Available online at www.sciencedirect.com

ScienceDirect

EJSO 42 (2016) 1420–1426

EJSO the Journal of Cancer Surgery

www.ejso.com

Worse outcome for patients with recurrent melanoma after negative sentinel lymph biopsy as compared to sentinel-positive patients

T. Gambichler*, L. Scholl, F.G. Bechara, E. Stockfleth, M. Stücker

Skin Cancer Center Ruhr-University, Department of Dermatology, Venereology and Allergology, Ruhr-University Bochum, Bochum, Germany

Accepted 31 March 2016
Available online 19 April 2016

Abstract

Background: The long-term outcome of patients with melanoma who had recurrence after negative sentinel lymph node (SLN) biopsy has rarely been evaluated systematically.
Methods: We searched our databases for melanoma patients with SLN biopsy from the end of 1999 and the beginning of 2011. Data was analyzed using uni- and multivariate statistics as well as Kaplan–Meier curves.
Results: Data of 651 patients with melanoma was available for statistics. We observed 451 (69.3%) patients with negative SLN who had no evidence of disease recurrence during follow-up. Recurrence in SLN negative patients was found in 50 (7.7%) cases. Tumor subtypes such as invasive lentigo maligna melanoma and acral melanoma (odds ratio 15.2, $P = 0.015$) and tumor thickness > 2 mm (odds ratio 3.1, $P = 0.0017$) were independent predictors for recurrence in patients with negative SLN. Patients with negative SLN and subsequent recurrence had a significantly ($P = 0.036$) reduced 5-year melanoma-specific survival (MSS) when compared with positive SLN patients. Recurrence of disease in positive SLN patients was observed after a median of 39 months when compared to patients with negative SLN and recurrence (28 months, $P = 0.0079$). Negative SLN with recurrence was an independent predictor for worse recurrence free and melanoma-related survival.
Conclusions: Patients with negative SLN and recurrence experience earlier disease relapses and poorer MSS when compared to patients with positive SLN status implicating that more stringent follow-up procedures are warranted in patients with higher tumor thickness and invasive lentigo maligna and acral melanoma, despite a negative SLN.

Keywords: Malignant melanoma; Sentinel lymph node biopsy; Recurrence; Invasive lentigo maligna; Acral melanoma

Introduction

Cutaneous melanoma is the major cause of skin cancer-associated mortality. Treatment and diagnostic strategies predominantly include wide excision of the primary tumor and sentinel lymph node (SLN) biopsy to assess the status of the regional nodal basin. With an about 20% likelihood of yielding positive results, it spares most patients to a complete lymph node dissection (CLND).[1–5] Breslow thickness of primary tumor is the most consistently reported and well-established predictor of SLN metastasis. Other reported predictive factors include age, gender, primary site, ulceration, tumor mitotic rate etc.[1–12]

On the one hand, the management of melanoma lymph node metastasis particularly when detected by SLN biopsy is still controversial with respect to prognosis and therapeutic value. Arguments against SLN biopsy procedure may include a false-negative SLN status, "prognostic false-positivity" in patients with nodal micrometastasis (<0.1 mm invasion depth), lack of highly effective adjuvant drugs, and questionable value of CLND following positive SLN status.[13–16] On the other hand, it has been reported that the strongest predictor for melanoma relapse is the status

* Corresponding author. Skin Cancer Center Ruhr-University, Department of Dermatology, Venereology and Allergology, Ruhr-University Bochum, St. Josef Hospital, Gudrunstr. 56, 44791, Bochum, Germany. Tel.: +49 234 5093458.
E-mail address: t.gambichler@klinikum-bochum.de (T. Gambichler).

http://dx.doi.org/10.1016/j.ejso.2016.03.038
0748-7983/

of the SLN.[17,18] Thus, SLN biopsy has been introduced as the standard of care.[19,20]

SLN status appears to be an important prognostic factor. Nevertheless, the accuracy and prognostic performance of this procedure are still under debate.[21–23] So far, only two studies addressed the performance of patients with negative SLN biopsy and subsequent relapse.[24,25]

We aimed to assess the frequency of recurrence and melanoma-specific deaths during 5-year follow-up of melanoma patients following a negative SLN biopsy result and to compare the data with SLN positive patients as well as SLN negative patients without evidence of tumor recurrence. Moreover, we sought to identify independent predictors for recurrences after a negative SLN result.

Material and methods

Patients

This monocenter study was performed at the Skin Cancer Center Ruhr-University (Bochum, North-Rhine-Westphalia, Germany). The study was approved by the ethics review board of the Ruhr-University Bochum and conducted according to the principles of the Declaration of Helsinki. We checked our database for melanoma patients who had undergone SLN biopsy between the end of 1999 and the beginning of 2011. All melanomas were diagnosed by primary excision. Predominant indication for SLN biopsy was a Breslow tumor thickness of 1 mm or more. Moreover upgrading in tumors less than 1 mm was considered in the presence of a Clark level of IV or higher, ulceration and lesions with signs of regression, or subungual localization of the primary melanoma. Macrometastatic disease in regional lymph nodes and distant metastases were ruled out by physical examination and individual staging procedures, such as ultrasound, chest X-ray, computed tomography, and magnetic resonance imaging, respectively.

Patients with metastatic SLNs were subjected to CLND. All patients with negative SLN and a primary melanoma thickness of 1.5 mm or more were considered for adjuvant low-dose interferon alfa-2a (Roferon; Roche Pharma AG, Grenzach-Wyhlen, Germany) therapy. Patients with melanoma-positive lymph nodes usually received adjuvant high-dose interferon alfa-2b (Intron; MSD, Munich, Germany) therapy. Clinical parameters such as age, sex, anatomic site of the primary melanoma, melanoma subtype, Clark level, and tumor regression, ulceration, and thickness (Breslow) were analyzed. In thin primary melanomas up to 1-mm tumor thickness, clinical examinations were performed at 6-month intervals and in thicker primary melanomas at 3-month intervals. Lymph node ultrasound and determination of the tumor marker protein S100β were also carried out. Additionally, in the stage of regional metastasis, whole body imaging was performed every 6 months; in the stage of distant metastasis, surveillance was scheduled individually. Survival data were also collected using chart review and contacting patients, relatives, and resident practitioners and dermatologists.

SLN biopsy procedure

Patients underwent lymphatic mapping and SLN biopsy as previously described in more detail by Wong et al.[4] In brief, lymphoscintigraphy was performed by intradermal injection of technetium-99 m sulfur colloid adjacent to the tumor or biopsy site to identify draining lymphatic basins by γ imaging. Intradermal injection of methylene blue dye was similarly performed during surgery. SLN biopsies were predominantly carried out under general anesthesia. Blue-stained and/or radioactive (>10% of the ex vivo counts) lymph nodes were removed and considered SLNs.

Histology and immunohistochemistry

Preparation, macroscopic examination, sampling, and microscopic examination were performed in line with the recommendations for pathologic examination of SLNs from patients with melanoma as proposed by Scolyer et al.[5] All SLNs were serially sectioned and stained with H&E and had immunohistochemical staining with S100 and Melan-A/MART-1 (DAKO, Hamburg, Germany). At time of diagnosis, all SLNs were assessed by 2 senior dermatohistopathologists. According to the study protocol re-assessment of SLNs was also performed by a senior dermatohistopathologist. In ambiguous cases, **re-evaluation** of sections was performed with additional immunohistology for HMB45 and Ki-67.

Statistics

Data analysis was performed using the statistical package MedCalc Software (Mariakerke, Belgium). Distribution of data was assessed by the D'Agostino-Pearson test. Data were analyzed using the χ^2 test, Mann–Whitney test, and a forward logistic regression model including coefficient of regression (CR), odds ratios (OR) and 95% confidence intervals (CI). 5-year recurrence-free and melanoma-specific survival (MSS) was examined using the Kaplan–Meier method; differences between the curves were assessed by the log-rank test. Survival curves were calculated from the time of diagnosis of the primary melanoma and considered censored for non-melanoma-related deaths and unavailable data. *P* values less than 0.05 were considered significant.

Results

651 patients with melanoma and SLN biopsy (303 males and 348 females; median age, 57 years; range, 15–85 years) were finally available for descriptive and analytical statistics. Hence, 117 (15.2%) patients were excluded predominantly because of missing critical data such as survival data. The overall median tumor thickness was 1.5 mm, ranging from 0.15 to 84 mm (mean ± SD,