In search of the sentinel node: validation and sophistication of lymphatic mapping and sentinel node biopsy in breast cancer and melanoma
van der Ploeg, I.M.C.

Citation for published version (APA):
van der Ploeg, I. M. C. (2009). In search of the sentinel node: validation and sophistication of lymphatic mapping and sentinel node biopsy in breast cancer and melanoma Amsterdam: Nederlands Kanker Instituut - Antoni Van Leeuwenhoekziekenhuis
CHAPTER 10

A tumour-positive sentinel node biopsy of the groin in clinically node-negative melanoma patients: superficial or superficial and deep lymph node dissection?

Van der Ploeg IMC, Kroon BBR, Valdés Olmos RA, Nieweg OE

Abstract

**Introduction:** The extent of a completion groin dissection in sentinel node-positive melanoma patients was guided by the location of the second-echelon nodes on the pre-operative lymphoscintigram. The purposes of the current study were to investigate the pathological findings, the lymph node recurrences and (disease-free) survival associated with this approach.

**Methods:** Between June 1996 and April 2007, 42 patients underwent completion groin dissection after a tumour-positive sentinel node biopsy. Eighteen patients had femoroinguinal second-echelon nodes on their lymphoscintigram and underwent a superficial lymph node dissection. Twenty-four patients had iliac-obturator second-echelon nodes on their scan and underwent a combined superficial and deep dissection.

**Results:** The median follow-up time was 61 months. One of the 18 patients who underwent a superficial groin dissection developed a deep (obturator) lymph node recurrence after 12 months. Revision of the lymphoscintigram showed that the images had been interpreted incorrectly and that the second-echelon node was located in the obturator area after all. A combined superficial and deep dissection revealed additional involved nodes in the deep lymph node compartment in two of the 24 patients. At five years, 77% of all patients were alive and 56% alive and disease-free. These figures were 76% and 53% respectively in the patients who underwent superficial dissection only, and 80% and 61% respectively in the patients who also underwent deep dissection.

**Conclusion:** This study suggests that the strategy to determine the extent of the groin dissection based on the location of the second-tier nodes may be valid.
Introduction

Melanoma patients with clinically palpable lymph node disease in the groin usually undergo both a superficial (femoro-inguinal) and a deep (iliac-obturator) lymph node dissection.\(^1\)-\(^4\) The extent of a groin dissection is more controversial in patients with non-palpable nodes in whom sentinel node biopsy reveals metastasis. Deep lymph nodes seem unlikely to be involved when a superficial sentinel node contains only a microscopic amount of disease.\(^5\)-\(^7\)

At the Netherlands Cancer Institute, the extent of a completion groin lymph node dissection in case of a positive sentinel node is based on the results of the anterior and lateral lymphoscintigrams that were obtained before sentinel node biopsy. A combined superficial and deep dissection is performed when the lymphoscintigram shows second-echelon nodes in the deep lymph node areas. Otherwise, only a superficial dissection is performed. This approach is based on the hypothesis that melanoma disseminates through the lymphatic system in a step-wise fashion. This would imply that second-echelon nodes are the next lymph nodes to be involved if the sentinel node appears to be tumour-positive. Patients with tumour-negative second-echelon nodes in the superficial lymph node area are less likely to have deep lymph node involvement and may be spared a more radical operation.

The purpose of the current study was to investigate the pathological findings, the incidence of lymph node recurrences, and the (disease-free) survival associated with this approach in clinically node-negative melanoma patients with a positive sentinel node in the groin.

Patients and methods

Between June 1996 and April 2007, 52 clinically node-negative patients with a cutaneous melanoma and a tumour-positive sentinel node biopsy of the groin were selected from a prospectively constructed database. Ten patients did not receive any further dissection due to the small tumour burden in their sentinel nodes and they are not part of this study. Patient and tumour characteristics of the remaining 42 patients are presented in table 1.

A two-day protocol was used for the sentinel node procedure. On the day before the operation, technetium-99m-labeled nanocolloid (Nanocoll\(^8\), Amersham Cygne, Eindhoven, the Netherlands) was injected intradermally around the biopsy site in a mean volume of 0.3 ml (range 0.1-0.5 ml) and a mean dose of 75.7 MBq (2.0 mCi) (range 37.1-141.0 MBq, 1.0-3.8 mCi). Approximately 95% of the radiopharmaceutical has a particle size of 80 nm or less. This small particle size means that second-echelon nodes are always depicted. Static images were performed at fifteen minutes and two
hours and were preceded by a dynamic study of ten minutes. A dual-head gamma camera equipped with low-energy high-resolution collimators (Vertex®, Philips, Eindhoven, the Netherlands) was used. Both anterior and lateral images were routinely made. Additional images were obtained if needed. A cobalt-57 flood source was placed behind the patient to outline the body contour. The location of the node was marked on the skin with indelible ink.

Table 1. Patient and tumour characteristics. N: number of patients; SSM= superficial spreading melanoma; NM= nodular melanoma; ALM= acral lentiginous melanoma; * A bold p-value is statistical significant (p<0.05); ** Number of additional involved lymph nodes detected in the completion dissection specimen.

The next day, patent blue dye (Laboratoire Guerbet, Aulnay-Sous-Bois, France) was administered intradermally in a mean volume of 1.0 ml, completely surrounding the tumour or biopsy site. Intra-operative detection of radioactivity was performed with a gamma ray detection probe (Neoprobe; Johnson & Johnson Medical, Hamburg, Germany). Both tracers were used to identify the sentinel node. A sentinel node was defined as a lymph node upon which the primary tumour drains directly. After sentinel node biopsy, a wide local excision was performed of the primary melanoma site with a 1 or 2 cm margin, depending on the Breslow thickness. All sentinel nodes were formalin-fixated, bisected, paraffin-embedded, and cut at a minimum of six levels at 50 to 150 µm intervals. Pathologic evaluation included haematoxylin and eosin and
immunohistochemical staining (S-100 and HMB-45).

Figure 1. A man with a melanoma on the medial side of his right thigh. Anterior lymphoscintigrams after fifteen minutes (A) and two hours (B) show two sentinel nodes (horizontal arrows), each with their own lymphatic vessel (horizontal dotted arrows). On the lateral views after fifteen minutes (C) and two hours (D), these same superficially located sentinel nodes are visualized, and also two deep second-echelon nodes (horizontal arrow points out the obturator node and descending arrow indicates iliac node). The lateral images led to the decision to perform both a superficial and deep completion groin dissection.

Before the completion groin node dissection, the surgeon and a nuclear physician reviewed the lymphoscintigraphic images that had been used for the sentinel node biopsy. The lateral images were particularly helpful to determine the location of the second-echelon node(s) (figure 1). A second-echelon node was defined by the lymph node that lies on a direct lymphatic pathway from the sentinel node. The location of the second-echelon node(s) guided the extent of the groin node dissection, while higher-echelon nodes were not considered for this purpose. A superficial dissection was performed if the second-echelon nodes were depicted in the femoro-inguinal area,
and second-echelon nodes in the iliac-obturator area meant that an external iliac and obturator fossa dissection was carried out as well. All harvested lymph nodes were examined in 4 mm sections stained by haematoxylin and eosin. All patients were followed at our institute. The median follow-up duration was 61 months. Analyses comparing groups of patients with different outcomes or dissimilar further treatment were calculated by non-parametric t-tests or non-parametric chi-square tests. The median follow-up times of all patients and of the two subgroups were calculated by a log-rank analysis. Survival curves were estimated with the Kaplan-Meier method and compared with the log-rank test. All statistical analyses were performed using SPSS 15 (Version 15, for Windows, SPSS Inc, Chicago, IL, USA).

Results

Eighteen of the 42 patients had superficial second-echelon nodes on their lymphoscintigram that had been performed before sentinel node biopsy, and they underwent a superficial lymph node dissection only. The other 24 patients had at least one deep second-echelon node depicted by lymphoscintigraphy and underwent a combined superficial and deep dissection. Differences in patient and tumour characteristics between the two dissection groups are shown in table 1.
Figure 2. A 30-year old man with a melanoma in the right gluteal area. The anterior image after 30 minutes (A) shows a sentinel node (descending arrow), a second-echelon node (horizontal arrow) next to it, and two more cranial second-echelon nodes are visualized indistinctly. The lateral lymphoscintigram after 30 minutes (B) more clearly points out the superficial sentinel node (horizontal arrow) with two separate afferent lymph channels entering the node on either side. The anterior image after two hours (C) seems to depict a deep (obturator) second-echelon node (horizontal arrow). The right lateral lymphoscintigram after two hours (D) indicates that this second-echelon node (upper horizontal arrow) is indeed located in the deep area. A superficially located second-echelon node (lower horizontal arrow) is also visualized. The deep second-echelon node on this lateral image should have prompted a deep node dissection, and was later found to be involved.

An additional involved lymph node was found in the superficial lymph node specimen in one of the eighteen patients who underwent a superficial dissection only. Because higher-echelon nodes could not be localized precisely, this prompted a subsequent complementary deep dissection that revealed two additional involved deep lymph nodes. This patient developed in-transit metastases and distant disease and died 23 months after initial treatment. Another patient who received a superficial dissection only developed a deep lymph node metastasis during follow-up. This was a 30-year old male with a nodular melanoma on his thigh, Breslow thickness 6.3 mm, Clark
level IV without ulceration. He had one sentinel node and it was tumour-positive. He received a superficial completion lymph node dissection that yielded no further metastases. A 3 cm metastatic lymph node was detected twelve months later in the obturator fossa. A complementary deep lymph node dissection revealed the one metastatic node but no further metastases. Because of a narrow margin, he received radiotherapy of the groin. Revision of the lymphoscintigram (figure 2) showed that the images had been interpreted incorrectly and that one second-echelon node was located in the obturator lymph node area after all. This patient is alive and without signs of disease eight years later.

In two of the 24 patients who received a combined superficial and deep dissection, two additional superficial involved lymph nodes were detected in the dissection specimen. Both patients are alive without signs of tumour-activity six and thirteen months after dissection. In two others, additional involved nodes were found in both the superficial and deep compartment. One of them developed local and distant metastases and died 26 months after the initial dissection, the other patient is alive without evidence of disease after fourteen months. During follow-up, no lymph node recurrences were detected in the group of patients who had a combined superficial and deep dissection. All follow-up events that occurred in either group and in the whole group are listed in table 2.

At five years, 77% (62% - 95% confidence interval) of all patients were alive and 56% (40% - 80% confidence interval) were alive and disease-free. The five-year survival in the patients who underwent only superficial dissection was 76% (56% - 100% confidence interval), and in the patients who underwent a combined superficial and deep dissection this was 80% (61% - 100% confidence interval) (p=0.80). These figures were 53% (31% - 90% confidence interval) and 61% (39% - 96% confidence interval) respectively for disease-free survival (p=0.69).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (42 patients) N (%)</th>
<th>Superficial dissection (18 patients) N (%)</th>
<th>Superficial and deep dissection (24 patients) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma-related event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph node recurrence (groin)</td>
<td>1 (2.4)</td>
<td>1 (5.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>3 (7.1)</td>
<td>1 (5.6)</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>In-transit metastases</td>
<td>12 (28.6)</td>
<td>7 (38.9)</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>Satellite metastases</td>
<td>3 (7.1)</td>
<td>1 (5.6)</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>11 (26.2)</td>
<td>6 (33.3)</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>Survival at last follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive without disease</td>
<td>29 (69.0)</td>
<td>11 (61.1)</td>
<td>18 (75.0)</td>
</tr>
<tr>
<td>Alive with disease</td>
<td>4 (9.5)</td>
<td>1 (5.6)</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>Deceased</td>
<td>9 (21.4)</td>
<td>6 (33.3)</td>
<td>3 (12.5)</td>
</tr>
</tbody>
</table>

Table 2. Follow-up events overall and in each group. N: number of patients.
Discussion

Before the era of the sentinel node procedure, some investigators questioned the need for a deep (iliac-obturator) lymph node dissection because involved deep nodes were thought to be associated with systemic and possible incurable disease.\textsuperscript{12-14} Any potential survival benefit was considered to be outweighed by the supposed high morbidity. Others demonstrated that five-year survival rates in patients with pathologically proven involved deep nodes who received adequate surgical therapy were not that disappointing and ranged from 20\% to 35\% without showing a substantial extra morbidity.\textsuperscript{15-20}

Lymphatic mapping has revived this debate. This elegant procedure identifies patients who are without lymph node metastases among those at considerable risk of having involved nodes based on their primary tumour characteristics. Patients with a negative sentinel node biopsy can be spared a regional node dissection. When sentinel node biopsy reveals metastasis, 16\% to 21\% of patients have additional involved nodes in the lymph node dissection specimen, of which a relatively small number will be situated in the deep area.\textsuperscript{21-24} Dr. Morton’s ongoing second Multicenter Selective Lymphadenectomy Trial focuses on sentinel node-positive patients and examines their need for a completion node dissection.\textsuperscript{9-11}

The current study examines the approach of adapting the extent of a completion groin dissection to the site most likely to contain additional metastases. A radiopharmaceutical with a small particle size passes through a sentinel (first-echelon) node and lodges in second-echelon nodes or even further downstream. The larger the particles, the smaller the fraction that will move on to subsequent nodes. Dynamic imaging immediately after injection of the radiopharmaceutical visualizes the lymphatic duct(s). Cross-connections of lymph ducts between nodes make it progressively more difficult to determine the exact echelon of nodes downstream from a sentinel node, but conscientious analysis of the images enables second-echelon nodes to be distinguished from both sentinel nodes and higher-echelon nodes. This feature can be used to tailor the extent of the node dissection to the needs of the individual patient. Patients with second-echelon nodes in the deep lymph node area seem more likely to have deep node involvement based on the concept of step-wise lymphatic spread of melanoma metastases. These patients may benefit from the radical approach of a combined superficial and deep node dissection if sentinel node biopsy reveals metastasis.

One of the eighteen patients in this study who underwent only a superficial lymph node dissection developed a deep (obturator) lymph node metastasis later. Retrospectively, the lymphoscintigram had been interpreted incorrectly which means that, according to our policy, he should have received a deep node dissection as well. Two of the twenty-four superficial and deep lymph node dissections revealed additional involved nodes in the deep dissection specimen. These findings seem to justify our approach and support...
the idea that melanoma spreads in a step-wise manner through the lymphatic system. The disease-free five-year survival in the present study was 56% and the overall five-year survival was 77%, similar to the 75% five-year overall survival mentioned by Essner et al. in a comparable group of patients. There were no distinct differences in (disease-free) survival figures between the two groups of patients in our study. The comment must be made that the median follow-up duration was significantly longer in the patients who underwent a superficial dissection only compared to the patients who also underwent deep dissection. This is attributable to the coincidence that shortly after the introduction of our strategy more patients had superficial second-tier nodes. Besides our approach to select patients for combined superficial and deep dissection, other factors have been mentioned that may indicate the risk of deep lymph node involvement. An example of such a predictive factor is the lymph node of Cloquet, which is typically described as the node that lies in the femoral canal between the femoral vein and the lacunar ligament. Coit et al. found a negative predictive value of 95% for this node. Others question the predictive value of the transitional node of Cloquet for the tumour-status of iliac-obturator nodes. Lymphatic drainage from the lower extremities and trunk does not always pass from the inguinal nodes to the deep nodes through the femoral canal and Cloquet’s node. A prospective study by Strobbe et al. of patients with palpable disease in the groin showed that Cloquet’s node has a limited sensitivity of 65% to predict involvement of deep nodes and a that the negative predictive value is 78%. Too many patients will be denied treatment for their deep lymph node metastases when Cloquet’s node guides the need for further dissection. A tumour-positive Cloquet’s node had a 69% risk (positive predictive value) of additional nodes that bear disease. Strobbe et al. also showed that the number of positive nodes in the inguinal region is not a reliable predictive factor for the deep nodal status with a sensitivity of 41% and a negative predictive value of 78%. The presence of more than three involved inguinal nodes carried a 69% risk of additional involved deep lymph nodes. Other studies reported a 32% risk of metastatic deep lymph nodes was noted when one to three superficial nodes were involved, ranging from a 17% risk when only one superficial node was tumour-positive to a 51% risk when more superficial nodes were affected. These observations indicate that the number of involved superficial nodes is not a good enough parameter to indicate the need for a deep lymph node dissection.

In conclusion, our approach led to one deep lymph node recurrence in a patient whose second-echelon nodes were (supposedly) superficial and who underwent a superficial groin dissection only. Retrospectively, this case was due to an incorrectly interpreted lymphoscintigram. Deep metastases were detected in two patients who underwent a combined superficial and deep dissection. The 56% disease-free survival and 77% overall survival are satisfying results. The promising results of this limited series suggest that the strategy to determine the extent of a groin dissection in sentinel node positive melanoma patients based on the location of the second-echelon nodes as shown by lymphoscintigraphy may be valid.
References


