



## Is skipped nodal metastasis a phenomenon of cutaneous melanoma?☆

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### ABSTRACT

**Background and Methods:** Skipped nodal metastasis (SNM) is a recognized phenomenon of visceral cancers when metastases bypass the regional basin and skip to a distant nodal basin without evidence of distant metastases. Its occurrence is undocumented in cutaneous melanoma patients but of potential prognostic significance. We therefore assessed the frequency of SNM in a large series of patients with limb melanomas.

**Patients and Methods:** We studied melanoma patients attending a tertiary oncology hospital in northwest England using two approaches. First, we systematically searched medical records of an unselected patient sample treated 2002–2015, and second, we studied lymphoscintigrams of all patients with limb melanoma who underwent sentinel node biopsy 2008–2019.

**Results:** Of 672 melanoma patients whose clinical records were examined, 16 had regional nodal metastases without apparent visceral spread and one appeared to have SNM but further scans were uncovered that showed concurrent pulmonary metastases. Of 667 limb melanoma patients with lymphoscintigrams, 7 showed dual lymphatic drainage patterns to distal as well as regional nodal basins, but none had micro-metastases solely in the distant basin.

**Conclusion:** Occurrence of SNM in cutaneous melanoma is highly unlikely.

### Introduction

Cutaneous melanoma, like other malignancies, has the potential to metastasize via the lymphatic or vascular systems to nodal basins and visceral organs. When melanoma metastases occur via the lymphatic system they largely involve lymph nodes in the major draining lymphatic basin, either cervical, axillary or inguinal, whichever is closest to the site of the primary tumor, with interval draining basins such as the epitrochlear or popliteal less frequently involved [1]. However, it is also possible that a skipped nodal metastasis (SNM) occurs if the first metastasis bypasses the lymph nodes in the first major draining basin and skip to a distant lymphatic basin without occurrence of visceral metastases.

SNM is a well-recognized phenomenon of several visceral cancers including oesophageal and gastric carcinomas [2], though precise

definitions vary. For example, SNM in oesophageal carcinoma is seen by some as a particular pattern of lymph node metastasis involving lymph nodes distant from the tumor site but not the peri-tumoral lymph nodes [3,4], while others have reported SNM in the lymph nodes of draining zones of the esophagus [5]. In gastric carcinoma patients, SNM has been defined as metastasis to an extra-gastric lymph node without peri-gastric involvement [2]. Despite numerous anecdotal reports amongst clinicians of SNM in primary cutaneous melanoma patients, only one study has defined the phenomenon, namely, a negative sentinel node but metastasis-positive nodes higher in the regional chain, or recurrence after a negative sentinel node biopsy [6]. In this study [6], authors assessed such ‘SNM’ of melanoma to be rare, consistent with another report [7] that SNM occurred in <1% of melanoma cases (no definition of SNM or supporting data were provided). Others have reported being unable to demonstrate SNM within a single drainage basin of primary

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cutaneous melanoma, for example, Hayashi et al. [8] in regard to the axillary basin found melanoma metastases did not involve higher tiered nodes without the involvement of the lower tiered nodes, and similarly Reintgen et al. [9] reported no SNM within specific nodal basins of 42 melanoma patients.

In summary, to date there appear to be no documented reports of SNM in cutaneous melanoma, beyond its rare occurrence in qualitative terms. However, it is worthwhile ascertaining if this phenomenon exists in cutaneous melanoma because of its prognostic significance as in other tumor groups [4], and because if the phenomenon existed, the clinical implications would be a requirement to routinely check all draining

nodal basins in primary melanoma patients on follow-up. We therefore sought to document SNM as a primary outcome in a large series of cutaneous melanoma patients in England.

**Materials and methods**

We performed two retrospective studies of primary melanoma patients in a tertiary oncology hospital in northwest England with institutional research ethics committee approval (16/LO/0387): first a records-based study and second, a review of lymphoscintigrams of melanoma patients who had undergone sentinel lymph node mapping

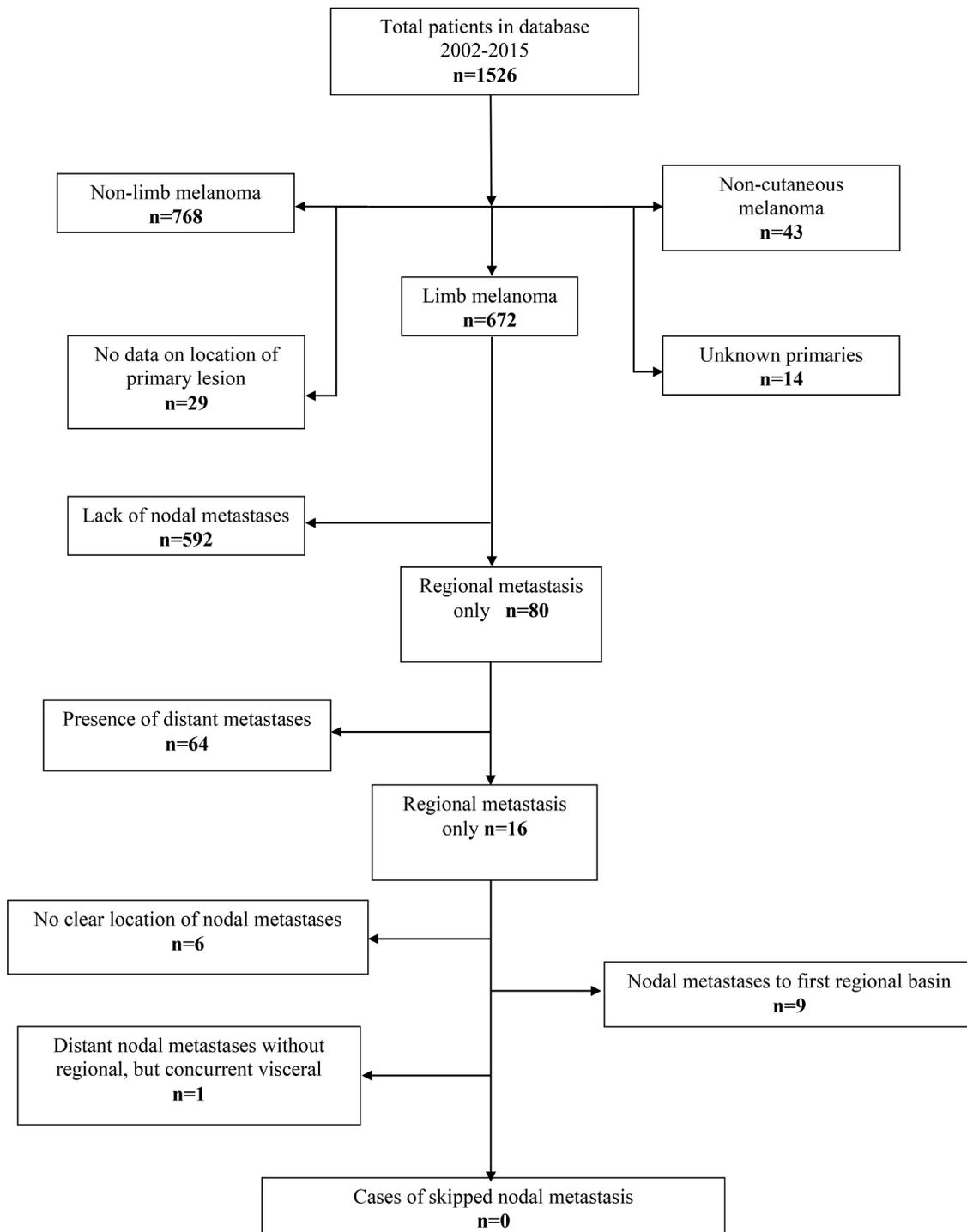


Fig. 1. Flowchart for search of clinical records, 2002-2015.

[7].

*Clinical records study*

Using a standard form, clinical information was extracted from case notes of unselected patients treated for melanoma between 2002 and 2015. We restricted our study to patients with primary melanoma of the upper or lower limb to be certain of the nearest regional draining basin, and to avoid the ambiguity in nominating the closest draining basins among patients with head and neck or trunk melanomas. Extracted data were compiled in an anonymized study database, and all patients with regional nodal involvement as the first presentation of metastasis, but no distant metastases, were selected from the database. For each study patient, the location of the nodal metastasis was matched to the primary site of the tumor to identify cases of distant nodal involvement only. In cases where there was uncertainty, details of the melanoma were checked against those recorded in the hospital's electronic record system.

*Lymphoscintigraphy study*

All patients with primary melanoma of the limbs undergoing lymphoscintigraphy prior to sentinel node biopsy from April 2008 to March 2019 were ascertained from the hospital electronic records system. We excluded patients with melanoma on the shoulder or deltoid region, or hip or buttock region, due to variable lymphatic drainage patterns from these sites, and cases with no identifiable sentinel nodes. Besides patients' electronic records, their clinical notes, lymphoscintigrams and lymphoscintigraphy records were retrieved and site of primary melanoma, drainage basin(s) of sentinel nodes and regional nodal basin (axillary or inguinal) were recorded in order to identify patients with only distant nodal micro-metastases.

**Results**

*Clinical records study*

From a total of some 4500 melanoma patients, information was extracted from the clinical records of an unselected sample of 1526. Of these, 672 presented with primary melanoma of the limbs, of whom 80 had nodal metastases, and 16 of these had no report of distant metastases (Fig 1). Of these 16, exact location of nodal metastases of 6 patients were unclear, leaving 10 patients with complete records of nodal metastases, 9 of which occurred in the proximal lymphatic basin. The remaining patient with primary melanoma on the sole of the left foot, but no clinical inguinal lymphadenopathy, presented with a rapidly growing mass in the left supraclavicular region, confirmed by cytology as metastatic melanoma. She had a history of previous primary melanoma of the third toe of the right foot, renal cell carcinoma and uterine carcinoma. On further investigation, a staging CT scan report was located that confirmed the supraclavicular mass to be in close contact with the chest wall but with no rib/clavicular erosion, no intra-thoracic extension, and no cervical or inguinal lymphadenopathy. However, the scan also revealed multiple pulmonary metastases, thereby excluding a diagnosis of SNM (Fig 1).

*Lymphoscintigraphy study*

The lymphoscintigrams of 1688 consecutive patients who underwent lymphoscintigraphy for identification of sentinel node(s) in the 12-year study period, 2008–2019, were examined. Of these, 667 patients with melanomas of the upper or lower limb had an available lymphoscintigraphy report, 620 of which showed conventional drainage to only the proximal nodal basin (Fig 2). Of the 28 patients with primary melanomas on the upper limb and unconventional drainage patterns, 22 had interval nodal drainage as well as axillary, while 6 had drainage to the supraclavicular as well as the axillary nodal basin (Fig 2). None of the 6 had supraclavicular micro-metastases without axillary micro-

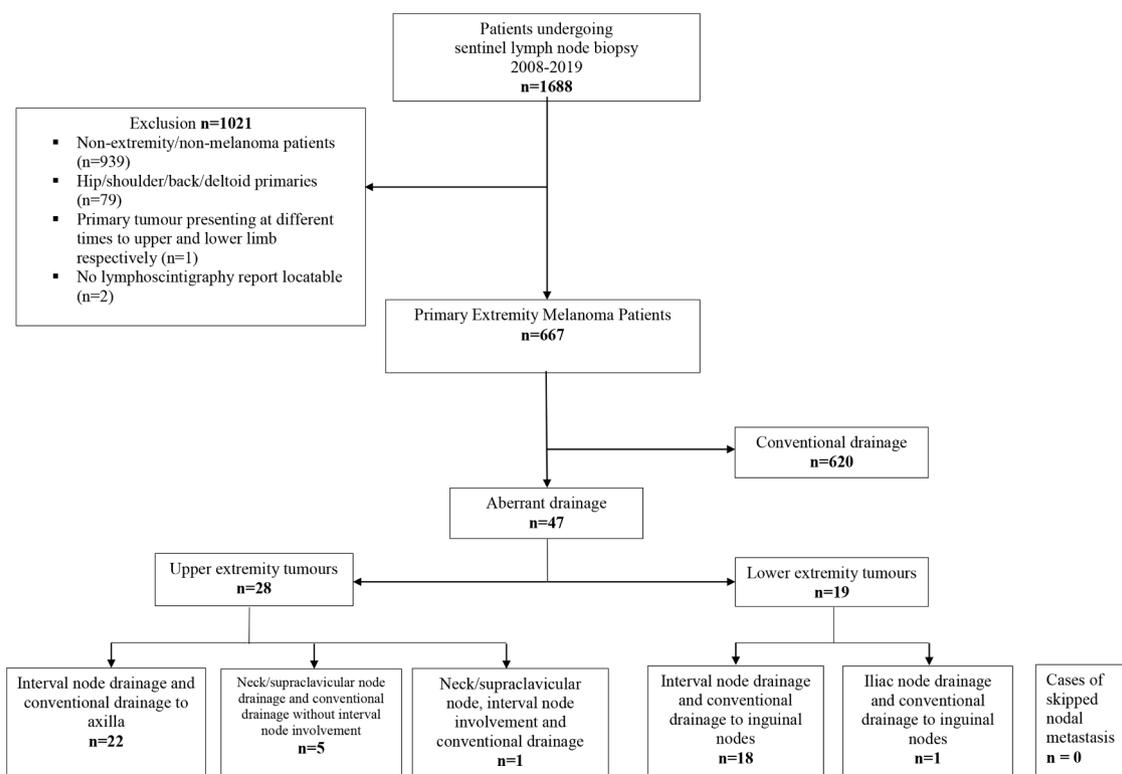


Fig. 2. Flowchart for lymphoscintigraphy study of limb melanoma patients who underwent sentinel lymph node biopsy, 2008–2019.

metastases. Of the 19 patients with lower limb primary melanomas whose lymphoscintigrams showed unconventional drainage patterns, 18 had drainage to interval as well as inguinal lymph nodes, and the single patient with dual drainage to external iliac as well as inguinal nodes showed no micro-metastasis to the distant node on sentinel lymph node biopsy.

## Discussion

We used two complementary approaches to search for unambiguous evidence of cases of SNM in cutaneous melanoma patients treated across two decades at a tertiary oncology center. On examination of clinical records of 80 patients with limb melanoma and regional node involvement with no apparent visceral disease across the period 2002–2015, there was one with a possible SNM, but further checking revealed a CT scan showing concurrent secondary lung deposits. We also reviewed the lymphoscintigrams of 1688 consecutive patients with melanoma of the extremities who had undergone sentinel lymph node biopsy in the study period 2008–2019, and to identify unusual lymphatic drainage from the skin site directly to distant lymph nodes. We found 7 cases with direct drainage from skin to nodes distal to the regional nodal basins, but all 7 had lymphatic drainage to the nodes in the regional nodal basin as well, and all positive sentinel lymph node biopsies involved the proximal basin. Thus, despite extensive searching, we found no cases of SNM.

Our working definition of SNM was the first occurrence of metastasis in a distant lymphatic basin that skips the lymph nodes in the first major draining basin, without the occurrence of distant visceral metastases. This pattern of SNM is well-documented in other tumor groups, and Virchow's node is a classic example [10]. Initially described as a supraclavicular nodal metastasis of gastric carcinoma, it is now known to occur in breast, oesophageal, pelvic and testicular cancer [11]. SNM in visceral tumors appears to be a more random pattern of drainage to nodes at higher levels than for skin cancer within a single drainage basin [12]. Indeed, several authors [8, 9] have shown that there is a proximal to distal order in the pattern of drainage even within a single nodal basin in patients with cutaneous melanomas consistent with our findings. Contrary to a previous report [6], we do not consider the development of positive nodes in patients following a negative sentinel lymph node biopsy can be considered SNM because these are temporally distinct clinical episodes.

The current standard of care for the management of patients with cutaneous melanoma is local surgery and further management depends on whether or not regional node disease or distant metastatic disease is present. Our findings provide evidence that if the immediate regional nodal basin is disease-free, including free from micro-metastases, then the tumor is unlikely to have metastasised via the lymphatic network to distant nodal basins. If a distant nodal basin is involved, the implications are that the metastasis has spread via the vascular network and other sites of visceral/distant metastases need to be investigated with a staging scan.

Similar to our finding that unusual drainage patterns are not rare in patients with cutaneous melanoma, Uren et al. [13] noted that 7% of over 2400 patients had drainage to interval nodes as well as to standard draining basins. However, we found no reports in English of confirmed SNM as defined, and we postulate that anecdotal cases of SNM in melanoma could be explained by distant melanoma deposits (nodal or extra-nodal) in patients who have unrecognized distant metastases.

Our study was limited by being retrospective and relying on information in clinical records, but this in turn allowed a far greater number of patients' records (over a thousand) to be included over a prolonged period than would have been possible in a prospective study.

There were limitations in each of the methods used to evaluate the lymph nodes. Clinical examination is limited by the experience of the clinician - small (<1 cm) nodal metastases maybe missed, and similarly ultrasound imaging is limited by the experience of the operator as well as the sensitivity of the probe. Magnetic resonance imaging is limited by

patient compliance and computer-assisted tomography carries with it risks associated with exposure to ionizing radiation. Although our two strategies for ascertaining cases of SNM involved some overlap in study cases, the complementary information allowed internal validation of the extent of nodal involvement in such cases, maximizing our ability to identify any true SNM cases. In addition, we avoided possible false positive SNM by excluding primary melanomas of hip, groin or buttock regions, as well as head and trunk melanomas, and specifically within the lymphoscintigraphy group, by excluding cases with melanoma on the shoulder, given the clear predilection for lymphatic drainage to the neck from primary tumours at this site [14].

## Conclusion

We searched for cases of SNM among over a thousand clinical records and lymphoscintigrams of melanoma cases and found none. We conclude that SNM are highly unlikely to occur between regional nodal basins in cutaneous melanoma. Future management of patients with limb melanomas should involve clinical examination and/or imaging of the immediate regional nodal basin, and if node-positive then examination should extend to adjacent nodal basins. Patients presenting with apparent first metastases to extra-regional nodal basins should be investigated for distant haematogenous metastases.

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## CRediT authorship contribution statement

**Omar El-Omar:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Sharanniyam Ragavan:** Data curation, Formal analysis, Writing – review & editing. **Won Young Yoon:** Data curation, Formal analysis, Writing – review & editing. **Megan E. Grant:** Data curation, Writing – review & editing. **Adele C. Green:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Deemesh Oudit:** Conceptualization, Writing – original draft, Writing – review & editing.

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**Omar El-Omar:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Sharanniyam Ragavan:** Data curation, Formal analysis, Writing – review & editing. **Won Young Yoon:** Data curation, Formal analysis, Writing – review & editing. **Megan E. Grant:** Data curation, Writing – review & editing. **Adele C. Green:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Deemesh Oudit:** Conceptualization, Writing – original draft, Writing – review & editing.

## Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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