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Prospective study of patterns of surgical management in adults with primary cutaneous melanoma at high risk of spread, in Queensland, Australia

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Synopsis for Table of Contents

Variations in diagnostic biopsy procedure and performance of sentinel node biopsy were assessed in 787 Australian patients with cutaneous melanoma clinical stage 1b or 2. Diagnostic procedure influenced initial tumor microstaging. Treating doctor, patient and tumor characteristics all influenced whether sentinel node biopsy was performed.

ABSTRACT

Background: Knowledge of variation in diagnosis and surgery in high-risk primary melanoma patients is limited. We assessed frequency and determinants of diagnostic procedures, wide local excision (WLE) and sentinel lymph node biopsy (SLNB).

Methods: People in Queensland newly diagnosed with melanoma, clinical stage 1b or 2, were recruited prospectively. Patient information was collected from questionnaires and pathology records. Differences in surgical procedures in relation to host and tumor characteristics were assessed.

Results*:* In 787 participants, primary melanoma was diagnosed by surgical excision (74%), shave (14%), punch (12%) or incisional (1%) biopsy. General practitioners (GPs) diagnosed 80%. Diagnostic procedure differed by remoteness of residence, health sector, treating doctor's specialty and melanoma site and thickness. 766 patients had WLE, 86% by surgeons. Of 134 residual melanomas, 13 (10%) were ≤1mm at diagnosis but >1mm at WLE, mostly after shave biopsy. SLNB was performed in 261 (33%) patients. SLNB was more common in those under 50, in remoter locations or treated by GP initially, and less common with head and neck melanoma.

Conclusion: Diagnostic and surgical procedures for primary melanoma vary substantially and partial biopsy can influence initial tumor microstaging. Patient, tumor and doctor characteristics influence SLNB practice.

Key Words: excision, melanoma, sentinel node

Introduction

Cutaneous melanoma continues to be a serious public health problem for white populations around the world, but the clinical picture has changed over the last 50 years. Formerly a rare cancer with high mortality, melanoma is now a cancer of relatively high incidence and low mortality as clinical and public awareness of the disease have risen [1]. The majority of melanomas are now thin (<1mm in thickness) when diagnosed and have not spread beyond the skin. In the Queensland population with the highest known incidence rates globally, 20-year survival for people presenting with thin melanoma is 96% [2]. Despite this favourable outlook for the majority, deaths from thin melanoma in high-incidence populations like Queensland are not uncommon, such that currently more people die from thin melanomas than from thick melanomas (>4 mm) in Queensland [3] . Primary melanomas thicker than 1mm have estimated 10-year survival rates ranging from 80% to 40% [4]. This is despite complete surgical excision of the primary with or without SLNB, though patterns of management from presentation to definitive surgical treatment can vary. Controversies exist about the method of diagnosis [5], timing of WLE [6] and whether SLNB should be routinely performed [7-9]. There is also a dearth of knowledge about how initial management decisions might affect not only ultimate survival, but also quality of life, particularly among patients who are at high risk of spread [10].

Several previous studies have focused on initial biopsy techniques [11-13] and the time from diagnostic biopsy to WLE [6,14]. For primary melanoma >1mm in thickness at time of diagnosis, studies of rates of SLNB [15,16] have often been limited by their reliance on clinical databases that lacked important clinicopathological factors or were hampered by missing information for sizable

numbers of patients. Given the high number of deaths due to primary melanoma in Australia, with over 9,300 deaths from thin melanomas in the state of Queensland alone in the most recent 5 years [3], we aimed to assess patterns of surgical management in the subgroup of primary melanoma patients who have a high risk of spread, namely those with stage 1b and 2 disease [4]. We also investigated potential change in staging of primary melanoma from diagnosis to definitive surgery according to diagnostic surgical technique used in this high-risk subgroup.

Patients and Methods

Case ascertainment

People diagnosed with a clinical stage 1b or 2 cutaneous melanoma [4] between October 2010 and October 2014 were recruited prospectively through a variety of clinics, namely the Multidisciplinary Melanoma Clinic at the Princess Alexandra Hospital and the Specialist Outpatient Department of the Royal Brisbane and Women's Hospital in Brisbane; through two regional hospitals, the Nambour General Hospital and the Specialist Outpatient Department of Townsville General Hospital in north Queensland, and through the private practices of surgeons associated with these hospitals who have an interest in managing cutaneous melanoma [10]. In addition people with stage 1b or 2 cutaneous melanomas initially managed by other private specialists and primary care practitioners were identified through 3 private pathology companies in Queensland.

Eligible patients ascertained through clinics or private practices were invited to participate by their treating doctors (or by study personnel with doctor's permission) and were provided with a patient information and consent form. For ascertainment

of patients in the community through pathology laboratories, pathologists identified eligible patients with newly-diagnosed melanoma and included a standard note on the computer-generated histopathology report. This note informed the treating doctors about the study and asked the doctors to inform the pathology company if their patients should not be contacted. When no objection was received within 2 weeks, the pathology company sent a standard introductory letter and study brochure to the potentially eligible patients with a request for permission to release their details to study personnel. Only the contact details of patients who actively granted permission were disclosed by the pathology company and these patients were then invited to participate in the study and provided with patient information and consent forms. Patients were excluded if they were aged less than 16 years (Queensland Health deems 16 years to be the age of consent), if they were physically or mentally unable to complete a written questionnaire, if subsequent definitive surgical diagnosis proved the primary melanoma was ineligible eg pathology showed presence of satellitosis. (Use of imaging techniques for staging following the primary diagnosis is not routine and was performed at the discretion of the treating surgeon.) All study participants provided written informed consent and the study was approved by the Ethics Committees of the Metro South Hospital and Health Service of the Princess Alexandra Hospital and the Queensland Institute of Medical Research.

Baseline data collection

Participants provided personal details including previous melanoma and family history using standard self-completed questionnaires. Patients' place of residence was categorised as major city, inner regional area, outer regional area or a remote

location using the Australian Statistical Geographical Standard Remoteness Structure (2001) [17,18]. Details of index primary melanomas were extracted from histopathology reports including anatomical site, histological classification, thickness (mm), presence of mitoses (per mm^2 or per hpf) and ulceration. In addition, information about the initial treating doctor (GP, GP in a skin cancer clinic, specialist), diagnostic biopsy procedure (excision, incision, shave, punch) and the surgical treatment performed (WLE including if residual tumor present or absent, with or without SLNB) was obtained from pathology records. Margin of excision was not recorded. For SLNB, specialty of treating doctor, interval (days) between diagnostic biopsy and definitive surgery, biopsy site, total number of sentinel lymph nodes removed, number of involved (positive) nodes and size of largest node (in mm) were recorded prospectively from pathology reports. Primary tumor and clinical staging of melanomas were determined [4].

Statistical analysis

Differences in diagnostic procedure and operative details of definitive surgery in relation to personal characteristics and site of melanoma were assessed using chi-squared tests for categorical or nominal variables, ANOVA for age and Wilcoxon rank sum test for time between diagnosis and surgery. Prevalence ratios (PR) and 95% confidence intervals (CI) were estimated using log binomial regression models to determine the associations between decision to undergo SLNB (yes/no) and personal characteristics, diagnostic procedure and histological characteristics of primary melanoma, and similarly for associations with occurrence of positive nodes (none/1 or more). These analyses were adjusted for other related factors, namely age, sex, melanoma thickness and ulceration for SLNB; and age and sex only (due to small number of people with positive nodes) for SLNB positivity. All analyses were

performed with Statistical Analysis Software, version 9.2 (SAS Institute, Cary, USA).

Results

We contacted 1254 patients newly diagnosed with primary invasive cutaneous melanoma, of whom 825 (66%) agreed to participate. Of these 825, 38 were found to be ineligible after consent leaving 787 participants. The mean age of participants at diagnosis was 62 years and 57% were male. The trunk was the most common site of melanoma (35%) while head and neck, upper limbs and lower limbs were each affected in similar proportions (around 22%)(Table I). Of the 787, 23% reported a previous melanoma and 30% a first-degree relative with melanoma. Comparison of our study cohort aged less than 80 years with the corresponding total number of cases diagnosed in Queensland within the study period as recorded by the Cancer Registry, showed no significant differences in the respective age or sex distributions.

GPs diagnosed 80% of the stage 1b or 2 melanomas, 24% of whom worked in dedicated skin cancer clinics. Overall the most common diagnostic method was surgical excision (74%), followed by shave (14%), punch (12%) or incisional (1%) biopsy. WLE was the diagnostic procedure in 16 patients. No further surgery was performed after diagnostic surgical excision in 9 patients either because clear margins had been achieved (n=4) or for reasons unstated (n=5).

Diagnostic procedure differed significantly by patient's place of residence, health care sector, specialty of treating doctor, site and thickness of the primary melanoma (Table II). Of 674 patients living in major cities and inner regional areas, 15% were diagnosed by shave biopsies compared with 7% of those in outer regional/remote

areas (p=0.007). Of patients treated in public hospitals, 79% and 9% had melanoma diagnosed by excision and shave biopsies respectively compared with 70% and 18% respectively among private patients (p=0.002) . Of the 633 diagnostic procedures performed by GPs, 75% were excision biopsies, 13% were punch biopsies and 12% were shave biopsies compared with 79 diagnostic procedures by dermatologists, 53% of which were excision, 8% punch and 39% shave biopsies. Surgeons mostly performed excision biopsies (85% of 68 diagnostic procedures) (Table II).

Melanomas on all sites were most commonly diagnosed by excision biopsy. Punch or incision biopsy was least used for melanomas on the trunk (Table II). The mean thickness of melanomas diagnosed by shave biopsy (1.1mm) was significantly less ($p<0.0001$) and time to definitive surgery significantly less on average (17 days) ($p<0.0001$) compared with melanomas diagnosed by other procedures (Table II).
A total of 766 patients had follow-up WLEs, 86% of which were performed by surgeons (Table I). Residual tumor was present in 203 (27%) of these 766, and the proportion varied significantly by diagnostic procedure with 83% of 96 punch biopsies and 48% of 111 shave biopsies having residual tumor, compared with 13% of 559 excision biopsies ($p<0.0001$). Tumor thickness after diagnostic surgery was available for 134 melanomas with residual tumor, of which 13 (10%) were reported ≤1mm thick at diagnosis, but >1mm at WLE. This change of measured thickness was significantly associated ($p=0.001$) with diagnostic procedure and occurred in 4 of 40 shave biopsies, 1 of 24 excisions and 2 of 70 punch/incision biopsies. In addition, 32 of the 766 patients underwent at least 2 WLEs (Table I), and this was also associated with diagnostic procedure, involving 9% of all shave (n=111) biopsies

compared with 3% of all (559) excision biopsies and 4% of all (96) punch biopsies (p=0.021).

Of the 766 patients who had follow-up WLEs, 261 (34%) also had a SLNB (Table I). After adjustment for age, sex, melanoma thickness and ulceration, the decision to undergo SLNB was significantly less common among those aged 50 or more compared with younger patients, and especially less frequent among those aged 70 years old or more (PRadj:0.31; 95% CI:0.23, 0.44) (Table III). A significantly higher proportion of outer regional/remote residents underwent SLNB (PRadj:1.41; 95%CI:1.14, 1.74) compared with residents of major cities (further adjustment by type of treating doctor did not alter this result), more of those who lived with a partner (PRadj: 1.25; 95%CI: 0.99, 1.58), as well as more of those with a first degree relative with melanoma than those without (PRadj:1.28; 95%CI:1.07, 1.53). SLNB was performed twice as frequently among patients with melanomas thicker than 1mm compared with stage 1b melanomas and in those with primary melanomas on sites other than the head and neck. People who had a past history of melanoma less commonly underwent SLNB compared to those without previous melanoma (PRadj: 0.65; 95%CI:0.48, 0.90) and significantly less patients initially treated by surgeons and other specialists elected to undergo SLNB compared with patients of GPs (PRadj: 0.75; 95%CI:0.59, 0.97) (Table III). Finally SLNB was significantly less prevalent among patients with melanomas lacking a common or clearly defined histological type (Table III).

The sentinel node was positive in 38 (15%) patients and a positive result was associated with increasing melanoma thickness, ulceration of the primary melanoma and increasing T-stage after adjustment for age and sex (see Supplemental Table).

There was no association between node positivity and sex, age at diagnosis, relationship status, remoteness of residence, previous melanoma history or immediate family history, health service sector, speciality of initial treating doctor, diagnostic procedure, site of melanoma or histologic classification of the primary, although numbers were small.

Discussion

We have shown that in Queensland patterns of surgical management vary widely for people diagnosed with primary melanoma stage 1b or 2 at high risk of spread. Primary care practitioners, a quarter of whom worked in dedicated skin cancer clinics, diagnosed 80% of the primary melanomas in this cohort, mostly by excision biopsy (74%). Surgeons diagnosed 9% of the melanomas, mostly by excision biopsy (85%). Dermatologists, who diagnosed 10%, performed excision biopsy for half the diagnoses and shave biopsy for around 40% (versus 12% among GPs). More people living in major cities and inner regional areas and those treated in the private sector were diagnosed by shave biopsies than those living in outer regional/remote areas and those treated in the public sector respectively. On the relatively few occasions that punch biopsies were performed, the melanomas tended to be thicker (1.9mm on average) and to be located on the head and neck or lower limb, perhaps partly reflecting that large lentigo maligna melanomas on cosmetically sensitive sites are difficult to remove entirely; or that thick melanomas may require partial biopsy for diagnosis. Melanomas diagnosed by shave biopsy were significantly thinner on average (1.1mm) than other melanomas perhaps reflecting a tendency for primary treating physicians to reserve shave biopsies for thin, flat lesions.

The overall low rate of 26% of diagnoses performed by non-excisional biopsy in our large unselected Queensland series was similar to the rate of 23% seen in another large Australian series in 2000, although the latter was not restricted to high-risk primary melanomas and included in situ melanomas[11]. Much higher non-excisional biopsy rates have been reported in North America. For example in a series of 709 primary melanoma patients who were clinically node–negative and had been referred to a surgical oncology department in Oregon between 1998 and 2012 for SLNB, non-excisional biopsies had been performed in over 50% (punch, 23%; shave, 34%) [12], and among a survey of some 100 Canadian family physicians, only 20% reported they would always perform an excisional biopsy of skin lesions suspicious for melanoma [19]. The main potential problem with partial biopsies relates to diagnostic accuracy and accuracy of microstaging of thicker lesions. In our series of 134 melanomas with complete thickness data available, 25% of melanomas diagnosed by shave biopsy were upstaged from $\leq$1mm to >1mm thickness compared with 3% diagnosed by punch biopsy and 4% by excisional biopsy, which could have influenced the potential to discuss the role of sentinel node biopsy in these patients. These findings are slightly at variance with the Oregon series, where the T stage changed after a punch biopsy in 23%, after a shave biopsy in 8% and after excision in 2%, and in particular in 13% of melanoma diagnosed by punch or shave biopsies, measured thickness changed from <1mm to >1mm [12]. Countering these data, a study assessing shave biopsy in 490 patients in a Texas Veterans' hospital found the T stage to be appropriately assessed in 99% of patients [13] when only 14% of patients had an excision biopsy, mostly for thicker lesions (mean 2.28mm) compared with a mean thickness of <1mm for punch and shave biopsied lesions. In an Australian study of melanoma (all stages) at a tertiary referral centre,

histopathologic misdiagnosis was more common for melanomas diagnosed with punch and shave biopsies than with excisional biopsy, and punch and shave biopsies also led to microstaging inaccuracy [20]. Tumor thickness was the most important factor associated with microstaging inaccuracy after partial biopsy: inaccuracy increased nearly 2-fold for every 1mm increase in tumor thickness[20]. To date most of the literature assessing non-excisional biopsies has not assessed the method or completeness of biopsy, or the training or experience of the person doing the partial biopsy. This may be relevant when it has been shown that a deep shave biopsy is superior to a punch or superficial shave biopsy for diagnostic accuracy[21]. Tumor seeding may also be a rare outcome of punch biopsy [22]. Despite these drawbacks, studies have reported that method of biopsy does not affect melanoma-specific survival [12,13,23].

In high-risk primary melanoma patients it is reasonable to consider a SLNB for improved staging and extra prognostic information [8,24]. SLNB was performed in a third of the 787 study patients, which is less than in other population studies [15,16,25] that were mostly performed prior to the publication of the MSLT 1 trial [8]. Our study began after that publication. Although most of study patients were initially managed by primary care practitioners as are most melanoma patients in Australia, 86% of patients were treated by surgeons for their WLE and potential SLNB. Notably many of these Queensland patients were at high risk of melanoma a priori because of a self-reported first-degree relative with melanoma (30%) (though this estimate is likely to be inflated by a degree of false-positive reporting [26]) or a previous melanoma (23%) yet paradoxically these risk factors significantly affected the decision to undergo SLNB in opposite ways; in the former 28% more, and the latter 33% less patients underwent SLNB than those without the respective histories.

Patients aged under 50, those living with a partner, and those initially treated by a GP opted for SLNB more than others in this high-risk cohort. In addition patients living in outer regional/remote locations were more likely to undergo SLNB than those living in or close to major cities. These patients from more remote locations are typically diagnosed by a GP and then referred to a major centre / specialist managing melanoma, often a substantial distance away. This referral pattern, together with the required travel, may have resulted in the observed tendency for a higher number to undergo SLNB. Factors associated with decreased prevalence of SLNB on the other hand, were having a melanoma on the head or neck, or a melanoma lacking a common or clearly defined histological type. The sentinel node was positive in 15% and a positive result was associated with increasing melanoma thickness, ulceration of the primary melanoma and increasing T stage. There was no association between sentinel node positivity and patient's sex, age at diagnosis, relationship status, remoteness of residence, previous melanoma history or immediate family history, health service sector, speciality of initial treating doctor, diagnostic procedure, site of melanoma or histologic classification of the primary.

In the US, the records of 18,499 patients in the SEER database who were diagnosed with Stage 1b and 2 melanoma from 1998 to 2001 showed a 43% SLNB biopsy rate with 12% of patients having an elective regional node dissection [25]. At the time the authors felt the procedure had been "under used" with lower rates in the elderly, minority populations and primary lesions on the head and neck and trunk. (A later survey of the SEER database in the period 2004 to 2006, showed that 53% of eligible patients had a SLNB [27].) In a separate population-based study of 1242 patients with invasive melanoma in North Carolina between 1999 and 2001, 48% of

patients had a SLNB. As in most other studies including the present Queensland study, the procedure was more common in patients under 50 years and for melanoma on sites other than the head and neck. Indeed in relation to anatomical site, the decision to proceed to SLNB may be influenced by the potential for morbidity such as risk of injury to the facial nerve for head and neck lesions, and groin wound complications in lower limb sites. In contrast to the Queensland primary melanoma patients, those with thicker melanomas (T3/4) in North Carolina were more likely to have SLNB compared with T2 [15]. A lower rate of SLNB of 34% was reported in a population-based study of people with primary melanoma >1mm in North East of France in 2004 [16]. Variation in rates of SLNB was related to geographical region, distance from a major referral centre and local health care patterns. Additionally, we have previously shown that patients who elected to undergo SLNB reported significantly worse melanoma-specific symptoms compared with those who did not undergo the procedure [10]. Taken together, it appears that patients' perception of the seriousness of the disease (as influenced by age, personal and family history for example) and non-medical parameters play key roles in the decision to undergo a SLNB.

With the recent publication of the long-term (10 year) outcomes from the MSLT I trial [24], positive prognostic implications for the subgroup of patients with melanoma between 1.2 – 3.5 mm were confirmed with survival benefit from SLNB followed by completion lymph node dissection in the subset of patients who had a positive biopsy. Although debated, it has been suggested that there may be a survival benefit for 3-4 patients for every 100 patients within this thickness range that have the procedure [7]. It is clear there is no survival benefit for patients with a melanoma

greater than 3.5mm thick, although there is still prognostic information and early diagnosis for regional disease in patients with a positive biopsy [7]. Whether the long-term outcomes from the MSLT I trial influence SLNB trends will be worthy of assessment in the future. We also note that at present several therapies are being assessed in phase III trials for their efficacy in patients with stage 3 melanoma. The role and indication for SLNB is therefore likely to expand in the next few years and this will influence the number of patients with high risk primary melanoma who undergo SLNB.

In conclusion, diagnosis and management of primary cutaneous melanoma requires rational guidelines based on evidence. Our study provides detailed information about the variation in current practices in patients with melanoma at high risk of spread, suggesting the need for further evaluation of patient outcome according to diagnostic and staging methods. Patients should receive appropriate counselling about the role of sentinel lymph node biopsy and general counselling regarding prognosis and future management.

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TABLE I. Personal characteristics, diagnostic procedure and treatment of 787 patients with primary stage 1b, 2 melanoma

Variable	N*	%
Age at diagnosis		
<50	149	19
50 – 69	388	49
70 +	250	32
Age at diagnosis (mean ± sd)	62 (±14)	
Sex		
Female	340	43
Male	447	57
Location of residence		
Major city	450	57
Inner regional	224	28
Outer regional/remote	113	14
Site of melanoma		
Head or neck	167	21
Trunk	273	35
Upper limb	165	21
Lower limb	182	23
Education		
Junior school or less	324	41
Completed senior school/trade/diploma	307	39
Completed university/college degree	155	20
Relationship status		
No partner	199	25
Partner	586	75
Previous melanoma diagnosis		
No	587	77
Yes	177	23
First degree blood relatives with melanoma		
No	547	70
Yes	230	30
Diagnostic procedure		
Excision	580	74
Incision	4	1
Shave	111	14
Punch	92	12
Health service sector		
Public	351	45
Private	436	55
Initial treating doctor		
GP	478	61
GP at Skin cancer clinic	155	20
General surgeon	27	3
Plastic surgeon	41	5
Dermatologist	79	10
Other specialist	7	1

Follow-up surgery performed	766	97
Time (in days) from diagnosis to follow-up surgery (mean ± sd)	27 (± 21)	
Type of follow-up surgery performed		
WLE only	505	66
WLE + SLNB	261	34
Underwent additional WLE	32	4
Definitive treating doctor		
GP	58	8
GP at Skin cancer clinic	36	5
General surgeon	410	54
Plastic surgeon	246	32
Dermatologist	14	2
Other specialist	2	0.3

* For some characteristics, the summed total is less than the number of patients because of missing values.

TABLE II. Location of residence, health service sector, treating doctor, site and thickness of primary melanoma by diagnostic procedure, n=787

		Diagnostic Procedure			
	Total	Excision	Shave	Punch/Incision	p-value
Location of residence					
Major city	450	322 (72)	79 (18)	49 (11)	
Inner regional	224	165 (74)	24 (11)	35 (16)	
Outer regional/remote	113	93 (82)	8 (7)	12 (11)	0.007
Health service sector					
Public	351	277 (79)	33 (9)	41 (12)	
Private	436	303 (70)	78 (18)	55 (13)	0.002
Initial treating doctor					
GP	478	355 (74)	51 (11)	72 (15)	
GP at Skin cancer clinic	155	120 (77)	24 (15)	11 (7)	
Surgeon	68	58 (85)	4 (6)	6 (9)	
Dermatologist	79	42 (53)	31 (39)	6 (8)	
Other specialist/Unknown	7	5 (71)	1 (14)	1 (14)	<0.0001
Site of Melanoma					
Head and neck	167	114 (68)	21 (13)	32 (19)	
Trunk	273	206 (75)	46 (17)	21 (8)	
Upper limb	165	132 (80)	17 (10)	16 (10)	
Lower limb	182	128 (70)	27 (15)	27 (15)	0.005
Thickness, mm (mean±sd)*	785	2.2 (1.8)	1.1 (0.6)	1.9 (1.3)	<0.0001
Time (in days) from initial to follow-up surgery† (mean±sd)	766	29 (22)	17 (12)	25 (16)	<0.0001

*n=2 with missing thickness

†Calculated only for those who had follow-up surgery (n=766)

TABLE III. Personal characteristics, treating doctor, diagnostic procedure and histological characteristics of primary melanoma by sentinel lymph node biopsy

	Number*	SLNB		Crude		Adjusted†	
		n	%	PR (95% CI)	p-value	PR (95% CI)	p-value
Sex							
Female	340	114	34	1.00		1.00	
Male	447	147	33	0.98 (0.80, 1.20)	0.85	1.06 (0.88, 1.28)	0.54
Age							
<50 yrs	149	76	51	1.00		1.00	
50 – 69	388	145	37	0.73 (0.60, 0.90)		0.75 (0.61, 0.91)	
70+	250	40	16	0.31 (0.23, 0.43)	<0.0001	0.31 (0.23, 0.44)	<0.0001
Location of residence							
Major city	450	134	30	1.00		1.00	
Inner regional	224	71	32	1.06 (0.84, 1.35)		1.06 (0.85, 1.32)	
Outer reg'n/remote	113	56	50	1.66 (1.32, 2.10)	0.0004	1.41 (1.14, 1.74)	0.010
Relationship status							
No partner	199	53	27	1.00		1.00	
Partner	586	208	35	1.33 (1.03, 1.72)	0.020	1.25 (0.99, 1.58)	0.051
Previous melanoma							
No	587	218	37	1.00		1.00	
Yes	177	33	19	0.50 (0.36, 0.70)	<0.0001	0.65 (0.48, 0.90)	0.004
1st degree blood relatives with melanoma							
No	547	164	30	1.00		1.00	
Yes	230	95	41	1.38 (1.13, 1.68)	0.003	1.28 (1.07, 1.53)	0.010
Health service sector							
Public	351	126	36	1.00		1.00	
Private	436	135	31	0.86 (0.71, 1.05)	0.144	0.96 (0.80, 1.15)	0.65
Initial treating doctor							
GPs	633	218	34	1.00		1.00	
Others	154	43	28	0.81 (0.62, 1.07)	0.119	0.75 (0.59, 0.97)	0.019
Diagnostic procedure							
Excision	580	208	36	1.00		1.00	
Shave	111	31	28	0.78 (0.57, 1.07)		0.93 (0.70, 1.23)	
Punch / Incision	96	22	23	0.64 (0.44, 0.94)	0.017	0.68 (0.48, 0.98)	0.064

Site of melanoma							
Head or neck	167	29	17	1.00		1.00	
Trunk	273	114	42	2.40 (1.68, 3.44)		2.12 (1.50, 2.99)	
Upper limb	165	57	35	1.99 (1.34, 2.94)		2.00 (1.38, 2.90)	
Lower limb	182	61	34	1.93 (1.31, 2.85)	<0.0001	1.92 (1.31, 2.79)	<0.0001
Histology							
SSM	333	116	35	1.00		1.00	
Nodular	177	70	40	1.14 (0.90, 1.43)		1.00 (0.80, 1.25)	
LMM	27	4	15	0.43 (0.17, 1.06)		0.54 (0.22, 1.32)	
Desmoplastic	43	13	30	0.87 (0.54, 1.40)		0.71 (0.45, 1.14)	
Other[‡]	207	58	28	0.80 (0.62, 1.05)	0.027	0.76 (0.60, 0.96)	0.036
Breslow thickness							
T1: >0.0 – 1.0	206	36	17	1.00		1.00	
T2: >1.0 – 2.0	333	143	43	2.46 (1.78, 3.39)		2.30 (1.67, 3.15)	
T3: >2.0 – 4.0	177	64	36	2.07 (1.45, 2.95)		2.15 (1.51, 3.04)	
T4: >4.0	69	18	26	1.49 (0.91, 2.45)	<0.0001	1.63 (1.00, 2.68)	<0.0001
Ulceration							
Absent	593	185	31	1.00		1.00	
Present	194	76	39	1.26 (1.02, 1.55)	0.042	1.15 (0.95, 1.40)	0.162
T classification							
1b	206	36	17	1.00		1.00	
2a	258	109	42	2.42 (1.74, 3.36)		2.34 (1.70, 3.23)	
2b	75	34	45	2.59 (1.76, 3.82)		2.41 (1.66, 3.51)	
3a	119	40	34	1.92 (1.30, 2.84)		2.02 (1.38, 2.95)	
3b	58	24	41	2.37 (1.55, 3.63)		2.61 (1.75, 3.90)	
4a	29	5	17	0.99 (0.42, 2.31)		1.21 (0.52, 2.80)	
4b	40	13	33	1.86 (1.09, 3.18)	<0.0001	2.08 (1.25, 3.48)	<0.0001

* For some factors, the summed total is less than 787 because of missing values.

[†] Adjusted for age, sex, thickness and ulceration; T stage adjusted for age and sex only;

[‡] Includes n=142 unable to classify/not stated, n=31 naevoid, n=12 mixed, n=22 other

PR – prevalence ratio

95% CI – 95% confidence interval

Supplemental Table. Personal characteristics, treating doctor, diagnostic procedure and histological characteristics of primary melanoma by sentinel lymph node biopsy result, n=261

	Number*	Positive†		Crude		Adjusted‡	
	of SLNB	n	%	PR (95% CI)	p-value	PR (95% CI)	p-value
Sex							
Female	114	16	14	1.00		1.00	
Male	147	22	15	1.07 (0.59, 1.93)	0.83	1.14 (0.62, 2.10)	0.66
Age							
<50 yrs	76	15	20	1.00		1.00	
50 – 69	145	16	11	0.56 (0.29, 1.07)		0.55 (0.28, 1.05)	
70+	40	7	18	0.89 (0.39, 2.00)	0.190	0.85 (0.37, 1.95)	0.176
Relationship status							
No partner	53	8	15	1.00		1.00	
Partner	208	30	14	0.96 (0.47, 1.96)	0.90	0.93 (0.45, 1.91)	0.84
Previous melanoma							
No	218	31	14	1.00		1.00	
Yes	33	6	18	1.28 (0.58, 2.83)	0.56	1.33 (0.60, 2.96)	0.50
1st degree blood relatives with melanoma							
No	164	24	15	1.00		1.00	
Yes	95	14	15	1.01 (0.55, 1.85)	0.98	1.00 (0.54, 1.86)	0.99
Location of residence							
Major city	134	24	18	1.00		1.00	
Inner regional	71	8	11	0.63 (0.30, 1.33)		0.66 (0.31, 1.40)	
Outer reg/remote	56	6	11	0.60 (0.26, 1.38)	0.28	0.61 (0.26, 1.41)	0.34
Health service sector							
Public	126	23	18	1.00		1.00	
Private	135	15	11	0.61 (0.33, 1.11)	0.101	0.62 (0.34, 1.14)	0.119
Initial treating doctor							
GPs	218	33	15	1.00		1.00	
Others	43	5	12	0.77 (0.32, 1.86)	0.54	0.75 (0.31, 1.82)	0.51
Diagnostic procedure							
Excision	208	28	13	1.00		1.00	
Shave	31	6	19	1.44 (0.65, 3.19)		1.54 (0.69, 3.45)	
Punch / Incision	22	4	18	1.35 (0.52, 3.50)	0.62	1.41 (0.54, 3.66)	0.53

Site of melanoma							
Head or neck	29	4	14	1.00		1.00	
Trunk	114	19	17	1.21 (0.45, 3.28)		1.18 (0.43, 3.21)	
Upper limb	57	4	7	0.51 (0.14, 1.89)		0.52 (0.14, 1.93)	
Lower limb	61	11	18	1.31 (0.46, 3.76)	0.25	1.32 (0.46, 3.82)	0.29
Histology							
SSM	116	16	14	1.00		1.00	
Nodular	70	15	21	1.55 (0.82, 2.94)		1.59 (0.84, 3.02)	
LMM	4	0	0	—		—	
Desmoplastic	13	1	8	0.56 (0.08, 3.87)		0.55 (0.08, 3.83)	
Other	58	6	10	0.75 (0.31, 1.81)	0.27	0.77 (0.32, 1.85)	0.25
Breslow thickness							
T1: >0.0 – 1.0	36	1	3	1.00		1.00	
T2: >1.0 – 2.0	143	18	13	4.53 (0.63, 32.8)		4.59 (0.63, 33.3)	
T3: >2.0 – 4.0	64	15	23	8.44 (1.16, 61.3)		8.46 (1.16, 61.5)	
T4: >4.0	18	4	22	8.00 (0.96, 66.4)	0.006[§]	8.57 (1.02, 72.3)	0.005[§]
Ulceration							
Absent	185	19	10	1.00		1.00	
Present	76	19	25	2.43 (1.37, 4.34)	0.003	2.43 (1.37, 4.33)	0.003
T classification							
1b	36	1	3	1.00		1.00	
2a	109	10	9	3.30 (0.44, 24.9)		3.35 (0.44, 25.2)	
2b	34	8	24	8.47 (1.12, 64.2)		8.56 (1.13, 64.8)	
3a	40	8	20	7.20 (0.95, 54.8)		7.18 (0.94, 54.6)	
3b	24	7	29	10.50 (1.38, 80.0)		10.75 (1.41, 82.0)	
4a	5	0	0	—		—	
4b	13	4	31	11.08 (1.36, 90.2)	0.005	11.36 (1.37, 94.3)	0.005

* For some factors, the summed total is less than 261 because of missing values.

[†] Consists of n=15 and 1 females with 1 and 2 positive nodes, respectively; and n=18, 2 and 2 males with 1, 2 and 3 positive nodes, respectively

[‡] Adjusted for age and sex

[§] p-value for trend

PR – prevalence ratio

95% CI – 95% confidence interval