I need an exact margin measurement for this basal cell carcinoma!

Ian Katz, Les Irwig, Kevin McGeechan, Katy Bell

Author Affiliations

Ian Katz	MBChB, BSc (Med)(Hons), FRCPA	Southern Sun Pathology, Sydney; School of Medicine, University of Queensland, Australia
Les Irwig	BSc, MBBCh, PhD	School of Public Health, Faculty of Medicine and Health, The University of Sydney, Australia
Kevin McGeechan	Bsc (Hons), PGDPH, GradCertPharmEc, MBiostat, PhD	School of Public Health, Faculty of Medicine and Health, The University of Sydney, Australia
Katy Bell	MBChB, MMed (Clin Epi), PhD	School of Public Health, Faculty of Medicine and Health, The University of Sydney, Australia

Corresponding Author

Dr Ian Katz

Southern Sun Pathology

Suite 16/7 Sefton Road

Thornleigh, NSW, 2075 Australia

Phone:+61 2 94735200

Email: driankatz@gmail.com

Key words: basal cell carcinoma, dermatopathologist, surgical margins, histological margins, observer variation

Word count: 1522

Reference count: 10

Abstract

Background/objectives.

Pathology laboratories are required to determine or estimate the measurement uncertainty for all quantitative results but there is no literature on the uncertainty in margin measurements for skin cancer excisions.

Methods

Six pathologists measured 4-14 histological margins in each of ten BCCs.

Results

The mean of measurements from all the margins from all the cases was 1.8mm (range 0 and 6mm). Regarding the overall variance in margin measurements across the ten cases, 25% was from variation within cases (differences in margin measurement for a given case, because of different margins and different pathologists measuring each margin, SD 0.7mm). For a given case, we estimate that 95% of margin measurements would fall approximately within +/- 1.4mm of the mean measurement for that case. When only pathologists' closest margin for each case were included (for the six cases with uninvolved margins), 6% of the overall variance was from differences within cases (because of different pathologists' measurements of the closest margin, SD 0.2mm). For a given case without an involved margin, 95% of closest margin measurements would fall approximately within +/- 0.5mm of the mean closest measurement for that case.

Conclusions

Clinicians should be aware there is uncertainty in reported histological margins

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Clinicians routinely request assessment of the histological margin status (clear vs involved) in excisions of skin tumours as inadequately excised lesions are at risk of local recurrence [1] and some also request exact measurement of the distance from the tumour to the surgical margins. In clinical chemistry and laboratory medicine, measurement uncertainty assessment is required in accordance with ISO 17025 and ISO 15189 [2]. In Australia, medical pathology laboratories are required, as part of their accreditation, to determine or estimate the measurement uncertainty for all quantitative results [3]. Despite this, anecdotally, it appears that anatomical pathologists are not aware of the concept of measurement uncertainty. For example, we could find no published studies on the measurement uncertainty for distance of tumour from surgical margins in histopathology samples of keratinocyte skin tumours, despite this being by far the most common type of cancer specimen examined in most pathology laboratories [4,5]. As well as uncertainty in measurement of each individual margin, perhaps the most clinically important information is the uncertainty in the closest margin for a specimen. Clinical decisions about further management are informed by whether a margin is likely involved by tumour (which may imply residual unexcised tumour). In this study we suggest a method to empirically estimate the variation in margin measurement between pathologists examining cases of basal cell carcinoma (BCC).

We retrieved routine diagnostic slides for a sample of ten cases of shave excision or formal excision of multifocal superficial BCC from an Australian laboratory (Southern Sun Pathology, Sydney, Australia) during January 2020. Routine laboratory processing produced from 2-7 pieces of tissue per case and 4 to 14 margins per case (each piece of tissue has two margins). Each margin was numbered with ink on the surface of the slide (Figure 1) and six experienced pathologists independently measured each margin, using their usual method, blinded to the original pathology report and to each other’s findings.

As a first step to analysis, we constructed plots to visualise each pathologists’ measurements for the ten cases. For completeness, we then estimated variation in the margin measurement between cases (average differences across different specimens). We then estimated variation within cases (variation between margins and between pathologists for a given specimen). To account for the clustering of measurements

within cases and within pathologists, we built mixed models (two level models with measurements nested within cases, and pathologist fitted as an independent variable). We first built models using all measurements each pathologist made for each case, and then built models using only the closest margin measurement a pathologist made for each case. All analyses were conducted using SAS 9.4; the MIXED procedure was used for the mixed models. The University of Sydney Human Research Ethics Committee approved the study on 20th March 2019 (#2018/553).

In total 432 margins were measured (6 pathologists x 10cases x (4 to14) margins/case). Variation across cases, pathologists, and margins, for each case where all measurements are included, is shown in the Figure 2. The mean of measurements from all the margins from all the cases was 1.8 mm, and the range was 0 to 6 mm. Variation across cases and pathologists in the closest margin for each case, is shown in Figure 3. For the four cases where at least one pathologist thought there was a margin involved with tumour, all six pathologists reported a closest margin of 0 mm for three of the cases (cases 3,4, and 10), and closest measurement ranged from 0 to 0.4 mm for one case (case 5). For the six cases where none of the pathologists thought there was an involved margin, the mean of the closest measurements was 1.6 mm and ranged from 0.2 mm to 5 mm.

Table 1 summarises the model estimates for within case variation in margin measurement. Where all margin measurements were included, of the overall variance in margin measurements across the ten cases, 25% was from variation within cases (differences in margin measurement for a given case, because of different margins and different pathologists measuring each margin, SD 0.7 mm). For a given case, we estimate that 95% of margin measurements would fall approximately within +/- 1.4 mm of the mean measurement for that case. When only pathologists' closest margin for each case were included (for the six cases with uninvolved margins), 6% of the overall variance was from differences within cases (from differences between pathologists' measurements, SD 0.2 mm). For a given case without an involved margin, 95% of closest margin measurements would fall approximately within +/- 0.5 mm of the mean closest measurement for that case.

Discussion

In this study of histopathology margin measurements of BCC, we found evidence that the apparent distance from tumour to the surgical margin varies, depending on the section examined, and the pathologist assessing it. We have shown that just like any quantitative measurement in the pathology laboratory [3], there is uncertainty when measuring margins for excision of BCC and that this measurement uncertainty has two major components: variation in where within the tissue block the margin is measured, and variation between pathologists who measure the margins.

Strengths of this study include the labelling of all margins for a specimen to allow measurements for each unique margin to be correlated, use of independent and masked evaluation by the pathologists, the large number of margins measured, and the robust statistical analysis. A weakness is that all the lesions were multifocal superficial BCC which tends to be poorly demarcated, and there may be different findings for other types of BCC.

To the best of our knowledge, this is the first report on the uncertainty when measuring histological margins for BCC excisions. In fact, we can find no published reports that quantify uncertainty in histological margin measurements for excisions of tumours of any tissue type. Some studies have documented inaccuracy in visual inspection of the surgical margin pre-excision, compared to histopathology margin measurement [6, 7], and the potential for retraction of the tumours and margins during formalin fixing before histopathology examination due to tissue shrinkage [8].

There is no literature on the sources of uncertainty in the measurement of histological margins but anecdotally, sources of uncertainty include: non-representative sampling (<2% of the sample is routinely examined), environmental effects on the measurement process (shrinkage of the sample in formalin may contribute to this variably), individual pathologist reading errors (measuring the closest margin out of many margins in different directions may be prone to error), finite instrument resolution of discrimination thresholds (some pathologists measure margins to 2 decimal places which is likely to be prone to error), inexact values of measurement standards (how exactly do we measure margins in curved samples, for example, which leads to inter-observer variation), approximations incorporated into the measurement (pathologists measure using many different methods e.g. stage micrometer, graticule, estimation of proportion of field diameter, again producing inter-observer variation).

Complicating the uncertainty in these measurements, or perhaps because of them, there are few recommendations about what to do with histological measurements of margins for BCC (and most other tumours). There is no evidence that measuring exact histological margins has clinical benefit. In fact, in many parts of the world this is not standard practice. The Australian Keratinocyte Carcinoma Guidelines recommend that excision margins should be measured if necessary and that this is particularly important with narrowly excised lesions [9], but do not provide further details. One of the only sources that suggest a method for reporting measurement of margins for BCC is the UK's Royal College of Pathologists dataset for the histopathological reporting of primary cutaneous BCC [10]. In this they suggest measuring peripheral and deep margins histologically as <1 mm, 1–5 mm and >5 mm. Measuring to a whole millimetre integer over 1 mm is included as a non-core item. They comment that adequacy of clearance is a risk assessment of the chance of recurrence, based on margin clearance and low/high-risk status of the tumour. By using ranges of margins, this implies that there is measurement uncertainty, although this is not explicitly stated.

Pathologists essentially have 3 ways to communicate a margin to a clinician: numerically, descriptively, and visually. As we have presented, there is uncertainty in the numeric assessment of a margin. Descriptive terms may be used in a report, such as "narrowly clear", "close" or "well clear", however, these terms are inherently subjective, and may not provide the clinician with sufficient information to determine management. Histologic images are also an effective way of highlighting the edges of BCC extension. Perhaps a judicious use of numeric, descriptive, and visual information may be a more effective way to communicate the significance of a BCC margin to the clinician.

In conclusion, despite that fact that in Australia, medical pathology laboratories are required, as part of their accreditation, to determine or estimate the measurement uncertainty for all quantitative results [3], there is little evidence that this is occurring with regards to margin measurements. Anatomical pathologists are not aware of the concepts of measurement uncertainty and there is a need to increase awareness of the uncertainty in histological margin measurements of BCC (and other tumours) among clinicians. We provide a framework for laboratories to perform the same study internally to comply with accreditation guidelines. Histopathology reports could incorporate this uncertainty into the margin measurement.

Funding: no funding was required.

There are no conflicts of interest.

The University of Sydney Human Research Ethics Committee approved the study on 20th March 2019 (#2018/553).

Contributorship Statement: IK, LI and KB were responsible for planning, conduct, reporting, conception and design, acquisition of data or analysis and interpretation of data, etc. KM was responsible for data analysis.

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Table 1: Within case variation in margin measurement for ten cases of basal cell carcinoma (BCC)		
	SD	**95% distribution**
All margin measurements for ten cases (n=4-14 measurements per pathologist per case)	0.7 mm	Mean +/- 1.4 mm
Closest margin measurement for six cases without involved margin (n=1 measurement per pathologist per case)	0.2 mm	Mean +/- 0.5 mm

Figure Legends

Figure 1
A low power (4x) view of Case 4, H&E slide shown how for one specimen with 2 pieces of tissue, and two levels produces 8 separate margins to be measured by each pathologist.

Figure 2
Each individual box represents one specimen with the 6 pathologists' margin measurements for each specimen.

Figure 3
Pathologists' closest margin measurements for each case.