In search of the sentinel node: validation and sophistication of lymphatic mapping and sentinel node biopsy in breast cancer and melanoma
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CHAPTER 9

Is completion lymph node dissection needed in case of minimal melanoma metastasis in the sentinel node?

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Ann Surg, in press
Abstract

Introduction: The micromorphometric Starz-classification suggests that melanoma patients with a sentinel node metastasis invading no more than 0.3 mm (S-I) or 0.31-1.0 mm (S-II) below the capsular level can be spared further surgery, while invasion of the metastasis of more than 1.0 mm (S-III) implies a need for completion dissection. The purpose of this study was to evaluate this approach in our melanoma patients.

Methods: Seventy patients with sentinel node metastases were studied. Twenty patients with an S-I or S-II classification were spared further surgery and 50 S-III patients underwent completion dissection. The median follow-up time was 33 months.

Results: No lymph node recurrences were detected in the twenty S-I,II patients. Six of the 50 S-III patients (12%) had additional involved nodes in the dissection specimen. In these patients no recurrences developed in the cleared regional basins. Overall three-year survival was 100% in the S-I,II patients and 80% in the S-III patients (p=0.04). Three-year disease-free survival rates were 83% and 60%, respectively (p=0.40).

Conclusion: This study suggests that further surgery is unnecessary in S-I and S-II patients, while it does seem prudent to carry out completion dissection in S-III patients. The distinct survival difference between the two groups of patients suggests that the S-classification also has prognostic implications.
**Introduction**

Detailed histopathological work-up has led to a higher detection rate of involved sentinel nodes.\(^1\)\(^-\)\(^4\) This increase in tumour-positive sentinel nodes most likely concerns lymph nodes with a small tumour burden and may signify less aggressive disease.\(^5\) Some 15-20% of the patients with a tumour-positive sentinel node have additional metastases in their regional basin, and this might be less in patients with minimal involvement.\(^6\)\(^-\)\(^9\) There is no consensus on the benefit of a completion dissection in melanoma patients with a small tumour burden in their sentinel node. The micromorphometric S-classification described by Starz and co-workers can guide the decision whether to perform completion dissection.\(^9\)\(^,\)\(^10\) This system is based on the depth of penetration of the metastasis from the surrounding capsule into the node. Patients categorized as S-I (≤ 0.3 mm invasion depth) and S-II (0.31 – 1.0 mm invasion depth) have a relatively small risk of additional lymph node disease.\(^9\)\(^,\)\(^11\) Our policy is to refrain from regional node dissection in these patients. S-III metastases are defined by a invasion depth of more than 1.0 mm, which has been reported to imply a more than 50% risk of additional lymph node metastases in the basin.\(^9\) A completion lymph node dissection is routinely carried out in such S-III patients.

The purpose of this study was to analyze our management of melanoma patients with involved sentinel nodes based on the Starz-classification. The incidence of lymph node recurrences was determined in the patients in whom no node dissection was performed and the occurrence of additional lymph node metastases was determined in the dissection specimens of the patients who did undergo a completion node dissection. Disease-free and overall survival rates were determined as well.

**Patients and methods**

Between October 2001 and July 2007, 344 melanoma patients underwent lymphatic mapping and sentinel node biopsy at our institute. Sentinel node biopsy revealed metastases in 94 of the 344 patients (27%). Twenty patients were excluded because they did not follow the protocol of the present study and four patients were lost to follow-up.

Patients with a cutaneous melanoma with a Breslow thickness of at least 1.0 mm or a Clark level of at least IV routinely undergo this procedure. A two-day protocol was used for the sentinel node procedure. On the day before surgery, 80 MBq \(99m\)Tc-nanocolloid (Nanocoll\(^\text{®}\); Amersham Cygne, Eindhoven, the Netherlands) was injected in a total volume of 0.4 ml in 4 peritumoural intradermal injections of 0.1 ml within 1 cm from the melanoma or the excisional biopsy site. Dynamic imaging was performed for the first ten minutes, followed by static imaging at fifteen minutes and...
two hours. 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. Since December 2006 additional SPECT/CT was performed when the lymphoscintigrams were inconclusive or no drainage was seen. The location of the node was marked on the skin with indelible ink.

The next day, 1.0 ml patent blue dye (Laboratoire Guerbet, Aulnay-Sous-Bois, France) was administered intradermally around the tumour or biopsy site. A gamma ray detection probe (Neoprobe, Johnson & Johnson Medical, Hamburg, Germany) was available. Both techniques were used to identify the sentinel node. A sentinel node was defined as a lymph node to which the primary tumour drains directly. After sentinel node biopsy, a wide local excision was performed of the primary melanoma site with 1.0 or 2.0 cm margins, 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 staining as well as immunohistochemical staining (S-100 and HMB-45 or MART-I).

The sentinel node metastases were originally categorized according to the Starz-classification as described in his first publication in 2001 and the patients were prospectively entered in a database separating those without dissection (S-I and S-II) from those who received further dissection (S-III). For the present study, we revised all pathology slides according to the new simplified version of the Starz-classification introduced in 2004, in which the maximum depth of invasion below the interior margin of the lymph node capsule is measured. In this system, tumour cells invading not deeper than 0.3 mm are classified as S-I, invasion up to and including 1.0 mm is classified as S-II, and S-III is defined as invasion of more than 1.0 mm below the capsular level. No patient was incorporated in another S-category using the more recent version. The S-classification was separately determined for all lymph node basins containing sentinel lymph nodes. The highest S-classification prevailed if metastases were present in more than one sentinel node in the same lymph node basin. All lymph nodes harvested by a completion dissection were examined in 4.0 mm sections stained by haematoxylin and eosin. If needed, more sections were cut to determine how many slides incorporated tumour cells. All patients were followed at our own institute.

Overall and disease-free survival were calculated from the date of sentinel node biopsy to the date of the first recurrence, death or to the date of the last follow-up visit. Overall and disease-free survival rates were estimated with the Kaplan-Meier method and compared by means of the log-rank test. Statistical analyses were performed using SPSS 15 (Version 15, for Windows, SPSS Inc, Chicago, IL, USA).

Results
Seventy patients (74% of those with involved sentinel nodes and 20% of the whole group) were enrolled in the present study. Twenty of them had either an S-I classification (sixteen patients) or S-II classification (four patients) and were spared further surgery. The remaining 50 patients had an S-III classification and underwent completion dissection. The median follow-up time was 32 months (range 8.4 – 71 months) in the S-I and S-II patients, and 34 months (range 4.5 – 72 months) in the S-III patients. The median Breslow thickness was 1.8 mm (range 1.0 – 3.0 mm) and 3.8 mm (range 1.0 – 12 mm) respectively. The median number of harvested sentinel nodes was two, ranging from one to six.

<table>
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Table 1. Characteristics of the six S-III patients with additional metastases in the dissection specimen. SN: sentinel lymph node; LN: additional lymph node(s); DM: distant metastasis, SM: satellite metastasis, ITM: in-transit metastasis, LNR: lymph node recurrence

Figure 1. Overall survival comparing the twenty S-I,II patients (dotted line) who did not receive completion dissection with the fifty S-III patients (solid line) who underwent this procedure (p-value = 0.04).
Six of the fifty S-III patients (12%) had additional involved lymph nodes in the dissection specimen (table 1). Four of these patients had one additional tumour-positive lymph node, one patient had two additional involved nodes, and another patient had six additional involved lymph nodes. One of these patients died of distant metastases, the others were alive at the last date of follow-up. The smallest penetration depth of the sentinel node metastasis associated with additional involvement (of nodes) was 1.1 mm.

No lymph node recurrences were detected in the twenty S-I and S-II patients and none of the S-III patients recurred in the cleared basin. Two S-III patients (4%) developed a supraclavicular lymph node recurrence, seven and eleven months after an axillary node dissection. One of these patients had concurrent distant metastases and passed away four months later. The lymph node recurrence in the other patient was followed by a local recurrence four months later and a satellite metastasis five months thereafter. This patient is alive without signs of tumour activity, now two years after the axillary dissection.

Five-year overall survival in our entire population was 79% and disease-free survival at five years was 53%. Overall three-year survival was 100% for S-I and S-II patients and 80% for the S-III patients (p= 0.04, figure 1). Disease-free survival at three years was 83% and 60%, respectively (p= 0.40, figure 2).

Figure 2. Disease-free survival comparing the twenty S-I,II patients (dotted line) who did not receive completion dissection with the fifty S-III patients (solid line) who underwent this procedure (p-value= 0.40).
Discussion

In the breast cancer staging system, tumour deposits with a size of 0.2 - 2.0 mm are defined as micrometastases and when smaller than 0.2 mm as sub-micrometastases.\textsuperscript{13-15} It is widely accepted that completion axillary dissection can be safely omitted in patients with sub-micrometastases in the sentinel node.\textsuperscript{16} In melanoma, the term micrometastasis has been formally defined as a metastasis that is ‘diagnosed after sentinel node biopsy or elective lymphadenectomy’.\textsuperscript{16} This definition means in essence that any non-palpable metastasis is a micrometastasis. There is thus no defined upper diameter and a micrometastasis may be quite sizeable depending on factors that are not associated with the actual tumour deposit. For instance, a metastasis in an obese patient will generally be larger before it becomes palpable compared to a slim patient, and the same applies to an obturator nodal metastasis compared to a superficial inguinal metastasis. We see a need for a definition based on an easily measurable parameter that separates patients who require further dissection from patients in whom observation is justified. The micromorphometric S-classification introduced by Starz et al. is an attempt to accomplish this and suggests that melanoma patients with an S-I,II sentinel node metastasis can be spared a lymph node dissection, while an S-III metastasis implies a need for completion dissection.\textsuperscript{9,10} The present prospectively performed study supports this guiding principle as no lymph node recurrence was detected in the twenty S-I and S-II patients who did not receive further surgery, while additional metastases were present in six of the 50 dissected S-III patients (12%). The smallest penetration depth of the sentinel node metastasis associated with additional nodes involved was 1.1 mm, confirming that Starz-III patients should undergo completion dissection.

To our knowledge, no other studies on the omission of a completion lymph node dissection based on the S-classification have been reported so far. More data on this issue are eagerly awaited, the more so as the incidence of additional involved nodes in the dissected S-classification patients varies in the published reports.\textsuperscript{9,11,17} In a study describing their new and simplified classification, Starz et al. found additional lymph node metastases in the dissection specimen in 11% to 13% of the S-I and S-II patients combined, compared to 53% of the patients with S-III sentinel node metastases.\textsuperscript{9} Fink and colleagues describe that only patients with an S-III stage were found to have further metastases in the dissection specimen.\textsuperscript{11} Van Akkooi et al. reported additional lymph node involvement in 23%, 8% and 13% of the S-I, S-II and S-III patients, respectively.\textsuperscript{17} The high incidence of additional lymph node disease in S-I patients in the study by Van Akkooi and their relatively high percentages in all three categories in the Starz study are remarkable. The first finding might be explained by their exclusion of patients with clusters of less than ten tumour cells in the sentinel node, while such patients may account for a relatively low risk of further lymph node metastases. The second observation may be explained by the thorough pathological work-up of the lymph nodes in the dissection specimen by Starz et al., which was done by
haematoxylin and eosin combined with immunohistochemistry (S-100) staining. The five-year overall survival mentioned in literature ranges from 85% to 95% for sentinel node-negative patients and from 47% to 65% for sentinel node-positive patients. The 79% five-year overall survival in our entire population of sentinel node-positive patients is higher than the latter described range. This could be a result of our thorough pathologic evaluation of the sentinel nodes and the resulting greater proportion of patients with small metastases. The difference in our series between the three-year overall survival of S-I,II patients (100%) and S-III patients (80%) is statistically significant (p= 0.04). This is in line with the results of Starz et al, who mentioned that their classification was a highly predictive factor for both the manifestation of distant metastases and overall survival (p<0.0001). Van Akkooi et al. observed a similar trend with a three-year overall survival of 96% in S-I patients, 80% in S-II patients and 57% in S-III patients (p=0.055).

Two patients with a solitary metastatic deposit centrally in the sentinel lymph node were excluded from our analysis because the Starz-classification is restricted to subcapsular lesions. Three other patients with bilateral tumour-positive sentinel nodes in the groin were excluded as well. Although S-I or S-II metastases were present in one groin, the largest lesions in the other groin were classified as S-III. The outcome of these patients would not necessarily have reflected the course of disease related to the S-I and S-II metastases.

We realize that our results are based on a modest size population, especially with respect to patients with S-I metastases, and that the 33 months median follow-up time may not be long enough for definitive conclusions. Another drawback of our study is that the histopathological work-up of the completion dissection specimen did not include immunohistochemistry staining. This may have caused underestimation of the number of additional involved nodes in the S-III category.

Several investigators have tried to find independent factors that predict the presence of additional involved lymph nodes in sentinel node-positive patients based on primary tumour and/or sentinel node characteristics (table 2). These investigators used a variety of protocols for lymphatic mapping and pathological work-up of the harvested nodes, and often small groups of patients were studied. In some studies the decision to perform a completion dissection was based on the size or on the invasion depth of the metastasis, in other studies the location of the metastasis within the sentinel node was the determining factor, or the number of affected nodes. These parameters have also been combined as predictive factors. Observational studies combining patients from multiple institutions should be able to provide us with the incidence of additional metastases associated with each of these parameters. Serial sectioning and immunohistochemistry staining should be done on all removed nodes in such a study. Although this approach will require a substantial effort from pathologists, it may be the quickest road to a parameter to guide the decision on whether to perform completion lymph node dissection or to wait and see.

In the second Multicenter Selective Lymphadenectomy Trial (MSLT-II), sentinel
node-positive patients are randomized to dissection or nodal observation regardless of the size of the tumour burden in the involved node but the results are not expected for a considerable number of years. If this trial shows a benefit of completion node dissection, a similar designed randomized study may be considered looking at the benefit of completion dissection in patients with a small sentinel node tumour burden. Finally, a predictive factor or a set of predictive factors that identifies patients in whom the survival benefit outweighs the disadvantages of further dissection may emerge. From this study it is concluded that it appears to be safe to refrain from completion lymph node dissection in patients with an S-I or S-II classification, while it seems prudent to carry out a dissection in S-III patients. We also found a clear survival difference between S-I,II patients and S-III patients. Therefore, we conclude that the S-classification has both practical and prognostic implications.
Acknowledgement

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Table 2. Studies describing sentinel node characteristics predictive of additional lymph node disease. The incidence of additional lymph node disease is given for the cut-off point, as suggested by the authors. N: number of patients, * primary tumour characteristics predictive of additional lymph node disease are not mentioned, ** Cochran et al. determined the area of the node occupied by tumour using a computer-assisted image analysis program and expressed this as a percentage of the total surface of the cut surface of the sentinel node.
References


17. Van Akkooi AC, De Wilt JH, Verhoef C et al. Clinical relevance of melanoma micrometastases (<0.1 mm) in sentinel nodes: are these nodes to be considered negative? Ann Oncol 2006; 17:1578-1585.


