

# Value of sentinel node status as a prognostic factor in melanoma: prospective observational study

Stephen Kettlewell, Colin Moyes, Caroline Bray, David Soutar, Alan MacKay, Dominique Byrne, Taimur Shoaib, Barun Majumder, Rona MacKie

## Abstract

**Objective** To establish the prognostic value of knowledge of sentinel node status in melanoma.

**Design** Single centre prospective observational study, with sentinel nodes identified by lymphoscintigraphy,  $\gamma$  probe, and intraoperative blue dye and examined by both conventional histopathology and immunopathology.

**Setting** Specialist surgical service in west of Scotland.

**Participants** 482 patients with melanoma who consented to sentinel node biopsy in 1996-2003.

**Main outcome measure** Time to recurrence of or death from melanoma.

**Results** Of 472 patients who consented to sentinel node biopsy and in whom at least one sentinel node was identified, 367 (78%) had no tumour in the sentinel node. At mean follow-up of 42 months, 299 (82%) of this group were alive and free from disease, 24 were alive with melanoma recurrence, and 31 had died of melanoma. Of 105 patients with a positive sentinel node biopsy, 44 (42%) were alive and disease free, 12 were alive with recurrence, and 46 had died of melanoma. The survival difference between patients who were negative and those who were positive for tumour in the sentinel node was highly significant at all thickness levels over 1.0 mm ( $P < 0.001$ ).

Multivariate analysis showed that sentinel node status was independent of tumour thickness and ulceration. 71/105 (68%) patients with a positive sentinel node had a negative completion lymphadenectomy, and 44/71 (62%) were alive and disease free at follow-up; 34 patients with a positive sentinel node had further nodes involved, and only 4 (12%) were disease free ( $P < 0.001$ ). 16 patients (13 sentinel node biopsy positive; 3 negative) died of other causes.

**Conclusion** Sentinel node status is a highly significant predictor of prognosis in melanoma and should be considered in adjuvant studies. However, it should not be regarded as a standard of care until mature data from ongoing randomised trials are available.

## Introduction

In breast cancer, sentinel node biopsy (SNB) is becoming a standard method of nodal sampling, and the presence or absence of tumour cells in the node determines the treatment pathway after surgery.<sup>1</sup> For melanoma, the lack of proved effective non-surgical adjuvant treatment precludes this approach. A multicentre randomised trial (MSLT1) is in progress with the aim of determining if patients with melanoma who have a positive SNB and proceed immediately to full node dissection have superior survival compared with patients who have node dissection only when nodes draining the site of the primary melanoma are clinically palpable.<sup>2</sup> We aimed to gain clinical

experience of the technique of SNB in a single centre and determine whether sentinel node status adds prognostic information to that gained from measuring tumour thickness.

## Methods

We identified 482 patients who had an appropriate wide excision of their primary melanoma and a primary lesion of 1 mm or thicker. We did all SNBs within eight weeks of surgery, and no patient had evidence of spread beyond the primary tumour site. Patients had lymphoscintigraphy to identify the appropriate draining nodal basin to sample. We used tracking of patent blue V dye to identify the sentinel node, confirmed by a collimated  $\gamma$  radiation detection probe.

The receiving pathologist tested the nodes for melanoma cells and recorded the volume and site within the node of melanoma cells. All patients with one or more positive SNB proceeded to completion lymphadenectomy within four weeks.

We followed up patients at intervals of three months after SNB with clinical, haematological, and biochemical examination and with chest radiography. We recorded the times to recurrence and to death.

## Results

We attempted 482 SNB procedures and identified one or more sentinel nodes in all but 10 cases. Five patients had primary melanomas  $< 1$  mm thick and are not considered further. The median number of sentinel nodes identified was two (range one to five). Most primary lesions (253/472, 54%) were superficial spreading melanomas, 125 (27%) were nodular primary tumours, 31 (7%) were acral melanomas, 10 (2%) were lentigo maligna melanomas, and 53 were unclassifiable. One hundred and five patients (22%) had one or more positive sentinel nodes, and 34 (32%) of these had further nodes containing melanoma identified at completion lymphadenectomy.

The incidence of positive SNBs rose from 12% to 19% to 30% to 34% with increasing thickness category (1-1.99 mm, 2-2.99 mm, 3-3.99 mm, and  $\geq 4$  mm), a statistically significant trend ( $P < 0.001$ ,  $\chi^2$  test for trend). Follow-up to a maximum of 130 months (mean 42 months) found that for all 367 SNB negative patients recurrence-free survival was 82%, whereas recurrence-free survival for all 105 SNB positive patients was 42%, a highly significant difference ( $P < 0.001$ ).

Twenty four of 367 SNB negative patients were alive with recurrent melanoma at follow-up, and 31

Hairmyres Hospital,  
Lanarkshire  
G75 8RG

Stephen Kettlewell  
consultant vascular  
surgeon

Royal Alexandra  
Hospital, Paisley  
PA2 9PN

Colin Moyes  
consultant pathologist

Greater Glasgow  
NHS Board,  
Glasgow G3 8YZ

Caroline Bray  
statistician

Canniesburn Plastic  
Surgery Unit,  
Glasgow Royal  
Infirmary, Glasgow  
G4 0SF

David Soutar  
consultant plastic  
surgeon

Taimur Shoaib  
specialist registrar in  
plastic surgery

General Surgery  
Unit, Glasgow Royal  
Infirmary  
Barun Majumder  
specialist surgical  
registrar

Gartnavel General  
Hospital, Glasgow  
G12 0YN

Alan MacKay  
consultant vascular  
surgeon

Dominique Byrne  
consultant vascular  
surgeon

Department of  
Public Health and  
Health Policy,  
University of  
Glasgow, Glasgow  
G12 8RZ

Rona MacKie  
senior research fellow

Correspondence to:  
R MacKie  
R.M.Mackie@  
clinmed.gla.ac.uk

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Cox's proportional hazard model comparing sentinel node status with other postulated prognostic factors as independent influences on survival

Factors	No*	Hazard ratio (95% CI)	P value
<b>Sentinel node biopsy</b>			
Positive	99	4.40 (2.91 to 6.64)	<0.001
Negative	352	1	
<b>Ulceration</b>			
Yes	124	1.80 (1.20 to 2.70)	0.005
Other	327	1	
<b>Tumour thickness (mm)</b>			
1-1.99	159	1	
2-2.99	96	2.41 (1.11 to 5.22)	0.026
3-3.99	58	1.70 (0.71 to 4.11)	0.236
≥4	138	4.36 (2.13 to 8.91)	<0.001
<b>Clark level</b>			
2	20	0.50 (0.12 to 2.06)	0.335
3	75	0.56 (0.25 to 1.24)	0.153
4	301	1	
5	44	1.08 (0.60 to 1.93)	0.801
Not assessable	11	0.47 (0.14 to 1.59)	0.225
<b>Age (years)</b>			
<40	93	0.46 (0.23 to 0.92)	0.028
40 to 59	174	1	
≥60	184	0.76 (0.48 to 1.21)	0.253
<b>Sex</b>			
Male	201	1.08 (0.69 to 1.69)	0.742
Female	250	1	
<b>Body site</b>			
Limbs	298	1	
Head and neck	48	1.14 (0.53 to 2.45)	0.731
Trunk	105	1.51 (0.90 to 2.53)	0.118

\*Number of patients included in analysis=451 (number of cases with complete data for all variables).

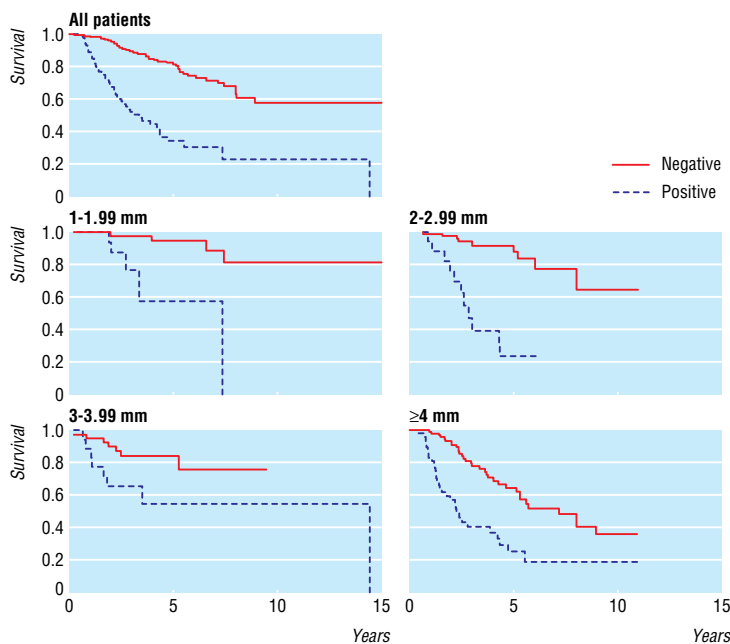
SNB negative patients had died of melanoma. Thus 55/367 (15%) of SNB negative patients had disease progression at follow-up. For comparison, 12 SNB positive patients were alive with recurrence and 46 had

died of melanoma, a combined recurrence rate of 58/105 (55%). More detailed analysis showed that 71/105 (67%) SNB positive patients had a negative completion lymphadenectomy, and 34 (32%) had additional nodes containing melanoma. Forty four (62%) of the 71 SNB positive, completion lymphadenectomy negative patients were alive and recurrence free, 4 were alive with recurrent melanoma, 19 had died of melanoma, and 3 had died of other causes. In contrast, only 4/34 (12%) SNB positive, completion lymphadenectomy positive patients were alive and recurrence free, 3 were alive with recurrence, and 27 had died of melanoma. This difference in survival was highly significant ( $P < 0.001$ ).

The first site of recurrence in the 31 SNB negative patients who died of melanoma was nodal in 12 (39%), distant in 14 (45%), and in transit in 5 (16%). For the 39 SNB positive patients the site was nodal in 4 (10%), distant in 30 (77%), and in transit in 4 (10%).

The table shows the multivariate analysis for the group. The most powerful prognostic factor for survival was the sentinel node status; ulceration and tumour thickness were independent prognostic factors. The hazard ratio for a positive sentinel node in a Cox model including only primary tumour thickness and ulceration as additional variables was 4.15 (95% confidence interval 2.82 to 6.11). Clark levels, age at diagnosis of melanoma, sex, and body site of primary tumour did not add any additional prognostic information. When we analysed the SNB negative and SNB positive groups separately, tumour thickness was retained in the model as significant for both groups but ulceration lost independent significance for the SNB positive group.

The figure shows Kaplan-Meier survival curves. They show statistically significant survival differences in all thickness categories between SNB positive and SNB negative patients ( $P < 0.001$ ).



Kaplan-Meier survival curves for patients with positive and negative sentinel node biopsies for all tumour thicknesses ( $P < 0.001$ ) and for patients in categories of 1-1.99 mm ( $P < 0.001$ ), 2-2.99 mm ( $P < 0.001$ ), 3-3.99 mm ( $P < 0.05$ ), and  $\geq 4$  mm ( $P < 0.001$ ) tumour thickness

## Discussion

Our single centre European study reviews a large series of patients who have had SNB to determine the relation between tumour thickness, SNB status, and survival. These data clearly show that SNB status adds important prognostic information to that provided by tumour thickness at the time of diagnosis in all thickness groupings. This is maintained for patients with primary melanomas thicker than 4 mm, and this group should not be regarded as having uniformly fatal disease. We have also shown the very poor prognosis for patients with primary melanomas of any thickness who have additional non-sentinel nodes involved at full node dissection, strongly implying that these patients already have disseminated disease. A strong case exists for a trial of adjuvant treatment directed specifically at patients with SNB positive, completion lymphadenectomy positive melanoma. The 15% disease recurrence rate in the 367 SNB negative patients in our study is similar to a 13% recurrence rate for SNB negative patients at three years' follow-up.<sup>3</sup> The pattern of recurrence in these patients suggests that they should not be regarded as nuclear medicine, surgical, or pathological "failures," but that up to 15% of melanoma patients have a pattern of lymphatic or haematogenous tumour dissemination that bypasses

the sentinel node or at the time of SNB have melanoma cells distal to the sentinel node and still in transit. Thus, although a negative SNB is an encouraging prognostic feature, patients will still need to be counselled that they may have a recurrence of their melanoma. In keeping with results from other groups, our data do not suggest that patients who have had SNB have a higher than expected incidence of in-transit recurrence.<sup>4</sup>

### Conclusions

Although knowledge of sentinel node status is an additional significant prognostic indicator, this knowledge does not change routine management of patients, as no widely accepted effective adjuvant treatment is available to SNB positive patients after node dissection. The recently reported results of EORTC 19852 adjuvant interferon therapy for stage 2b and 3 melanoma showed no overall survival benefit,<sup>5</sup> and the early report of the benefit of interferon in the US study ECOG 1684 was not confirmed by the same group in ECOG 1690.<sup>6,7</sup>

Until the full results of MSLT1 are published, sentinel node biopsy should not be a routine procedure for melanoma patients but should be used as a staging procedure in centres entering patients into adjuvant trials for patients with stage 3 melanoma. Knowledge of sentinel node status is necessary to stratify melanoma patients being entered into these trials and should be part of the protocol.

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### What is already known on this topic

Before 1990, common practice in Europe was to widely excise the primary melanoma and then observe the patient, delaying lymph node surgery until nodes were palpable

North American practice was to offer elective node dissection of the appropriate draining nodal basin to most patients with primary melanomas thicker than 1 mm

Many European centres are introducing sentinel node biopsy as a routine procedure despite the lack of evidence that this and completion lymphadenectomy extend overall survival

### What this study adds

This prospective observational study shows that sentinel node status is a significant prognostic factor and is independent of both tumour thickness and ulceration

Until data from randomised trials are available, sentinel node biopsy status should be considered in patients entering adjuvant trials but should not become a routine standard of care

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## Immediate, underlying, and macro-underlying causes

When filling in death certificates, doctors list both the immediate cause of death and the underlying cause, be that a disease which initiated the train of morbidity leading to death or the circumstances surrounding the accident which produced a fatal injury. Identifying underlying causes in this way provides information of great importance to public health by highlighting the main sources of avoidable mortality in a population.

I wonder, however, whether doctors have yet realised the full scope of the death certificate as a tool for compiling information to be used in guiding policy makers to the best way of promoting public health and wellbeing. For example, when recording the underlying cause of a heart attack in a manual labourer in his 50s, how about digging a little deeper than coronary artery disease to note the socioeconomic disadvantages that constrained this person's ability to quit smoking and take more exercise compared with people of higher socioeconomic status? Or, when recording

the death of a teenager who crashed her car while over the legal alcohol limit, why not note the concerted efforts by the alcohol industry in the past decade to increase sales by marketing drinks aimed at young women?

Of course, doctors are unlikely to be called on to make sociopolitical and economic judgments of this kind any time in the near future, and probably rightly so. As a thought exercise, however, I find the idea of introducing a "macro-underlying" section to the death certificate rather compelling. After all, what better way could there be for stimulating government action on issues of social justice than a sudden, sharp epidemic of deaths due to social inequality?

Anna Goodman *masters student, London School of Hygiene and Tropical Medicine, London* ([anna.goodman@lshtm.ac.uk](mailto:anna.goodman@lshtm.ac.uk))