Results, morbidity, and quality of life of melanoma patients undergoing sentinel lymph node staging
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Morbidity after axillary sentinel lymph node biopsy in patients with cutaneous melanoma

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ABSTRACT

Aim: In this study, the short-term and long-term morbidity was assessed after axillary sentinel lymph node biopsy (SLNB) with or without completion axillary lymph node dissection (SLNB/ALND) in patients with cutaneous melanoma.

Methods: Between 1995 and 2003, 119 axillary SLNBs were performed for cutaneous melanoma. Fifty-eight patients met the inclusion criteria and entered the study.

Results: Forty-four patients underwent SLNB alone and 14 patients underwent axillary lymph node dissection after positive SLNB. Complications after SLNB alone: post-operative bleeding (n=2), seroma (n=1), and slight lymphedema 11%. Complications after SLNB/ALND: wound infections (n=2), seroma (n=5), and slight lymphedema 7%. There were differences between the two groups in short-term complications (p<0.001) and functional limitations of the shoulder (p=0.011).

Conclusion: Axillary SLNB alone had a low complication rate. However, SLNB followed by completion ALND was associated with an increased risk of short-term and long-term complications.
INTRODUCTION

In order to achieve better staging of patients with clinical stage I and II melanomas, Morton introduced the concept of sentinel lymph node biopsy (SLNB) at the beginning of the 1990s.\textsuperscript{1} Research has shown that sentinel lymph node biopsy does indeed lead to better staging of stage I and II patients.\textsuperscript{1-8} When metastases are found in the sentinel lymph node, completion lymph node dissection is recommended. At present, studies are underway to establish whether lymph node dissection influences survival improvement in melanoma patients.\textsuperscript{9} It will take a number of years before the results of this multicentre selective lymphadenectomy trial (MSLT) become available.

Sentinel lymph node biopsy in itself seems to be a minimally invasive procedure. Various studies have shown that axillary SLNB in breast cancer patients is associated with less morbidity than SLNB and/or axillary lymph node dissection (ALND).\textsuperscript{10-15} We reviewed axillary SLNB and possible completion axillary lymph node dissection in patients with cutaneous melanoma to gain insight in the short- and long-term morbidity.

PATIENTS AND METHODS

Patient population

Patients were included who had undergone axillary SLNB as staging procedure for cutaneous melanoma ($\geq$ 1.0 mm) at the Groningen University and University Medical Center Groningen in the period 1995-2003. Positive SLNB had been followed by completion axillary lymph node dissection.

Patients were excluded on the basis of the following characteristics: bilateral SLNB, undergoing follow-up elsewhere, pre-existing functional limitations and/or previous operations on the extremity concerned, pre-existing volume difference between the two extremities, severe comorbidity such as dementia, disseminated disease or patients receiving palliative care. Patients were also excluded if they were receiving treatment for local or loco-regional recurrence at the time of the study.

Between 1995 and 2003, 277 patients had undergone SLNB for cutaneous melanoma. In 119 of these patients, axillary SLNB had been performed. On the basis of the above-mentioned criteria, 36 patients had to be excluded from the study; 21 patients had died (17 patients died of disease related death). The remaining 62 patients were eligible for the retrospective study and informed consent was ultimately obtained from 58. The clinical and pathological data on these 58 melanoma patients are summarized in Table 1. This study evaluated morbidity after axillary SLNB alone (SLNB) and after completion axillary lymph node dissection (SLNB/ALND). Short-term morbidity was measured as the number of post-operative complications. Long-term morbidity was analysed in the form of lymphedema and range of motion restriction of the affected extremity.
TABLE 1 Clinical and pathological characteristics (n=58)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>33</td>
</tr>
<tr>
<td>Women</td>
<td>25</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>50</td>
</tr>
<tr>
<td>Range</td>
<td>24-75</td>
</tr>
<tr>
<td>Localization of primary melanoma</td>
<td></td>
</tr>
<tr>
<td>Arm</td>
<td>25</td>
</tr>
<tr>
<td>Trunk</td>
<td>33</td>
</tr>
<tr>
<td>Breslow thickness (mm)</td>
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</tr>
<tr>
<td>Median</td>
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<tr>
<td>Range</td>
<td>1.08-13.0</td>
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<tr>
<td>1.0-2.0</td>
<td>21</td>
</tr>
<tr>
<td>2.01-4.0</td>
<td>24</td>
</tr>
<tr>
<td>&gt;4.0</td>
<td>13</td>
</tr>
<tr>
<td>Clark’s level</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>12</td>
</tr>
<tr>
<td>IV</td>
<td>44</td>
</tr>
<tr>
<td>V</td>
<td>2</td>
</tr>
<tr>
<td>Ulceration</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>19</td>
</tr>
<tr>
<td>Absent</td>
<td>38</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Superficial spreading</td>
<td>28</td>
</tr>
<tr>
<td>Nodular</td>
<td>26</td>
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<tr>
<td>Desmoplastic</td>
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<tr>
<td>Unknown</td>
<td>3</td>
</tr>
<tr>
<td>Localization SLNB</td>
<td></td>
</tr>
<tr>
<td>Right axilla</td>
<td>33</td>
</tr>
<tr>
<td>Left axilla</td>
<td>25</td>
</tr>
<tr>
<td>Tumour status SLNB</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>14</td>
</tr>
<tr>
<td>Negative</td>
<td>44</td>
</tr>
<tr>
<td>Follow-up in months</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>53</td>
</tr>
<tr>
<td>Range</td>
<td>5-89</td>
</tr>
</tbody>
</table>

SLN biopsy technique

The sentinel lymph node biopsy procedure, re-excision of the scar and possible completion lymph node dissection were conducted on an inpatient basis. The procedure was performed by a combination of lymphoscintigraphy, patent blue dye and a gamma ray detection. The technique has been described extensively in a previous study. SLNB was followed by re-excision of the scar of the primary melanoma with a margin of 1 or 2 cm, depending on the thickness of the melanoma (< 2 mm, 1 cm; > 2 mm, 2 cm margin). The excised lymph nodes were sent for routine histological examination with haematoxylin-eosin staining (HE staining) and when the HE staining was negative, specific immunohistochemical staining (IHC) was conducted for the protein S100 and melanoma-associated antigen HMB45. If histological examination showed that the sentinel node contained metastatic melanoma tissue, the patient was considered for completion axillary lymphadenectomy. ALND comprised Level I-III axillary dissection.

Complications and lymphedema

In all the patients, a note was made of post-operative complications that had occurred within 30 days. Between January and July 2003, the patients were invited for volume measurements and a function evaluation of both arms. The volume of the arms was determined with the aid of an adapted version of the water-displacement technique described by Kissin et al. Both the
affected and the unaffected arms were measured. An increased volume of 10% or more of
the affected extremity was classified as lymphedema. Lymphedema was defined according
to the classification of Stillwell (0-10% insignificant, 11-20% slight edema, 21-40% moderate
edema, 41-80% marked edema, and > 80% severe edema).¹⁷

**Functional evaluation**

The functional evaluation comprised abduction, anteflexion, external rotation and external
rotation in 90° abduction of the shoulder joint. Range of motion was measured in degrees
with a goniometer with the patient in the standing position according to a standardised
protocol. Both the affected and unaffected arms were evaluated. Functional limitation
(clinically relevant functional loss) was defined as a difference in range of motion of 20° or
more compared to the contralateral joint.¹⁸

**Statistical analysis**

Statistical differences were analysed with the t-test and the chi-square test. Differences with
a p value of < 0.05 were considered to be significant. All the analyses were performed with
the SPSS software version 11.0 (SPSS Inc., Chicago, IL, USA).

**RESULTS**

SLNB had been conducted in 33 men and 25 women. In 25 patients (12 men and 13
women) the primary melanoma was localized on the arm, while in 33 patients (21 men
and 12 women) the melanoma was localized on the trunk. Median age at the time of
diagnosis was 50 (24-75) years. There was no difference in age between the SLNB group
and the SLNB/ALND group. Median follow-up at the time of the study was 59 (5-89)
months; duration of follow-up did not differ between the two groups. Although SLNB can
be performed on a day treatment basis, all the patients in this study had been hospitalized.
Median duration of hospitalization in patients with axillary SLNB combined with re-excision
and possible free split skin grafting was 4 (2-10) days; in patients with SLNB/ALND, median
duration after axillary lymph node dissection was 7 (5-12) days (p<0.001). Primary closure
of the melanoma excision had been possible in 51 patients (88%), while 7 patients had
required free split skin grafting to close the wound.

Sentinel node metastases were found in 14 out of the 58 patients, which formed an
indication for completion axillary lymph node dissection. In four patients, one additional
tumour-positive lymph node was found in the resection specimen. Median duration
between SLNB and ALND was 35 (18-56) days. The remaining 44 patients had undergone
SLNB alone.
Complications

None of the patients had died as a result of the surgical intervention. After SLNB, three patients developed one complication: postoperative bleeding (n=2) and seroma (n=1). After SLNB/ALND, two patients developed wound infection that could be treated with incision and drainage. Five patients developed seromas that were treated by means of aspiration. Thus, after SLNB, three complications occurred (7%) vs seven complications after SLNB/ALND (50%; p<0.001). The complications are summarized in Table 2.

<table>
<thead>
<tr>
<th>Complication</th>
<th>SLNB n=44</th>
<th>SLNB/ALND n=14</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>44</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Wound infection</td>
<td>0</td>
<td>2</td>
<td>0.01</td>
</tr>
<tr>
<td>Seroma</td>
<td>1</td>
<td>5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postoperative bleeding</td>
<td>2</td>
<td>0</td>
<td>0.4</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>5</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Functional limitation</td>
<td>0</td>
<td>2</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*All slight lymphedema (volume difference 10-20%) according to Stillwell.*

Volume

In the total group of patients, who had undergone axillary SLNB, there was no volume difference between the patients with a primary melanoma localized on the trunk and those with a primary melanoma localized on the arm (p=0.8). No volume difference was found between primary closure of the excision wound and closure by means of free split skin grafting (p=0.3). Five patients (11%) in the SLNB group and two patients in the SLNB/ALND group had undergone free split skin grafting (p=0.8). No differences in the volume of the arms was observed between the men and the women (p=1.0). Furthermore, there were no differences regarding body mass index between the SLNB group and the SLNB/ALND group (p=0.1).

In the patients, who had undergone SLNB alone, five had slight lymphedema. In the patients, who had undergone SLNB/ALND, one had slight lymphedema (Table 2). In both groups there was no moderate, marked or severe lymphedema and the body mass indices were the same as in the group without lymphedema (p=0.4). No volume difference was found between the SLNB group and the SLNB/ALND group (p=1.0).

Function

There were no functional limitations in the SLNB group. In the SLNB/ALND group, two patients had functional limitations of the affected extremity. One patient had abduction limitation of the shoulder of 30° and anteflexion limitation of the shoulder of 40° and one patient had abduction limitation of the shoulder of 24°.
Until now, only one prospective study has been published on complications after SLNB in melanoma patients. Wrightson et al. found complication rates of 4.4% after axillary SLNB and 19.9% after SLNB/ALND.\textsuperscript{19} No further distinction was made between the complications. Particularly, the complication rate after SLNB/ALND was low compared to the present study (19.9 vs 50%) and compared to complications described after therapeutic axillary lymph node dissections, with complication rates that varied between 35 and 51%.\textsuperscript{20-24} Wrightson et al. also reported low rates of lymphedema (SLNB alone: 0.3% and SLNB/ALND: 4.6%).\textsuperscript{19} However, in contrast with the present study, lymphedema was not measured objectively in the study by Wrightson et al. and the patients were not classified according to severity. This means that the reliability of their rates can be questioned.

A recently published retrospective study from Wasserberg et al. showed some morbidity after SLNB in patients with melanoma.\textsuperscript{25} They found an overall wound complication rate of 13.6%. However, this was significantly associated with groin SLNB. Their wound complication rate was 9.8% for axillary SLNB. These findings are comparable to the present study, with an overall wound complication rate of 7% for axillary SLNB.

Various studies reported less long-term morbidity after SLNB than after ALND in breast cancer patients.\textsuperscript{10-13,15,26-30} However, a wide diversity of assessment instruments were used: from self-constructed questionnaires to physical examination and a few validated questionnaires. In addition, the duration of follow-up varied from two weeks to three years after treatment. In our study, we aimed to measure long-term morbidity using two objective assessments: lymphedema and range of motion.

**Lymphedema**

In this paper, lymphedema was classified as a volume difference of $> 10\%$ between the affected arm and the contralateral arm. We found one study in which volume differences were expressed in percentages and in which an SLNB alone group was compared to an SLNB/ALND group in breast cancer patients. The study in question by Sener et al. showed that after SLNB/ALND, there was a higher risk (17.1\%) of lymphedema than after SLNB alone (3.0\%).\textsuperscript{31} Patients with breast cancer underwent mastectomy or breast-conserving treatment. In the latter case, radiotherapy formed part of the regimen. A positive sentinel lymph node meant that there was an indication for completion axillary lymph node dissection and possible adjuvant radiotherapy to the axilla. Radiotherapy to the breast disrupts the lymphatic drainage and radiotherapy after axillary lymph node dissection increases the risk to develop lymphedema of the arm.\textsuperscript{16} Therefore, it is not surprising that in the study by Sener et al. the risk of lymphedema in breast cancer patients was higher after SLNB/ALND than after SLNB alone.\textsuperscript{31} Although it might be expected that the risk of lymphedema after SLNB or SLNB/ALND in melanoma patients is higher in women than in men, the present study did not find any difference in volume difference between the sexes.
Functional outcome

In a number of studies, upper limb morbidity was measured in terms of range of motion limitations.\textsuperscript{10,18,27,28,32} All these studies were conducted on patients with breast cancer after axillary SLNB with or without completion ALND. Differences in abduction and anteflexion were particularly noticeable between the ALND group and the SLNB group. In the study by Rietman et al., it was concluded that ALND was a predictor of upper limb morbidity in the form of range of motion restrictions.\textsuperscript{32} The present study confirmed that ALND after SLNB led to more range of motion restrictions in the upper extremity than SLNB alone.

The place of sentinel node biopsy in the treatment of patients with cutaneous melanoma has not yet been defined and we must wait for the results of the MSLT I. In the meantime, few studies were describing possible complications after this technique, such as an increased risk of in-transit metastases.\textsuperscript{33,34} The present study showed that the short-term and long-term morbidity after axillary SLNB was minimal. Patients with combined SLNB/ALND had an increased risk of short-term and long-term morbidity, such as wound infections and reduced range of motion of the shoulder.

Prospective randomized studies performed in the 1990s conclusively proved the value of prophylactic antibiotic treatment in patients with axillary lymph node dissection.\textsuperscript{35,36} Prophylactic antibiotic treatment in the case of ALND after positive SLNB seems to be indicated to reduce the risk of wound infection.

In conclusion, the risk of lymphedema in patients with cutaneous melanoma after SLNB/ALND was not increased, compared to SLNB alone, while there was an increased risk of short-term complications and clinical functional limitations of the affected arm after SLNB/ALND.
REFERENCES


8. Statusz Muller MG, van Leeuwen PA, de Lange-De Klerk ES et al. The sentinel lymph node status is an important factor for predicting clinical outcome in patients with Stage I or II cutaneous melanoma. Cancer 2001; 91: 2401-8.


