Melanoma surgery and the impact of sentinel node biopsy

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Chapter 6

Five year follow up of sixteen melanoma patients with a Starz I involved sentinel node in whom completion lymph node dissection was omitted

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I.M.C. van der Ploeg
B.B.R. Kroon
O.E. Nieweg

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ABSTRACT

Objectives: To determine the incidence of lymph node recurrence in sixteen melanoma patients with a minimal metastasis (Starz level I) in a sentinel node in whom a completion lymph node dissection was omitted. A secondary aim was to examine whether other melanoma-related recurrences developed.

Methods: Sixteen melanoma patients with an SI involved sentinel node, who did not receive completion lymph node dissection, were followed for a median 66 of months.

Results: Lymph node recurrences did not occur. One of the sixteen patients developed a local recurrence and another developed satellite metastases.

Conclusion: None of the sixteen patients with an SI positive sentinel node developed a nodal recurrence, which suggests that the risk of refraining from node dissection in such patients is small. This option could be considered and discussed with the patient regarding the risk of non-sentinel node involvement and the unsolved problem of unknown overall survival advantage.
INTRODUCTION

Since the introduction of sentinel node biopsy, the need for completion lymph node dissection in case of an involved sentinel node has been challenged in melanoma patients, particularly in the presence of a minimal tumour burden.[1,2] Additional lymph node metastases are found in only 10 - 20% of sentinel node positive patients and it is unclear whether their chance of survival increases by the early dissection.[3-6] The remaining patients do not benefit, but they are exposed to the significant morbidity of this procedure.[7] Criteria have been suggested to determine the risk that more nodes are involved in order to enable the selection of patients who may benefit from completion node dissection. The largest diameter of a metastasis, the total metastatic area, the number and location of tumour deposits within the sentinel node are among the micromorphic characteristics used to this end.[6,8-10]

In 2001, Starz et al introduced the micromorphometric S-classification, which is based on the depth of infiltration of a subcapsular metastasis into the sentinel node (Table 1).[11] The S-classification is appealing because it not only considers the size of the metastasis but also other parameters that appear to have prognostic value like its location and growth pattern. The S-classification, therefore, can be conceived to resemble tumour biology comparable to the Breslow thickness. Using completion lymph node dissection specimens, Starz et al showed that the presence of additional lymph node metastasis is significantly related to this S-classification and that the most favourable category is not associated with other involved nodes.[11] Based on these findings, we refrained from completion node dissection in sixteen patients with a tumour infiltration depth of not more than 0.30 mm in a sentinel node (S1). [12] These patients were a subgroup in an earlier study in which no lymph node recurrences were detected with a limited follow-up duration of 34 months. We kept a close eye on these patients and the median duration of the follow up is now more than five years. Since this issue is subject of considerable debate, this seems an appropriate moment to re-evaluate our regimen. The purpose of the study was to explore the omission of completion node dissection in a limited group of patients with an SI tumour-positive sentinel node. The main purpose was to determine the incidence of lymph node recurrence. A secondary aim was to examine whether other melanoma-related recurrences developed.
Table 1. New simplified Starz classification based on the depth of infiltration of a subcapsular metastasis into the sentinel node.[6]

<table>
<thead>
<tr>
<th>Starz classification</th>
<th>Infiltration depth from capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>SI</td>
<td>≤ 0.30 mm</td>
</tr>
<tr>
<td>SII</td>
<td>0.31 - 1.0 mm</td>
</tr>
<tr>
<td>SIII</td>
<td>&gt; 1.0 mm</td>
</tr>
</tbody>
</table>

PATIENTS AND METHODS

Patients
The patients in the present study are a subgroup of an original population of 70 melanoma patients who underwent lymphatic mapping and sentinel node biopsy at The Netherlands Cancer Institute between October 2001 and July 2007 and whose results have been published before.[12] The current sixteen patients had an SI involved sentinel node and did not undergo completion lymph node dissection, because they participated in a study or refused completion lymph node dissection. The overall patient characteristics are presented in table 2. The mean age was 45 years and the gender distribution was eight males and eight females. The median Breslow thickness was 1.6 mm (range: 1.0 - 3.6 mm). Three melanomas were located on the upper extremity, eight on the lower extremity, two in the head and neck region and three on the trunk. Informed consent was obtained and the ethics committee of The Netherlands Cancer Institute approved the use of human tissue.

Methods
Sentinel node biopsy was carried out if the primary tumour had a Breslow thickness of at least 1.0 mm or less if the Clark level was IV. The sentinel node biopsy technique has been described in detail.[13] Briefly, technetium-99m-labeled nanocolloid (Nanocoll, Amersham Cygne, Eindhoven, the Netherlands) was injected intradermally around the biopsy site and dynamic and static lymphoscintigraphy was then performed. Hybrid SPECT/CT was introduced in 2006 and was used when conventional images were difficult to interpret and for research purposes.[14,15] Sentinel node(s) retrieval was performed using patent blue dye (Laboratoire Guerbet, Aulnay-Sous-Bois, France) and a gamma ray detection probe (Neoprobe, Johnson & Johnson Medical, Hamburg, Germany). A sentinel node was defined as a lymph node upon which the primary tumour drains directly.[16] 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.

### Table 2. Characteristics of the 16 melanoma patients with a SI tumour-positive sentinel node.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age in years</th>
<th>Tumour location</th>
<th>Breslow thickness in mm</th>
<th>Number of sentinel nodes</th>
<th>Nodal basin</th>
<th>Follow-up in months</th>
<th>melanoma-related recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>64</td>
<td>arm</td>
<td>3.2</td>
<td>2</td>
<td>axilla</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>24</td>
<td>leg</td>
<td>2.0</td>
<td>1</td>
<td>inguinal</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>58</td>
<td>leg</td>
<td>1.5</td>
<td>1</td>
<td>inguinal</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>44</td>
<td>leg</td>
<td>1.0</td>
<td>4</td>
<td>popliteal (2), inguinal (2)</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>37</td>
<td>leg</td>
<td>1.1</td>
<td>2</td>
<td>inguinal</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>43</td>
<td>arm</td>
<td>1.7</td>
<td>1</td>
<td>axilla</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>62</td>
<td>head</td>
<td>1.0</td>
<td>5</td>
<td>pre-auriculair (1), level II (3), level III (1)</td>
<td>74</td>
<td>Loco-regional</td>
</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>43</td>
<td>leg</td>
<td>1.4</td>
<td>2</td>
<td>inguinal</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>61</td>
<td>arm</td>
<td>2.0</td>
<td>1</td>
<td>axilla</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Female</td>
<td>20</td>
<td>trunk</td>
<td>1.0</td>
<td>1</td>
<td>axilla</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Male</td>
<td>44</td>
<td>leg</td>
<td>1.2</td>
<td>1</td>
<td>axilla</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Female</td>
<td>40</td>
<td>head</td>
<td>1.8</td>
<td>1</td>
<td>parotid gland</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Male</td>
<td>35</td>
<td>trunk</td>
<td>3.6</td>
<td>4</td>
<td>left and right axilla</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Female</td>
<td>51</td>
<td>leg</td>
<td>2.3</td>
<td>2</td>
<td>inguinal</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Female</td>
<td>55</td>
<td>leg</td>
<td>2.6</td>
<td>1</td>
<td>inguinal</td>
<td>44</td>
<td>Loco-regional</td>
</tr>
<tr>
<td>16</td>
<td>Female</td>
<td>44</td>
<td>trunk</td>
<td>2.0</td>
<td>1</td>
<td>axilla</td>
<td>37</td>
<td></td>
</tr>
</tbody>
</table>

Between parentheses: number of sentinel nodes in that particular nodal basin

All sentinel nodes were formalin-fixed, bisected, paraffin-embedded, and cut at a minimum of six levels at 50 µm intervals. Pathologic evaluation included hematoxylin and eosin and immunohistochemical staining (S-100 and HMB-45 or MART-I). The pathology slides were reviewed by a senior pathologist with a particular interest in melanoma and the metastases were classified according to the new simplified version of the S-classification.[6,12] The highest S-classification was used if multiple metastases were present. A lymph node recurrence was defined as a nodal recurrence in the field from which the tumour-positive sentinel node had been harvested without previous or concurrent tumour reappearance elsewhere in the region.
All sixteen patients with an SI tumour-positive sentinel node were rigorously followed at our institution. The first two years, patients were seen every three months, in the third year every four months, in the fourth and fifth years every six months, and yearly thereafter. A follow up consisted of a history, a physical examination and ultrasound examination with fine needle aspiration cytology in case of uncertainty. The median follow up duration was 66 months (range: 37 - 99 months).

RESULTS

Lymph node recurrences were not encountered in the sixteen patients with an involved sentinel node in whom no nodal clearance had been performed. Two patients (13%) developed another type of melanoma-related recurrence. The first patient was a 62-year old gentleman with a left pre-auricular melanoma with a Breslow thickness of 1.0 mm and an ipsilateral SI sentinel node at level II in the neck. Nine months later, a local recurrence was excised after which he remained free of disease (four years). The second patient was a 55-year old lady with a 2.6 mm thick melanoma on the left calf and an SI sentinel node in the left groin. She developed two satellite metastases that were excised seven months later. At that time no lymph node metastases were found at physical examination or with ultrasonography. Eight months later, regional perfusion with Melphalan was performed because of extensive satellite, in-transit and lymph node metastases found. Currently, 34 months after sentinel node biopsy, she receives systemic therapy for multiple subcutaneous and intramuscular metastases of the left leg. All sixteen patients were still alive at the time this manuscript was finalised (July 2012).

DISCUSSION

None of the sixteen patients with an SI positive sentinel node in whom a completion lymph node dissection was omitted developed a nodal recurrence during a median follow up period of five and a half years, although one patient developed a local recurrence and another satellite metastases. The limited number of patients in our study leaves room for a type II error. However, the long median follow up duration, the notion that 80% of the recurrences become evident within three years after the diagnosis of the primary tumour, the paucity of data on this subject and its controversial nature may render the results meaningful.[17]

As far as we know, no other studies on the omission of completion lymph node dissection in case of a SI positive sentinel node have been published, but several investigators studied
the correlation between some form of tumour burden in the sentinel node and the presence of additional positive lymph nodes in the subsequent completion node dissection specimen. [6,8,18-20] Younan et al did not find additional tumour-positive lymph nodes in SI melanoma patients either, but they did find additional metastases in 11% of the SII patients and in 22% of the SIII patients (P=0.04).[20] Rossi et al described that none of their SI patients, 19% of SII patients and 31% of SIII patients had additional positive lymph nodes.[19] Still, some investigators did report metastases in other nodes in patients with SI involvement. Fink et al found that completion node dissection revealed additional lymph node metastases in 4% of the SI patients.[18] In their second study in 2004, Starz et al noted that the incidence of additional positive lymph nodes was 11% in SI patients, 13% in SII patients and 53% in SIII patients.[6] Van Akkooi et al reported that positive nodes were found in 23% of 26 SI patients after completion lymph node dissection, in 8% of 25 SII patients and 13% of 16 SIII patients.[8] The finding that 23% of patients with SI positive sentinel nodes harbour metastases in non-sentinel nodes is remarkable. A possible explanation may lie in the exclusion of patients with clusters of less then ten tumour cells in the sentinel node. Also, this high number may be based on chance in this relative small group of patients (n=26). From a series of 313 melanoma patients with a tumour-positive sentinel node, Kingham et al concluded that it remains unclear whether completion node dissection must be performed in all melanoma patients with a positive sentinel node and that for selected informed patients nodal observation may be an acceptable option. However, this was a small, retrospective study from a single institution in which the tumour burden in the sentinel node was not quantified.[21] Gershenwald et al. searched for factors predictive of additional regional lymph node involvement in patients with a tumour-positive sentinel node.[22] They concluded that primary tumour thickness, sentinel lymph node tumour burden, and the number of lymph nodes harvested may be useful in identifying a group at low risk for positive non-sentinel nodes that can be spared additional lymph node dissection.

More than thirty patient factors, primary tumour characteristics or sentinel node aspects have been published to have prognostic relevance when it comes to the involvement of other nodes. There is no lower limit identifiable below which no other nodes are ever involved. Other factors than the size of a metastasis clearly determine the biology of the disease as well. In this respect, the S classification appears attractive because it incorporates an element of the size of the lesion but it also incorporates parameters that are associated with the biology of the metastasis like the depth of invasion into lymph node and its location within the node.
So far, we must conclude that there is no parameter that reliably dictates whether a completion node dissection needs to be performed. The studies that have been carried out concern patients who underwent completion node dissection, but the number of identified nodes was not the number of nodes that are known to be present in the nodal basins and their pathology evaluation did not include step-sectioning and immunohistochemistry staining. Our current study does not address the presence of metastases in other nodes per se but their clinical relevance, which better reflects our ultimate concerns, which are regional control and survival.

Summarizing the current body of evidence one can say that few patients with an S1 sentinel node have more involved nodes and whether such involvement is relevant is subject of debate. None of our patients with S1 involvement developed a nodal recurrence during the median follow up period of five and a half years. Based on these observations and given the notion that some 90% of the recurrences – if they do occur – become evident within five years, the risk of a future recurrence appears remote. Also, a third of the patients in whom a nodal recurrence does happen can still be cured. So, does the potential small benefit from a routine completion node dissection justify its associated useless morbidity in the vast majority of patients?

Two ongoing studies currently address this issue. Morton’s Multicenter Selective Lymphadenectomy Trial II compares node dissection versus observation in patients with an involved sentinel node, and Van Akkooi’s MINITUB study observes patients in whom no dissection is carried out. We expect these studies to shed some light on the poignant questions that we are facing. One may even speculate that gene expression profiles may provide the desired prognostic information before the results of these long-term studies become available.

In the meantime, we discuss with our patients the pro’s and cons of completion node dissection as well as we can. We tell them that most melanomologists would proceed with a node dissection. The option of omitting a completion lymph node dissection in case of a S1 tumour positive sentinel node could be considered and discussed with the patient regarding the risk of non-sentinel node involvement and the unsolved problem of unknown overall survival advantage. It is understandable that some patients with minimal sentinel node involvement opt for a wait and see policy, particularly if operation would mean an inguinal node dissection.
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