IN ATOPIC DERMATITIS,

EPISODIC CONTROL MAY NOT GET TO THE CORE OF THE PROBLEM

UNDERLYING, PERSISTENT INFLAMMATION IS A CAUSE OF LESIONS AND ITCH, THE PRIMARY SIGNS AND SYMPTOMS OF ATOPIC DERMATITIS[1-3]

Addressing the source of this inflammation may be key to keeping current and future disease signs and symptoms, including itch, at bay.[1,2]

Some patients may need strategies that manage the overall disease course of atopic dermatitis, instead of reacting only to episodic flares on the superficial layers.[4]

A proactive approach is warranted for management of the persistent inflammatory process, which, even if subclinical, is always present.[5]

SANOFI GENZYME

References: 1. Leung DYM, *et al. J Clin Invest*. 2004;113(5):651-657. **2.** Suárez-Fariñas M, *et al. J Allergy Clin Immunol*. 2011;127(4):954-964. **3.** Gittler JK, *et al. J Allergy Clin Immunol*. 2012;130(6):1344-1354. **4.** Bieber T. N *Engl J Med*. 2008:358(14):1483-1494. **5.** Wollenberg A, *et al. Dtsch Dermatol Ges*. 2009;7(2):117-121.

Sanofi-Aventis Australia Pty Ltd trading as Sanofi Genzyme ABN 31 008 558 807. Talavera Corporate Centre. Building D, 12-24 Talavera Road, Macquarie Park, NSW 2113. www.sanofi.com.au

Date of preparation November 2018. GZANZ.DUP.18.11.0311.

Australasian Journal of Dermatology

Australasian Journal of Dermatology (2019) ••, ••–•• doi: 10.1111/ajd.13004

ORIGINAL RESEARCH

Accuracy of partial biopsies in the management of cutaneous melanoma

Brent J Doolan[1,2] | Aaron J Robinson[1] | Rory Wolfe[3] | John W Kelly[2] | Catriona McLean[4] | Chris McCormack[1] | Michael A Henderson[1] | Yan Pan[1,2]

[1]Melanoma and Skin Service and Division of Cancer Surgery, Peter MacCallum Cancer Centre, [2]Victorian Melanoma Service, The Alfred Hospital, [3]Department of Epidemiology and Preventative Medicine, Monash University, and [4]Department of Anatomical Pathology, The Alfred Hospital, Melbourne, Victoria, Australia

ABSTRACT

Background: The recommended method for histopathological diagnosis of cutaneous melanoma is excisional biopsy, although partial biopsies (shave and punch) are often used. Following a partial biopsy, treatment guidelines recommend a narrow excisional biopsy to plan definitive management. There is limited evidence on the benefits of direct wide local excision (WLE) following diagnostic partial biopsies.

Methods: Retrospective cohort study of cutaneous melanoma cases, from two tertiary referral centres from January 2013 to December 2015. Demographic and histopathological data, including tumour thickness (T-stage) from initial biopsy and subsequent excisions, were collected. Logistic regression was used to examine histopathological T-staging between biopsy and subsequent excisions (upstaging).

Results: 2304 melanomas (2157 patients) were identified; 455 shave, 308 punch, 14 incisional and 1527 excisional biopsies. Out of 1527, 5 (<1%) excisional biopsies were upstaged from original biopsy T-stage to final WLE; compared to 28/455 (6%) for shave, 45/308 (15%) for punch and 2/14 (14%) for incisional biopsies. Histopathology upstaging were increased with punch (OR, 52.1; 95% CI, 20.5–132.4. $P < 0.001$) and shave biopsy (OR, 20.0; 95% CI, 7.7–52.0. $P < 0.001$) compared to excisional biopsy. Upstaging rates of 9.4% for desmoplastic (OR, 6.9; 95% CI, 2.4–19.7. $P < 0.001$) and 21.9% for acral lentiginous (OR, 18.4; 95% CI, 6.9–49.2. $P < 0.001$) melanomas were elevated compared to 1.4% for superficial spreading melanoma.

Conclusions: In most cases, partial biopsy (particularly shave biopsy) can provide sufficient information to plan for definitive surgical melanoma management. Punch and incisional biopsies have elevated upstaging rates, a consideration in planning therapy. Partial biopsies of desmoplastic or acral lentiginous melanomas have high rates of upstaging and should have a complete excision prior to definitive treatment.

Key words: Australia, biopsy, melanoma, shave, skin neoplasms, staging.

INTRODUCTION

Cutaneous melanoma was the 4th most commonly diagnosed cancer in Australia in 2012, and an estimated 14 000 new cases were diagnosed in 2017.[1] An accurate diagnosis is essential in planning surgical treatment. The current

Correspondence: Dr Brent J Doolan, Melanoma and Skin Service and Division of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne, Victoria 3050, Australia and Victorian Melanoma Service, The Alfred Hospital, Melbourne, Victoria 3000, Australia. Email: brentjamesdoolan@gmail.com

Brent J Doolan, BSc, MBBS. Aaron J Robinson, BBiotech (Hons.), MBBS, PhD. Rory Wolfe, BSc, PhD. John W Kelly, MBBS, PhD, FACD. Catriona McLean, MBBS, PhD, FRCPA. Chris McCormack, MBBS, FACD. Michael A Henderson, BMedSc, MBBS, MD, FRACS. Yan Pan, BMedSc, MBBS, FACD.

Financial and Material Support: None identified.

Previous Presentations: This study was presented in part at the 50th Annual Scientific Meeting of the Australasian College of Dermatologists; 6 May 2017; Sydney, Australia; at the 9th World Congress of Melanoma; 18 October 2017; Brisbane, Australia; at the American Academy Of Dermatology Annual Meeting; 18 February 2018; San Diego, United States of America; at the 51st Annual Scientific Meeting of the Australasian College of Dermatologists; 19 May 2018; Gold Coast, Australia.

Conflicts of Interest/Disclosures: The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication. There was no funding supplied from any source.

Submitted 9 November 2018; accepted 22 January 2019.

Australian clinical practice guidelines recommend complete excision biopsy with a narrow (2 mm) margin for definitive diagnosis of primary melanoma.[2] Partial biopsy techniques such as shave and punch biopsies are often used for the initial investigation, and different techniques have particular strengths and weaknesses.[3,4] Indications for partial biopsies include tumours too large to primarily excise, lesions on cosmetically sensitive areas or on certain sites where excision may be impractical such as the ear, palm, sole or distal digit.[3,5]

After diagnosis of a melanoma by partial biopsy, the current Australian clinical practice guidelines recommend a narrow excisional biopsy to plan definitive melanoma management.[2] The American Academy of Dermatology guidelines state that if a partial biopsy specimen is inadequate to make a histopathological diagnosis or accurately microstage for treatment planning, then a repeat biopsy should be performed prior to WLE.[6,7]

Current literature indicates wide variation in the accuracy of microstaging for partial biopsy (67–84%).[4,8–10] However, these studies were limited by many factors, including varying definition of partial biopsy (including deep and superficial shave), inclusion of curettage (tissue fragments) and lack of a pathology review panel.[4,8,9] The aim of the present study was to undertake a retrospective review of a large number of melanoma cases presenting to two tertiary melanoma units, to assess the accuracy of partial biopsies for microstaging. By establishing the accuracy of initial partial biopsy, we sought to determine whether information from partial biopsies was sufficient to justify progressing directly to definitive surgical management.

METHODS

The Peter MacCallum Cancer Centre and The Victorian Melanoma Service are the two major tertiary melanoma referral centres in the State of Victoria, Australia. A retrospective review of 2304 consecutive cases of new primary cutaneous melanoma from these centres was performed.

For each melanoma, information on patient age, gender, anatomical site and type of physician that performed the initial biopsy and biopsy type (shave, punch, incisional or excisional) were recorded. Biopsy definitions were derived from the clinical practice guidelines for the management of melanoma in Australia and New Zealand.[2] There was no distinction made between superficial and deep shave biopsy. Subungual melanomas and cutaneous metastases were excluded. Histopathological features including melanoma subtype, Breslow thickness (categorised into *in situ* (Tis), ≤1.0 mm (T1), >1.0–2.0 mm (T2), >2.0–4.0 mm (T3) and >4.0 mm (T4)), mitotic rate (per mm^2) and absence or presence of ulceration were recorded.

Data were also collected on the subsequent narrow excision and/or WLE for each case. Residual disease was defined as histopathological evidence of residual melanoma in the WLE. For shave biopsy-proven melanoma, base transection information was also collected. Microstaging accuracy was assessed based on comparison between the initial histopathological assessment of the biopsy (both partial and excisional) and the final histopathological result of the WLE. Staging definitions were derived from the 8th Edition: American Joint Committee on Cancer (AJCC) Staging Manual.[11]

Statistical analysis

Summary statistics are presented as median and interquartile range (IQR). Logistic regression was used to estimate odds ratios (OR) with a 95% confidence interval (CI) that describe the relationships between: (i) accuracy of microstaging and type of biopsy, (ii) tumour upstaging post-biopsy and melanoma subtype, and (iii) shave biopsy transection and operator subtype. These relationships were examined in univariable and multivariable models. Statistical significance was defined as $P < 0.05$. All analyses were performed using Stata Statistical Software: Release 15.0. College Station, TX: StataCorp LP.

RESULTS

Over the study period, 2521 patients were referred with a diagnosis of melanoma. There were a total of 2796 biopsies, and of these, 492 cases were excluded, as they did not meet the criteria for diagnosis of primary cutaneous melanoma after pathology review (Supplementary Fig. 1). Amongst the remaining 2304 biopsies (2157 patients), there were 455 (20%) shave biopsies, 308 (13%) punch biopsies, 14 (<1%) partial incisional biopsies and 1527 (66%) excisional biopsies. Patient demographics, clinicopathological characteristics and frequency and distribution by biopsy technique are presented in Table 1.

The median (IQR) Breslow thickness of melanomas biopsied by excision, incision, punch and shave biopsy was 1.2 (1.8) mm, 1.4 (3.2) mm, 1.2 (1.7) mm and 0.8 (1.1) mm, respectively. The depth of tissue removed at the initial biopsy varied by biopsy type. The median (IQR) depth for excision, incision, punch and shave biopsy was 5.0 (3.7) mm, 3.0 (3.0) mm, 3.0 (2.0) mm and 2.0 (2.0) mm, respectively. Whilst tumour thickness was similar across biopsy types, the depth of the tissue sample was more superficial for partial biopsies compared to excisional biopsies.

All biopsy types had a proportion of lesions that were upstaged upon completion of definitive WLE – 28/455 (6%) shave, 45/308 (15%) punch, 2/14 (14%) partial incisional and 5/1527 (0.003%) excisional biopsies. Amongst these upstaged melanomas, a proportion influenced subsequent management with 7/28 (25%) shave, 13/45 (29%) punch, 1/2 (50%) partial incisional and 3/5 (60%) excisional biopsies requiring a further surgical resection for adequate clearance margins. The rate of overall upstaging of biopsies post-WLE by operator type was 7% for surgeons, 5% for hospital, 4% for dermatologists and 3% for general practitioners, with no significant differences in upstaging between operators ($P = 0.07$).

The increased upstaging risks associated with punch and shave biopsies compared to excisional biopsies were consistent across the common sites (head and neck,

upper limb, chest/abdomen, back and lower limb; $P = 0.99$ for interaction of site and biopsy type). Odds of histopathologic upstaging are presented in Table 2. OR for the likelihood of upstaging following partial biopsy were higher for desmoplastic (OR 6.9) and acral lentiginous (OR 18.4) melanoma compared to superficial spreading melanoma.

There were 40/781 partial biopsies (14 shave, 25 punch and 1 incisional) that underwent a narrow excision prior to WLE. Of these biopsies, there were 0/10 (0%) shave and 4/18 (22%) punch biopsies that had upstaging from Tis/T1 (≤1.0 mm) to T2 (>1.0 mm) or greater and provided clinically important information in planning WLE. In comparison, for partial biopsies that proceeded directly to WLE there were 10/341 (3%) shave and 12/167 (7%) punch biopsies that showed clinically important upstaging from Tis/T1 to T2 or greater. A subanalysis of shave biopsies for invasive melanoma showed base transection in 58/120 (48.3%) of T1 melanomas, 41/58 (70.7%) of T2 melanomas, 27/30 (90.0%) of T3 melanomas and 8/9 (89.9%) of T4 melanomas. Furthermore, of those shave biopsies that did not have melanoma base transection, 5/214 (2.3%) had subsequent upstaging following definitive WLE.

DISCUSSION

Previous studies have established that Breslow thickness is the most important factor determining prognosis and treatment recommendations for localised cutaneous melanoma.[10,11] Tumour thickness is the primary factor that all national guidelines recommend to determine the margin at WLE and eligibility for sentinel lymph node biopsy (SLNB).[2,5] Partial biopsies are widely practiced, and clinicians are often faced with decisions for surgical management based on incomplete histopathological assessment. Therefore, this study aimed to assess the potential negative impact of proceeding directly to definitive surgery, rather than undertaking an intermediate step of complete excisional biopsy, prior to definitive surgical therapy.

Potential negative impacts by proceeding directly to definitive WLE include failure to perform SLNB and failure to undertake a sufficient excision margin at WLE, when these would have been indicated with full knowledge of tumour depth. Whilst, the latter can be retrieved in many cases from further excision, the SLNB can no longer be performed with the same level of accuracy.[12]

The recent evidence of prolonged disease-free survival and likely overall survival benefit from adjuvant therapy following a positive sentinel node biopsy,[13,14] as well as the commencement of adjuvant trials for stage II melanoma patients, have focused new attention on the importance of accurate assessment of tumour depth.[15] Studies have shown underestimation of tumour thickness from transection of the melanoma base with shave biopsies.[7,16] It has also been shown that tumour upstaging rates are higher for punch biopsy than for shave biopsy.

Our results demonstrated higher rates of upstaging for punch biopsy than shave biopsy, whether or not an intermediate excisional biopsy was undertaken prior to WLE. Therefore, given the high rates of punch biopsy upstaging, caution should be advised for interpretation of small tissue sample biopsies. In a prospective study ($n = 709$) by Mills and colleagues,[17] results comparable to the present study were found. About 23% of melanomas that underwent a punch biopsy for diagnosis prior to WLE were upstaged, compared to 8% of those that were diagnosed by shave biopsy.

It was noted by Ng and colleagues[18] that punch biopsy had an OR of 5.1 (95% CI, 3.4–7.6) and shave biopsy had an OR of 2.3 (95% CI, 1.5–3.6) of microstaging inaccuracy over excisional biopsy. We found an increased OR of 20.0 for shave biopsy and 52.1 for punch biopsy compared to initial excisional biopsy. These ratios were greater than those found by Ng and colleagues[18] and can be partly attributed to our low level of upstaging of excisional biopsy (0.33%) compared to a twofold upstaging for excisional biopsy (0.70%) in their study.

Our results also showed that there were only a small proportion of cases (3% shave and 7% of punch biopsies) that underwent clinically important upstaging from Tis/T1 to T2 or higher when proceeding from partial biopsy directly to WLE. It was also noteworthy that even though current guidelines recommend narrow excision prior to WLE for partial biopsy-proven cutaneous melanoma, only 2% of cases in our retrospective review followed this protocol.

As recommended by the National Comprehensive Cancer Network, the approach of performing an excisional biopsy, postpartial biopsy allows consideration and discussion of SLNB for patients with melanomas ≥0.8 to 1.0 mm with ulceration and mitosis or ≥1.0 mm.[5] According to current guidelines, in situations where a partial biopsy demonstrates a melanoma Breslow thickness >1.0 mm, the decision for SLNB will not be altered by further narrow excisional biopsy prior to definitive WLE.[3,11] Our data suggest that in clinical situations where partial biopsies (particularly shave) show melanoma subtypes other than desmoplastic or acral lentiginous melanoma, adequate information is available to proceed directly to WLE and in some cases SLNB, avoiding the need for the additional step of narrow excision prior to definitive wide local excision.

Possible limitations of this study include the use of institutional data sets with potential referral biases and its retrospective design. We noted that 199/413 (48.18%) of shave biopsies transected the melanoma base. Such transection may cause destruction of residual tumour through haemostatic procedures, inflammation and wound healing. Tumour destruction following base transection may have contributed to underestimation of tumour thickness and associated upstaging in this study.[7,17] A further limitation was our inability to determine the extent to which shave biopsies were attempts to completely remove tumour rather than to take a limited sample for diagnosis.

Our study provides evidence that in many clinical situations, partial biopsy alone may be sufficient to safely plan

Table 1 Patient, tumour and nodal characteristics, by biopsy technique for cutaneous melanoma

Characteristic	Total (n = 2304)	Biopsy type			
		Shave (n = 455)	Punch (n = 308)	Incisional (n = 14)	Excisional (n = 1527)
Gender					
Male	1261 (55%)	236 (52%)	145 (47%)	10 (71%)	870 (57%)
Female	1043 (45%)	219 (48%)	163 (53%)	4 (29%)	657 (43%)
Age (years)					
Mean ± SD	60.6 ± 15.8	63.8 ± 16.3	61.9 ± 16.6	70.9 ± 14.4	59.3 ± 15.4
Primary site					
Head and neck	616 (27%)	204 (45%)	111 (36%)	9 (64%)	292 (19%)
Upper extremity	548 (24%)	84 (18%)	52 (17%)	2 (14%)	410 (27%)
Chest/Abdomen	152 (7%)	22 (5%)	19 (6%)	0 (0%)	111 (7%)
Back	518 (22%)	68 (15%)	48 (16%)	0 (0%)	402 (26%)
Lower extremity	458 (20%)	75 (17%)	75 (24%)	3 (21%)	305 (20%)
Other	12 (1%)	2 (<1%)	3 (1%)	0 (0%)	7 (<1%)
Clinician performing biopsy					
General practitioner	1542 (67%)	216 (47%)	225 (73%)	10 (71%)	1091 (71%)
Dermatologist	400 (17%)	173 (38%)	47 (15%)	1 (7%)	179 (12%)
Surgeon	229 (10%)	24 (5%)	23 (8%)	1 (7%)	181 (12%)
Hospital	133 (6%)	42 (9%)	13 (4%)	2 (14%)	76 (5%)
Biopsy T-stage (mm)					
Tis (*In situ*)	663 (29%)	215 (47%)	95 (31%)	4 (29%)	349 (23%)
T1 (≤1.0)	721 (31%)	135 (29%)	89 (28%)	2 (14%)	495 (32%)
T2 (>1.0–2.0)	438 (19%)	61 (13%)	60 (19%)	5 (36%)	312 (20%)
T3 (>2.0–4.0)	315 (14%)	34 (7%)	44 (14%)	1 (7%)	236 (15%)
T4 (>4.0)	167 (7%)	10 (2%)	20 (6%)	2 (14%)	135 (9%)

SD, Standard deviation.

Table 2 Odds of histopathologic upstaging of melanoma following definitive surgery

Upstaging comparison	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Biopsy type				
Shave (n = 455) *vs* excisional (n = 1527)	20.0 (7.7–52.0)	<0.001	18.8 (6.9–51.7)	<0.001
Punch (n = 308) *vs* excisional	52.1 (20.5–132.4)	<0.001	43.3 (16.3–115.2)	<0.001
Incisional (n = 14) *vs* excisional	50.7 (8.9–287.7)	<0.001	41.3 (6.7–253.5)	<0.001
Melanoma subtype				
Desmoplastic melanoma (n = 25) *vs* SSM (n = 1003)	6.9 (2.4–19.7)	<0.001	4.5 (1.3–15.3)	0.015
ALM (n = 32) *vs* SSM	18.4 (6.9–49.2)	<0.001	3.2 (1.0–10.1)	0.05
Nodular melanoma (282) *vs* SSM	2.2 (0.94–5.1)	0.07	1.8 (0.7–4.5)	0.21
LMM (n = 140) *vs* SSM	1.9 (0.6–5.9)	0.25	0.9 (0.3–3.0)	0.87
Primary site				
Head & neck location (n = 616) *vs* back (n = 518)	4.4 (1.9–10.0)	<0.001	1.6 (0.6–4.0)	0.34
Upper extremity location (n = 548) *vs* back	1.4 (0.5–3.6)	0.54	1.1 (0.4–3.3)	0.81
Lower extremity location (n = 458) *vs* back	4.0 (1.7–9.5)	0.001	2.4 (0.9–6.4)	0.08
Age (years)				
50–69 (n = 181) *vs* <50 (n = 149)	2.3 (1.1–5.1)	0.03	2.8 (1.1–7.2)	0.03
>70 (n = 128) *vs* <50	3.9 (1.8–8.5)	<0.001	2.7 (1.1–6.9)	0.04
Shave biopsy with melanoma base transection (n = 199) *vs* shave biopsy with nontransection (n = 214)[†]	4.2 (1.5–11.5)	0.006		

[†]Not included in multivariable analysis as relevance only to partial biopsy. ALM, acral lentiginous melanoma; CI, confidence interval; LMM, lentigo maligna melanoma; OR, odds ratio; SSM, superficial spreading melanoma.

definitive melanoma management, with caution recommended for definitive surgical management of partial biopsy diagnosed desmoplastic or acral lentiginous melanoma. We noted that in only 3% of our cases, initial staging was significantly underestimated by shave biopsy, and in these cases, management was subsequently altered following histopathological findings from WLE. Given the higher upstaging rates of punch and incisional biopsies compared to shave biopsies, these techniques should be more scrutinised for T2 to T4 melanomas.

This study has implications in clinical practice in cases where there is sufficient diagnostic information from initial partial biopsy to justify proceeding directly to WLE, obviating the need for an intermediate narrow excisional biopsy.

This could provide a significant psychosocial and financial benefit for both patients and the medical tertiary referral service, by reducing additional procedures, potential complications and the cost to the healthcare system for theatre times and staffing.

ACKNOWLEDGEMENTS

Carlo Russo, BSc, provided collation of initial data sets from Peter MacCallum Cancer Centre. Karen Scott provided the preliminary comparative data set from The Alfred Hospital.

ETHICS

Ethics and governance were approved by Peter MacCallum Cancer Centre: Human Research Ethics Committee (LNR/17/PMCC/98) and The Alfred Hospital: Office of Ethics & Research Governance (LNRSSA/17/Alfred/184).

REFERENCES

1. Australian Government. *Cancer in Australia 2017: Cancer series no. 101*.
2. Australian Cancer Network. Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand: Evidence-Based Best Practice Guidelines. National Health and Medical Research Council. Wellington, New Zealand: New Zealand Guidelines Group, 2008.
3. Coit DG, Thompson JA, Algazi A *et al.* Melanoma, Version 2.2016. *J. Natl. Compr. Canc. Netw.* 2016; **14**: 450–73.
4. Cancer Council Australia Melanoma Guidelines Working Party. *Clinical practice guidelines for the diagnosis and management of melanoma*. Available from URL: https://wiki.cancer.org.au/australiawiki/index.php?oldid=186215. (Accessed 8 October 2018.)
5. Karimipour DJ, Schwartz JL, Wang TS *et al.* Microstaging accuracy after subtotal incisional biopsy of cutaneous melanoma. *J. Am. Acad. Dermatol.* 2005; **52**: 798–802.
6. Marsden JR, Newton-Bishop JA, Burrows L *et al.* Revised U.K. guidelines for the management of cutaneous melanoma 2010. *Br. J. Dermatol.* 2010; **163**: 238–56.
7. Bichakjian CK, Halpern AC, Johnson TM *et al.* Guidelines of care for the management of primary cutaneous melanoma. American Academy of Dermatology. *J. Am. Acad. Dermatol.* 2011; **65**: 1032–47.
8. Martin RC 2nd, Scoggins CR, Ross MI *et al.* Is incisional biopsy of melanoma harmful? *Am. J. Surg.* 2005; **190**: 913–7.
9. Pariser RJ, Divers A, Nassar A. The relationship between biopsy technique and uncertainty in the histopathologic diagnosis of melanoma. *Dermatol. Online J.* 1999; **5**: 4.
10. Ng PC, Barzilai DA, Ismail SA *et al.* Evaluating invasive cutaneous melanoma. *J. Am. Acad. Dermatol.* 2003; **48**: 420–4.
11. Amin MB, Edge S, Greene F *et al.* AJCC Cancer Staging Manual, 8th edn. New York, NY: Springer International Publishing, 2017.
12. Perissinotti A, Rietbergen DD, Vidal-Sicart S *et al.* Melanoma & nuclear medicine: new insights & advances. *Melanoma Manag.* 2018; **5**: MMT06.
13. Faries MB, Thompson JF, Cochran AJ *et al.* Completion dissection or observation for sentinel-node metastasis in melanoma. *N. Engl. J. Med.* 2017; **376**: 2211–22.
14. Eggermont AMM, Chiario-Sileni V, Grob JJ *et al.* Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. *N. Engl. J. Med.* 2016; **375**: 1845–55.
15. Van Zeijl MC, Van Den Eerwegh AJ, Haanen JB *et al.* (Neo)adjuvant systemic therapy for melanoma. *Eur. J. Surg. Oncol.* 2017; **43**: 534–43.
16. Tadiparthi S, Panchani S, Iqbal A. Biopsy for malignant melanoma – Are we following the guidelines? *Ann. R. Coll. Surg. Engl.* 2008; **90**: 322–5.
17. Mills JK, White I, Diggs B *et al.* Effect of biopsy type on outcomes in the treatment of primary cutaneous melanoma. *Am. J. Surg.* 2013; **205**: 585–90.
18. Ng JC, Swain S, Dowling JP *et al.* The impact of partial biopsy on histopathologic diagnosis of cutaneous melanoma. *Arch. Dermatol.* 2010; **146**: 234–9.

Supporting Information

Additional Supporting Information may be found online in Supporting Information:

Figure S1. Flow chart of included and excluded cases.