Towards a tailored therapeutic approach for vulvar cancer patients

Kortekaas, K.E.

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PRACTICAL GUIDANCE FOR MEASURING AND REPORTING SURGICAL MARGINS IN VULVAR CANCER

K.E. Kortekaas, K.K. Van de Vijver, M.I.E. van Poelgeest, C.B. Gilks, V.T.H.B.M. Smit, S. Arif, D. Arora, A. Faruqi, R. Ganesan, N.R Griffin, R. Hale, Y.L. Hock, L-C Horn, W. Glenn McCluggage, P. Mukonoweshuro, K.J. Park, B. Rous, B. Tanchel, A.S. Van Rompuy, G. van Schalkwyk, J. Vella, M. Vergine, N. Singh, T. Bosse

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ABSTRACT

Objective

Surgical resection with free surgical margins is the cornerstone of successful primary treatment of vulvar squamous cell carcinoma (VSCC). In general re-excision is recommended when the minimum peripheral surgical margin (MPSM) is <8mm microscopically. Pathologists are therefore required to report the minimum distance from the tumor to the surgical margin. Currently there are no guidelines on how to make this measurement, as this is often considered straightforward. However, during the 2018 Annual Meeting of the British Association of Gynaecological Pathologists (BAGP), a discussion on this topic revealed a variety of opinions with regard to reporting and method of measuring margin clearance in VSCC specimens.

Methods

Given the need for uniformity and the lack of guidance in the literature, we initiated an online survey in order to deliver a consensus-based definition of peripheral surgical margins in VSCC resections. The survey included questions and representative diagrams of peripheral margin measurements. In total 57 pathologists participated in this survey.

Results

Based on the consensus results, we propose to define MPSM in VSCC as the minimum distance from the peripheral edge of the invasive tumor nests towards the inked peripheral surgical margin reported in millimetres. This MPSM measurement should run through tissue and preferably be measured in a straight line. Along with MPSM, other relevant measurements such as depth of invasion or tumor thickness and distance to deep margins should be reported.

Conclusion

This manuscript provides guidance to the practicing pathologist in measuring MPSM in VSCC resection specimens, in order to promote uniformity in measuring and reporting.

INTRODUCTION

Vulvar squamous cell carcinoma (VSCC), the most common vulvar malignancy[1], is notorious for its high recurrence rates, with a reported local recurrence frequency of up to 40% ten years after primary treatment.[2] In an effort to limit these recurrence rates, most guidelines including The Royal College of Obstetricians & Gynaecologists (RCOG) in United Kingdom, recommend surgical excision with a histological minimum tumor-free peripheral surgical margin (MPSM) of >8mm.[3-6] Retrospective cohort studies support this approach, showing 0% recurrence rates for >8mm margins and 47% when the margins are ≤8mm[4, 7, 8], although recent studies have argued that the 8mm threshold might be too stringent.[9-12] The concept of ontogenic cancer fields might explain why the width of the tumor-free resection margin is not a consistent predictor of local recurrence.[13] However, when surgical treatment of VSCC in respect to the theory of cancer as inverse morphogenesis, it is still important to measure the MPSM as a pathological quality. In order to achieve this requirement, surgeons often need to sacrifice critical structures adjacent to the VSCC (eg. clitoris, urethra, and anus) with subsequent morbidities.[14] If the 8mm MPSM is not reached, most guidelines recommend consideration of re-excision and/or adjuvant radiotherapy to reduce the chance of local recurrence.[9] Therefore, MPSM measurement is a mandatory and clinically important item in pathology reporting and clinical care.

Despite its clinical relevance, practical guidelines on how to measure the MPSM is lacking in the current literature. This is in contrast to depth of stromal invasion and/or tumor thickness for which definitions and guidance on measurement have been published.[15, 16] During the British Association of Gynaecologic Pathologists (BAGP) Annual Meeting in 2018, an ad-hoc pilot-survey revealed considerable disagreement among pathologists on how to measure MPSM. This topic appears particularly relevant to vulvar resections as the vulva has natural folds that form the anatomical landmarks such as the labia, and tumors are often exophytic, resulting in scenarios in which the correct measurement is not obvious. This is compounded by a lack of agreement between the naked eye measurement made at the time of surgery and that reported histologically after formalin-fixation.[17] Surgical assessment of margin clearance is based on measuring skin adjacent to tumour when the skin has been pulled taut/flat. Various factors may affect the histological assessment including variation in laboratory protocols with regard to pinning specimens prior to fixation, shrinkage as a result of fixation and/or the presence of microscopic tumor deep to the surface extending closer to the margin than is apparent from assessment of the skin surface. Since patient care and future research studies would clearly benefit from an uniform and standardized approach towards measuring MPSM in VSCC, we undertook an online survey amongst members of the BAGP in order to formulate recommendations for uniform MPSM measurement and reporting. These recommendations are likely not only relevant for VSCC, but also for other skin/mucosal resections for which peripheral margin measurements are required.

METHODS

Four pathologists with a specialist interest in gynecological, including vulvar, pathology (KvdV, BG, NS, TB) discussed the common problems encountered in MPSM measurement of VSCC following the 2018 BAGP meeting. This group designed a survey including questions and challenging scenarios for MPSM measurement. The questions were sent to members of the BAGP council for comments. A link to the final agreed electronic online survey was sent to all members of the BAGP in November 2018.

The survey included five diagrams representing potential problematic areas in MPSM measurement. In each diagram, multiple options for measuring margin distance were drawn and the participants were asked to select their preferred MPSM (only one answer allowed). The first diagram represents a straightforward MPSM measurement (supplemental figure 1), and was included to make participants familiar with the online webtool. Five multiple-choice questions were also included in the survey (figure 1). Participants were encouraged to submit comments related to the topic, which have been incorporated in the discussion of this manuscript. Responses received until the end of December 2018 were analysed, excluding any that were incomplete.

RESULTS

A total of 57 BAGP members responded and all these participants fully completed the survey. Importantly, an overwhelming majority (96%) replied that recommendations for measuring MPSM would be useful in daily practice. This was reinforced by responses to the question on whether they experienced difficulties in measuring MPSM in daily practice, to which 14% and 68% respondents respectively selected 'often' and 'occasionally', as opposed to 12% and 5% respectively stating that they rarely or never experienced difficulties when measuring MPSM (figure 1).

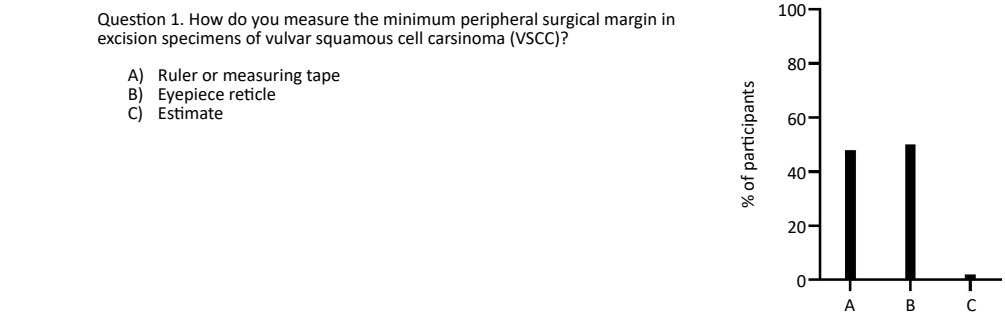
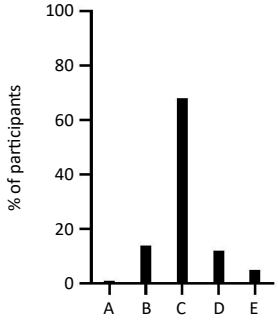


Figure 1. Five multiple choice questions were asked to all participating pathologists on how to measure and report on minimal peripheral surgical margin.

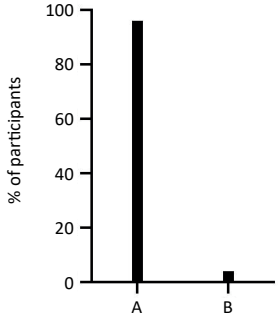
Question 2. Do you experience difficulties measuring minimum peripheral surgical margins in daily practice?

A) Usually
B) Often
C) Occasionally
D) Rarely
E) Never



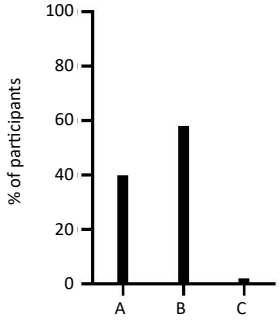
Question 3. Do you think a practical guideline for measuring margins would be useful?

A) Yes
B) No



Question 4. HoDo you report on the relationship of “in situ” lesions (HSIL/dVIN) in the peripheral resection margins of the specimen?

A) Yes, always; but I only state if the margins are clear or involved (with or without the use of IHC).
B) Yes, always; and if margins are clear I also report the distance of VIN to margins (with or without the use of IHC).
C) No, only when specifically asked for by clinician.



Question 5. Do you report on deep surgical margins?

A) Yes, always; independent of peripheral surgical margin (two measurements in report).
B) Yes, but only when deep surgical margin is more closely aproached by tumor than the peripheral margin.
C) No, I don’t report deel surgical margin status separately unless it is involved.

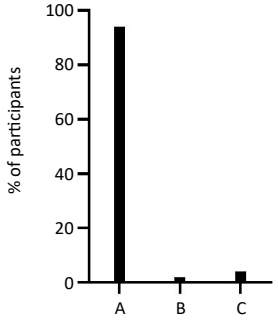


Figure 1. Continued

Problematic area 1: Should the MPSM always be measured towards the peripheral surface edge?

Due to the irregular vulvar surface or to dermal extension of the tumor, a measurement toward the peripheral inked epithelial-surface edge may not always represent the shortest distance. As illustrated in figure 2A, the shortest measurement from the tumor to the resection edge, in this scenario, is towards the inked soft tissue edge. In keeping with measuring the shortest distance, the majority of the participants (86%) chose option B, measuring from the peripheral edge of the invasive tumor to the peripheral inked soft tissue edge. Interestingly, a significant minority (14%) chose option A, in which the distance is larger, but the measurement is towards the epithelial-surface edge.

Comments

Most participants strictly applied the simple rule that the MSPM is the shortest measurement towards the peripheral inked edge even though this is a stromal and not an epithelial margin. Some participants however, commented that it may be challenging to decide where the peripheral margin stops and "the deep surgical margin" begins. Another remark made by one of the participants, was that measurement A is more representative of what the surgeon measures during the operation. Reporting measurement B (only) could potentially result in a negative impact on surgical audit, and therefore it was suggested (in these scenarios) to report on both the MPSM (option B) and also the "surface epithelial margin" (option A). Providing both may be worthy of consideration albeit after good communication with local surgeons, as long as it is clearly emphasised in the report that for decisions regarding the patient's adjuvant treatment plan measurement B is the most relevant.

Problematic area 2: How should MPSM be measured when the epithelial surface is irregular/curved?

Given the normal vulvar anatomy, an irregular or curved surface is frequent in VSCC resection specimens and may complicate the measurement of the MSPM (figure 2B). Curved skin may be neutralized in part by pulling the skin taut. However, artificial folds due to processing can still appear and are difficult to distinguish from natural irregularities. Depending on how extreme this irregularity is, pathologists may favour a curved line instead of a straight line. Curved line measurements are impractical when using a microscope, but as the field moves towards digital pathology this practical problem becomes obsolete. Interestingly, when faced with this scenario in our survey, 98% of the participants considered that the straight-line measurement is preferred.

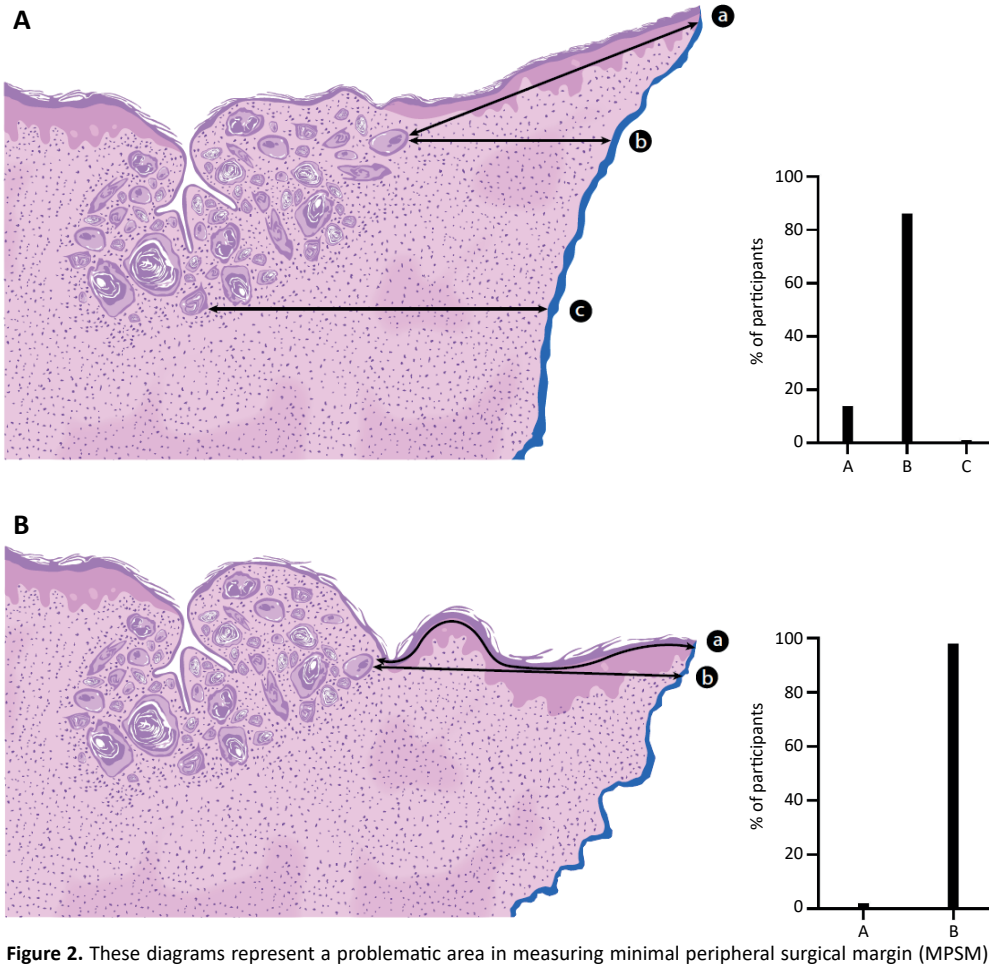


Figure 2. These diagrams represent a problematic area in measuring minimal peripheral surgical margin (MPSM) in vulvar cancer. In each diagram, multiple options were drawn, and participants selected their preferred MPSM via an online survey. The results of this survey are shown in the corresponding bar graph. The first question was: Should the minimal peripheral surgical margin always be measured towards the peripheral surface edge? The diagram and answer to this question are depicted in A. The next question was: How to measure minimal peripheral surgical margin when the epithelial surface is irregular/curved (B)?

Comments

The outcome of figure 2B may have been influenced by the fact that it is likely that few or none of the participants have already moved towards digital pathology in daily routine. The participants reported that they used eyepiece recticles (50%), a ruler (either stage vernier scale of the magnificying glass fixed with a rule (48%), or simply estimated the MPSM distance (2%) in practice (figure 1). With the introduction of digital pathology, more accurate margin measurements can be anticipated. This will increase accuracy and introduces another interesting question raised by one of the participants; how accurately do we need to measure? Most pathologists currently record measurements rounded to the nearest

whole millimetre; however digital pathology will allow for measurements of hundredths of millimetres or less. There is currently no evidence that this level of accuracy is required, and therefore we would recommend rounded millimetres should remain the standard. Digital pathology will also simplify measuring curved lines; however, unless a curved measurement clearly represents the true shortest distance towards the periphery, e.g., when a length of uninvolved skin is embedded curved/folded in order to fit into a paraffin block, this should be avoided. In addition, a pitfall is not to overstretch the skin, because this might lead to overestimation of the MPSM. It is unknown whether measuring in a straight line compared to curved line will influence clinical outcome. Uniform use of the recommendations from this manuscript will help resolve this in the near future.

Problematic Area 3: How to measure MPSM when an exophytic tumor protrudes above the adjacent surface epithelium?

Often VSCC have an exophytic component, which protrudes above the adjacent surface epithelium (figure 3A). In these cases, the shortest distance from the tumor to the periphery can be measured by drawing a line outside the tissue (option A). The participants in the survey agreed in an overwhelming majority (98%) that in this scenario, option A does not represent the MPSM. We can deduct from this answer that the MPSM measurement should not be outside the tissue. This is informative; as this provides a useful “rule” for measuring MPSM in cases with surface irregularities.

Problematic Area 4: Should MPSM always be measured as a straight uninterrupted line?

Figure 3B represents a case of an exophytic tumor where the deepest point of invasion is above a collarette of uninvolved skin. In this case, two ways to measure the MPSM by a straight uninterrupted line were presented (option A and option D) as well as two ways in which the line was interrupted at the collarette (option B and C). The shortest distance is measurement A; however, following the rule for not measuring outside the tissue (described above, figure 3A), this would be incorrect. The alternative straight uninterrupted line (option D) is the largest distance of all options and was not the preferred option by the participants (2%). The majority voted for option C (95%), which represents the shortest distance through tissue in a line with an angle at the collarette. From this we can conclude that the participants are familiar with this scenario and allow for MPSM with an angle.

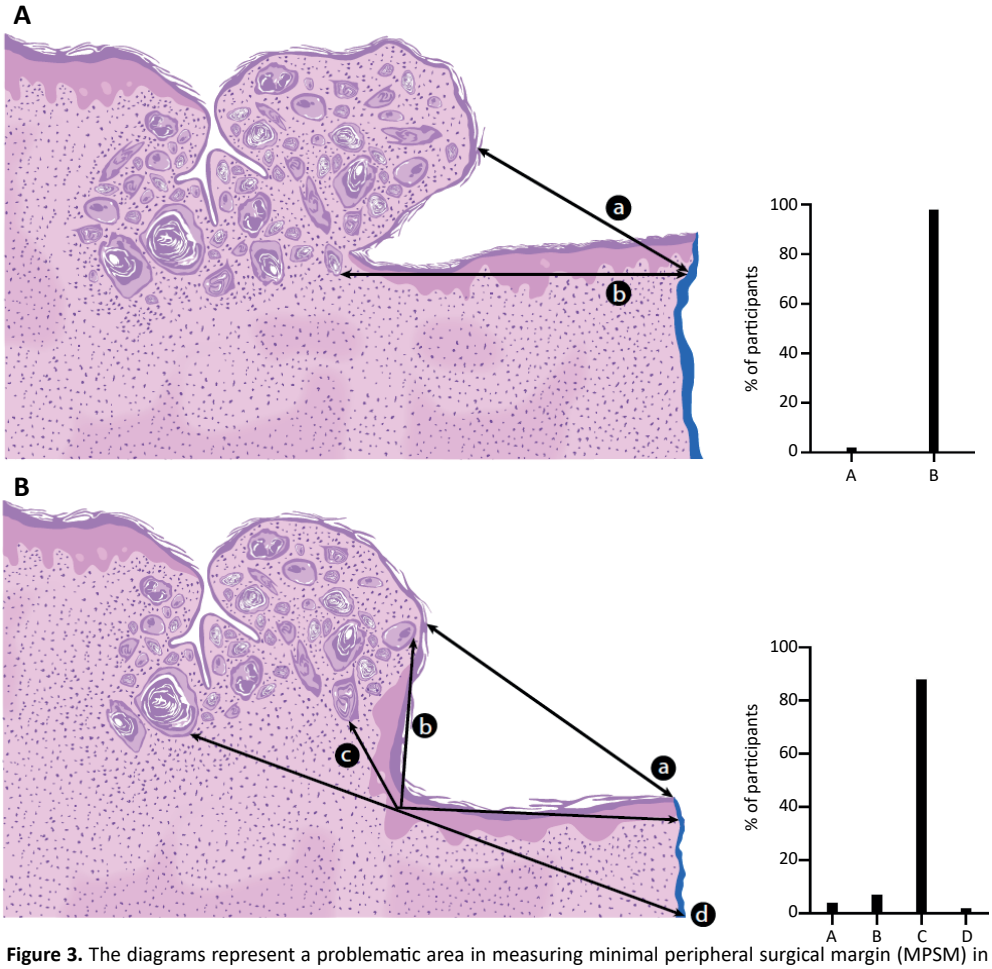


Figure 3. The diagrams represent a problematic area in measuring minimal peripheral surgical margin (MPSM) in vulvar cancer. In each diagram, multiple options were drawn, and participants selected their preferred MPSM via an online survey. The results of this survey are shown in the corresponding bar graph. The first figure (A) refers to the question: How to measure the minimal peripheral surgical margin when an exophytic tumor is overarching the adjacent surface epithelium? The second figure (B) answers the question: Should the minimal peripheral surgical margin always be measured as a straight uninterrupted line?

In addition to the questions relating to illustrated scenarios, a few additional questions were asked as below.

Should the presence of a precursor lesion at the lateral epithelial MPSM be reported?

VSCC has two well-defined precancerous lesions that are frequently recognised in the epithelial surface adjacent to the tumor, high-grade squamous intraepithelial lesion of usual type (HSIL / usual high-grade vulvar intraepithelial neoplasia (uVIN)) and differentiated vulval intraepithelial neoplasia (dVIN). It is possible that recurrent disease is not only determined by the margin status of the invasive tumor, but also by the presence and

distance of the precancerous lesion to the surgical margin. Here, the measurement itself is more straightforward as the precancer will always be measured along the epithelial surface. Interestingly, with the exception of the RCOG and College of American Pathologist (CAP) guideline[3,18], most guidelines do not consider reporting precancerous lesions in VSCC resection specimens mandatory. Despite this, most of the survey participants report upon the presence or absence of precancerous lesions (98%) adjacent to the VSCC at the peripheral margin. 42% of these participants also include a measurement of the in-situ lesion to the peripheral margin. The remaining 56% do not include a measurement and limit the comment on the in-situ lesion to its presence/absence at the surgical margin (figure 1).

Should a measurement of the deep soft tissue margin also be included in the report?
Most participants (95%) also report on deep soft tissue margins, in addition to the MPSM in their VSCC resection specimens (figure 1). This is in line with most guidelines[7], in which a minimum of three measurements are listed: 1) tumor thickness/depth of invasion, 2) the MPSM, and 3) the deep soft tissue margin.[3] One participant remarked to not limit the measurement to the minimal margin, but report a clockwise margin status. Measurement of distance to multiple cutaneous margins has limited relevance; the margins are approximated and stitched together at the end of surgery (unless a skin flap has been used to fill the gap), and therefore it is the involvement of/proximity to the closest margin that is required by clinicians to plan further management. Histology reports should not be crowded with irrelevant measurements. In many practices clockwise measurements are the standard during grossing, but these measurements should not be included in the report to avoid potential confusion.

SUMMARY

This is the first study to survey current practice in measuring the MPSM in VSCC specimens. By presenting five margin scenarios to 57 trained pathologists with an interest in gynaecological pathology we can propose some broad rules that will help the community arrive at more reproducible and accurate MPSM measurements and uniform reporting. Based on this, we propose the following:

- The MPSM is defined as: “the minimum distance from invasive carcinoma to the inked peripheral surgical margin reported in millimetres”.
- The peripheral margin is roughly perpendicular to the skin surface; this includes the epithelial surface and deeper soft tissue; the MPSM should therefore be measured towards the peripheral stromal edge or surface-epithelial edge, whichever is the shortest.
- Reporting both the MPSM and the distance to the surface-epithelial edge is not mandatory for invasive tumor, but may be considered for the purpose of surgical audit. Additionally, reporting on both margins is recommended for HSIL and dVIN.

- The MPSM should be measured through tissue and preferably in a straight uninterrupted line, however in some situations (collarette) a composite measurement including separate linear measurements joined at an angle may be required.
- Measuring the MPSM by a curved line in the context of an irregular surface, which is now possible due to the increased use of digital pathology, is not recommended, unless this is felt to represent a truer measurement, for example when a length of uninvolved skin is embedded curved/folded in order to fit into a paraffin block.
- The presence or absence of precancerous lesions at the surgical margin should be included in the report.
- Although there is no clear evidence to support the value of recording the distance of precancerous lesions from the nearest epithelial margin, it is recommended that for uniformity in current practice this measurement should be included in the report; this measurement is made along the epithelial surface.
- The minimal deep surgical margin is generally understood to be measured from the deepest infiltrating tumor nest to the inked dorsal soft tissue margin.

It is hoped that these recommendations will help to uniform current clinical practice and can be used as a reference for future guidelines and clinical studies to correlate MPSM with patient outcome.

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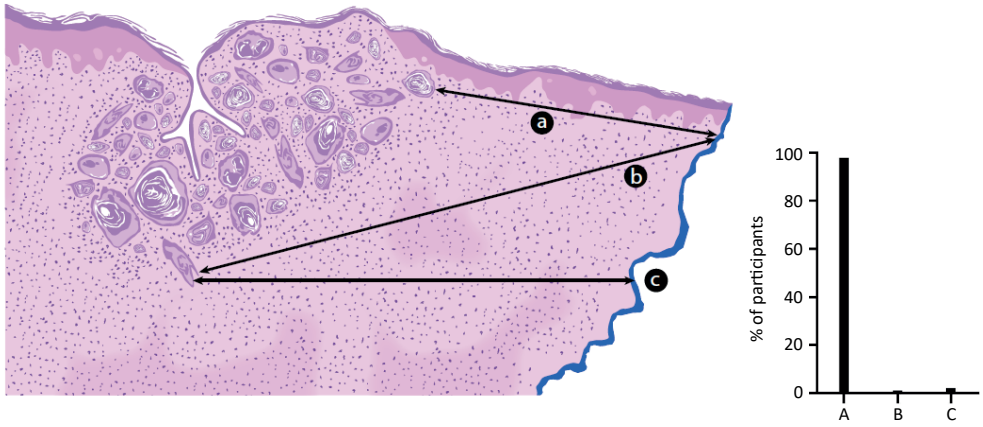
SUPPLEMENTAL MATERIALS



Supplemental figure 1. This figure was the first included in our online survey and was used as a practical exercise for the participants. The shortest distance in this figure is measurement A, which measures from the most lateral invasive tumor edge towards the inked epithelial-stromal junction. The vast majority of participants (98%) chose line A as the preferred MPSM.