clark level	
I[b]	4 (2%)
II	14 (6%)
III	82 (34%)
IV	93 (39%)
V	6 (3%)
Unclassifiable[a]	41 (17%)
Not registered	1 (0.4%)
Tumour type	
SSM	159 (66%)
NM	32 (13%)
ALM	4 (2%)
LM	1 (0.4%)
Unclassifiable[a]	44 (18%)
Not registered	1 (0.4%)
Ulceration (micro- or macroscopic)	70 (29%)
Regression (micro- or macroscopic)	31 (13%)

ALM, acral lentiginous melanoma; LM, lentigo maligna melanoma; NM, nodular melanoma; SSM, superficial spreading melanoma.
[a]Non-radical primary resection or marked regression.
[b]Included because of immeasurable tumour thickness.

from the prospectively registered Danish Melanoma Group database; SNB data were registered retrospectively).

The inclusion criteria were primary cutaneous melanomas of Breslow thickness >1.0 mm, or thinner lesions exhibiting marked regression or ulceration, and clinically localized disease (clinically N0 patients). Two patients were excluded, one because of severe aortic stenosis and one because of pregnancy, resulting in a final study group of 241 patients. No patient refused to participate. Informed consent was obtained from all patients. Preoperative assessment included histopathology of the melanoma and clinical examination. All 241 patients underwent preoperative lymphoscintigraphy and intraoperative SN detection with a hand-held gamma-probe. Intraoperative SN detection with blue dye was also performed in 194 patients. The other 47 patients did not have blue dye injected. In one case, the reason was a history of Quinckes oedema of unknown cause and for the rest (46/47) the reason was unknown. Table 1 shows the characteristics of the 241 patients.

Methods

Lymphoscintigraphy

Static lymphoscintigraphy with intradermal injection of radiolabelled colloid was performed on the day before surgery. The radiocolloid used was Nanocoll (^{99m}Tc-albumin nanocolloid, Nycomed Amersham, Amersham, Bucks, UK) in 230 patients and rhenium (^{99m}Tc-rhenium sulphide colloid, CIS, Elektra-Box, Gif-Sur-Yvetts Cedex, France) in 11 patients. The injected activity was 2–160 MBq in a volume of around 0.2 ml. Before January 2001, the injected radioactivity was a median of 20 MBq, and from January 2001 it was increased to a median of 100 MBq. The patients were injected with radiocolloid at two to four sites around the biopsy scar. Two to twenty-four hours after colloid injection, the regional lymph node basins were imaged with a single-headed gamma-camera (General Electric Wisconsin, USA) in anterior and lateral views with a low-energy, high-resolution collimator. The body contour was shown by a brief ^{57}Co flatfield transmission scan, and a skin mark was made over the SN(s). Focal accumulations were considered SN(s). Images were described by the nuclear medicine physician on duty, who also performed the tracer injection.

Surgery

Five to fifteen minutes before opening of the regional lymph node basin(s), 194 (80%) of the patients were injected intradermally with a median of 0.4 ml of Patent Blue V dye (H:S Apoteket, CAS-nr. 68238-36-8, Copenhagen, Denmark) around the excisional biopsy scar. The lymph node basin(s) in question was then opened with the intention of harvesting the SNs after careful dissection of eventual blue-stained lymphatic vessels and detection of radioactivity with a hand-held gamma-probe. The gamma-probe was used in all patients: a C-track gamma-probe (Care Wise Medical Products Corporation, CA, USA) was used for the first 3.5 years and a Neoprobe (neo2000 Model 2100, Neoprobe Corporation, OH, USA) for the last 6 months of the study. Hot and/or blue nodes were regarded as SNs. Once the first and hottest radioactive SN was harvested and verified with the gamma-probe *ex vivo*, the operating field was re-examined for other radioactive nodes, which were also removed. Diffuse activity up to 10% of the count of the SN with the highest count was disregarded. Suspected enlarged lymph nodes, whether hot/blue or not, were also removed. In the neck and axilla regions, SNs were searched for within the whole lymph node basin. In the groin, the iliac and intra-abdominal SNs were left – extensive surgical procedures (intra-abdominal or retroperitoneal) were avoided, as SNB is regarded as a diagnostic staging procedure. If hot nodes were left in order to avoid extensive surgery, or if the SN procedure failed because of a lack of dissemination of the tracer to the lymph node region in question, the patient was followed by ultrasound investigation every 6 months for 5 years. Thirty-four surgeons performed the surgery,

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ranging from very experienced specialists to young residents, who were supervised during the operation. The false negative rate of the SNB procedure is defined as the number of false negative procedures/(number of false negative procedures + number of true positive procedures).

Regional lymphadenectomy was performed shortly after SNB in the case of micro- or macroscopic metastasis. In the axilla, lymphadenectomy was performed to level III. In the case of positive SNs in the groin, preoperative ultrasound investigation of the abdomen was performed; if ultrasound suspected iliac lymph nodes, both inguinal and iliac lymphadenectomy was performed. In the case of a negative ultrasound scan, inguinal lymphadenectomy only was performed. Neck dissection was always selective depending on the location of the positive SNs in the neck region.

Pathology

All nodes were submitted fresh to the Department of Pathology, where they were fixed in buffered formalin 4%, bisected along the long axis to 2–3 mm tissue blocks and embedded in paraffin. From each block, three sections were cut and underwent histological analysis with haematoxylin and eosin (HE) followed by immunohistochemical analysis for S100 protein and HMB45.

Statistics

Statistical analysis was performed using the chi-squared test, where 0.05 was chosen as the significance level.

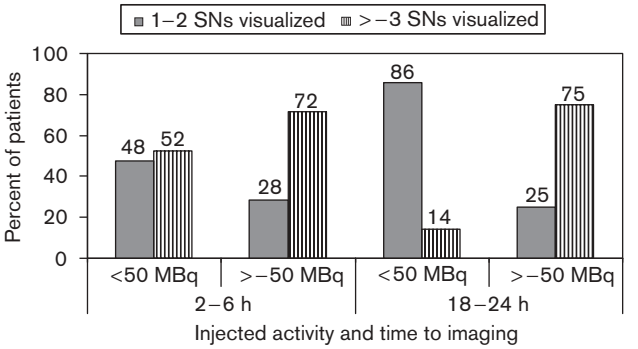
Results

Lymphoscintigraphy

Lymphoscintigraphy showed drainage to 314 lymph node basins: 50% (158) were in the axilla, 37% (115) in the groin, 6% (19) in the neck and 7% (22) in unusual regions (knee, elbow, upper arm, breast, hip, retroperitoneum and melanoma site). Of the 241 patients 177 (73%) had SNs visualized in one basin, 54 (22%) in two basins and 10 (4%) in three or more basins. The median number of SNs visualized per patient was three (range, 0–10).

One hundred and eighty-nine (78%) of the 241 patients were injected with less than 50 MBq of tracer, and 52 (22%) were injected with 50 MBq or more. Images were acquired after 2–6 h for 224 (93%) patients, whereas 15 (7%) had image acquisition after 18–24 h. There was a significant increase in the number of visualized SNs at lymphoscintigraphy for patients receiving high radioactivity ($\geq$ 50 MBq) compared with those receiving low radioactivity ($<$ 50 MBq), regardless of the time to imaging ($P < 0.0001$ with imaging after 2–6 h and $P = 0.003$ with imaging after 18–24 h). For patients injected with a low tracer activity, the number of visualized SNs decreased when images were acquired late compared with early (Fig. 1).

Fig. 1



High injected activity ($\geq$ 50 MBq) increases the number of visualized sentinel nodes (SNs) at lymphoscintigraphy and can compensate for late imaging ($\geq$ 12 h).

Sentinel node biopsy

In total, 618 SNs were surgically removed from 285 lymph node basins. At least one SN was removed in 98% (236) of patients (median, 2; range, 0–9). The gamma-probe was used for all 241 patients, while Patent Blue V was used for only 194 patients (80%). All 618 removed SNs were radioactive. For the 194 patients receiving blue dye, 74% (248/335) of the removed SNs were blue. There was a significant increase in the number of surgically removed SNs (0–1 vs. $\geq$ 2) for patients receiving high radioactivity ($\geq$ 50 MBq) compared with those receiving low radioactivity ($<$ 50 MBq) ($P = 0.012$).

For 144 (46%) of the lymph node basins, there was a discrepancy between the number of SNs visualized at scintigraphy and the number removed at surgery; in 115 (37%) basins, nodes were not excised in accordance with the protocol, either because of deep localization (34) or because they had a count rate of less than 10% of the SN with the highest count and therefore were not regarded as SNs (81); in 29 (9%) basins, additional SNs, not visualized at scintigraphy, were removed surgically because they had a count rate of at least 10% of the SN with the highest count.

Twenty-two patients (9%) showed 38 SNs in unusual regions at scintigraphy; four of these patients only had SNs in that region. We were able to remove eight of these SNs, and none contained metastases. None of the remaining patients had recurrence during the follow-up time and were therefore not considered to be false negatives. For two of the four patients with unusual localization of SNs only, the SNs were not found surgically. Because these two patients had high-risk

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Table 2 Complications of surgery in the 241 patients

Complication	Melanoma site (241 patients)	Sentinel node biopsy site (241 patients)	Complete node dissection site (49 patients)
Infection (superficial wound infection, abscess)	17	5	7
Seroma	2	7	8
Lymphoedema	–	2	6
Haematoma	–	2	–
Wound rupture	2	–	–
Anaphylactic reaction	1	–	–
No take of skin graft	4	–	–
Total	26 complications in 21 patients	16 complications in 14 patients	21 complications in 14 patients

melanomas (nodular melanoma and Breslow thickness >4 mm), regional lymphadenectomy was performed prophylactically; one patient had metastatic lymph nodes and was therefore considered a false negative.

Pathology

Fifty-three (22%) of the 241 patients had at least one SN containing melanoma metastasis. Sixty-eight (11%) of the removed SNs contained metastases. In nine SNs (1%), metastases were not detected in HE-stained sections, but were seen in S100- or HMB45-stained sections. There was no significant relationship between the number of SN metastases and the radioactivity injected or the number of SNs removed ($P = 0.536$ and $P = 0.700$, respectively).

The risk of SN metastases increases almost linearly with increasing thickness of the melanoma ($P < 0.0001$); SN metastases were not found in any of the patients with T1 melanomas, but were found in 13% (13) of the patients with T2 melanomas, in 38% (22) of the patients with T3 melanomas and in 50% (14) of the patients with T4 melanomas.

Fifty-two regional lymphadenectomies were performed on 51 patients with positive SNs (two patients refused): 27 axillary, 22 superficial groin and three neck dissections. Residual metastatic lymph nodes (median, 2; range, 1–18) were seen in 14 patients (6% of the study population).

Complications of surgery

Complications were defined as incidents that demanded treatment, i.e. antibiotics, evacuation or surgical treatment (Table 2). No patients died of the procedure. There were 63 complications in 42 patients (17%); 9% had complications at the site of the primary melanoma, 6% had complications to the SNB and 29% had complications after regional lymphadenectomy. The more SNs removed, the greater the risk of complications at the SNB site: 3% of patients who had up to one SN removed vs. 8% of patients who had two or more SNs removed ($P = 0.053$).

Recurrence and survival

The median follow-up time was 15 months (range, 10 days to 43 months), and 188 (78%) of the patients were followed for at least 6 months. Thirteen (5%) of the 241 patients had recurrence during the observation period, a median of 16 months (range, 3–31 months) after primary surgery: six of the patients were SN-negative, seven were SN-positive.

Of the six SN-negative patients, five had local recurrence in the skin and four had distant metastases. Three patients had nodal recurrences, two in non-SN basins. One had recurrence in the SN basin in nodes that were left at surgery as they were only discretely visualized at lymphoscintigraphy and were therefore not classified as SNs (high tracer activity and early imaging). This patient is a false negative of the SNB procedure. With regard to the seven patients with positive SNs, two patients had local skin recurrence and six had distant metastases. One patient had nodal recurrence in a non-SN lymph node basin.

Skin and distant metastases were considered to be manifestations of progressive disease as part of the natural history of the disease. This gives a recurrence rate in patients with negative SNs of 3% (6/188), compared with 13% (7/53) for patients with at least one positive SN. Overall, two patients had failure of the SNB procedure, giving a false negative rate of 4% (2/55).

In total, 13 (5%) of the 241 patients died during the observation period, a median of 17 months (range, 3–37 months) after primary surgery. The reason for death was melanoma in seven patients (3%), four of whom had no positive SNs. For the remainder, the aetiology was not related to melanoma (two pneumonia, one malfunctioning kidneys, one cardiac disease and two unknown reason).

Ulceration

Seventy (29%) of the patients had micro- or macroscopic ulceration in their melanoma. Seventeen (24%) of these had a positive SN, and nine (13%) had recurrence during the observation period. The median Breslow thickness of the ulcerated tumours was 2.8 mm.

Discussion

With regard to preoperative lymphoscintigraphy on the day before surgery, our data suggest that high tracer

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activity ($\geq$ 50 MBq) significantly increases the number of SNs visualized compared with low injected activity ($<$ 50 MBq), regardless of time to imaging (Fig. 1). High tracer activity also significantly increases the number of SNs detected with the gamma-probe. This may lead to the suggestion of the injection of high radioactivity, as the risk of overlooking SNs is expected to be higher with the injection of low radioactivity. Furthermore, the radiation dose to the patients and staff for SNB is low [13]. However, no significant relationship was demonstrated between the number of SN metastases and injected radioactivity or the number of removed SNs. The number of patients was low, however, and additional studies are required to confirm our findings.

According to our results, there was a discrepancy between scintigraphically visualized and surgically removed SNs of 13%. One explanation could be the prolonged interval between injection of the tracer and surgery, sometimes longer than 24 h, resulting in the disappearance of the tracer from the SNs or trapping of the tracer in second tier nodes before surgery. Performing surgery shortly after lymphoscintigraphy may minimize this problem. Adding a dynamic study to static lymphoscintigraphy might also reduce the difference [14,15].

In the current study, SNs were identified by the gamma-probe in 98% of patients, which is comparable with other studies [6,16–18]. Of the patients injected with blue dye, 74% of the SNs removed were stained. Blue dye did not increase the SN detection rate of the gamma-probe, as all SNs removed were radioactive, but may have helped the surgeon to find the SNs via its dynamic nature. Some papers have shown an increase in the rate of successful SN detection from 80–85% by blue dye alone to more than 95% by a combination of blue dye and gamma-probe [6,17,18]. We detected metastatic SNs in only seven basins without blue staining. This might suggest that non-blue lymph nodes are not true SNs, as reported by Morton [15]. The SNs were not recorded separately with regard to radioactivity and blue staining, and were not sent node by node to pathology.

Five per cent of the study population had interval nodes at lymphoscintigraphy, 21% of which were removed at surgery, none containing metastases. The remainder could not be identified at surgery. No recurrences were seen in these basins, suggesting that these nodes may not be true SNs. Uren *et al.* [12] found 7.2% interval SNs, 14% of which contained metastases, whilst McMasters *et al.* [19] showed 3.1% interval nodes, 19.5% of which contained metastases. Summer *et al.* [16] recommended the thorough use of the gamma-probe to identify unusual SN drainage patterns, as lymphoscintigraphy only visualized unusual SN locations in 29%. However, we detected no unusually situated sentinel lymph nodes with the gamma-probe, which had not been identified at lymphoscintigraphy.

In the present study, 22% of the patients had at least one metastatic SN. This agrees well with McMasters *et al.* [20] and Wagner *et al.* [10] in comparable patient populations (24.3% and 20.1%, respectively). HE staining alone detected 89% of the SNs containing metastases, and 11% HE-negatives were caught by S100 and/or HMB45 staining. This was also shown by Morton *et al.* [21]. The study by Gibbs *et al.* [22] suggests that these deposits are seen with careful examination in HE sections, although S100 and HMB45 may assist in visualizing small foci of metastases. They therefore recommend multiple-level HE sections with S100 immunohistochemistry in all SNBs that are negative in routine HE sections.

All patients with SNs positive by pathology underwent complete node dissection in our study. Twenty seven per cent had additional nodal metastases, in agreement with Morton *et al.* [21].

Like most other studies, we found a strong correlation between the incidence of subclinical micrometastases and tumour thickness [10,11,23]. In our study, 29% of the melanomas showed ulceration. Ulcerated melanomas had a greater median thickness than melanomas overall (2.8 mm vs. 1.8 mm), which partly explains why the number of patients with positive SNs was slightly greater in patients with ulcerated melanomas compared with the total study population (24% vs. 22%). However, the recurrence rate for patients with ulcerated melanomas was more than twice that for those with non-ulcerated melanomas. This is in agreement with the upstaging of primary melanoma with ulceration in the new American Joint Committee on Cancer (AJCC) staging system, because ulceration has been shown to worsen the prognosis for patients [24].

With a median follow-up of 15 months (range, 10 days to 43 months) in this study, 5% of the patients showed recurrence, and slightly more than half of the patients with recurrence died of melanoma. There were no recurrences in SNs left behind at surgery. The recurrence rate was 3% in SN-negative patients. In comparison, Wagner *et al.* [10] found recurrence in 1.7% of their SN-negative patients after a median follow-up of 13.8 months. Gershenwald *et al.* [3] found 11% recurrence in SN-negative patients after a median follow-up of 35 months. The recurrence rate in SN-negative patients is expected to increase with the observation time. Another registration of recurrences in our study population after a mean follow-up of 5 years would be appropriate, as most recurrences appear in this period [25].

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The morbidity associated with SNB was 6% in our study, compared with 29% for complete node dissection. This is slightly lower than that suggested by Morton *et al.* [21] and comparable with the results of Wrightson *et al.* [26]. Furthermore, we showed that the risk of complications of SNB increased with increasing number of SNs removed.

The primary limitation of this study was its retrospective design. However, the patient data were recorded consecutively and most in a prospective database. We changed the amount of injected activity during the study period; thus, the influence of activity injected and retained in the patient could be analysed, but with the risk of introducing a confounding factor of temporal influence. The two levels of injected activity were used fairly systematically over the whole study period, thus enabling us to compare the effect of different tracer activities on the SNB result. Two other potentially interesting factors with possible impact on the outcome of SNB could not be analysed in this study: the choice of tracer and the coincidence between blue and radioactive SNs; these remain to be analysed.

Conclusion

This study confirms that the SN status is a strong prognostic factor in melanoma patients, and that SNB is a reliable diagnostic procedure for the staging of > 1 mm thick cutaneous melanomas without clinical suspicion of regional lymph node metastases. Many patients who, without SNB, would have been classified as N0 were changed to N1. The combination of blue dye and gamma-probe made the procedure more accurate, and the method provides a more rational approach to complete regional lymph node dissection. A longer follow-up is necessary to confirm our findings and to assess the power of SNB as a predictor of recurrence in SN-positive and SN-negative patients.

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