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Clinical significance of intra-nodal naevi in sentinel node biopsies for malignant melanoma

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Abstract

Background: Intra-nodal naevi (INN) identified during assessment of a sentinel lymph node for melanoma are not an uncommon finding. Little is known about their clinical significance. Patients with INN are treated as sentinel node biopsy (SNB) negative currently. Our aim was to assess the significance of INN in patients who undergo SNB for melanoma.
Methods: 353 melanoma patients who underwent a SNB between November 1999 and June 2012 were retrospectively analysed from a prospectively collected database. The patients were divided into SNB negative, INN, isolated tumour cells (ITC) and SNB positive groups. Outcome measures of nodal recurrence, distal recurrence and survival were used to assess the differences between the groups.
Results: 203 patients were SNB negative, 103 were positive of which 13 had ITC, 47 had INN (13%). Overall median follow up was 2.3 years (range 0.1–14.1 years). Our data demonstrated a statistically significant survival benefit for patients who had an INN compared to the SNB positive and ITC group. INN patients also had significantly better nodal and regional recurrence compared to SNB positive patients. There was no difference between INN and SNB negative patients.
Conclusion: We have clinically demonstrated that patients with INN on SNB can be adequately treated as SNB negative patients.

Keywords: Melanoma; Metastatic melanoma; Sentinel node biopsy; Intra-nodal naevi; Isolated tumour cells

Introduction

Sentinel node biopsy (SNB) is a well established and accepted staging tool for malignant melanoma (MM) patients. It involves a triple diagnostic technique, using lymphoscintigraphy, blue dye and radio colloid with gamma probe detection. SNB allows upstaging of patients with isolated melanoma cells and micrometastasis which can permit early intervention with nodal basin clearance before potential progression into palpable stage III disease. However the benefits of early intervention for micrometastasis have not been proven by clinical trial and await the results of the Multicenter selective lymphadenectomy trial II (MSLT-II).

The detection of micrometastases and isolated tumour cells within sentinel node biopsies has been improved by advances in immunohistochemistry techniques. INN (also referred to as nodal naevi and naevus cell aggregates) are not an uncommon finding in sentinel node biopsies, particularly in axillary nodes.[1–3] They are less frequently found in lymphadenectomy specimens, most likely due to the more thorough sectioning techniques used in SNB. INN are often found as isolated clusters of normal-appearing melanocytes within the capsule, trabeculae, and rarely the parenchyma or lymphatic channels, of a lymph node.[3,4] A histological example of an INN is shown in Fig. 1. INN can be present in several malignancies including breast carcinoma, squamous cell carcinoma of the skin and most commonly melanoma, with the incidence of INN in all malignancies reported as 1–24%.[2,5,6]

Two controversial hypotheses regarding their origin exist: I) there is regional embolic drainage of melanocytes from a naevus to a lymph node via the lymphatics[7,8]; II) embryological neural crest derived melanocytes are transported to lymph nodes during in-utero migration.[7,9]

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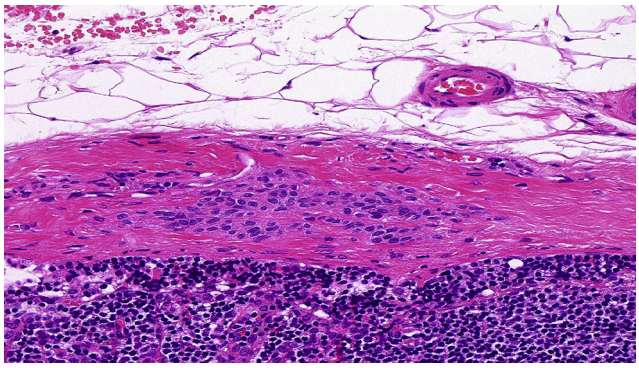

Figure 1. Histology slide illustrating an INN within a lymph node capsule.

Histologically it can be difficult to differentiate INN from nodal metastases and a combination of immunohistochemistry, location and morphology must be used although this is not consistently reliable. This provides significant diagnostic challenges where false positive and negative SNB findings could lead to over or under treatment.

Evidence of the clinical significance of INN is limited with only one study evaluating the clinical outcome of patients with INN versus positive SNB.[10] Several authors have noted a significant association between primary cutaneous melanoma and the presence of INN.[2,8,10–12] Some authors even suggest an, as yet unproven, association between INN and melanoma of unknown primary.[5]

Current British Association of Dermatology/British Association of Plastic, Reconstructive and Aesthetic Surgery (BAD/BAPRAS) guidelines do not recommend a specific treatment option for INN in SNB.[13] MSLT-I classified INN as SNB negative however they did not analyse these patients as a specific subgroup.[14] Current standard practice in the UK sees patients with INN treated as SNB negative.

The aim of this paper is to evaluate the clinical significance of INN in patients who undergo SNB for MM and to assess whether they should be classified as SNB negative.

Methods

This study was carried out at the Christie Hospital in Manchester, UK. All the patients in this study were consented for sentinel node biopsy and the data was collected as part of an on going audit into the use of sentinel node biopsy. No specific ethical approval was obtained for this study. Patients with malignant melanoma confirmed on excision of primary tumour who underwent a SNB between November 1999 and June 2012 were retrospectively analysed from a prospectively collected database. Indication for SNB was a primary tumour Breslow thickness of 1–4 mm, or patients with tumours less than 1 mm with additional high risk factors including ulceration, high mitotic count, perineural spread, Clark level IV or greater. All patients undergoing SNB had clinical disease excluded through examination and staging CT.

SNB was carried out using a standard triple diagnostic technique with lymphoscintigraphy, blue dye and gamma probe assessment. Histopathological assessment of the lymph nodes was performed using a standardised method, as recommended by the European Organisation for Research and Treatment of Cancer (EORTC).[15] This involved a dedicated histopathology team using serial sectioning at 50 microns, H&E and S100 stains with additional immunohistochemistry staining as required. Positive SNB results were classified as ITC, metastases 0.1–2 mm and metastases >2 mm in line with previously published studies.[16,17] All patients with positive SNB underwent completion lymphadenectomy, those that declined further surgery were excluded from the study.

Data was collected with regard to demographics, location of the primary, Breslow thickness, histology of the SNB, local and distant recurrence and survival. All follow-up data was added prospectively to the database.

The patients were divided into SNB positive, ITC on SNB, SNB negative and INN groups. Patients with ITC were chosen as a separate comparative group as they contain the lowest burden of metastasis within a positive sentinel lymph node. INN identified at completion lymphadenectomy were excluded from the study.

Outcome measures of nodal recurrence, distal recurrence and 5-year survival were used to assess the differences between the groups. Difference between INN patients and sentinel node positive, sentinel node negative and ITC patients were analysed. Recurrence and survival were calculated from the time of diagnosis of primary melanoma. Breslow thickness, ulceration, histological subtype and location of primary were all evaluated for an effect on survival. Clark level and mitotic rate were not included in the analysis due to insufficient data.

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) Version 16 (IBM, USA). Estimated survival was calculated using Kaplan–Meier curves. Significance was calculated using log rank tests and chi squared tests for categorical data. A p-value of <0.05 was considered significant.

Results

Between November 1999 and June 2012, 353 patients with a median age of 53.5 years, underwent SNB for MM and were included in the study. Demographics of all included patients are summarised in Table 1.

Forty seven patients (13%), 16 male and 31 female, with a median age of 52.5, had INN detected within their SNB. Median Breslow thickness was 1.5 mm (range 0.6–4 mm).

203 patients (58%) were sentinel node negative. 103 patients were sentinel node positive (29%), of these 13 (4%) had isolated tumour cells, 63 (18%) had metastases 0.1–2 mm, and 27 (8%) had metastases >2 mm. A higher Breslow thickness