

Journal Pre-proof

Prognostic implications of biopsy with tumour transection for high-risk primary melanoma patients

Lena A. von Schuckmann, MBBS, MPH, Kiarash Khosrotehrani, MD, PhD, Maria Celia B Hughes, MMedSci, Jolieke C. van der Pols, PhD, Maryrose Malt, B.Bus, B Mark Smithers, MBBS, Adele C. Green, MBBS, PhD

PII: S0190-9622(20)30153-5

DOI: <https://doi.org/10.1016/j.jaad.2020.01.067>

Reference: YMJD 14201

To appear in: *Journal of the American Academy of Dermatology*

Received Date: 12 September 2019

Revised Date: 21 January 2020

Accepted Date: 29 January 2020

Please cite this article as: von Schuckmann LA, Khosrotehrani K, Celia B Hughes M, van der Pols JC, Malt M, Smithers BM, Green AC, Prognostic implications of biopsy with tumour transection for high-risk primary melanoma patients, *Journal of the American Academy of Dermatology* (2020), doi: <https://doi.org/10.1016/j.jaad.2020.01.067>.

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1 **Article type:** Research letter

2 **Title:** Prognostic implications of biopsy with tumour transection for high-risk primary
3 melanoma patients

4 Lena A von Schuckmann, MBBS, MPH^{1,2}, Kiarash Khosrotehrani, MD, PhD^{3,4}, Maria Celia B Hughes,
5 MMedSci¹, Jolieke C van der Pols, PhD⁵, Maryrose Malt, B.Bus¹, B Mark Smithers MBBS⁶, Adele C
6 Green, MBBS, PhD^{1,7}

7 1. *Population Health Department, QIMR Berghofer Medical Research Institute, Australia*

8 2. *School of Public Health, The University of Queensland, Australia*

9 3. *Experimental dermatology group, The University of Queensland Diamantina Institute, Translational
10 research institute, Brisbane, Australia*

11 4. *Department of Dermatology, Princess Alexandra Hospital, Brisbane, Australia*

12 5. *School of Exercise and Nutrition Sciences, Queensland University of Technology, Australia*

13 6. *Queensland Melanoma Project, Princess Alexandra Hospital, The University of Queensland, Australia*

14 7. *CRUK Manchester and Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK*

15

16 **Corresponding author:**

17 Lena von Schuckmann

18 QIMR Berghofer Institute of Medical Research, 300 Herston Road, 4006 Herston, Australia

19 Phone +61 7 3362 3226, Fax +61 7 3845 3502

20 Email: lena.vonschuckmann@uqconnect.edu.au

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22 **Funding:** The study is supported by NHMRC Program Grants 1073898 and 552429. LAVs is funded by

23 NHMRC Postgraduate Scholarship 1133317 and KK is funded by a NHMRC Career Development

24 Fellowship. The funding body played no role in study design; in the collection, analysis and

25 interpretation of data; in the writing of the report; or in the decision to submit the article for
26 publication.

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28 **Word count (main text): 500**

29 **Number of references: 5**

30 **Number of tables: 2**

31

32 **Conflicts of interest: None.**

33 **Abbreviations:**

34 CI- confidence interval

35 HR- hazard ratio

36 OR- odds ratio

37 SLNB- sentinel lymph node biopsy

38 Introduction

39 Excisional biopsies with narrow margins are optimal for histopathological diagnosis of
40 melanoma. However, many clinicians have adopted quicker and cheaper partial biopsy
41 techniques that have high rates of tumor transection and staging inaccuracies. Another
42 potential concern is disease spread by direct displacement of tumor cells or modifying the
43 microenvironment during wound healing to favor metastasis.

44 We used data from a prospective study of patients diagnosed with high-risk primary
45 melanoma to examine whether tumor transection in biopsy specimens increased melanoma
46 recurrence.

47

48 Methods

49 We prospectively recruited patients with tumor-stage T1b to T4b melanoma between 2010
50 and 2014 in Queensland, Australia, and examined the associations between tumor
51 transection during biopsy with sentinel lymph node biopsy (SLNB) positivity and melanoma
52 recurrence using logistic regression and proportional-hazard regression analyses
53 respectively (methods determined *a priori*). Those with no recurrence, and those who died
54 within 3 years before a recurrence occurred (n=10) were censored at 36 months or date of
55 death respectively. We assessed confounding by patient and tumor characteristics and
56 adjusted the final model for age, sex, thickness, ulceration, mitotic rate, site of primary and
57 melanoma subtype. Proportionality was assessed using time-dependent covariates.

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60 Results

61 Of 700 participants with T1b to T4b melanoma (59% male; mean age 62), 119 (13%) patients
62 developed a recurrence within 3 years of diagnosis, during 22562.54 person-months of
63 follow-up. Base transection was associated with shave biopsies and tumour thickness >2mm
64 in univariate analyses ($p < 0.01$) (Table 1). After final model adjustment, patients with any
65 primary tumour transection did not have an increased risk of melanoma recurrence (HR_{adj}
66 1.28, 95% CI 0.85-1.93), nor when only tumour base or only lateral margin was transected
67 (Table 2). Amongst patients who had a SLNB procedure ($n=258$), those with transected
68 tumours had higher likelihood of positive SLNB (OR_{adj} 2.31, 95% CI 1.01-5.29).

69

70 Discussion

71 Our study of 700 patients with high-risk primary melanoma indicated that partial biopsy was
72 not associated with melanoma recurrence. Whilst we observed an association between
73 transected biopsies and SLNB positivity, the relationship may, at least in part, be explained
74 by the strong correlation with tumour thickness and SLNB micrometastases.

75 A small number of retrospective clinical studies have shown an increased risk of recurrence
76 and/or poorer survival with incisional biopsies, yet these were limited by their retrospective
77 design, lack of histopathological (thickness) information and small sample size. Evidence
78 supporting the safety of partial biopsies is limited by retrospective designs, exclusion of
79 shave biopsy results, lack of information of margin involvement, small samples¹⁻³, limited
80 follow-up⁴, and potential confounding³⁻⁵.

81 Study strengths were prospective design and detailed clinical documentation. Limitations
82 were lack of information regarding biopsy intent (shave excision vs shave biopsy), lower
83 SLNBs of head and neck melanoma, and relatively short follow-up. Larger and more
84 problematic lesions may have been selected for partial biopsy leading to biased results that
85 reflected lesion characteristics as well as biopsy technique.

86 In summary, all published results to date (including these) have inherent limitations and we
87 call for high-quality evidence before confident acceptance of the safety of partial biopsies.

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108 **Table I.** Patient, clinical and tumour characteristics and their association with tumour transection of
 109 initial biopsy

	Total N=700	Clear margins 410 (59%) N (%)	Deep transection 142 (20%) N (%)	Lateral transection 148 (21%) N (%)	P-value
Patient factors					
Age					
< 65	360 (51)	240 (59)	57 (40)	63 (43)	0.003
≥65	340 (49)	170 (42)	85 (60)	85 (57)	
Sex					0.19
Male	410 (59)	248 (60)	85 (60)	77 (52)	
Female	290 (41)	162 (40)	57 (40)	71 (48)	
Previous melanoma					0.01
No	563 (82)	342 (84)	103 (74)	118 (80)	
Yes	137 (20)	68 (16)	39 (26)	30 (20)	
Clinical factors					
Diagnostic biopsy					<0.0001
Excision	485 (69)	384 (94)	22 (16)	79 (54)	
Shave	110 (16)	16 (4)	83 (58)	11 (7)	
Punch/ incision	105 (15)	10 (2)	37 (26)	58 (39)	
Initial treating Dr					0.04
GP	568 (82)	338 (83)	106 (75)	124 (84)	
Surgeon	65 (9)	38 (9)	14 (10)	13 (9)	
Dermatologist	62 (9)	30 (8)	22 (15)	10 (7)	
Time from dx to surgery					<0.0001
Mean (days)	27 (± 20)	29 (±20)	23 (± 16)	27 (±16)	
SLNB					0.04
No	442 (62)	245 (60)	101 (71)	96 (65)	
Yes	258 (38)	165 (40)	41 (29)	52 (35)	
SLNB result					0.17
Negative	220 (85)	143 (87)	32 (78)	45 (87)	
Positive	38 (15)	22 (13)	9 (22)	7 (13)	
Tumour factors					
Thickness (mm)					0.04
≤2	433 (62)	257 (63)	76 (53)	100 (68)	
>2	267 (38)	153 (37)	66 (47)	48 (32)	
Ulceration					0.38
No	504 (72)	299 (73)	96 (68)	109 (74)	
Yes	196 (28)	111 (27)	46 (32)	39 (26)	
Mitosis (no./mm ²)					0.48
<1	96 (14)	63 (15)	16 (11)	17 (11)	
1-3	302 (43)	175 (43)	58 (41)	69 (47)	
>3	302 (43)	172 (42)	68 (48)	62 (42)	
Site of melanoma					<0.0001
Trunk	247 (35)	168 (41)	38 (27)	41 (28)	
Head/neck	154 (22)	70 (17)	48 (34)	36 (24)	
Upper limb	143 (20)	90 (22)	21 (15)	32 (22)	
Lower limb	156 (22)	82 (20)	35 (25)	39 (26)	
Subtype					<0.0001
SSM	278 (40)	172 (42)	32 (23)	74 (50)	
Nodular	172 (24)	122 (30)	35 (25)	15 (10)	
Other	118 (17)	51 (12)	42 (30)	25 (17)	
Not classified	132 (19)	65 (16)	33 (23)	34 (23)	

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111 **Table II.** Risk of melanoma recurrence in relation to tumour transection of biopsy specimen

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	No recurrence	Recurrence	Adjusted ¹ HR (95% CI)
Clear	353 (61)	57 (48)	1.00
Deep +/- lateral	103 (18)	39 (33)	1.45 (0.91-2.30)
Lateral only	125 (21)	23 (19)	1.10 (0.66-1.83)
Any margin	228 (39)	62 (52)	1.28 (0.85-1.92)
	SLNB negative	SLNB positive	Adjusted ¹ OR (95% CI)
Clear	143 (65)	22 (58)	1.00
Any margin	77 (35)	16 (42)	2.31 (1.01-5.29)

120 **Adjusted for age, sex, thickness, ulceration, mitoses, site and subtype**