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Title: Melanoma staging: Varying precision and terminal digit clustering in Breslow thickness data is evident in a population based study

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Abbreviations used:

AJCC:	American Joint Committee of Cancer
ALM:	acral lentiginous melanoma
CM:	cutaneous melanoma
CRN:	Cancer Registry of Norway
ICDO-3:	International Classification of Diseases for Oncology, Third Edition
LMM:	lentigo maligna melanoma
NM:	nodular melanoma
NMMR:	Norwegian Malignant Melanoma Registry
NOS:	melanoma unspecified
SEER:	Surveillance, Epidemiology and End Results
SSM:	superficial spreading melanoma
TNM:	tumour, node, metastasis

Abstract

Background: Errors in Breslow thickness reporting can give misclassification of T category, an important classifier in melanoma staging.

Objective: Investigate precision (number of digits) and terminal digit clustering in Breslow thickness, and potential consequences for T category.

Methods: All first primary invasive melanomas in Norway, 2008–2015, were included. A smoothing model was fitted to estimate the underlying Breslow thickness distribution without digit clustering.

Results: Thickness was reported for 13 057 (97.5%) patients, median 1.0 mm (range 0.09–85). It was reported as whole numbers (15.6%), to one decimal (78.2%) and two decimal places (6.2%); thin tumours with more precision than thicker. Terminal digit clustering was found with marked peaks in the observed frequency distribution for terminal digits 0 and 5, and with drops around these peaks. Terminal digit clustering increased proportions of patients classified with T1 and T4 tumours and decreased proportions classified with T2 and T3.

Limitations: 2.5% missing.

Conclusions: Norwegian recommendation of measurement to the nearest 0.1 mm was not followed. Terminal digit clustering was marked, with consequences for T category. Pathologists, clinicians and epidemiologists should know that clustering of thickness data around T-category cut-points can impact melanoma staging with consequent effect on patient management and prognosis.

Capsule summary

- Terminal digit preference with abnormal clustering of Breslow thickness data has been reported from Australia.
- Measurement precision varied and terminal digit bias was evident.
- Pathologists, clinicians and epidemiologists should take into account that clustering around T-category cut-points can impact melanoma staging with consequent effect on patient management and prognosis.

Background

Vertical tumour (Breslow) thickness is the cornerstone for classifying cutaneous melanoma (CM) and the most important prognostic factor for clinically localized primary CM.[1,2] Prior editions of the American Joint Committee of Cancer (AJCC) tumour staging manual implied thickness measurements recorded to the nearest 0.01 mm, while the new 8th edition explicitly stated recording to the nearest 0.1 mm.[3] Recently Ge et al. pointed on imprecision in Breslow thickness measurements and the phenomenon of terminal digit bias as a reason for abnormal clustering in Australian thickness data.[4] Moreover, substantial numbers of thin CMs with terminal digits 0 and 5 were found in a recent Surveillance, Epidemiology and End Results (SEER) Registry study.[5] Overrepresentation of certain numbers due to strong preference is not a new phenomenon in pathology[6,7] or other areas of medicine.[8-10] Yet, except for the Australian study,[4] this kind of observer error has not been investigated for CM.

Breslow thickness is the primary determinant of T category in the AJCC tumour, node, metastasis (TNM) staging system.[11] T category forms basis for assessment of CM status at the specific time, estimates of prognosis, recommendations for minimal excision margins, whether sentinel node dissection is routinely offered and frequency and extent of follow-up examinations[2,12] Imprecision in reporting of Breslow thickness will have significant impact on patient management.

Breslow thickness has been recorded on a national basis in Norway since 2008, and national guidelines have advised thickness reported in mm to 1 decimal point.[13] The aim of this study was to investigate precision (i.e. the reported number of digits after the decimal point) and occurrence of terminal digit clustering in Breslow thickness of primary CMs diagnosed in 2008–2015, and to estimate the underlying Breslow thickness density distribution to quantify potential misclassification of T category.

Material and methods

Data sources

The Cancer Registry of Norway (CRN) has recorded all cancer diagnoses nationwide since 1953. The Norwegian Malignant Melanoma Registry (NMMR) was established under the CRN in 2008, adding Breslow thickness and other histopathological and clinical information to each CM case. We included all patients diagnosed with a first primary invasive CM in Norway in 2008–2015 and with Breslow thickness recorded in the NMMR.

Extracting data from cancer specific registries and working with de-identified data is regulated by the law of health registries. No further ethical approval is needed to describe these data.

Variables

Norwegian guidelines (2008–2015) advised thickness measured (in mm) on histological haematoxylin and eosin stained sections (preferably by micrometer equipped microscope), reported to 1 decimal point.[13] It was assessed by the vertical distance from the granular layer of the epidermis (or if the surface is ulcerated, from the base of the ulcer) to the deepest dermal (invasive) tumour cell. Thickness is recorded in the NMMR with the same number of digits as in the pathologist report. We categorized Breslow thickness in T category according to the AJCC staging manuals in 2008-2015. The 6th (2001-2009) and 7th (2010-2017) editions both used T1 (≤1.0 mm), T2 (1.01–2.0 mm), T3 (2.01–4.0 mm) and T4 (>4.0 mm).[11]

We categorized age (<50, 50–69 and ≥70 years) and residential municipality at the time of diagnosis (South-Eastern, Western, Central and Northern Norway Health Authority). The International Classification of Diseases for Oncology, Third Edition (ICDO-3)[14] was used to categorize primary tumour localization (head/neck (190.0), trunk (190.1/190.7), upper extremity (190.2), lower extremity (190.3/190.4), other (190.5/190.6/190.8) and skin

unspecified (190.9)) and morphological subtype (superficial spreading melanoma (SSM) (M87433), nodular melanoma (NM) (M87213), lentigo maligna melanoma (LMM) (M87423), acral lentiginous melanoma (ALM) (M87443), melanoma unspecified (NOS) (M87203) or other (M87403/M87223/M87303/M87453/M87703/M87713/M87723/M87803)). Ulceration (yes/no) is also recorded in the NMMR.

Statistical analysis

Descriptive results are presented as medians (minimum–maximum or 25^{th}–75^{th} percentiles), frequencies (%) and histograms of frequency distributions. Patients were grouped according to the number of digits after the decimal point of Breslow thickness reported to the NMMR (0, 1 or 2 digits). One-way analysis of variance was used to test differences in Breslow thickness ($\log_e$ transformed) between the three groups, and chi-squared test to test differences in other characteristics.

To study T-category misclassification, we estimated the underlying density distribution of Breslow thickness by the Wang method[15,16] (using generalized lambda distribution, bin size 0.1 mm; R package bda, version 5.1.6.[17]) assuming no systematic measurement bias. This method of smoothing the observed distribution was recently used to study terminal digit preference bias in colorectal polyp size measurements.[7] The Breslow thickness distribution is highly skewed to the right, with few observations in the long tail. Thus we performed the method on two limited intervals, CMs≤10 mm and CMs≤5 mm, to illustrate the uncertainty of the results. CMs reported with 2 digits after the decimal place were excluded (since mainly used for thin CMs). Expected numbers and difference between observed and expected numbers were estimated for each T category.

We explored the Breslow thickness frequency distribution stratified by ulceration, since thickness may be underestimated in ulcerated lesions.[1]

Results

In 2008–2015, 13 386 Norwegians were diagnosed with a first primary invasive CM. Mean age at diagnosis was 62.8 years (range 2–98 years). Breslow thickness was recorded for 13 057 (97.5%) of these patients (6470 men and 6587 women) with a median of 1.0 mm (range 0.09–85 mm). Thickness was reported to 1 decimal place for 10 211 of the patients (78.2%; range 0.1–25.5 mm), but also as whole numbers (n=2032, 15.6%; range 1–85 mm) and with 2 digits after the decimal point (n=814, 6.2%; range 0.09–11.01 mm).

Thin tumours were reported with more precision than thicker (Table I, $p<0.001$). Whole number reporting decreased by calendar year in parallel with increased reporting with 1 (and 2) digits after the decimal point ($p<0.001$). Whole numbers were more frequent in men than women, in older patients, in the Central Norway Health Authority, for head/neck and 'other' localization, for nodular NMs and 'other' morphology, for T4s and for ulcerated CMs and CMs with no information on ulceration ($p<0.001$ for all) (Table I).

Figure 1 shows the distribution of Breslow thickness for tumours ≤10 mm in the total population and in the subsamples with 0, 1 and 2 digits after the decimal point, and displays high frequencies of the values 1.0, 2.0,…, 10.0 mm and 0.5, 1.5,…, 9.5 mm. Around the peaks, drops are found for thicknesses ending in 1, 4, 6 and 9. Figure 2 focuses on the distribution in the interval 0–1.5 mm, displaying high frequencies of the terminal digit 5, especially among those reported with 2 digits after the decimal point (Fig 2D). Figures 3A and 3B show histograms of the terminal digits when thickness was reported with 1 and 2 digits after the decimal point, respectively, in the total sample. Five was the dominating terminal digit, and the terminal digit 1 was reported in lower frequencies than other terminal digits. A corresponding drop in frequency was seen for the terminal digit 9 when thickness was reported to 1 decimal place (Fig 3A).

198 The use of the terminal digits 0 and 5 increased with increasing thickness. In the
199 intervals 0.3–0.7 and 0.8–1.2, 27–28% were reported as 0.5 and 1.0, respectively, while 69.2%
200 were 9.5 in the interval 9.3–9.7 and 97.4% were 10.0 in the interval 9.8–10.2 (Supplementary
201 Table I).
202 Table II shows the results of fitting the smoothing model to Breslow thickness data of
203 CMs≤10 mm and CMs≤5mm. Terminal digit clustering increased the proportion of patients
204 classified with T1 and T4 tumours and decreased the proportions classified with T2 and T3.
205 Clustering at 0.5 mm intervals was evident both in absence and presence of ulceration
206 (Fig 4; tumours ≤10 mm). Ulcerated lesions were generally thicker (median (25^{th}–75^{th}
207 percentile): 0.9 (0.6–1.5) for non-ulcerated and 3.4 (2.0–6.0) for ulcerated).
208
209

Discussion

In this national study of Breslow thickness data, thin tumours were reported with more precision than thicker tumours. Reporting of thickness to the nearest 0.1 mm increased by calendar year. Terminal digit clustering was found with marked peaks in the observed frequency distribution for terminal digits 0 and 5, and with drops around these peaks. Smoothing of the observed Breslow thickness distribution demonstrated that terminal digit clustering increased proportions of tumours classified as T1 and T4, and decreased proportions of T2 and T3. Clustering at 0.5 mm intervals was evident both in absence and presence of ulceration.

In this large dataset, all p-values were <0.001 when comparing characteristics of patients categorised according to the number of digits after the decimal point in reported thickness. Reporting with more precision in thin tumours is likely why precision was lower in men versus women (larger proportions of CMs are diagnosed in an advanced stage in Norwegian men than women[18]), at older age (delayed diagnosis, comorbidity[19]), in head/neck CMs,[20] in NMs versus SSMs, in T4s versus T1s and in ulcerated vs non-ulcerated CMs.

Norwegian guidelines in the period of our data explicitly advised reporting in mm to 1 decimal point,[13] and was followed for 78.2% of the lesions. The lower bars for lesions with terminal digit 0 as compared to terminal digit 5 in lesions reported with 1 or 2 digits after the decimal point (Figs. 1C–D, 2C–D and 3A–B) demonstrated that less digits were reported when the terminal digit was 0. Importantly, the 8th edition of the AJCC staging system described the convention for rounding decimal values and stated recording to the nearest 0.1 mm, and not 0.01 mm, because of measurement impracticality and imprecision.[21]

Substantial clustering at 0.5 mm intervals is likely due to preferences in reporting. Our findings are in line with the findings from two Australian registries (2003–2013), where no biological plausible basis was found for the clustering.[4] We know of no specific events in the

past that may have resulted in a frequency distribution with such clear peaks. When the Australian group re-measured 125 invasive CMs (diagnosed in 1993–2013) with a reported thickness of 0.9–1.1 mm, the clustering at 0.9, 1.0 and 1.1 mm disappeared.[4] Thus, a smooth true distribution is reasonable. The drops found in our data for thicknesses ending in 1, 4, 6 and 9 support the conclusion that the peaks at 0.5 mm intervals include misclassified cases from the neighbouring values. Terminal digit preference was reported previously for a variety of measurements.[6-10,22-24]

Smoothing of the observed frequency distribution cannot accurately model the true underlying distribution, and gives misclassification on the group level and not for each specific patient. The estimated distribution (and thereby the expected number in each T category) will depend on the choice of statistical method. Unfortunately, statistical methods for estimating terminal digit preference are relatively under-developed.[7] The long tail of the distribution is challenging and the choice of interval length may influence the results. Therefore, we applied the smoothing to CMs ≤10 mm and ≤5 mm, with similar conclusions. In the latter case, the long tail was less captured giving a larger difference between observed and expected for T4 tumours than when truncated at 10 mm.

Fitting a smoothing model to the data demonstrated important alterations of staging, consistent with the Australian finding: The number of CMs classified as T1 was too high and the number of T2s too low.[4] Moreover, we found that the number of T4s was too high and the number of T3s too low. Clinical implications, even of errors of 0.1 mm, may be significant. Tumour thickness is an important predictor in prognostic tools used to individualize prognostication and facilitate clinical decision making.[26] Thickness forms basis for primary treatment (minimal excision margins, sentinel node dissection), frequency and extent of follow-up examinations and responsibility during follow-up (dermatologist or general

practitioner).[2,12,13] Finally, T category is used to study the importance of prognostic factors and stage specific survival.[5,27,28]

Thickness may be underestimated in ulcerated lesions.[1] Clustering at 0.5 mm intervals was evident both in the absence and presence of ulceration. Ulceration was not addressed in the Australian study.[4]

Mandatory reporting from independent sources (hospitals, laboratories, general practitioners and the Cause of Death Registry) to the CRN ensures completeness and high quality data.[18] After 2000, >99% of all CM cases are morphologically verified.[18,29] Missing in Breslow thickness (2.5%) was less than e.g. reported from SEER (9%, 2004-2008).[30] Lack of information may result from incomplete diagnostic procedures in cases with thick tumours.

In summary, the national guideline of reporting Breslow thickness to one decimal point was followed for 78% of CMs. Our findings elucidate the need of more detailed guidelines of precision in reporting, as outlined in the new AJCC staging manual.[21] The results add materially to the very limited evidence that terminal digit preference is an under-recognized source of error leading to over- or underestimation of actual Breslow thickness. The observed frequent reports of 1.0, 2.0 and 4.0 mm have consequences for T categorization and thereby the communication of CM stage and prognosis at the specific time and for patient management. These observations are important for pathologists, clinicians and epidemiologists.

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Figure legends

Figure 1. Breslow thickness ≤10 mm in Norwegian melanoma patients diagnosed in 2008–2015. (A) All, n=12 809; (B) Reported as whole numbers, n=1823; (C) Reported with 1 digit after the decimal point, n=10 173; (D) Reported with 2 digits after the decimal point, n=813.

Figure 2. Breslow thickness ≤1.5 mm in Norwegian melanoma patients diagnosed in 2008–2015. (A) All, n=8590; (B) Reported as whole numbers, n=506; (C) Reported with 1 digit after the decimal point, n=7352; (D) Reported with 2 digits after the decimal point, n=732.

Figure 3. Terminal digits of Breslow thickness in Norwegian melanoma patients diagnosed in 2008–2015. (A) Reported with 1 digit after the decimal point, n=10 211, (B) Reported with 2 digits after the decimal point, n=814.

Figure 4. Breslow thickness ≤10 mm in Norwegian melanoma patients diagnosed in 2008–2015 stratified by ulceration. (A) No, n=7333; (B) Yes, n=2068; (C) Unspecified, n=3408.

[Figures 1 and 2 each have 4 parts and we expect these are 2 column fitting images. Figures 3 (2 parts) and 4 (3 parts) can be presented in one column if preferred.]

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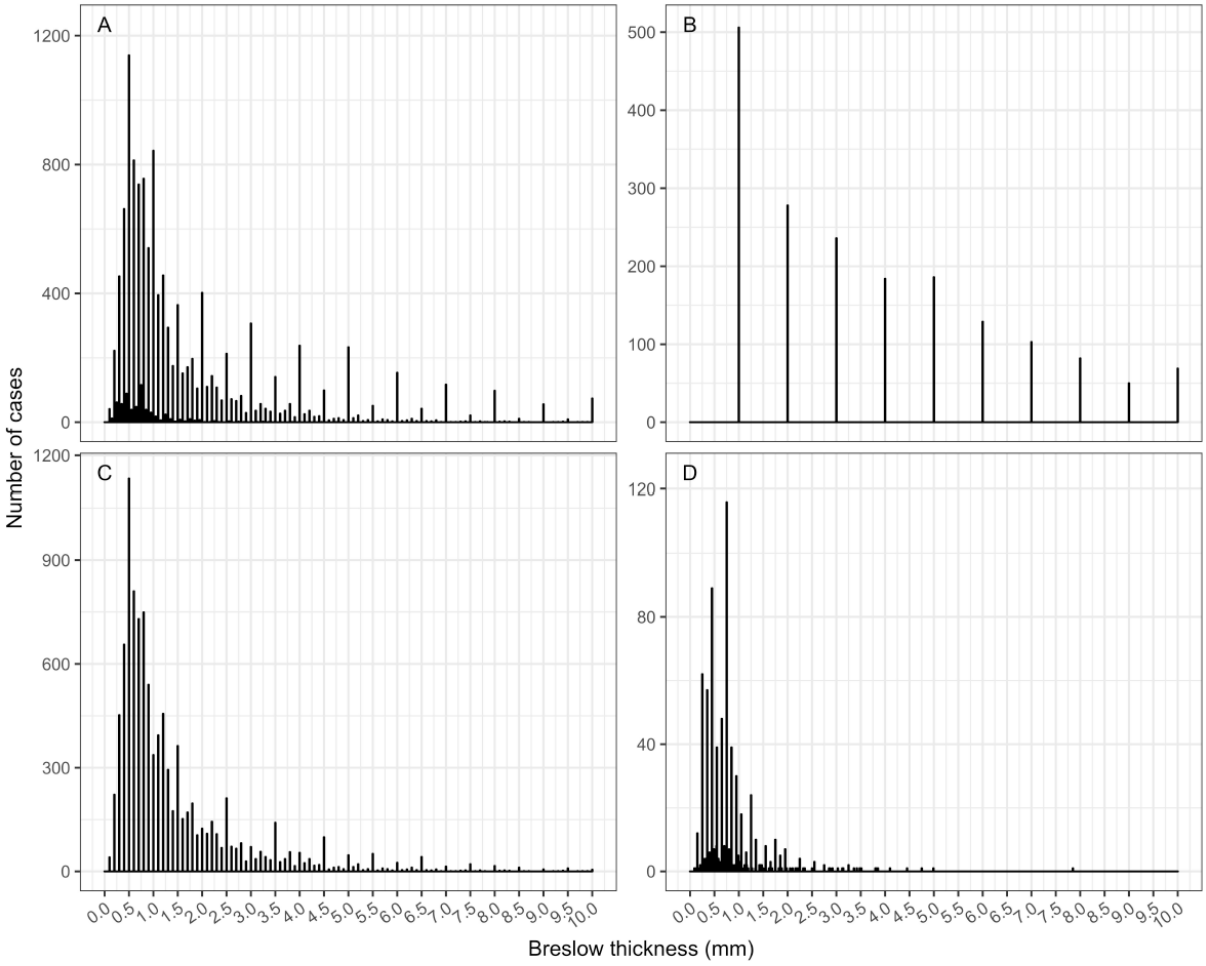

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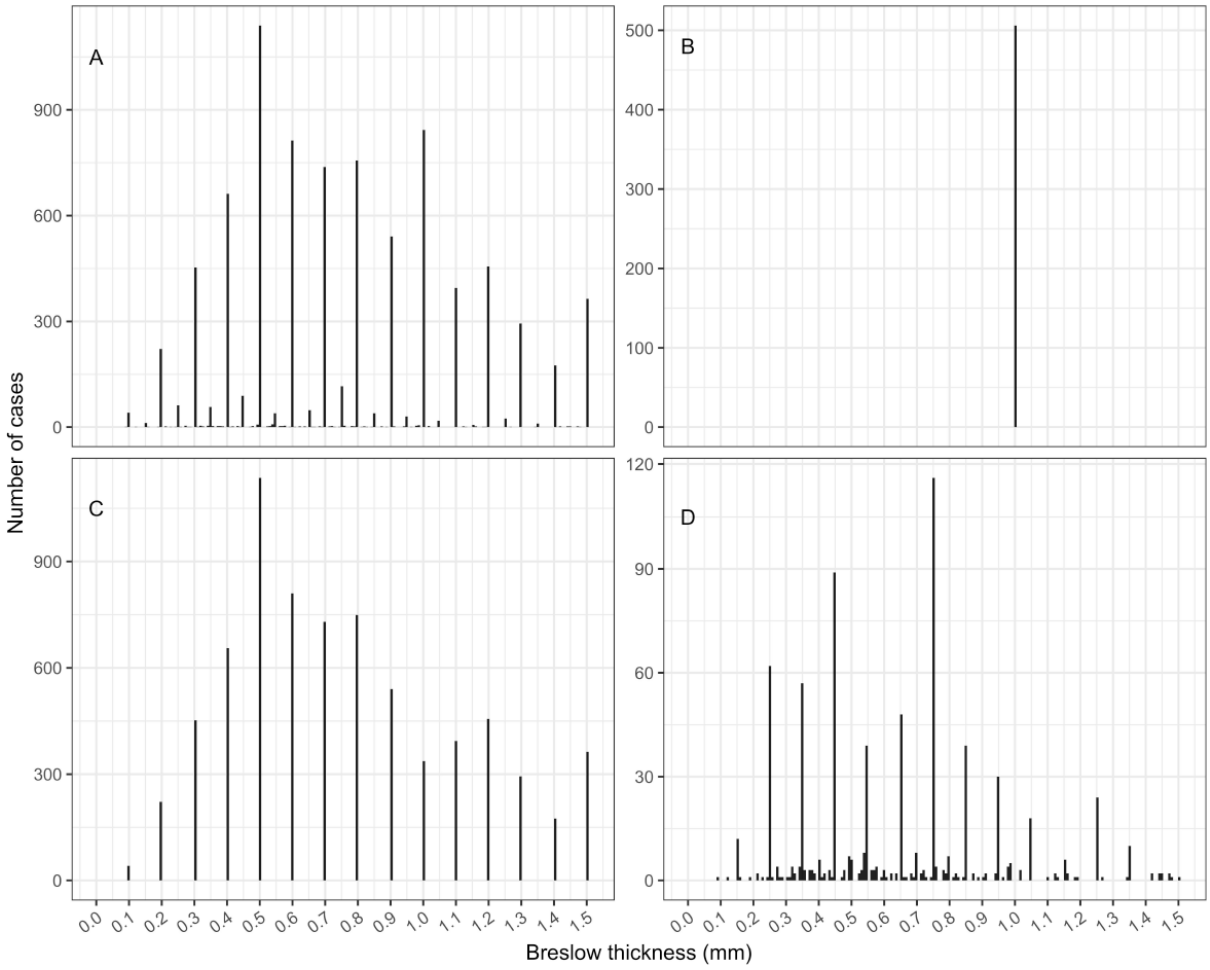

386 Figure 3. Terminal digits of Breslow thickness in Norwegian melanoma patients diagnosed in
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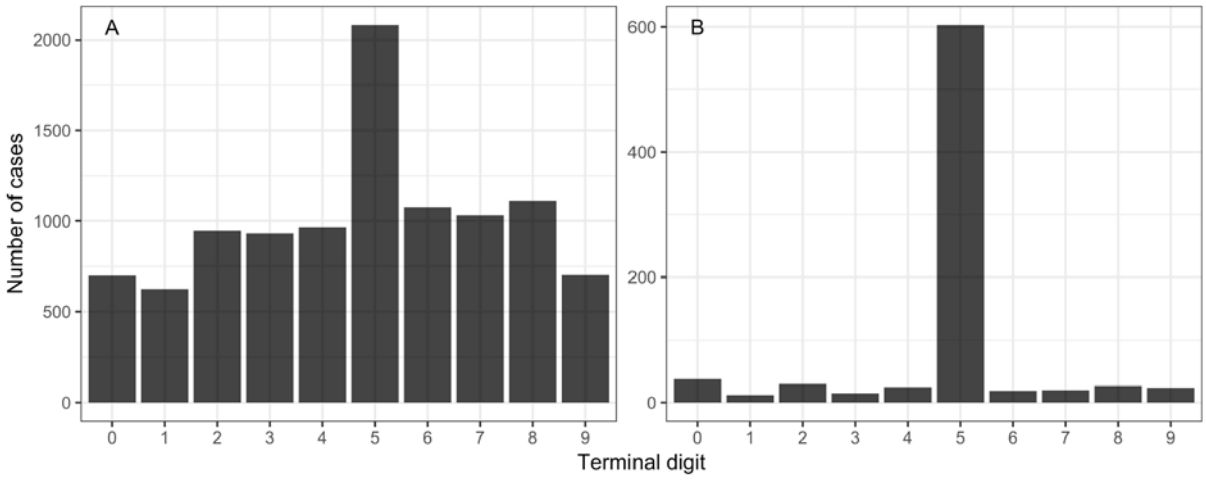

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391 Figure 4. Breslow thickness ≤10 mm in Norwegian melanoma patients diagnosed in 2008–

392 2015 stratified by ulceration. (A) No, n=7333; (B) Yes, n=2068; (C) Unspecified, n=3408.

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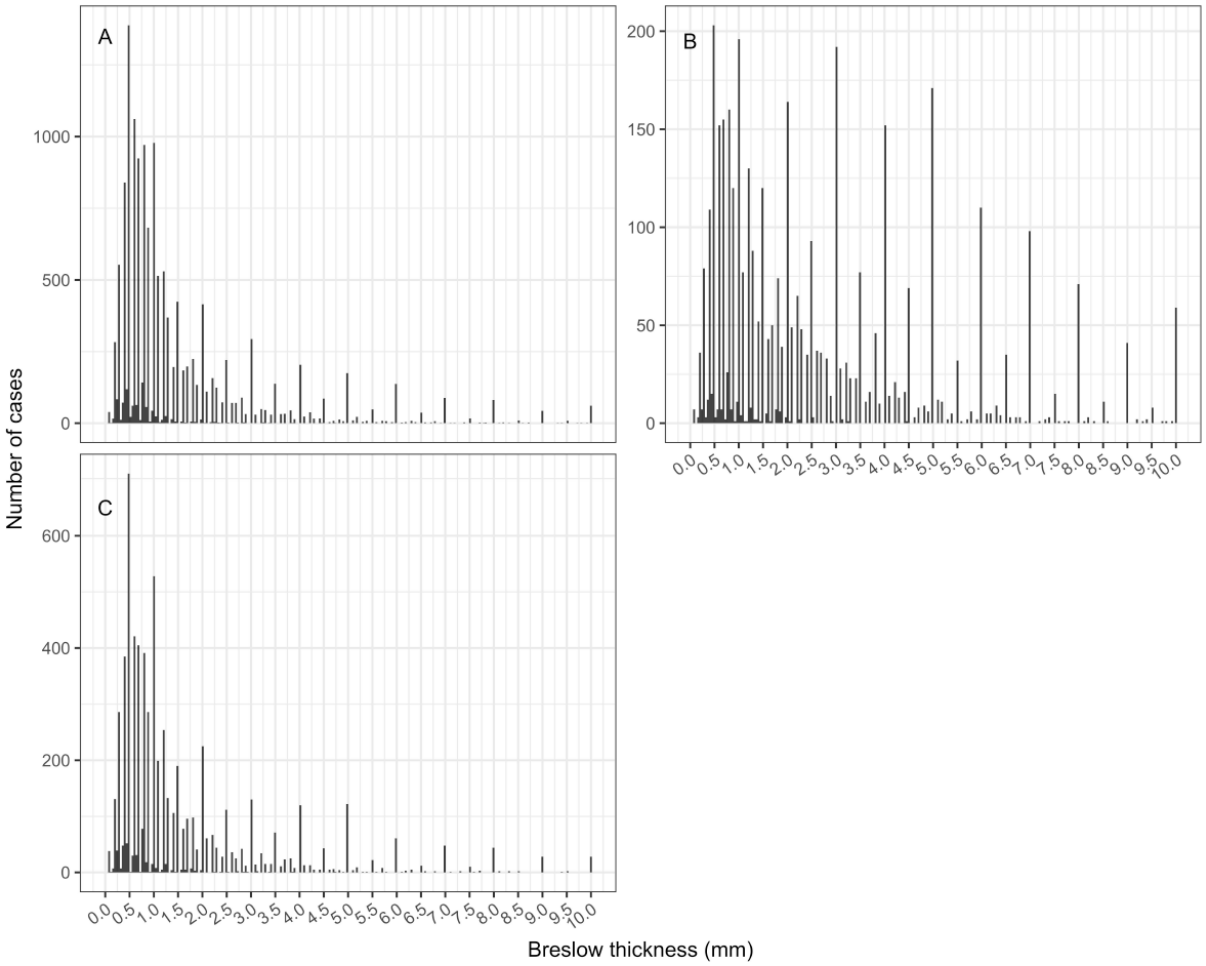

394

395 Table I. Number of digits after the decimal point and selected characteristics of Norwegian
396 melanoma patients diagnosed in 2008-2015,

397 n=13 057.

		No. of digits after the decimal point			
	Total (n=13057)	0 (n=2032)	1 (n=10211)	2 (n=814)	p-value‡
	Median (25^{th}–75^{th} percentile)	Median (25^{th}–75^{th} percentile)	Median (25^{th}–75^{th} percentile)	Median (25^{th}–75^{th} percentile)	
Breslow thickness, mm	1.0 (0.60-2.20)	3 (2-7)	0.9 (0.6-1.7)	0.66 (0.45-0.94)	<0.001
	Frequency (%)*	Frequency (%)†	Frequency (%)†	Frequency (%)†	
Year of diagnosis					
2008	1238 (9.5)	292 (23.6)	886 (71.6)	60 (4.9)	
2009	1356 (10.4)	289 (31.3)	993 (73.2)	74 (5.5)	
2010	1510 (11.6)	265 (17.6)	1126 (74.6)	119 (7.9)	
2011	1696 (13.0)	261 (15.4)	1313 (77.4)	122 (7.2)	
2012	1739 (13.3)	247 (14.2)	1373 (79.0)	119 (6.8)	
2013	1708 (13.1)	214 (12.5)	1400 (82.0)	94 (5.5)	
2014	1946 (14.9)	247 (12.7)	1590 (81.7)	109 (5.6)	
2015	1864 (14.3)	217 (11.6)	1530 (82.1)	117 (6.3)	<0.001
Gender					
Men	6470 (49.6)	1100 (17.0)	5007 (77.4)	363 (5.6)	
Women	6587 (50.4)	932 (14.1)	5204 (79.0)	451 (6.9)	<0.001
Age (years)					
<50	2859 (21.9)	295 (10.3)	2371 (82.9)	193 (6.7)	
50-69	5513 (42.2)	702 (12.7)	4425 (80.3)	386 (7.0)	
≥70	4685 (35.9)	1035 (22.1)	3415 (72.9)	235 (5.0)	<0.001
Health authority of residence					
South-East	7858 (60.3)	1241 (15.8)	6101 (77.6)	516 (6.6)	
West	2801 (21.5)	414 (14.8)	2219 (79.2)	168 (6.0)	
Middle	1597 (12.3)	272 (17.0)	1230 (77.0)	95 (6.0)	
North	769 (5.9)	97 (12.6)	637 (82.8)	35 (4.5)	
Tumour localization					
Head/neck	1726 (13.2)	376 (21.8)	1260 (73.0)	90 (5.2)	
Trunk	6245 (47.8)	880 (14.1)	4960 (79.4)	405 (6.5)	
Arm	1793 (13.7)	280 (15.6)	1405 (78.4)	108 (6.0)	
Leg	3082 (23.6)	456 (14.8)	2427 (78.7)	199 (6.5)	
Other	56 (0.4)	23 (41.1)	31 (55.4)	2 (3.6)	
Unspecified	155 (1.2)	17 (11.0)	128 (82.6)	10 (6.4)	<0.001
Morphology					

SSM	7324 (56.1)	574 (7.8)	6170 (84.2)	580 (7.9)	
NM	2566 (19.6)	839 (33.0)	1684 (65.6)	43 (1.7)	
LM	414 (3.2)	29 (7.0)	344 (83.1)	41 (9.9)	
ALM	65 (0.5)	12 (18.5)	48 (73.8)	5 (7.7)	
Other	135 (1.0)	59 (43.7)	75 (55.6)	1 (0.7)	
Unspecified	2553 (19.5)	519 (20.3)	1890 (74.0)	144 (5.6)	<0.001
T category					
T1, ≤1.0 mm	6831 (52.3)	507 (7.4)	5673 (83.0)	651 (9.5)	
T2, 1.01–2.0 mm	2836 (21.7)	278 (9.8)	2433 (85.8)	125 (4.4)	
T3, 2.01–4.0 mm	1911 (14.6)	420 (22.0)	1459 (76.3)	32 (1.7)	
T4, >4.0 mm	1479 (11.3)	827 (55.9)	646 (43.7)	6 (0.4)	<0.001
Ulceration					
Yes	2257 (16.9)	806 (35.7)	1390 (61.6)	61 (2.7)	
No	7414 (55.7)	735 (9.9)	6153 (83.0)	526 (9.1)	
Unspecified	3645 (27.4)	779 (21.4)	2640 (72.4)	226 (6.2)	<0.001

No., number; SSM, Superficial spreading melanoma; NM, Nodular melanoma; LMM, Lentigo maligna melanoma, ALM, Acral lentiginous melanoma.

*Frequency (column %).

†Frequency (row %).

‡One-way analysis of variance on $\log_e$transformed data for Breslow thickness and chi-squared test for all other variables.

406 Table II. Observed[*] and estimated[†] number of patients according to T category for melanomas
407 ≤10 mm and melanomas ≤5 mm.

	T1 (≤1.0 mm)	T2 (1.01–2.0 mm)	T3 (2.01–4.0 mm)	T4 (>4.0 mm)
Melanomas ≤10 mm				
Observed, n (%)	6176 (51.5)	2709 (22.6)	1879 (15.6)	1232 (10.3)
Estimated, n (%)	5582 (46.9)	3069 (25.8)	2223 (18.7)	1023 (8.6)
Difference, n	594	-360	-344	209
Misclassified[‡], %	9.6	-13.3	-18.3	17.0
Melanomas ≤5 mm				
Observed, n (%)	6176 (55.0)	2709 (24.1)	1879 (16.8)	465 (4.1)
Estimated, n (%)	5450 (49.2)	3310 (29.9)	2061 (18.6)	255 (2.3)
Difference, n	726	-601	-182	210
Misclassified[‡], %	11.8	-22.2	-9.7	45.2

408 [*]Patients recorded in the Norwegian Malignant Melanoma Registry (excluding patients with
409 thickness reported with two digits after the decimal point).
410 [†]Estimated by the Wang method.
411 [‡]Difference/observed.
412

413 Supplementary Table I. Percentages of terminal digits 5 and 0 within selected intervals in the
414 recordings of Breslow thickness in Norwegian melanoma patients diagnosed in 2008–2015,
415 n=13 057.

Terminal digit 5			Terminal digit 0		
Interval	n	Percentage at 5 (midpoint)	Interval	n	Percentage at 0 (midpoint)
All, n=13057					
0.3–0.7	4112	27.7	0.8–1.2	3120	27.1
1.3–1.7	1191	30.6	1.8–2.2	982	40.9
2.3–2.7	532	40.0	2.8–3.2	517	59.4
3.3–3.7	283	49.8	3.8–4.2	374	63.6
4.3–4.7	153	64.7	4.8–5.2	288	80.9
5.3–5.7	74	68.9	5.8–6.2	174	88.5
6.3–6.7	64	65.6	6.8–7.2	126	92.9
7.3–7.7	30	70.0	7.8–8.2	105	93.3
8.3–8.7	15	73.3	8.8–9.2	57	98.3
9.3–9.7	13	69.2	9.8–10.2	76	97.4
1 digit after the decimal point, n=10211					
0.3–0.7	3781	30.0	0.8–1.2	2479	13.6
1.3–1.7	1156	31.4	1.8–2.2	680	18.2
2.3–2.7	526	40.3	2.8–3.2	275	25.8
3.3–3.7	279	50.5	3.8–4.2	186	29.0
4.3–4.7	152	65.1	4.8–5.2	101	46.5
5.3–5.7	74	68.9	5.8–6.2	45	55.6
6.3–6.7	64	65.6	6.8–7.2	23	60.9
7.3–7.7	30	70.0	7.8–8.2	22	72.7
8.3–8.7	15	73.3	8.8–9.2	7	85.7
9.3–9.7	13	69.2	9.8–10.2	7	71.4
2 digits after the decimal point, n=814					
0.30–0.70	331	1.8	0.80–1.20	134	0
1.30–1.70	35	2.9	1.80–2.20	24	0
2.30–2.70	6	16.7	2.80–3.20	6	0
3.30–3.70	4	0	3.80–4.20	4	0
4.30–4.70	1	0	4.80–5.20	1	0
5.30–5.70	0	–	5.80–6.20	0	–
6.30–6.70	0	–	6.80–7.20	0	–
7.30–7.70	0	–	7.80–8.20	1	0
8.30–8.70	0	–	8.80–9.20	0	–
9.30–9.70	0	–	9.80–10.20	0	–

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