Analysis of predictive factors for the outcome of complete lymph node dissection in melanoma patients with metastatic sentinel lymph nodes

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Background: Sentinel lymph node biopsy (SLNB) is a widely accepted procedure to accurately stage patients with melanoma. However, there is no consensus concerning the practical consequences of a positive SLN, since a survival benefit of a complete lymph node dissection (CLND) has not yet been demonstrated.

Objective: We wondered whether we could identify a subgroup of patients with metastatic involvement of the SLN who could be excluded from the recommendation to undergo CLND.

Methods: At the Department of Dermatology at the University of Munich, a total of 213 patients with metastatic SLNs (24.9%) were identified among 854 patients who had undergone SLNB between 1996 and 2007. All SLN-positive patients had been advised to have CLND. Survival analyses were performed by using the Kaplan-Meier approach.

Results: A total of 176 (82.6%) of 213 SLN-positive patients underwent CLND. In this group, 26 patients (14.8%) showed metastatic disease in non-sentinel lymph nodes (NSLN). The 5-year overall survival (OS) was 26.1% in NSLN-positive patients and 74% in NSLN-negative patients. SLN-positive patients who refused CLND had a better prognosis than patients with CLND. Breslow tumor thickness was significantly associated with positive CLND status with higher median values in CLND-positive than CLND-negative patients (3.03 vs 2.22 mm).

Limitations: The subgroup of patients with metastatic disease in CLND may have been too small to reach statistical significance for other tumor- or patient-related parameters. Mitotic indices of the primary melanomas had not been determined in this retrospective study; thus a possible correlation with lymph node status could not be tested.

Conclusion: Among SLN-positive patients, the presence of metastatic NSLN is a highly significant poor prognostic factor. Tumor thickness is a significant prognostic parameter for positive CLND status and might be considered in the decision to perform CLND in case of metastatic SLN. (J Am Acad Dermatol 2011;64:655-62.)

Key words: complete lymph node dissection; disease-free survival; melanoma; overall survival; sentinel lymph node.

In patients with stage I/II melanomas, elective lymph node dissection (ELND) of regional lymph nodes had been carried out as a standard procedure in many centers over nearly two decades. However, several trials demonstrated a lack of benefit for overall survival (OS) comparing ELND with follow-up only.[1-4] In 1992, Morton and co-workers[5] introduced the sentinel lymph node (SLN) concept as

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Funding sources: None.
Conflicts of interest: None declared.

Accepted for publication February 18, 2010.
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Published online February 14, 2011.
0190-9622/$36.00

doi:10.1016/j.jaad.2010.02.047

an innovative approach in oncologic surgery to replace the blind ELND. Since then, numerous studies have proven the prognostic value of the SLN concept in the management of patients with cutaneous melanoma.[6-8]

However, no study has confirmed a survival benefit in melanoma patients undergoing SLN biopsy (SLNB).[9] Nevertheless, the result of SLNB is the most important prognostic factor for both disease-free survival (DFS) and OS. It is still controversial whether, in the case of a positive SLN, a complete lymph node dissection (CLND) should always be performed, regardless of the type of SLN involvement (eg, micrometastasis or macrometastasis).[10-13]

We performed a retrospective study including 213 SLN-positive melanoma patients who underwent CLND or refused it. Apart from DFS and OS, patient- and tumor-related parameters were analyzed for an association with the occurrence of metastatic disease in non-sentinel lymph nodes (NSLN) as detected by CLND.

CAPSULE SUMMARY

- In a retrospective study, 213 sentinel lymph node (SLN) positive melanoma patients were included to evaluate the effect of complete lymph node dissection (CLND) on disease-free survival (DSF), overall survival (OS), and other parameters possibly associated with CLND outcome.
- Independent significant prognostic factors for poor outcome were tumor thickness and presence of metastatic non-sentinel lymph nodes (NSLN).
- Predictive factors for positive NSLN in CLND were presence of ulceration and regression of the primary tumor.
- Ulceration and regression were found to be associated with shorter DFS and OS.

PATIENTS AND METHODS

Study population

A total of 1049 consecutive patients with SLNB were identified at the Department of Dermatology and Allergology, University of Munich, between September 1996 and November 2007. Most of them presented with cutaneous melanoma with a Breslow tumor thickness greater than 1 mm or with other possible risk factors, such as ulceration of the primary melanoma as well as Clark level IV or V.[14]

In 166 patients, lack of detailed information concerning the primary melanoma, such as tumor type, tumor thickness or Clark level, or lack of further follow-up data led to exclusion from the study. Thus a total of 854 patients with SLNB remained for further analysis. From these patients, 213 (24.9%) showed a positive SLN and were advised to undergo CLND according to the current German melanoma guidelines.[14] These 213 patients constituted the study population of the present analysis.

If excisional biopsy of the primary tumor had been performed elsewhere, the original slides were re-examined by an experienced dermatopathologist (M. F.) in our department. Primary tumors were removed within 4 weeks prior to SLNB or excised concurrently with SLNB.

SLN procedure

Two to 16 hours before SLNB, dynamic lymphoscintigraphy was performed using technetium 99m—labeled human serum albumin colloid (Solco-Nanokoll, Sorin-Biomedica, Munich, Germany) in collaboration with the Department of Nuclear Medicine, University of Munich. The skin site corresponding to the hottest emission point was marked. On the day of surgery, a hand-held gamma camera (C-Trak-System, Care Wise, Morgan Hill, CA) was used to measure background and SLN radioactivity preoperatively and intraoperatively. In addition, intradermal injection of 0.5-1.0 mL of patent Blue V (Guerbet, Sulzbach, Germany) was performed 10 to 15 minutes preoperatively approximately 0.5 cm around the primary tumor or excision scar. The SLN was identified as a hot and blue-stained lymph node (LN). SLNB was performed using standard procedures. All LNs exhibiting radioactive impulse rates of at least 10% of the LN with the maximal radioactive impulse rate were also removed.[15]

Histopathologic evaluation

For histopathologic examination, SLNs were bisected along the long axis after formalin fixation. From each paraffin block, 8 to 12 sections were prepared for staining with hematoxylin-eosin and Giemsa as well as for immunohistochemical analysis (S-100, HMB45, NKI/C3, Melan A).

The metastatic status was documented for each SLN. Positive SLN specimens were subdivided histopathologically into micrometastasis or macrometastasis according to Carlson et al.[10] Micrometastasis was defined as a cluster of up to 15 tumor cells. Primary tumors and the specimens from CLND were examined by using routine histology.

Surgical and adjuvant therapies

Patients with positive SLNs were advised to have CLND of the regional basin (modified neck