Five years of sentinel node biopsy for melanoma: the St George’s Melanoma Unit experience

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Summary Sentinel node biopsy has become an integral part of the management of malignant melanoma. Here, the authors describe the technique that is used at the St George’s Hospital Melanoma Unit. Results obtained over the past 5 years on a cohort of patients are presented. Three hundred and forty seven patients were entered in the study. Population demographics were analysed for both the primary melanoma and for sentinel node positive status. Histological features of the primary, particularly regression were noted and, in addition to metastatic disease, the presence of capsular naevus cells within the node also recorded. Complications associated with the procedure have been presented along with the specificity and sensitivity of the technique. The relative influence of both Breslow thickness and sentinel node positivity were analysed statistically and Kaplan–Meier survival curves produced for the cohort as a whole. This confirmed the accuracy of sentinel node biopsy and its role as a prognostic indicator.

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Sentinel lymph node biopsy (SNB) is at present the most effective method of determining the presence of lymphatic involvement with metastatic melanoma. It has been stated that it is the most important predictor of prognosis, better than both Breslow thickness and ulceration.1 Prior to its use, further melanoma management after histological confirmation, relied upon a depth-related wider excision margin and whether elective (ELND) or observation and therapeutic lymph node dissection (TLND) was the correct protocol to follow. Subsequent studies analysing ELND, however, showed only a beneficial outcome in patients that were observed retrospectively.2–5 Prospectively designed studies did not confirm a survival benefit, only in subgroups for example, males with truncal primaries and in addition, complication rates following this surgery were extensive.6–9 Following the concept of a step-wise progression of melanoma,10 Morton et al. in 1992 subsequently proposed SNB, lymphatic mapping and so nodal staging for melanoma patients.11 This theoretically would discern those patients who had developed micrometastases and could therefore benefit from an early completion lymphadenectomy before further lymphatic spread had occurred, from those not needing further nodal surgery.

Throughout the 1990’s, the technique of SNB has been refined to include not only an intraoperative
vital dye injection to identify the sentinel node as originally described by Morton (success rate 90%) but also a dermal injection of a radiolabelled tracer colloid preoperatively. Reports now state an accuracy of between 96% and 99% using this combination. Although controversy exists over the role of SNB in the further management of malignant melanoma, the technique now forms an integral part of the AJCC classification for the staging of melanoma and the World Health Organisation has issued a statement supporting its use in the care of patients with melanoma.

SNB for melanoma has been performed by the senior author at the Melanoma Unit, St George’s Hospital since 1996. This study reports on the experience of the past 5 years looking particularly at surgical outcome, histological features, complications and overall survival rates to date.

Method

Three hundred and forty seven patients underwent SNB at the Melanoma Unit, St George’s Hospital between 1996 and 2001. Data were filed prospectively in the notes and then added to a database retrospectively. All patients had undergone an excision biopsy confirming the diagnosis and establishing the histological features such as Breslow thickness, regression, growth phase and lymphovascular invasion. Patients whose tumour had a Breslow thickness greater than 1 mm were included. Patients whose tumour had a Breslow thickness less than 1 mm were included if the tumour reached Clark’s level 3 or greater. Histological evidence of a vertical growth phase, features of regression or lymphatic involvement also were inclusion criteria. All patients were clinically stage I or II and were medically fit to undergo a completion lymphadenectomy should the result be positive. All had agreed to partake in the SNB study being made fully aware of its potential benefits and side-effects.

The patients were admitted to hospital and underwent lymphoscintigraphy using radiolabelled colloid (Solco Nanocoll, Sorin Biomedica, Vercelli, Italy) on the morning of the operation. The sentinel node(s) were identified using a gamma camera and marked on the skin with an estimated depth. The patient went to theatre in the afternoon and had the sentinel node biopsy performed. An intraoperative dermal injection of patent blue V dye (Laboratoire Guerbet, Aulney-sous-bois, France) was given around the excision scar prior to the procedure to help locate the nodes.

Previous reports by the senior author highlighted the benefits of lymphoscintigraphy by showing that aberrant sentinel lymph nodes do exist which undoubtedly would not have been harvested if vital dye alone was used. A hand-held gamma probe (Neoprobe Corp, Dublin, OH, USA) was used intraoperatively to locate the nodes. A depth-related wide local excision of the scar (1 mm or less a 1 cm margin and greater than 1 mm a 2 cm margin) was also performed.

Patients were discharged home the following day and all SNB specimens were histologically examined by a single pathologist. Nodes were assessed according to the protocol described by Cochran et al. using both routine histological techniques and in addition, immunohistochemical staining for S-100, HMB45, melan-A and tyrosinase. Clinic review took place 3-4 weeks post-biopsy and further management was dependant upon the result. The patient was offered a completion lymphadenectomy if the result was positive with oncological assessment at the time of admission for this procedure. The patient with a negative result had regular clinic follow-up. Should disease manifest in this group at a later date, then the patient was restaged and offered TLND if positive nodal involvement was confirmed.

Results

There were 185 female patients and 162 male patients. Mean age at diagnosis was 48.9 years (range 14-88). The primary lesions in the females were sited on the lower limb 70 (38%), upper limb 43 (23%), back 28 (15%), head and neck 21 (11%), foot 15 (8%), chest and abdomen each four (2%) (Fig. 1). The primary lesions in the males were sited on the back 43 (27%), upper limb 36 (22%), lower limb 30 (18%), head and neck 21 (13%), chest 13 (8%), foot 11 (7%) and abdomen eight (5%) (Fig. 2).

Figure 1 Anatomical distribution of female melanomas.
The mean thickness of the primary tumour was 2.04 mm (SD ± 2.32) with three melanocytic intraepithelial neoplasias (MIN) which had features of regression.

Two hundred and eighty six (82.4%) had a negative SNB whilst 61 (17.6%) had a positive result. The male to female ratio for a negative result was 1:1.3 and for a positive 1:0.6. The most common positive primary site in both males and females was the lower limb (32 and 48%, respectively) (Figs. 3 and 4). The mean positive SNB primary thickness was 3.13 mm (SD ± 2.19) with one positive MIN, whilst that for negatives was 1.81 mm (SD ± 2.28) with two negative MIN’s. Statistical analysis using the Mann–Whitney rank sum test revealed the differences to be statistically significant (p < 0.001). Ranking of the Breslow thicknesses according to thin (<1 mm), intermediate (1–2 mm) or thick (>2 mm) melanomas and representing these graphically according to either a positive or negative result showed an increasing tendency to a positive result with thicker primary melanomas. In the thin group the ratio of negatives to positives was 29:1, with the intermediate group this was 5:1 and for the thick group 2:1 (Fig. 5). Four patients or 3.5% of the thin group had a positive SNB. The mean number of sentinel nodes taken at operation was 2.1 (range 0–7). The mean number taken from subsequently positive patients was 1.3 (range 1–4). Successful SNB harvesting overall was 99%. Features of regression were noted in 27 specimens (7.8%) of the total number and all had a negative SNB. Capsular naevus cells, which are a potential source of a false positive result, were present in the sentinel nodes of 21 (7.3%) of patients who obtained a negative result.

Analysis of surgical complications revealed an overall complication rate of 16.5% (57 in total) (Table 1). The number of patients experiencing complications who were SNB negative was 49 (14% of the total or 17% of total number of negatives) whilst for positive 8 (2% of total or 13% of the positives) (Fig. 6). Although all positive patients had a completion lymphadenectomy within 3 weeks of diagnosis, there were nevertheless some complications experienced by a few within this time scale.

Figure 2 Anatomical distribution of male melanomas.

Figure 3 Anatomical distribution of melanoma primary sites in female patients with a positive sentinel node.

Figure 4 Anatomical distribution of melanoma primary sites in male patients with a positive sentinel node.

Figure 5 Plot of the number of patients with either a positive or negative SNB according to the depth of the primary lesion.
Six patients had lymphocele formation (75% of the total complications for positives) of which one subsequently developed lymphoedema whilst waiting for an abscess to resolve prior to nodal clearance. Of the negative patients, the main complication was lymphocele formation (31 or 63% of the total complications) of which five (10%) subsequently developed lymphoedema whilst the remainder resolved. One patient had lymphoedema, which resolved and then subsequently recurred when she became pregnant. Overall nine patients (18%) or 3% of the negative patients had permanent lymphoedema. Four patients (1.4% of the complications for negatives) had a culture-proven infection with one developing an abscess requiring drainage. Three patients had a wound dehiscence (1%) whilst two had a haematoma requiring drainage (0.7%). One patient developed an allergy to patent blue V dye intraoperatively which resolved spontaneously without any other sign of systemic upset (Fig. 6).

All patients with a positive result underwent a completion lymphadenectomy. Of the 61 patients that had this procedure, 53 (87%) had no further nodal involvement with melanoma. The remaining eight patients had a mean positive number of nodes of 2.7 (range 1-9). A graph was plotted (Fig. 7) of the thickness of the melanoma (<1 mm or thin, 1-2 mm or intermediate, >2 mm or thick) against the total number of involved nodes (sentinel nodes plus completion lymphadenectomy positive nodes). Statistical analysis revealed no significant difference between depth of the melanoma and the number of lymph nodes containing metastatic melanoma.

At 5 years, the total number of deaths in this cohort numbers 21 (6% of total) with one having died from a myocardial infarction (5.5% dying from melanoma). Eleven have died in the positive group representing 3% of the total number or 18% of the positives. In the negative group, nine patients or 2.6% of the total number have died representing 3% of the negatives. Therefore, in this study, positive patients are six times more likely to die from their disease than negatives. Of the 11 positive patients that have died, only two had further nodal involvement on completion lymphadenectomy. All 11 had visceral recurrence with two having additional cutaneous recurrence. Therefore the remaining six patients who had additional positive nodes on completion lymphadenectomy (10% of the positives or 2% of the total cohort) may have benefited from this procedure halting the further spread of lymphatic disease.

Overall recurrence rate for melanoma (including the deaths) totals 30 (9% of cohort). For patients who had a positive SNB, melanoma recurrence totals 14 (4% of the cohort or 23% of positive patients) and so with 11 having died from the disease, three are presently alive. For SNB negative patients the number is 16 (4.5% of the cohort or 6% of negatives). Therefore, there is a four-fold

### Table 1

<table>
<thead>
<tr>
<th>Complication</th>
<th>Number of SNB negative patients</th>
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<td>Major</td>
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<tr>
<td>Lymphoedema</td>
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<td>Infection/abscess</td>
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<tr>
<td>Wound dehiscence</td>
<td>3</td>
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<tr>
<td>Haematoma</td>
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<tr>
<td>Allergy</td>
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</tr>
<tr>
<td>Minor</td>
<td></td>
</tr>
<tr>
<td>Lymphocele</td>
<td>31 (11%)</td>
</tr>
<tr>
<td></td>
<td>50 (14.5%)</td>
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![Figure 6](allergic_reaction_to_vital_blue_dye.png) **Figure 6** Allergic reaction to vital blue dye.

![Figure 7](mean_number_of_positive_nodes.png) **Figure 7** Graph showing mean number of positive nodes (SNB and nodal clearance (±SD)) according to thickness of melanoma.
greater chance of a melanoma recurrence if the SNB is positive compared to having a negative result. Of the 16 negatives with recurrence, eight had a visceral recurrence and six have died, five a nodal recurrence giving a false negative SNB rate of 2%, two in-transit recurrence and one local recurrence. The sensitivity of the procedure was 92% with a specificity of 99%. Four percent of the negative group had a non-nodal recurrence representing the number in this study for which SNB will not detect advanced disease as the path of dissemination was not lymphatic.

A graph was plotted of the thickness of the melanomas against the number of deaths/recurrences and those without disease/recurrence (Fig. 8). There was a statistically significant difference upon analysis by the Student paired t-test between the Breslow thickness of those patients who had a recurrence or had died compared to those who had not ($p = 0.0006$). A further graph was plotted of the total number of disease-involved nodes against death/recurrence of the disease in patients and those who had no recurrence (Fig. 9). Statistical analysis by the Mann–Whitney rank sum test showed there to be a statistically significant difference between the number of patients with disease recurrence and the number of involved nodes with a greater number of involved nodes leading to an increased chance of recurrence ($p = 0.002$).

Cox’s proportional hazard model was used to determine the relative influence of primary thickness and sentinel node positivity upon the likelihood of the patient dying from the disease. When analysed, both factors had a significant influence on survival rates. The hazard ratio for thickness was 9.45 meaning that moving from thin to intermediate grouping raised the likelihood of death by this figure and moving from intermediate to thick increased the likelihood still further by this amount. This was significant ($p = 0.0018$). Having a positive sentinel node result gave a hazard ratio of 4.27 meaning that an individual who was positive had an increased likelihood of mortality by this amount ($p = 0.0024$). Kaplan–Meier survival curves were drawn to represent these figures graphically over time (Figs. 10 and 11).

**Discussion**

This paper represents a 5 year analysis of the largest UK series to date of SNB for the management of melanoma. It confirms the accuracy of the technique with a low false negative result (2%) and supports our previous findings of a high percentage SNB retrieval (from 98 to 99%).

**Figure 8** Graph showing the mean thickness (±SD) of the primary melanoma plotted against whether the patient is alive or not.

**Figure 9** Graph showing the mean number of positive nodes in all patients (SNB’s plus completion lymphadenectomy specimens) (±SD) plotted against whether the patient is alive or not.

**Figure 10** Kaplan–Meier survival curves of patients grouped for thin and thick primary melanomas. The intermediate group is not shown as although recurrences were present, there were no deaths at the time of assessment.
primary sites for the disease were lower limb in females and back in males. Interestingly the location of the primary site, whose draining nodal basin had the greatest number of positive sentinel nodes, changed in males to the lower limb (still lower limb in females). From the 347 patients in this study, 17.6% returned a positive SNB result. This is in line with other studies (Morton et al.—15%, Gershenwald et al.—16%) but the histological protocol has recently been changed in our group appearing to yield a greater number of positive findings not only from the use of reverse transcriptase-polymerase chain reaction (RT-PCR) but also more closer sectioning (personal communication Professor Cook) and this is a standard that has now been adopted by the European Organisation for the Research and Treatment of Cancer melanoma group (EORTC). This finding could well account for the 99% specificity in this study but it also could be argued that the original finding was a genuine negative and a delay was present in the lymphatic dissemination of the metastatic melanoma such that it had not reached the sentinel node prior to its harvest.

Three patients had MIN’s with one returning a positive SNB. The graph in Fig. 5 shows that in total, four patients with Breslow thicknesses less than 1 mm had a positive SNB (1% of the total or 3.5% of the thin group) which would suggest that certain melanomas could contain histological features more aggressive than their depth would suggest. In contrast to the policy described by Muller et al. who identified no metastatic melanoma in SNB’s under 0.9 mm, the authors would still continue with SNB upon thin melanomas regarding them as ‘at one end of a continuous spectrum of biological activity’.

Breslow thickness was confirmed in this study to be an important predictor of prognosis. There was an increasing tendency to have a positive SNB result the thicker the primary melanoma plus a greater number of patients had a recurrence or died from the disease the greater the thickness of the melanoma, a finding which was statistically significant ($p = 0.0006$). In addition, this study has shown that those patients with a positive SNB had a statistically significant greater primary Breslow thickness than those with a negative result. Ulceration was a feature that was not confirmed as a prognostic indicator until year 2000 and so for this study was not originally included as a variable.

Histological features of regression present within the primary melanoma have either been described as being a sinister feature or having a protective effect upon patient survival. A literature search has not discovered any report to date as to the effect of regression on sentinel node result. In this study, all patients who had features of regression in the primary melanoma did not have a positive SNB which was statistically significant ($p < 0.0001$) and as such the authors believe that this is the first report of this finding. One patient of the 27 did develop a local recurrence of the disease representing 3.7% of the total number of regression specimens. The recurrence rate for the remaining negative patients is 5.8% confirming that regression does not appear to influence recurrence rates as it was in line with the general trend.

An additional finding was that of capsular naevus cells within the lymph nodes which can stain positive for all stains used and therefore be a source of potential false positive result. Importantly these cells appear cytologically benign. Of the patients with a negative SNB, 7.3% had capsular naevus cells, which suggests that they are a relatively common finding and must be accurately discerned from micrometastatic disease. The importance of a pathologist used to assessing such lymph nodes is therefore apparent.

There was no statistical difference between the thickness of the primary melanoma and the number of lymph nodes involved with metastases (positive sentinel nodes plus further positive completion lymphadenectomy nodes). However, it was found that there was an association between the number of involved nodes and death from the disease or recurrence of the disease, which was statistically significant ($p = 0.002$). This would be expected being associated with a more advanced disease status.

To date, there are no reports of complication rates for SNB other than that published by this centre 2 years ago. The initial findings from the first 100 consecutive patients within this cohort found a high complication rate of 33%. This has now been
reduced to 16.5% including the positives, or 14% of the negatives. In this study features such as hypertrophic scarring, parasthesia, persistent staining and incorrect histological reporting were no longer included, as it was felt particularly that the scarring and the parasthesia would be observer and patient-dependent and difficult to quantify. The permanent and debilitating complication of lymphoedema represented 2.6% of the negative sentinel node group which the authors believe should not in itself detract from the use of SNB in melanoma management, but that its use should still be confined to trials.

The role of SNB has been defined by Mc Masters et al. as improved accuracy of staging for further treatment decisions and prognosis with additional psychological benefits for the patients (as shown by our group)\(^3\), early completion lymphadenectomy hopefully preventing further spread of disease (to be confirmed by the multicentre lymphadenectomy trial), discerning candidates for adjuvant therapy with interferon alfa-2b and finally identifying patient cohorts for subsequent trials of therapy.\(^\text{19}\)

For prognostic information, in our study it was found that having a positive SNB made it six times more likely that the individual would die from their disease as compared with an SNB negative individual. Taking recurrence overall, which included the number of deaths, this figure dropped to four times. An interesting finding was that of the positive patients who had completion lymphadenectomy, only eight of the 61 (13%) had further disease in the nodes. Eleven patients have subsequently died in the positive group but only two of these had had further nodal involvement on lymphadenectomy. This would suggest that completion lymphadenectomy to date has potentially been beneficial for the remaining six patients that had further nodal involvement representing 10% of the positive group or 2% of the cohort. Eighty seven percent of positive SNB patients had no further nodal involvement with melanoma suggesting that if these patients could be identified, then there would be scope to prevent an unnecessary completion lymphadenectomy. However, to date nine positive patients within this group have died from their disease due to other modes of metastasis. From the negative group 4% of patients had a non-nodal recurrence which suggests that SNB in this study would not detect any evidence of metastatic disease in this number of patients.

To determine the relative influence of primary thickness and sentinel node positivity on mortality rates, a statistical test was performed. This confirmed the fact that Breslow thickness is an important prognostic indicator for survival. The hazard ratio of 9.45 for thickness is not exact, as no patients as yet have died within the intermediate group. However, the analysis takes this into account and so the figure is the lowest that it is likely to be. In our study, sentinel node positivity was also a strong indicator for survival but not as great as Breslow thickness. It does confirm the usefulness of the technique as well as the accuracy in the unit’s hands.

This paper reviews 5 years of SNB for melanoma particularly with regard to population demographics, complication rates and survival data. Although the follow-up period is short at 5 years, it has been stated that 80% of melanoma recurrence will be within the first 3 years of diagnosis\(^3\) and that the hazard ratios for both thickness of primary and sentinel node positivity both reached statistical significance.

The authors believe that the study gives a good indication as to the status of SNB within the unit. In our hands, SNB is a good prognostic indicator, has a high sensitivity and specificity and a low false negative rate with minimal associated morbidity. The next stage would be to assess whether it infers a survival benefit in its own right compared to patients who have not undergone SNB. Until this happens then it will always have its detractors.

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