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Original Research

Risk stratification of sentinel node–positive melanoma patients defines surgical management and adjuvant therapy treatment considerations

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Abstract ***Background:*** In light of the evolving landscape of adjuvant therapy in melanoma and the recently confirmed absent survival benefit of completion lymph node dissection (CLND), it becomes important to explore possible consequences of omitting CLND, and whether it is possible to adequately stratify positive sentinel node (SN) patients solely based on information retrieved from the melanoma up to the sentinel lymph node biopsy (SLNB).

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Staging;
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Methods: A retrospective cohort from nine European Organization for Research and Treatment of Cancer Melanoma Group centres was used. Patients were staged based on SLNB and CLND result according to the American Joint Committee on Cancer (AJCC) criteria and stratified by ulceration and SN tumour burden. These were incorporated in Cox regression models. Predictive ability was assessed using Harrell's concordance index (c-index) and the Akaike information criterion (AIC).
Results: In total, 1015 patients were eligible. CLND led to upstaging in N-category in 19% and in AJCC stage in 5–6%. The model incorporating only ulceration and SN tumour burden performed equally well as the model incorporating substages after CLND. The model incorporating substages based on SLNB had the lowest predictive ability. Stratifying by ulceration and SN tumour burden resulted in four positive SN groups from which low-, intermediate- and high-risk prognostic classes could be derived.
Conclusions: Adequate stratification of positive SN patients was possible based on ulceration and SN tumour burden category. The identification of low-, intermediate- and high-risk patients could guide adjuvant therapy in clinical practice. Omitting CLND seems to have little consequences.

1. Introduction

The landscape of systemic therapy for melanoma is evolving rapidly, both in the metastatic setting as in the potentially curative adjuvant setting. The introduction of immune checkpoint inhibitors and BRAF/MEK inhibitors has significantly improved the perspective of patients with stage IV melanoma [1,2]. This success has led to various clinical trials evaluating the potential of these therapies in the adjuvant setting in high-risk stage III melanoma. Positive results in this setting have already been published [3–5].

Until recently, complete nodal staging through lymph node dissection was standard-of-care in stage III melanoma, either as a therapeutic lymph node dissection for clinically apparent disease, or as a completion lymph node dissection (CLND) preceded by a positive sentinel lymph node biopsy (SLNB; occult disease). As such, complete nodal staging was, and still is, a prerequisite for inclusion in clinical trials in the adjuvant setting. However, the landmark Multicentre Selective Lymphadenectomy Trial (MSLT) II trial lately concluded that CLND was not associated with a significant survival benefit compared with nodal observation [6]. These results are supported by the underpowered DeCOG-SLT trial with similar conclusions [7]. Consequently, clinical practice will change dramatically since CLND is expected to no longer be standard procedure after a positive sentinel node (SN). In the current landscape of (systemic) adjuvant therapy, a vacuum remains for patients classified stage III solely based on the SLNB result since results from published trials cannot be extrapolated, nor do these patients qualify for trial participation due to the present inclusion criteria. In that light, CLND after a positive SLNB may remain valuable since it could potentially lead to upstaging and subsequently yield additional prognostic information.

Considering the recent developments, it becomes important to adequately identify those positive SN patients that are at high-risk of recurrence and/or melanoma-specific death, preferably by only using information retrieved from the primary melanoma up to the SLNB. The number of positive lymph nodes, Breslow thickness and the presence of ulceration in the primary tumour have long been identified as poor prognostic characteristics [8–11]. Sentinel node tumour burden, according for example to the Rotterdam and/or Dewar criteria, has also been identified as an important prognostic factor for survival and also as a predictive factor for additional positive (non-sentinel) lymph nodes [12–14]. The current 8th and previous 7th American Joint Committee on Cancer (AJCC) staging editions, however, do not account for SN tumour burden [10,11]. On the contrary, the maximum diameter of the largest tumour lesion in the SN ($\leq$1.0 mm versus >1.0 mm) has already been implemented as an additional criterion for participation in adjuvant clinical trials [3,5]. The aim of the present study was to explore the potential upstaging of CLND, its prognostic value and whether patients with a positive SN could be adequately stratified into distinct risk classes solely based on information retrieved from the melanoma up to the SLNB procedure, including ulceration status and SN tumour burden category.

2. Methods

For purposes of the present study, a retrospective cohort of SN-positive patients previously collected and described, was used [15–17]. This cohort contained 1080 SN-positive melanoma patients that underwent a SLNB between 1993 and 2008 in one of nine European Organization for Research and Treatment of Cancer (EORTC) Melanoma Group centres. The study was