Sentinel lymph node biopsy in breast cancer and melanoma
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Chapter VI

Is sentinel lymph node biopsy beneficial in melanoma patients? A report on 200 patients with cutaneous melanoma

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Introduction
Throughout the past century, there has been controversy about the role of elective lymph node dissection (ELND) of clinically negative lymph nodes in patients with cutaneous melanoma.1-3 Before the introduction of sentinel lymph node biopsy in 1992 by Morton et al.4 the ‘watch-and-wait policy’ was generally applied to melanoma patients with clinically negative lymph nodes. Patients with clinically negative lymph nodes underwent wide excision only of the primary melanoma with a one or two centimeter margin according to the Breslow thickness.5-7 When lymph nodes became palpable during follow-up, therapeutic lymph node dissection was performed. Sentinel lymph node biopsy is known to be a reliable method for assessing the status of regional lymph node basins.4,8-11 This technique is based on the hypothesis that lymphatic drainage from the primary tumour follows an orderly pattern through afferent lymphatic vessels into sentinel lymph node(s) before flowing into non-sentinel lymph node(s) in the regional lymphatic basin.4 The tumour status of the sentinel lymph node has been found to be the strongest prognostic factor for recurrence and survival in melanoma patients with clinically-negative lymph nodes.12 Sentinel lymph node biopsy can identify patients who may benefit from complete lymph node dissection. Dissection of clinically undetectable regional lymph node metastases at an early stage may improve long-term survival.13 Besides a strong prognostic factor and a tool for selecting patients for therapeutic lymph node dissection, sentinel lymph node biopsy can also determine the tumour status of the regional lymph nodes, which is important for directing the use of adjuvant therapy.14,15

The aim of this study was to evaluate reliability and clinical impact of sentinel lymph node biopsy in patients with cutaneous melanoma of the head, neck, trunk or extremities.

Patients and methods
Patients
From May 1995 to January 2000, 200 patients with cutaneous melanoma ≥1.0 mm Breslow thickness were enrolled in a prospective study at the Division of Surgical Oncology of the UMCG. All primary melanomas were diagnosed by excisional biopsy. None of the patients had undergone excision of the primary tumour with margins of >1.5 cm or a prior procedure that could have disrupted lymphatic drainage to the regional nodal basin. Patients with palpable regional lymph nodes, clinical evidence of distant metastases and pregnant women, children and adolescents (<18 years) were excluded from this study. The sentinel lymph node biopsy protocol was approved by the Institutional Review Board (IRB). The third patient in this series was excluded afterwards, because the radioactive tracer was spilled due to a loose needle. The clinical and pathological characteristics of the 200 melanoma patients are summarized in Table 1.
Table 1.
Clinical and pathological characteristics (n=200)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>97</td>
<td>49</td>
</tr>
<tr>
<td>Female</td>
<td>103</td>
<td>51</td>
</tr>
<tr>
<td>Age (years) Median</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>21-86</td>
<td></td>
</tr>
<tr>
<td>Site of primary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head or neck</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>Trunk</td>
<td>67</td>
<td>34</td>
</tr>
<tr>
<td>Arm</td>
<td>29</td>
<td>14</td>
</tr>
<tr>
<td>Leg</td>
<td>82</td>
<td>41</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0-2.0</td>
<td>77</td>
<td>38</td>
</tr>
<tr>
<td>2.01-4.0</td>
<td>79</td>
<td>40</td>
</tr>
<tr>
<td>&gt; 4.0</td>
<td>44</td>
<td>22</td>
</tr>
<tr>
<td>Clark level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>44</td>
<td>22</td>
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<td>IV</td>
<td>138</td>
<td>69</td>
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<tr>
<td>V</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Unclassified</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Ulceration</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>Histological subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial spreading</td>
<td>97</td>
<td>48</td>
</tr>
<tr>
<td>Nodular</td>
<td>89</td>
<td>44</td>
</tr>
<tr>
<td>Acrolentiginous</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Lentigo maligna</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Unclassified</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

**Lymphoscintigraphy**

The whole procedure was performed on an inpatient basis. Patients underwent lymphoscintigraphy on the day before surgery, to identify all basins at risk for disease and any possible interval sentinel lymph nodes. Interval nodes are defined as lymph nodes that lie along the course of a lymphatic collecting vessel between a primary melanoma site and a draining node field (i.e. axillary, groin, cervical, epitrochlear, popliteal and occipital). A single dose of 40-60 MBq $^{99m}$Tc nanocolloid (Nanocoll; Amersham Cygne, Eindhoven, the Netherlands) with a particle size of < 80 nm in 0.2 ml of normal saline was injected intradermally around the biopsy site with a 27 Gauge needle at two to four points, depending on the size of the biopsy site. Dynamic imaging with a low energy high resolution collimator to visualize lymph flow was commenced immediately after tracer administration and continued for 20 minutes at a frame rate of 30 sec/image. Subsequently, static scintigrams were acquired. A radioactive flood source
was used to outline the body contour. Another set of static images was taken two hours later. All possible lymph drainage regions were imaged. If two or more pathways drain a primary tumour site, there are generally two or more sentinel lymph nodes, because the first node reached along the path of each individual channel is a sentinel lymph node. If there is an interval node on a lymphatic drainage pathway outside a recognized lymph node field, it will be a sentinel lymph node if it receives drainage directly from the tumour site. The position of the sentinel lymph node(s) was marked on the skin with indelible ink. The images were discussed interdisciplinary between the nuclear physician and the surgical oncologist prior to the operation.

**Surgery**

The sentinel lymph nodes were excised within 30 hours after lymphoscintigraphy. Subsequent to the induction of anaesthesia, 15-20 minutes before surgery, an injection of 0.3-1.0 ml Patent Blue V (Bleu Patenté V; Laboratoire Guerbet, Aulnaysous-Bois, France) was administered intradermally with a 25 Gauge needle at the same sites as the \(^{99m}\text{Tc}-\text{nanocolloid. All basins identified by lymphoscintigraphy were explored surgically through limited incisions. The possible need for therapeutic lymph node dissection was kept in mind while making the incisions. Surgical dissection was guided by a hand-held gamma detection probe (Neoprobe®1000 and 1500, Johnson & Johnson Medical BV) and by looking for blue-stained afferent lymphatic vessels that led to blue-stained sentinel lymph nodes. Once the sentinel lymph node had been identified, excised and measured for radioactivity, the probe was used to search the resection bed to ensure that there were no residual areas of high radioactivity. If necessary, additional hot nodes were removed until the ratio of the hottest ex vivo sentinel lymph node to the residual basin was >10:1.**

After sentinel lymph node biopsy, wide local excision of the primary melanoma scar with 1 or 2 cm margin was performed according to the tumour thickness (Breslow) and invasion of the skin (Clark). If primary closure was not possible, the skin defect was closed with the use of a split-skin graft.

When we were unable to localize a sentinel lymph node transcutaneously prior to making an incision, we tried to visually identify the sentinel lymph node with the blue dye. If no blue-stained lymphatic vessels and/or sentinel lymph nodes could be found, we excised the primary injection site to remove the high background counts. In this way, radioactivity within the sentinel lymph node could be more easily detected with the probe.

**Pathology**

After marking the hottest part of the sentinel lymph node with a stitch, the harvested sentinel lymph nodes were sent for definitive pathological examination. Frozen section microscopy with HE was discontinued after the first 58 patients because of low
sensitivity (38%). The sentinel lymph nodes were fixed in 10% neutral buffered formalin and blocked in paraffin. All paraffin-embedded material was evaluated with serial 4 μm thick sections for routine HE and immunohistochemical (IHC) staining for S100 protein and melanoma-associated antigen HMB45. This procedure was repeated at levels of 500 μm until all the tissue was sectioned (average: 9 levels). Two paraffin-embedded cross-sections of each lymph node of the therapeutic lymph node dissection were stained with HE without additional IHC.

Follow-up
Patients were seen for physical examination every 3, 4 and 6 months in the 1st, 2nd and 3rd-10th year respectively. A chest x-ray was taken once a year. In patients who developed a recurrence in the same basin, recurrence patterns were analysed and all previously identified tumour-negative sentinel lymph nodes were re-evaluated histologically.

Statistical analysis
Recurrence-free and overall survival curves were constructed using the Kaplan-Meier method and analyzed using the log-rank procedure. Significance was defined as P<0.05.

Results
The sentinel lymph node(s) could be identified during surgery in 197 out of the 200 patients (identification rate 99%). A total of 393 sentinel lymph nodes (mean: 2.0 per patient, range 1-7) were removed from 241 basins. Sentinel lymph nodes were removed from one basin in 155 patients (78%) and from two basins in 43 patients (22%). In 168 patients, the sentinel lymph nodes were both stained blue and radioactive (85%). In 26 patients the sentinel lymph nodes were only radioactive (13%) and in 4 patients the sentinel lymph nodes were only stained blue (2%). Postoperative complications occurred in 5% of the patients and were minor and transient, including wound infection, haematoma, seroma and neurapraxia. There were no anaphylactic reactions to the blue dye. In three out of the 22 head and neck region patients, no sentinel lymph node(s) could be identified with lymphoscintigraphy or blue dye (identification-rate head and neck region: 86%). Lymphoscintigraphy identified sentinel lymph nodes outside the standard node fields (i.e. outside the axillary, inguinal, parotid and cervical regions) in 17 patients (9%) (Table 2) of which interval nodes in four patients (2%). Ten patients had a sentinel lymph node in the parotid gland and all were explored. In three patients the sentinel lymph node in the parotid gland was tumour-positive, in six patients tumour-negative and in one out of the 10 patients (10%) the melanoma was located on the ear lobe and showed drainage to the parotid and subdigastric regions. The subdigastric sentinel lymph node was successfully identified and tumour-negative
Table 2.

<table>
<thead>
<tr>
<th>Sentinel lymph node location</th>
<th>n</th>
<th>Identified (n)</th>
<th>Tumour status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retroauricular</td>
<td>4</td>
<td>4</td>
<td>4-</td>
</tr>
<tr>
<td>Occipital</td>
<td>1</td>
<td>1</td>
<td>1-</td>
</tr>
<tr>
<td>Right costal margin</td>
<td>2</td>
<td>1</td>
<td>1-</td>
</tr>
<tr>
<td>Tri-angular intermuscular space</td>
<td>1</td>
<td>1</td>
<td>1+</td>
</tr>
<tr>
<td>Supraclavicular</td>
<td>3</td>
<td>2</td>
<td>1-/1+</td>
</tr>
<tr>
<td>Epitrochlear</td>
<td>2</td>
<td>2</td>
<td>2-</td>
</tr>
<tr>
<td>Popliteal</td>
<td>3</td>
<td>1</td>
<td>1-</td>
</tr>
<tr>
<td>Upper arm</td>
<td>1</td>
<td>1</td>
<td>1-</td>
</tr>
</tbody>
</table>

| Tumour status 4-=4 sentinel lymph nodes tumour-negative; 1+=1 sentinel lymph node tumour-positive. |

on pathological examination. The parotid node could not be identified. This patient is still recurrence-free.

There were no temporary or permanent injuries to the facial nerve due to exploration of the parotid gland.

Sentinel lymph nodes were pathologically tumour-positive in 48 out of the 198 patients (24%). HE stained slides (slides 1,3,5 and/or 9) provided the diagnosis in 43 out of the 48 patients (90%), whereas IHC examination provided the diagnosis in the remaining five patients (10%). Frozen section microscopy of the sentinel lymph node(s) was performed in the first 58 patients, but was discontinued after its sensitivity appeared to be only 38% in this series.18 Therapeutic lymph node dissection was performed in all (n=48) of the patients with tumour-positive sentinel lymph nodes. In 12 out of these 48 patients (25%) at least one additional tumour-positive non-sentinel lymph node was identified with HE staining (Table 3).

During follow-up, six patients developed ‘recurrence’ in a previously-mapped negative node basin after 13, 18, 20, 23, 30 and 32 months. No tumour cells have been found in a re-analysis of the sentinel lymph node in retrospect in all six patients. In two of these patients, there was no evidence of concomitant locoregional recurrence.

In four patients, nodal recurrence may have resulted from spread from local, in-transit and/or distant metastases. When those patients are not considered as false-negatives, the false-negative rate is 2/50 (4%). When all six patients are considered as false-negative procedures, the false-negative rate is 6/54 (11%). Recurrence-free and overall survival were significantly associated with the results of the sentinel lymph node biopsy. Three-year recurrence-free survival in patients with tumour-negative and tumour-positive sentinel lymph nodes was 83% and 66% respectively (P<0.05) (Figure 1). The corresponding overall survival rates were 92% and 73% respectively (P<0.05) (Figure 2).
Table 3.

Therapeutic lymph node dissection results after tumour-positive sentinel lymph node biopsy

<table>
<thead>
<tr>
<th>Breslow thickness (mm)</th>
<th>n patients (%)</th>
<th>n patients with tumour-positive SLN (%)</th>
<th>additional tumour-positive nodes after TLND (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0-2.0</td>
<td>77 (38)</td>
<td>13 (17)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>2.01-4.0</td>
<td>79 (40)</td>
<td>26 (33)</td>
<td>6 (23)</td>
</tr>
<tr>
<td>&gt; 4.0</td>
<td>44 (22)</td>
<td>9 (21)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Total</td>
<td>200 (100)</td>
<td>48 (24)</td>
<td>12 (25)</td>
</tr>
</tbody>
</table>

SLN=sentinel lymph node; TLND=therapeutic lymph node dissection.

Figure 1.

Recurrence-free survival plot according to Kaplan-Meier

Recurrence-free survival plot according to Kaplan-Meier
Figure 2.
Overall survival plot according to Kaplan-Meier

Discussion
The sentinel lymph node(s) could be identified by the combined detection technique in 197 patients (99%). In only three patients the technique failed. The three failures were all located in the head and neck region (i.e. angulus mandibulae, ear lobe and parietofrontal). Thus the procedural identification rate in the head and neck region was 86% (19 out of the 22) versus 100% in extremity and truncal primaries. Explanations for the failed identification include non-optimal resolution of the gamma camera; obscuration by scattered radiation at the primary injection site, because the injection site and draining basin in the head and neck region are in close proximity.
Prospective clinical trials have suggested that occult melanoma nodal metastases are clinically important and that early therapeutic lymph node dissection may improve survival. Therefore, therapeutic lymph node dissection was considered to be the most appropriate therapy after a tumour-positive sentinel lymph node biopsy result. All the patients with tumour-positive sentinel lymph node biopsy results were advised to undergo therapeutic lymph node dissection (e.g. axillary, inguinal or popliteal lymph node dissection). In the head and neck region, modified cervical lymph node dissection was performed, including subtotal parotidectomy or posterolateral neck dissection.
The sentinel lymph nodes were blue but not radioactive in 4% of the patients in our series. In only one patient the blue, non-radioactive sentinel lymph node was tumour-positive (1/48=2%). The use of blue dye is questionable, because of this low yield, but also for the risk of tattooing the skin and anaphylactic reactions. The risk of leaving a tattoo in the head and neck region is higher, due to the smaller excision margins.
(1 cm instead of 2 cm). Therefore in the head and neck region, sometimes only colloid injections are used.\(^{21}\)

The false-negative rate of 6/54 (11%) is in comparison with the results of others.\(^{22-24}\) According to Ross there might be three potential reasons for false-negative sentinel lymph node biopsy results: (1) biological failure - recurrence as a result of residual microscopic satellites or in-transit metastases left behind after wide excision of the primary lesion; (2) technical failure - the true sentinel lymph node was not found; (3) pathological failure - the sentinel lymph node was excised, but histological evaluation failed.\(^{21}\) The histopathologic false-negative rate may decrease when carbon particles are used as an aid to direct the pathologist to the sentinel lymph nodes most likely to contain tumour.\(^{25}\)

It must be emphasized that the false-negative rate of 11% was based on a median follow-up period of 47 months (range, 24-79 months) and may increase with a longer period of observation.

Lymphoscintigraphy showed four interval nodes in four patients (2%), which could be intraoperatively identified. Interval nodes are encountered in around 7% of melanoma patients.\(^{26}\) It is interesting to speculate how often in-transit metastases might actually have been metastases in previously undetected or unrecognised interval nodes. It may well be that many so-called in-transit metastases found before lymphoscintigraphy was routinely used, were in fact metastases in interval nodes, which were actually sentinel lymph nodes in those patients.

In an editorial Thomas raised the concern of potential entrapment of melanoma cells, causing higher incidence of in-transit metastases.\(^{27}\) The surgical treatment of these in-transit metastases might be extremely difficult and even impossible.\(^{28}\) By increasing the time between the primary excision and sentinel lymph node biopsy, the theoretical risk of entrapment might be reduced. In this series isolated in-transit metastases after tumour-positive sentinel lymph node biopsy and tumour-negative sentinel lymph node biopsy were found in 4 patients (8%) and 6 patients (4%) respectively, which was not significantly different. Our tumour-negative in-transit rate of 4% is comparable with that reported by Essner, who did not find any significant difference in the incidence of in-transit metastases after tumour-negative dissections between the sentinel lymph node biopsy group and the elective lymph node dissection group (2.6% versus 3.8%, \(P=0.48\)).\(^{29}\) The true incidence of in-transit metastases after sentinel lymph node biopsy should be compared to the true incidence of in-transit metastases during watch-and-wait policy and after elective lymph node dissection.\(^{30-33}\)

Advantage of lymphatic mapping is that drainage to sentinel lymph nodes in unusual locations is identified, leading to more accurate staging than could be achieved with routine dissection of the closest lymph node field.\(^{34}\) In our study 8% of the sentinel lymph nodes were identified outside the standard node fields, which is comparable with the results of others.\(^{35-37}\) Sentinel lymph node biopsy is of established diagnostic and prognostic value. Beyond improving the selection of patients for adjuvant therapy it will
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not have direct therapeutic relevance unless early excision of lymph node metastases leads to survival benefit. Demonstration of the therapeutic value of this procedure awaits the analysis of survival data from the multicenter randomized trials: wide excision alone versus wide excision plus sentinel lymph node biopsy, the so-called MSLT-study and the Sunbelt Melanoma Trial.\textsuperscript{38,39} Sentinel lymph lymph node biopsy in the treatment of melanoma is of unproven benefit and should be performed only in surgical trials.

Acknowledgement
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