Melanoma surgery and the impact of sentinel node biopsy

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Chapter 3

Less false-negative sentinel node procedures in melanoma patients with experience and proper collaboration

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ABSTRACT

Background and objectives: The aims of the study were to determine the percentage of false-negative sentinel node procedures in melanoma patients, to investigate the time cohort of these recurrences, whether a learning phase was involved and to search for causes of the failures.

Methods: Between December 1993 and December 2008, 708 melanoma patients underwent a sentinel node biopsy. The procedure was considered false-negative if a recurrence developed in the basin from which a tumor-free sentinel node had been removed. Of all false-negative cases, the pre-operative images, operative report and pathology slides were reviewed.

Results: Sentinel node biopsy was positive in 164 (23%) of the patients and false-negative in ten (1.4%), which results in a false negative rate of 5.7%. Five of the ten failures occurred in the first year after the sentinel node biopsy was introduced. Causes for these false-negative procedures could be attributed once to the nuclear medicine physician, once to the surgeon and twice to the pathologist.

Conclusion: The sentinel node procedure failed to identify involvement in 5.7% of the patients with lymph node metastases. Half of the false-negative biopsies took place in the first year after the procedure was introduced, illustrating the existence of a learning period.
INTRODUCTION

Sentinel node biopsy allows patients with nodal metastasis to be treated in a relative early phase of their disease. The sentinel node is found in almost 100% of the patients in specialized melanoma institutes. In non-specialized institutes, this percentage lies between 94 and 98.[1-3] The initial publications showed that no metastases were found in the dissection specimen of the regional lymph node basin when the sentinel node was free of metastases. [4-6] The tumor status of the sentinel node now is the most important prognostic factor and a valuable diagnostic test to determine further disease management.[1,7] Interim-results of a randomized controlled trial show that five-year overall survival of patients with a positive sentinel node in whom an early completion lymph node dissection is carried out is better compared to patients in whom a late dissection is carried out for palpable nodal metastases (72.3% and 54.2% respectively, p=0.02).[8]

Now that the duration of follow-up of patients after sentinel node biopsy is increasing, a considerable incidence of recurrences is noticed in nodal fields from which a tumor-negative sentinel node was excised.[9] False-negative percentages from eight to 32 have been reported from renowned melanoma institutes.[3,8,10-16] The median follow up of one study was less than two years.[17] At our own institute, this percentage was eleven in the first 200 patients who were analyzed in 2000.[1] This high incidence of false-negative procedures is reason for concern and one wonder what the causes may be. The nuclear physician, surgeon and pathologist perform the sentinel node procedure in close collaboration. The cause of a false-negative sentinel node biopsy may be present at each of these pillars of the procedure.[18]

Now that the number of melanoma patients who received a sentinel node biopsy at our institute has increased to 708 and the median follow-up has surpassed five years, it seems useful to further examine this question.

The first aim of this study was to determine the percentage of false-negative sentinel node procedures. The other aims were to investigate the time cohort of these recurrences, to analyze whether a learning phase was involved and to search for possible causes of the failures.

PATIENTS AND METHODS

Between December 1993 and December 2008, 708 melanoma patients underwent sentinel node biopsy at The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital. The first
250 patients were also included in previous studies. Sentinel node biopsy was carried out if the primary tumor had a Breslow thickness of at least 1 mm or less if the Clark level was IV. A two-day protocol was used. On the day before the operation, technetium-99m-labeled nanocolloid (Nanocoll, Amersham Cygne, Eindhoven, the Netherlands) was injected intradermally around the biopsy site in a mean volume of 0.4 ml and a mean dosage of 76 MBq (2 mCi). Static images were performed at fifteen minutes and two hours and were preceded by a dynamic study of ten minutes. Both anterior and lateral images were routinely made. Hybrid single photon emission computed tomography with radiographic computed tomography (SPECT/CT) was introduced in 2006 and was performed when conventional images were difficult to interpret and for research purposes. The location of the node was marked on the skin with indelible ink. 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 tumor 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 tumor drains directly. After sentinel node biopsy, 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. Pathology evaluation included hematoxylin and eosin and immunohistochemical staining (S-100 and MART-1). With the exception of some patients with minimal nodal involvement, patients with a positive sentinel node received a regional node dissection. This was a modified radical neck dissection, level I-III axilla dissection or a superficial inguinal node dissection that was usually accompanied by a dissection of the obturator and external iliac nodes. The biopsy was considered false-negative if a primary recurrence developed in the regional lymph node basin from which a tumor-free sentinel node had been removed. The mean follow-up of all 708 patients was 54 months.

The sentinel node procedure consists of three main pillars: the pre-operative imaging, the operation and the microscopic analysis of the node. The pre-operative images, the operation report and the microscopic analysis of the patients with a false-negative sentinel node procedure were reviewed in an attempt to trace the causes of these failures.
RESULTS

A median of 2.4 sentinel nodes per patient were excised. The sentinel nodes were tumor-negative in 534 patients (75%) and they received no further treatment. A total of 141 patients (20%) had a tumor-positive sentinel node and underwent completion lymph node dissection. Twenty-three patients (3.3%) with a minimally involved sentinel node did not receive any further dissection. Ten patients (1.4%) had a false-negative sentinel node procedure, which means that 5.7% of the patients with an involved lymph node basin were not identified by the procedure (false-negative rate 5.7; 95% confidence interval (CI) 2.8% - 10.3%). The sensitivity of the sentinel node biopsy is 94.3% (95% confidence interval (CI) 89.7% - 97.2%). The percentage of false-negative procedures (false-negative ratio) was 29.4 in the first year, 3.0% in the subsequent years and in the last four years this was 1.4. Five of the ten false-negative biopsies happened in the first year after sentinel node biopsy was introduced at our institute. In the subsequent years only sporadic a false-negative biopsy occurred and in the last three years there were none. The mean interval to discovery of the missed metastases in the regional lymph node field was 28 months (4.6 - 106 months).

The causes of these false negative procedures were pursued. One patient recurred in a lymph node in the triangular intermuscular space lateral from the right scapula. Although it had not been described by the nuclear medicine physician, this sentinel node was visible on the lymphoscintigram in hindsight. In a second case, the surgeon failed to excise a para-iliac sentinel node that was reported by the nuclear physician. Two false-negative sentinel node procedures became apparent when the pathologist made additional slides of the sentinel node after a recurrence developed in the nodal basin. No cause could be found in the remaining six false-negative cases.

DISCUSSION

The sentinel node biopsy failed to identify disease in ten of the 164 patients who had an involved nodal basin, which corresponds with a false-negative ratio of 5.7%. Some investigators calculate this rate of false-negative outcomes over the total number of patients who underwent sentinel node biopsy or in the group of sentinel node-negative patients.[24] This approach does not follow the formal definition of a false-negative test result.[9] The false-negative rate intends to tell us how often a diagnostic test fails to show an abnormality when it is present. Because it is not possible to miss a metastasis in a patient who has no metastasis, this ratio...
should be calculated only over the group of patients with tumor-positive sentinel nodes.[9] This is an important point because the choice of the definition has substantial implications for the outcome of this rate. When calculated in the correct fashion, the percentages of false-negative procedures in some reputable melanoma institutes are still unfavourable, e.g.18% and 32%. [25,26] The percentage was 18 in an interim analysis of the Multicenter Selective Lymphadenectomy Trial (Table).[8]

**Table.** False-negative rate in various studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>False-negative ratio</th>
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<tbody>
<tr>
<td>Present study</td>
<td>5.7%</td>
</tr>
<tr>
<td>Vuylsteke et al 2003</td>
<td>9.0%</td>
</tr>
<tr>
<td>Scoggins et al 2010</td>
<td>10.8%</td>
</tr>
<tr>
<td>Doting et al 2002</td>
<td>11.0%</td>
</tr>
<tr>
<td>Yee et al 2005</td>
<td>13.2%</td>
</tr>
<tr>
<td>Gershenwald et al 2007</td>
<td>16.1%</td>
</tr>
<tr>
<td>Clary et al 2001</td>
<td>16.4%</td>
</tr>
<tr>
<td>Caraco et al 2007</td>
<td>18.4%</td>
</tr>
<tr>
<td>Morton et al 2006</td>
<td>18.0%</td>
</tr>
<tr>
<td>Leiter et al 2010</td>
<td>32.0%</td>
</tr>
</tbody>
</table>

The nuclear medicine physician and the surgeon were responsible for one false negative case each and two had to do with the pathology evaluation. These causes could be identified, but there are other factors that can play a role. The lymph drainage is variable and not always follows the same lymph track to the same node. This is illustrated by the observation that pre-operative lymphoscintigraphy does not always show all the sentinel nodes when performed twice.[27,28] The recently introduced SPECT/CT sometimes shows more sentinel nodes than conventional lymphoscintigraphy.[20] Another possible explanation is that a large metastasis in the sentinel node blocks the lymph flow. The radioactive tracer and blue dye will then be diverted to another node, a ‘neo-sentinel node’, that may not harbor tumor cells yet.[29,30] Although we know that lymph fluid drains fast, little is known about the kinetics of melanoma cells in this fluid.[31] It is possible that melanoma cells are still in-transit at the time of the sentinel node procedure, only to end up later in another lymph node to cause a false negative result.
What are the possibilities to make the sentinel node procedure more sensitive and to decrease the number of false-negative biopsy in melanoma patients? One important factor is the collaboration between nuclear physician, surgeon and the pathologist. At our own institute all the lymphoscintigrams, operations and results of the procedures are discussed at a weekly multidisciplinary sentinel node conference. Our observation that five of the ten failures occurred in the first year after the procedure was introduced, suggests that these meetings and the increased experience with the procedure are responsible for the reduction of the percentage of false-negative procedures. The aforementioned SPECT/CT is expected to improve sentinel node detection in patients with a complex drainage region like the head and neck or the peri-scapulair area.[32] Another improvement is the refinement of the pathology analysis. The use of the polymerase chain reaction with multiple biomarkers could make the detection of tumor cells more sensitive.[33,34] Unfortunately, some normal cells like nevus cells, macrophages or antigen-presenting dendritic cells in a lymph node also contain these biomarkers, which limits the specificity.[35] The identification of minimal metastases still is difficult. Nodal minimal metastases may be missed if the lesion happens to be in-between slides. A technique like carbon dye mapping is used by some investigators to help the pathologist identify the region within the node where metastases are most likely to be found and may make the sentinel node procedure more sensitive.[36,37]

CONCLUSION

In 5.7% of the patients with metastasis in the regional lymph node field we were not able to detect this with the sentinel node biopsy. Half of these false-negative sentinel node biopsies took place in the first year after the procedure was introduced at our institute. The percentage false-negative procedures (false-negative ratio) in the first year was 29.4 and in the last four years this was 1.4. There appears to be a learning phase. The cause of a failed procedure was not identifiable in six of the ten cases.
REFERENCES