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The prognostic significance of sentinel node tumour burden in melanoma patients: An international, multicenter study of 1539 sentinel node-positive melanoma patients ☆,☆☆

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KEYWORDS
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Abstract ***Introduction:*** Sentinel node (SN) biopsy (SNB) and completion lymph node dissection (CLND) when SN-positive have become standard of care in most cancer centres for melanoma. Various SN tumour burden parameters are assessed to determine the heterogeneity of SN-positivity. The aim of the present study was to validate the prognostic significance of various SN tumour burden micromorphometric features and classification schemes in a large cohort of SN-positive melanoma patients.
Methods: In 1539 SN-positive patients treated between 1993 and 2008 at 11 melanoma treatment centres in Europe and Australia, indices of SN tumour burden (intranodal location, tumour penetrative depth (TPD) and maximum size of SN tumour deposits) were evaluated.
Results: Non-subcapsular location, increasing TPD and increasing maximum size were all predictive factors for non-SN (NSN) status and were independently associated with poorer melanoma-specific survival (MSS). Patients with subcapsular micrometastases <0.1 mm in maximum dimension had the lowest frequency of NSN metastasis (5.5%). Despite differences in SN biopsy protocols and clinicopathologic features of the patient cohorts (between centres),

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most SN parameters remained predictive in individual centre populations. Maximum SN tumour size > 1 mm was the most reliable and consistent parameter independently associated with higher non-SN-positivity, poorer disease-free survival (DFS) and poorer MSS.

Conclusions: In this large retrospective, multicenter cohort study, several parameters of SN tumour burden including intranodal location, TPD and maximum size provided prognostic information, but their prognostic significance varied considerably between the different centres. This could be due to sample size limitations or to differences in SN detection, removal and examination techniques.

1. Introduction

Twenty years ago, sentinel node (SN) biopsy (SNB) was introduced as a staging technique for patients with early-stage melanoma [1,2]. Since then, SN status has been shown to be the strongest independent prognostic factor in patients with clinically localised primary cutaneous melanoma [3–6].

First introduced in the 6th edition (2001) of the American Joint Commission on Cancer (AJCC)/Union Internationale Contre le Cancer (UICC) staging system for cutaneous melanoma, sentinel lymph node tumour burden is now established as an N1–2a staging criterion in the tumour-node-metastasis (TNM) staging system [7–9]. However, specific sub-groups of SN-positive patients have vastly differing survival rates, ranging from approximately 30% to over 90% [3,10–14]. Patient characteristics, primary tumour and SN parameters and models for risk stratification of SN-positive patients have been assessed in numerous studies with respect to prediction of non-SN (NSN) status and survival [11–21]. Ideally, the parameters utilised for prognostic stratification must be easy and quick to assess and reproducible [22,23]. The best validated prognostic SN tumour burden parameters to date are: tumour penetrative depth beneath the SN capsule, maximum size of SN tumour deposits and intranodal location of SN tumour [6,11,13,15–18,21,24–30].

In recent years, the European Organisation for Research and Treatment of Cancer (EORTC) Melanoma Group (MG) and Melanoma Institute Australia (MIA) have each gathered large independent datasets of SN-positive patients, assessed micromorphometric parameters of tumour in SNs and demonstrated the prognostic importance of these factors [6,15,27]. The aim of the current study was to combine the large European and Australian patient cohorts, and evaluate the prognostic significance of SN tumour burden parameters and classification schemes overall. A secondary aim was to assess and compare the predictive power of these parameters in individual melanoma treatment centres.

2. Patients and methods

2.1. Patients

Patients diagnosed between 1993 and 2008 with primary melanoma and a positive SN, at eleven melanoma treatment centres (10 EORTC MG centres in six different countries and one centre, MIA, Sydney, Australia) were studied. Patient demographics, information on previous medical history and follow-up data were collected by each centre. SN tumour burden was measured and classified by at least two of the following morphometric parameters: intranodal location (9/11 centres) [16], maximum size of the largest discrete SN tumour deposit (11/11 centres) [13,30]) and tumour penetrative depth (7/11 centres; [11,18,29]). The RDC (Rotterdam–Dewar Combined) classification was derived from the Rotterdam classification and the modified Dewar classification (9/11 centres) [6].

2.2. Lymphatic mapping, sentinel node biopsy and completion lymph node dissection

At all centres, SNB was offered to patients with Breslow thickness $\geqslant$ 1 mm or to patients with thinner tumours with adverse prognostic features such as ulceration, a high mitotic rate or Clark level IV or V invasion. SNB was performed using the triple technique identifying SNs with a combination of lymphoscintigraphy, preoperative injection of blue dye at the primary melanoma site and intraoperative use of a gamma probe. Full details have been reported previously [14,31–34]. However, there were some differences in the procedures for identifying and removing SNs at the different centres. These included differences in the radiocolloids used for pre-operative lymphoscintigraphy, the timing and planes of view utilised for lymphoscintigraphy, the type and volume of blue dye used, the type and sensitivity of the hand-held gamma probe and the criteria utilised for defining a SN, as well as the experience of the nuclear medicine physicians, radiologists and surgical oncologists performing these procedures. Excised SNs were fixed in buffered formalin and sent for pathologic examination. Subsequently, SN tumour burden was determined by histopathologic review of available tissue sections. Completion lymph node dissection (CLND) was performed in 1381 of 1539 (90%) SN-positive patients. Reasons for not performing CLND were eligibility for the EORTC 1208 (Minitub) study (Clinicaltrials.gov identifier NCT01942603), the presence of micrometastases <0.1 mm in maximum dimension since an excellent survival is to be expected, enrolment in the observation