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Original Research

The sentinel lymph node spread determines quantitatively melanoma seeding to non-sentinel lymph nodes and survival

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KEYWORDS
Sentinel lymph node biopsy;
Lymph node dissection;

Abstract ***Introduction:*** Complete lymph node dissection (CLND) after a positive sentinel node (SN) biopsy provides important prognostic information in melanoma patients but has been questioned for therapeutic use recently. We explored whether quantification of the tumour spread to SNs may replace histopathology of non-sentinel nodes (NSNs) for staging purposes.

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Malignant melanoma;
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Patients and methods: We quantified melanoma spread in SNs and NSNs in 128 patients undergoing CLND for a positive SN. In addition to routine histopathology, one-half of each of all 1496 SNs and NSNs was disaggregated into a single cell suspension and stained immunocytochemically to determine the number of melanoma cells per 10^6 lymph node cells, i.e. the disseminated cancer cell density (DCCD).

Results: We uncovered melanoma spread to NSNs in the majority of patients; however, the tumour load and the proportion of positive nodes were significantly lower in NSNs than in SNs. The relation between SN and NSN spread could be described by a mathematical function with $DCCD_{NSN} = DCCD_{SN}^{c}/10^{1-c}$ (c = 0.69; 95% confidence interval [CI]: 0.62–0.76). At a median follow-up of 67 months, multivariable Cox regression analyses revealed that $DCCD_{SN}$ (p = 0.02; HR 1.34, 95% CI: 1.05–1.71) and the total number of pathologically positive nodes (p = 0.02; HR 1.53, 95% CI: 1.07–2.22) were significant risk factors after controlling for age, gender, thickness of melanoma and ulceration status. A prognostic model based on $DCCD_{SN}$ and melanoma thickness predicted outcome as accurately as a model including pathological information of both SNs and NSNs.

Conclusion: The assessment of $DCCD_{SN}$ renders CLND for staging purposes unnecessary.
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1. Introduction

Melanoma spread to the sentinel nodes (SNs) and to non-sentinel nodes (NSNs) of the regional nodal basin are major predictors for melanoma outcome [1–8], and the total number of histopathologically positive nodes is part of the American Joint Committee on Cancer staging (AJCC) 2009 staging system for stage III melanoma [9].

A very recently published international multicenter randomized phase III trial (the second Multicenter Selective Lymphadenectomy Trial (MSLT II)) evaluated the therapeutic benefit of complete nodal dissection in patients with melanoma and a positive sentinel node. Besides reducing nodal relapse in SN-positive patients by nearly 70%, patient survival was not improved [3]. If, as a consequence of this trial, SN-positive patients will be spared from CLND, essential AJCC staging information on the NSN status will no longer be available.

Histopathology, the current gold standard for detecting melanoma spread in lymph nodes has limited power to quantify melanoma spread to SN and NSN. It is a two dimensional method, which impedes the quantitative assessment of a three-dimensional and possibly multilocular tumour load, and its sensitivity depends directly on the number of slides examined, which has not been standardized [10]. As complete serial sectioning of nodes is not possible, for practical reasons, a considerable (and not standardized) part of the lymphatic tissue remains unexamined [11,12]. Most importantly, it may be questioned whether the available non-standardized protocols for detecting SN spread are suitable for adequate patient stratification needed for upcoming adjuvant therapies [13–17].

Using a novel approach of quantitative immunocytology, we have previously shown that disseminated melanoma cells with genetically proven malignant origin are frequently detected in histopathologically negative nodes [18]. For this, the lymph node was bi-halved: one half was subjected to routine histopathology, and the other half of the lymph node was disaggregated into a single cell suspension resulting in a homogeneous distribution of melanoma cells among lymph node cells, thereby reducing the risk of false-negative samples. Two million cells per node were then stained by immunocytochemistry with gp100, positive cells were quantified and recorded as disseminated cancer cell density (DCCD, i.e. the number of gp100 positive cells per million mononuclear cells). With this approach, we showed that (i) the risk to die from melanoma correlates with increasing DCCD, (ii) already a very low DCCD ($0 < DCCD \leq 3$) significantly decreases patient survival and (iii) the DCCD of the sentinel node outperforms routine histopathology regarding outcome prediction [19]. We further demonstrated that gp100 staining is highly specific and that addition of Melan-A staining does not improve diagnostic and prognostic accuracy [19].

Here, we applied this highly sensitive and standardized assay to precisely quantify the metastatic spread to SN and NSNs and define the relative impact of the $DCCD_{SN}$ and $DCCD_{NSN}$ on melanoma outcome. We hypothesized that SN and NSN spread are quantitatively related and that quantification of SN spread is sufficient for outcome prediction.

2. Materials and methods

2.1. Patients

From 2002 to 2008, we enrolled 130 patients who underwent complete lymph node dissection at the University Hospital Tübingen, Germany after the detection

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