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Unexpectedly high variability in determining tumour extent in prostatic biopsies: implications for active surveillance

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Unexpectedly high variability in determining tumour extent in prostatic biopsies: implications for active surveillance

Aims: Tumour content in prostatic biopsies is an important indicator of prostate cancer volume and patient prognosis. Consequently, guidelines typically recommend reporting it as a percentage or linear length (mm). This study aimed to determine the current practices for reporting tumour content in

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Abbreviations: AS, active surveillance; CAP, College of American Pathologists; DGP, German Society of Pathology / Deutsche Gesellschaft für Pathology; GG, Grade Group; ICCR, International Collaboration on Cancer Reporting; ISUP, International Society of Urological Pathology; MRI, magnetic resoncance imaging; PI-RADS, Prostate Imaging-Reporting and Data System; PSA, prostate-specific antigen.

prostatic biopsies and evaluated the consistency among pathologists in diagnosing 10 standard biopsy cases of prostate cancer to assess interobserver variability.

Methods and results: A web-based survey gathered data on demographics, experience and attitudes regarding the reporting of prostate cancer and its extent in biopsies. Virtual microscopy allowed analysis of 10 biopsy cases, each consisting of a single slide of prostate cancer. Self-reports from 304 participants recruited via the International Society of Urological Pathology and the German Society of Pathology were analysed. Most participants (43.4%) reported tumour extent as percentage of the biopsy core, 37.6% reported percentages and mm and 18.3% reported mm exclusively. The methods used to determine percentages showed an unexpected spread of choices, leading to considerable variability in results. Additionally, 40.8% of participants took part in the practical segment of the survey. The reported measures of tumour extent confirmed a notable interobserver variability, which was significantly higher for reported percentages.

Conclusion: A high rate of interobserver variability in reporting tumour content in prostatic biopsies was found. This matter is especially critical for patients who are candidates for active surveillance. Reporting absolute measures of tumour content has the advantage of lower variability in comparison to percentages.

Keywords: active surveillance, milimeters, percentages, prostate cancer, tumour content

Introduction

Prostatic biopsy remains the mainstay to diagnose prostate cancer. The histology, grade and extent of tumours are crucial parameters for therapy planning in newly diagnosed cases of prostate cancer.[1–3] These details have gained increased significance, especially in light of the recognised potential for overtreatment, estimated to affect approximately 38% (ranging from 12 to 63%) of cases.[4] Active surveillance (AS) has emerged as a treatment strategy that aims to defer active therapy in eligible patients, but inclusion criteria vary among protocols. Most protocols consider factors such as International Society of Urological Pathology (ISUP) grade group 1, clinical stage cT1c or cT2a, PSA serum levels < 10 ng/ml and PSA density < 0.15 ng/ml/cc.[5] In addition, the fraction, of biopsy cores involved by tumour is taken into account. In approximately 40% of published protocols, the tumour content in each core is also relevant for eligibility for active surveillance. Herein, involvement of the cores has to be less than 50 or 20%, respectively.[6] The amount and linear extent of tumour detected in core needle biopsies correlates with tumour volume, postoperative stage and outcome after subsequent radical prostatectomy.[3] Pathology societies recommend reporting of tumour content in biopsies, preferably on individual cores.[3,7–9] This study aimed to evaluate how pathologists reported tumour content in prostatic biopsies and to elucidate interobserver variability.

Materials and methods

SURVEY CONSTRUCTION AND DISTRIBUTION

A survey was distributed (www.surveymonkey.com) between December 2023 and February 2024 using the mailing lists of the ISUP and the German Society of Pathology (DGP), with an open invitation to share the survey to other pathologists. The survey polled demographics data and queried methods for determining tumour content (Figures 1–3; Supplementary Information 1). Depending on the channel of recrution, participants will be referred to as members of ISUP or DGP irrespective of formal membership status. In addition to the poll, participants were also asked to report whole-slide images of a series of 10 typical prostate cancer biopsy cases.

CASES

Ten prostate cancer cases were selected to represent a variety of grade groups (GG) (GG1, three cases; GG2, three cases; GG3, two cases; GG5, two cases), tumour cell/tumour gland distribution and tumour content and presence or absence of periprostatic soft tissue, following central review (G.K., M.B.). Patient age and serum PSA levels were provided for all cases; prostate imaging—reporting and data system (PI-RADS) scores were available for seven cases.

Tumour parameters (length, area) were determined for all 10 cases using the digitised slides provided to

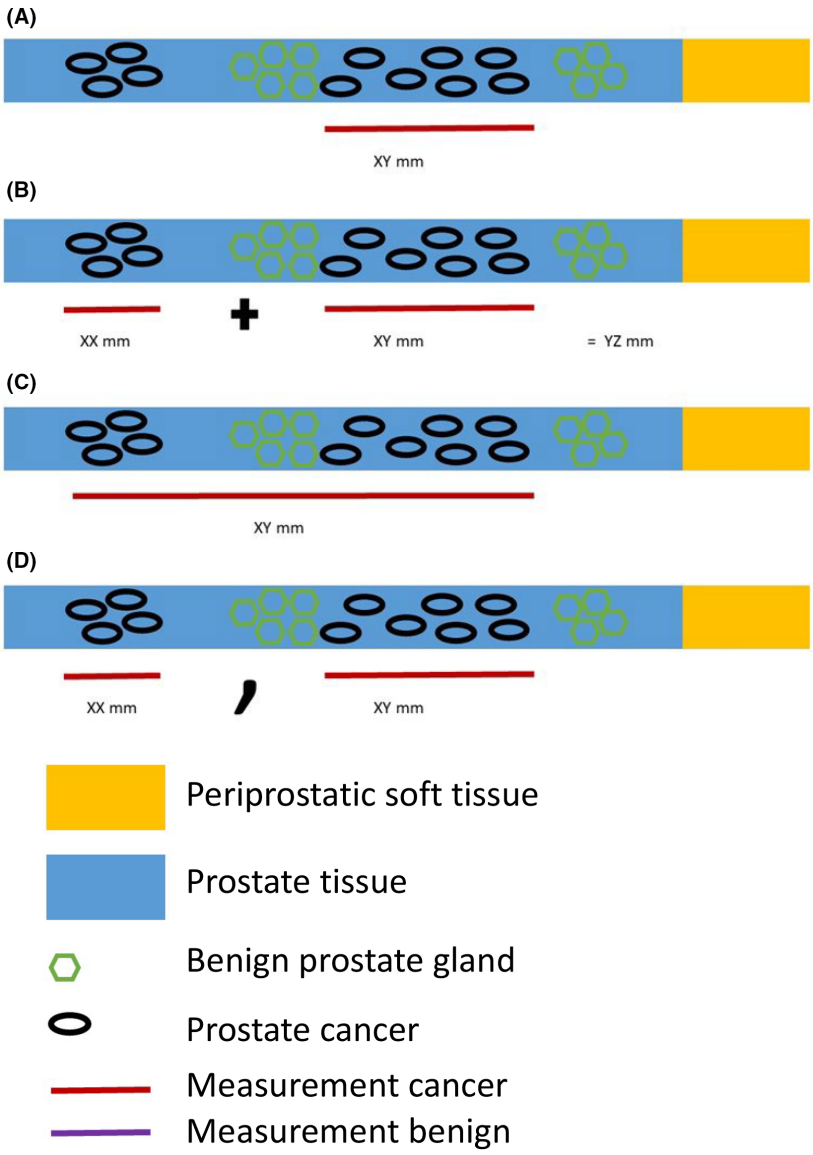

Figure 1. Overview of different methodologies for determining tumour content in prostatic biopsies: length. As illustrated, several structures may be observed in a tumour-bearing prostate biopsy. Apart from tumour (black circles) and benign prostatic glands (green hexagons), periprostatic soft tissue or tissue from the access route of the punch biopsy may be present (yellow rectangles). Benign glands may be found in between tumour infiltrates, and the tumour is present in a discontinuous or multifocal fashion within one core. Should only the greatest tumour length be included in the individual determination of tumour size (**A**), or should multiple foci be summed up (**B**)? Alternatively, the greatest dimension from first to last tumour gland may be measured if the tumour grows discontinuously (**C**) or tumour extent may be reported as a list of lengths of each tumour focus observed (**D**).

the participants. For measurements, the open-source software QuPath (version 0.4.4) was used.[10]

SLIDES

Slides were digitised using the Leica Aperio GT 450 DX Slide Scanner (Leica, Wetzlar, Germany) and uploaded to PathoZoom© Slide Cloud (Smart in Media AG, Köln, Germany) (Supplementary Information 2).

STATISTICS

Statistical analysis was performed using R Statistical Software (version 4.4.0; R Core Team 2021) and SPSS (IBM SPSS Statistics for Windows, version 28.0.

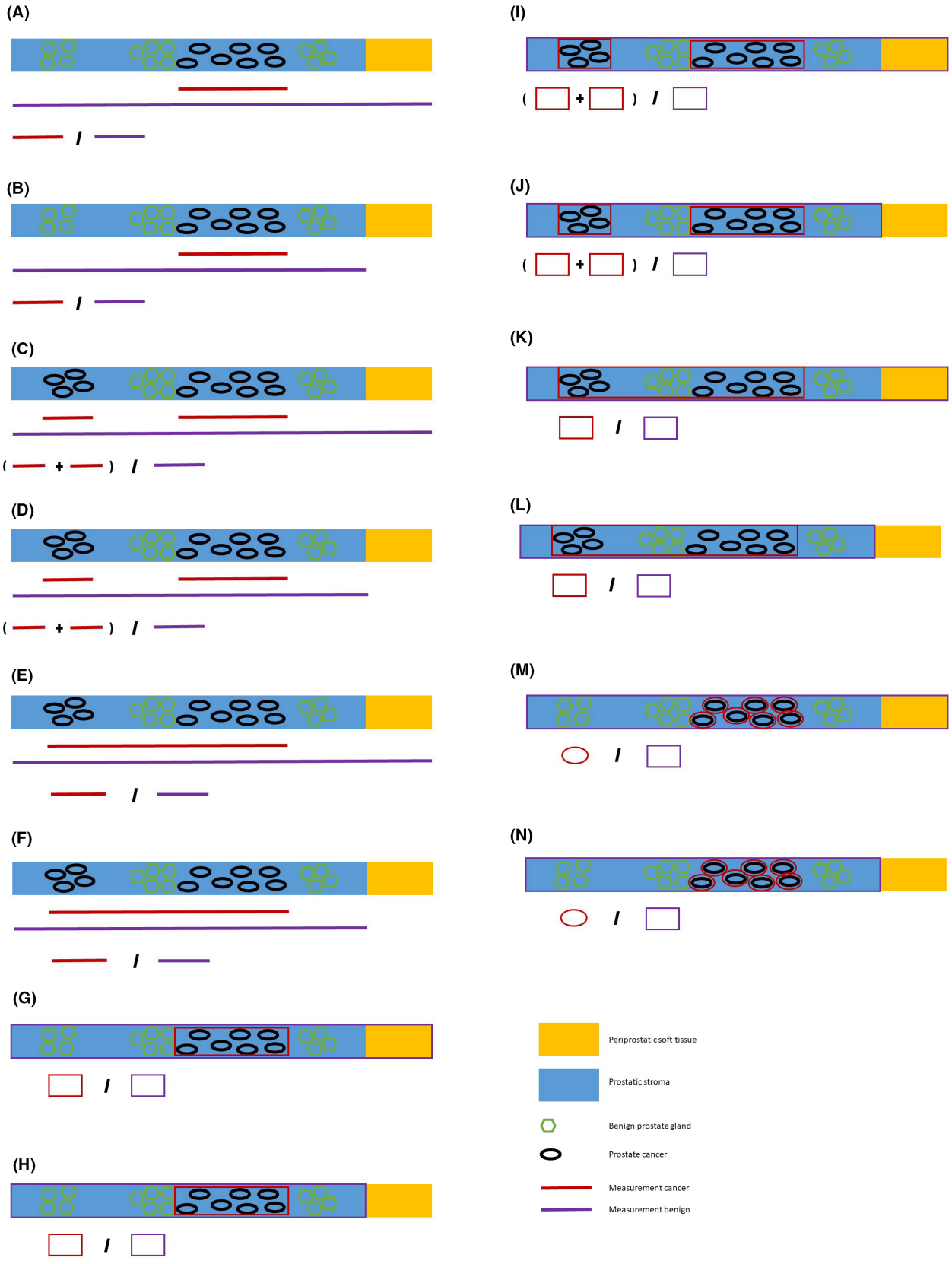
(A)
(B)
(C)
(D)
(E)
(F)
(G)
(H)
(I)
(J)
(K)
(L)
(M)
(N)
Periprostatic soft tissue
Prostatic stroma
Benign prostate gland
Prostate cancer
Measurement cancer
Measurement benign

Figure 2. Overview of different methodologies for determining tumour content in prostatic biopsies: percentage. As illustrated, several structures may be observed in a tumour-bearing prostatic biopsy. Apart from tumour (black circles) and benign prostatic glands (green hexagons), periprostatic soft tissue or tissue from the access route of the punch biopsy may be present (yellow rectangles). Benign glands may be found in between tumour infiltrates, and the tumour is present in a discontinuous or multifocal fashion within one core. To determine tumour extent one may divide the greatest length of a tumour focus by dividing it by the total length of the core, considering (**A**) or disregarding (**B**) periprostatic soft tissue. Here, too, the question remains if length of discontinuous tumour foci should be measured from first to last tumour cell (**E**,**F**) or as a sum of tumour gland extent only (**C**,**D**). Many biomarker scoring systems in which a percentage is specified (e.g. programmed cell death ligand) refer to a specific area occupied by the corresponding target structure (i.e. positive cells). This may represent a different approach, although the problem of any periprostatic soft tissue that may be included would not be solved here. The question also remains as to whether the tumour-associated stroma immediately adjacent to the tumour epithelia should be included in the calculation (**G**,**H**,**M**,**N**). Moreover, the optimal approach for managing the intervening benign stroma remains uncertain (**I**,**J**,**K**,**L**).

Armonk, NY, USA). In order to compare results in the different units mm and percentage, a non-parametric coefficient of variation was calculated. Essentially, in comparison to a conventional calculation of the coefficient of variation, the standard deviation is replaced by the median absolute deviations and divided by the median.[11,12] Confidence intervals were calculated by bootstrapping (1000 replicates). Statistical significance was defined by P-value < 0.05. To assess the interobserver variability according to ISUP grade groups, a weighted (ordinal) Fleiss' kappa was calculated.

Results

SURVEY RESPONDENTS

Two hundred and thirty-eight ISUP members participated in the study, practising in 52 countries on all continents: United States (24.8%), United Kingdom (7.6%), Australia (7.1%), Spain (4.2%), Switzerland (4.2%) and others (52.1%). The majority practised at university hospitals/academic settings (57.1%) or community hospitals (24.4%), with a minority in private practice (15.5%) or other settings (1.7%). Median work experience after board certification was between 11 and 20 years after board examination. The majority of participants described themselves as either uropathologists (70.6%) or generalists (19.4%), and reported prostatic needle core biopsies on a daily basis or several days per week (87.1%).

Sixty-six DGP members answered the survey. With the exception of two respondents (3%), who were located in Switzerland, all were practising in Germany. The workplace was most commonly in an academic setting (57.6%) or community hospital (24.2%) rather than in private practice (18.2%). Median work experience was between 11 and 20 years after board examination. Approximately half the pathologists considered themselves as generalists (45.5%), followed by gynaecological/breast (19.7%) and uropathologists (19.7%). The majority of respondents stated that they reported prostatic biopsies on a daily basis or on several days per week (74.2%).

TUMOUR CONTENT DETERMINATION

In both groups (ISUP/DGP) the majority of participants reported tumour content either as percentage alone (43.4%; 41.5% ISUP; 50.0% DGP) or both as percentage and mm (37.6%; 40.6% ISUP; 27.5% DGP), with the remainder solely reporting mm (18.3%; 17.0% ISUP; 22.5% DGP). Among participants, 0.72% (ISUP 0.9%; DGP 0%) reported ISUP grade group alone without tumour content. Within the 14 options for reporting percentages representing both scenarios with single as well as multiple tumour foci (multiselection possible) and four options for reporting tumour length, the answers displayed a wide spread (Figure 4). In the ISUP group the most commonly chosen ($n = 53$, 24.6%) option to report percentages was to divide the (discontinuous) tumour length by the total core length, including periprostatic tissue. In contrast, the DGP group preferred ($n = 15$, 25%) to calculate the percentage by the total sum of infiltration length of individual tumour infiltrates divided by length of prostatic parenchyma, excluding extraprostatic soft tissue.

Participants most commonly reported the length of tumour tissue by considering all tumour infiltrates. In contrast to the respondents from the ISUP, who preferentially reported tumour length which included intervening benign tissue (51.2% ISUP versus 14.5% DGP), respondents from the DGP preferred to ignore intervening benign tissue and restricted the report to the sum of lengths of all individual tumour spots in the biopsy (57.1% DGP versus 21.4% ISUP). An overview of the poll responses is given in Supplementary Information 3.

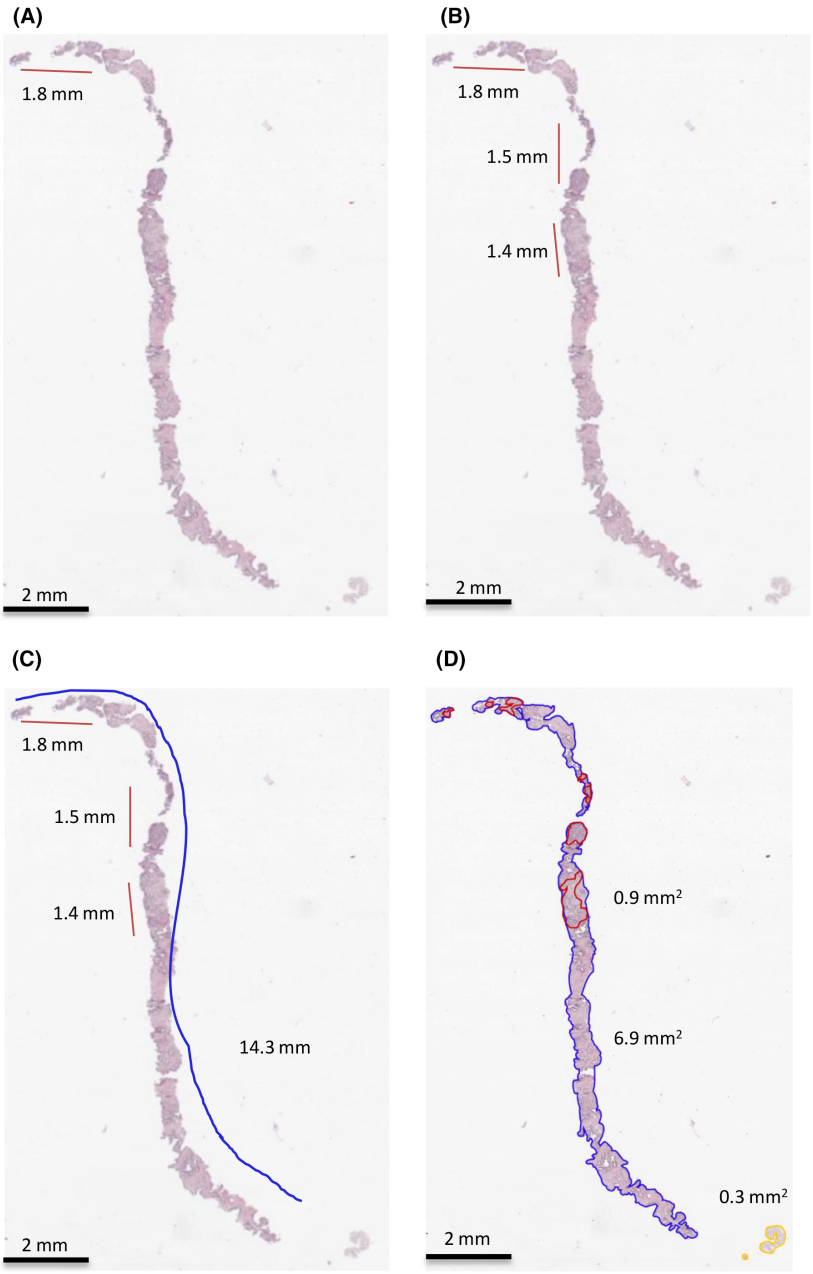

Figure 3. Exemplary application of the various methods to case 9. Tumour highlighted in red, benign prostatic tissue in blue, periprostatic tissue in yellow (**D** only). Determination of length in mm according to methods A (**A**) and D (**B**); determination of tumour extent in percentage according to methods D (**C**) and H (**D**).

PRACTICAL SLIDE REVIEW

Theoretical tumour extent

To demonstrate the variability of tumour extent as a function of the method applied, all 10 slides were reviewed by two experienced uropathologists (G.K., M.B.) and the tumour content for percentages and absolute measures in mm was determined applying all 18 methods. Minimum and maximum results per case were identified for lengths (Figure 5A) and percentages (Figure 5B). For lengths, identical values were obtained in six cases. In the other four cases, the discrepancy of measurements ranged from 0.98 to 5.7 mm (Figure 5A). For percentages, only a single identical value was obtained and the discrepancies of percentage points ranged from 1.2 to 77.0%

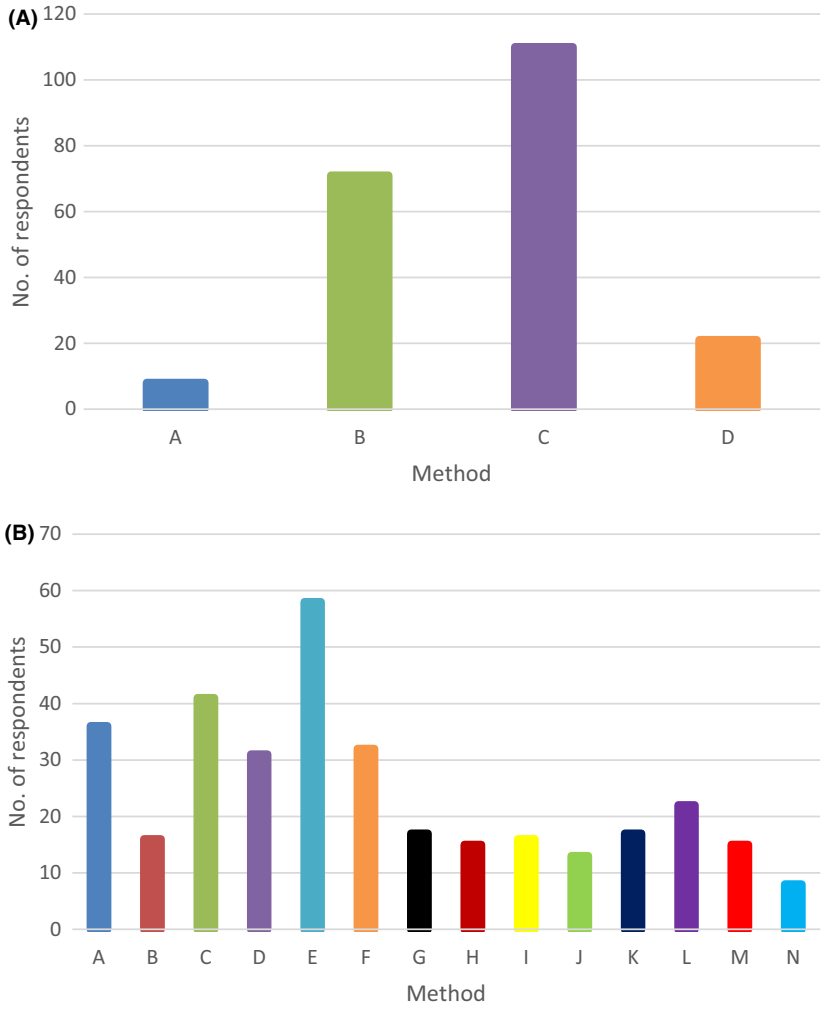

Figure 4. Participants' responses on the preferred methodology for determining tumour content. (**A**) Determination of tumour length; (**B**) determination of tumour involvement in percentage, chosen methods (A–D) or (A–N), respectively, correspond to the methods presented in Figures 1 and 2.

(Figure 5B). This illustrates the higher theoretical variability of percentages in reporting tumour extent.

For the practical test, results were available from 92 participants from the ISUP and 32 from the DGP. The range of minimal and maximal values obtained from the survey for all cases is depicted in mm (Figure 5C) and percentage (Figure 5D). Additionally, the median results +/− 1 standard deviation are shown in mm (Figure 5E) and percentage (Figure 5F).

Comparison of variation: percentages versus absolute length

A non-parametric version of the coefficient of variation was calculated. Herein, the coefficient of variation was 0.00–0.63 (ISUP 0.00–0.57; DGP 0.00–1.48) for tumour length in mm and 0.08–1.48 (ISUP 0.08–0.73; DGP 0.08–1.48) for tumour percentage. Generally, cases with higher variability for tumour content in mm also showed higher variability in the percentage group. Overall, tumour content reported as percentage showed significantly higher variability both for all participants ($P = 0.014$), as well as in the two groups of participants (ISUP $P = 0.014$; DGP $P = 0.016$) (Figure 6).

Concordance of theoretical and practical performance

Among respondents who provided information both in the survey and the practical performance, 30 (24.2%) claimed to report tumour in mm, 48 (38.7%) reported in percentage and 44 (35.5%) both in mm and percentage. Regarding the actual results

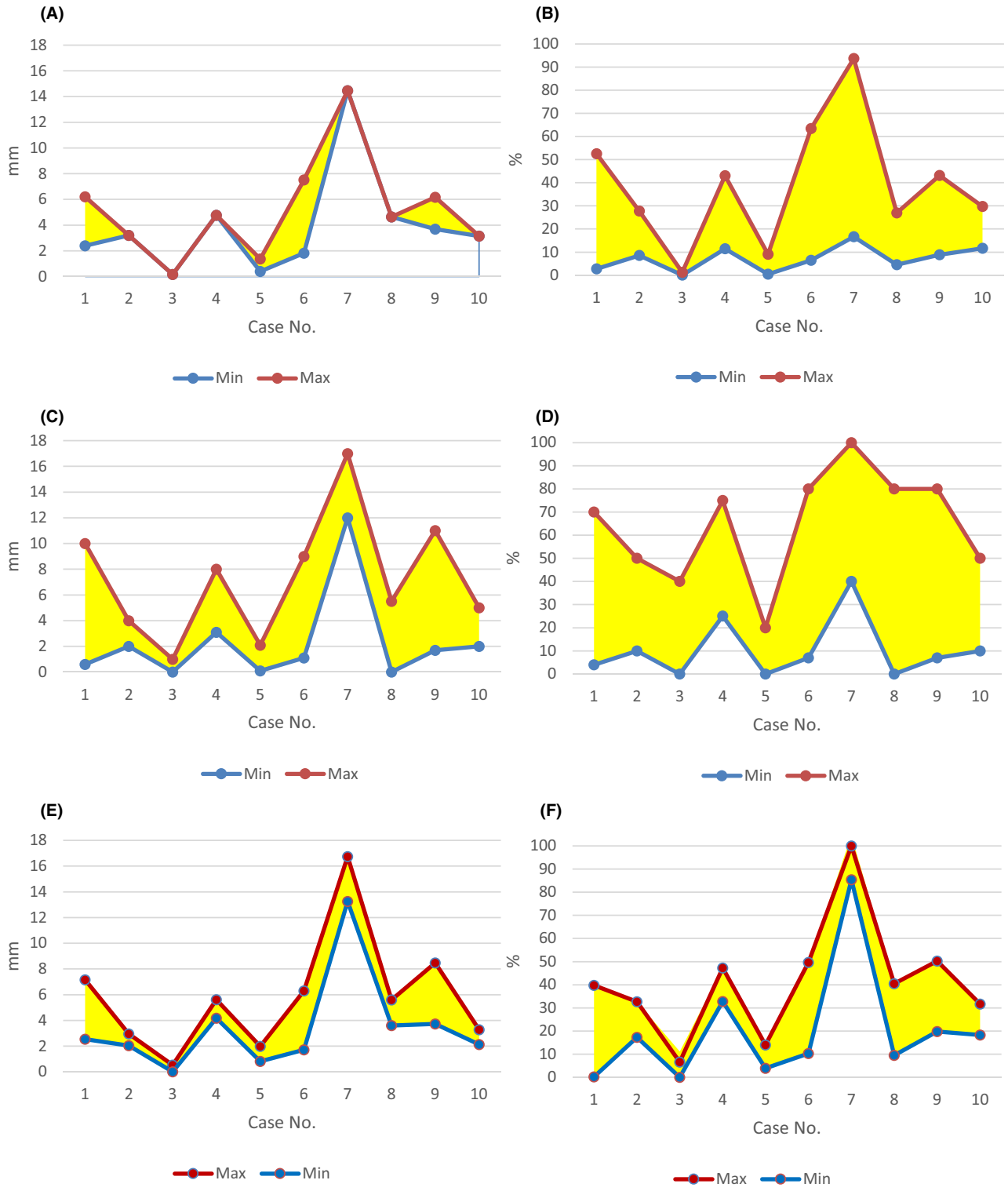

Figure 5. Expected and observed range of tumour content depending on method used: mm versus percentage. (**A**,**B**) Expected range when using either the length method (**A**) or percentage method (**B**); (**C**–**F**) definitive range provided by participants illustrated as range from minimal to maximal values (**C**, **D**) and as median +/− 1 standard deviation (**E**, **F**) for length and percentage, respectively.

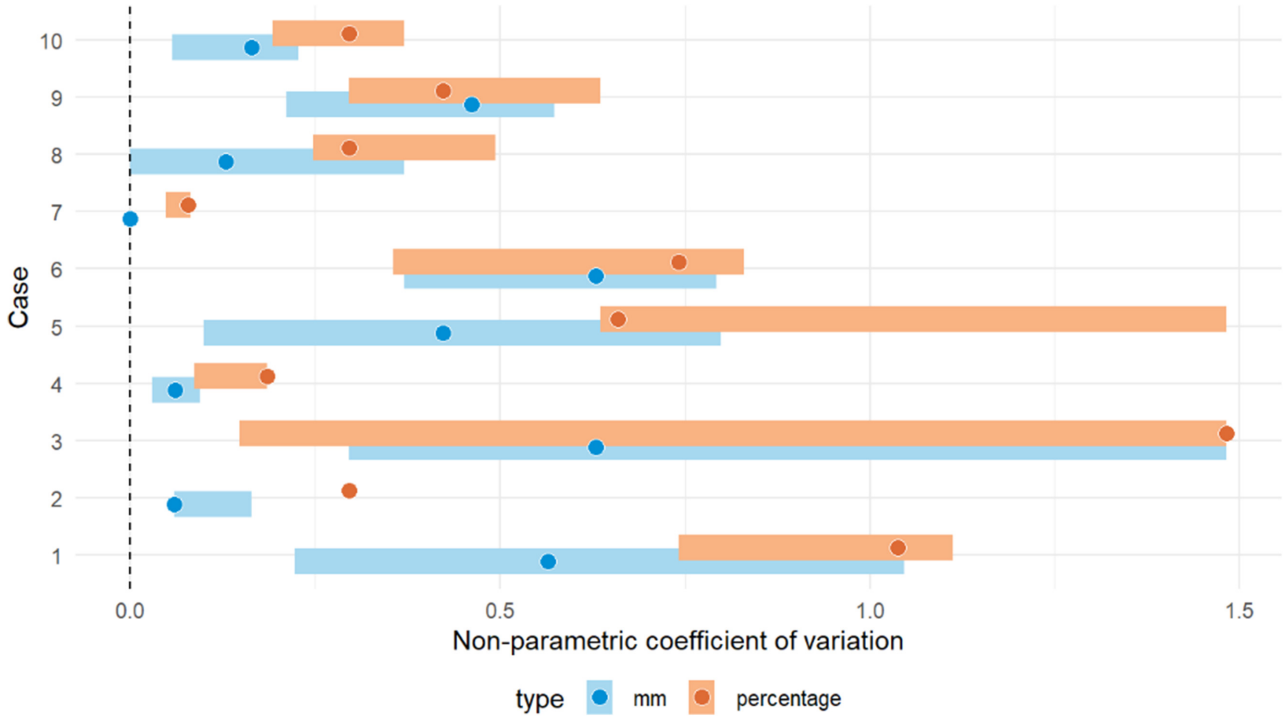

Figure 6. Non-parametric coefficient of variation for tumour content in mm (blue) and percentage (orange). The further to the right, the higher the coefficient and the greater the variability of the result obtained.

in the practical performance, the method reported and the method used were concordant for 90 participants (78.3%). Nine respondents were excluded from the analysis because only ISUP GG was provided.

Tumour grade

ISUP GG were provided by 123 participants (32 DGP, 91 ISUP), summarised in Table 1. Apart from case 1, the majority of participants diagnosed the same tumour grades that the authors had signed out originally, which were considered as the gold standard (Table 1). Weighted Fleiss' kappa was 0.769 for all participants (ISUP 0.778, DGP 0.751).

Discussion

This study provides results from a survey on the reporting practices for prostatic biopsies. The majority of participants (43.4%) reported tumour extent in percentages alone, closely followed by those who reported both percentage and absolute length in mm (37.6%), while only 18.3% reported absolute length in mm exclusively. The overwhelming preference for percentages (81.0%) was unexpected, especially given that in a 2014 poll by the members of the European Network for Uropathology (ENUP), 53% of participants favoured absolute measures in mm.[13] Reporting tumour content in percentages is the exception in histopathology and is used primarily in bone marrow and prostate assessments. In both organs, it was difficult to visualise tumour infiltrates radiologically in the past, so assessing the ratio of benign to tumourous tissue in a biopsy was crucial to estimate tumour size. The introduction of multiparametric MRI, which finally made it possible to visualise clinically relevant prostate cancer, was a turning point in the diagnosis of prostate biopsies.[14]

Currently, the guidelines that were established in the pre-magnetic resonance imaging (MRI) era are still relevant and percentage reporting still has a place.[15,16] Prostate cancer patients face a great risk of overtreatment.[4] AS is a therapy strategy designed to minimise overtreatment for low-risk prostate cancer patients.[6] Most AS protocols base inclusion on serum PSA, ISUP grade group and clinical tumour stage, as well as number/percentage and amount of involved cores.[6,17] Risk stratification on biopsy is crucial, as it is known that tumour extent both as number and proportion of involved cores, as well as linear tumour extent, correlate with tumour volume at radical prostatectomy.[3,18] The percentage of carcinoma

Table 1. Overview of ISUP grades provided by the participants

Case no.	Gold-standard	Benign or ASAP (%)	ISUP 1 (%)	ISUP 2 (%)	ISUP 3 (%)	ISUP 4 (%)	ISUP 5 (%)
1	ISUP 2	0	81.3	17.9	0	0.8	0
2	ISUP 1	0	51.2	43.0	4.1	1.7	0
3	ISUP 1	37.7	61.3	1	0	0	0
4	ISUP 3	0	0	20.2	46.2	19.3	14.3
5	ISUP 1	7.55	81.9	8.55	1	1	0
6	ISUP 5	0	0	0.9	5.2	19.8	74.1
7	ISUP 5	0	0	0	3.4	12.1	84.5
8	ISUP 2	2.8	8.3	58.3	28.7	0.95	0.95
9	ISUP 3	0	0.9	41.0	45.3	12.8	0
10	ISUP 2	0	34.2	50.4	10.3	5.1	0

ASAP, atypical small acinar proliferation; ISUP, International Society of Urological Pathology.

infiltration per core (< 50%) is among the inclusion criteria for AS of the Johns Hopkins Medical Institutions and the Memorial Sloane Kettering Cancer Center, whereas the Royal Marsden Hospital requires absolute measures (< 10 mm per core).[19] A recent systematic review on AS also recommended cancer involvement of less than 50% per core as a crucial inclusion criterium.[6]

The optimal diagnostic method for the quantification of carcinoma infiltrates in prostate biopsies has long been disputed.[18,20] Some argue that the percentage measurements on biopsies may be more robust, because fixation and tissue processing may lead to a shrinkage of tissues.[21] In fact, the shrinkage of tissues revolves approximately 5–10%, but this bias affects all laboratories equally.[22]

An argument in favour of reporting percentages is their ease of use, as many pathologists estimate by visual assessment ('eyeballing') rather than precise measurements. However, the major drawback of using percentages is that the representativeness of the biopsy core is ignored. A 2-mm cancer focus in a 3-mm biopsy core will result in 66% carcinoma extent, disqualifying this patient for many AS regimens, whereas an 8-mm carcinoma of the same grade sampled in a 19-mm core implies inclusion. Recommendations from the ICCR, CAP, the Royal College of Pathologists and the German S3 guideline allow both percentages and absolute measures.[7,9,23,24] However, with regard to CAP, measurement in percentage is a core element, while reporting tumour content in mm remains optional. In addition, percentages are not reported as absolute values but in steps of 5–10%.[7] Given the large number of participants from the United States in the present study, and the difference between CAP recommendations and those of other societies, this may have influenced the data obtained. However, participants were free to choose the methodology with which they were most familiar, so that lack of experience should not be a limiting factor in the result. Nevertheless, harmonisation of guidelines is desirable. The introduction of standardised reporting schemes, such as those developed by ICCR, could help to achieve this. The implementation of ICCR data sets is becoming more common in a variety of countries, enabling pathologists to both follow national guidelines as well as providing diagnoses that are comparable in an international setting.[9,25] Recently, Berney *et al.* demonstrated that linear tumour length in biopsies was a prognosticator of disease progression, yet in a multivariate setting the percentage of positive cores clearly outperformed measures from individual biopsies. Nevertheless, the authors advocate the relevance of individual measures for AS inclusion.[26]

As percentages of areas of tumours that do not exhibit full-thickness infiltration of the biopsy core allows for a more precise estimation of tumour content, we had expected that more pathologists would consider tumour areas instead of lengths in relation to the biopsy core area to define percentages, but the majority of respondents combined lengths to calculate percentages. An even more surprising finding was the diversity in how percentages were defined among

participants. Among the 14 permutations we envisioned initially, the results show an almost even spread among these options with minor but decisive differences. The most common method among ISUP members (24.7%) was to calculate percentages by dividing the length of tumour, including intervening benign tissue, by the core length, including periprostatic tissue. Members of the DGP favoured (25.0%) dividing the total sum of infiltration length of individual tumour infiltrates by length of prostatic parenchyma, excluding extraprostatic soft tissue and intervening benign prostate parenchyma. To include periprostatic tissue in a quotient that is meant to quantify intraprostatic tumour content is obviously questionable, but this may indicate that the total length of the core is taken from the gross report (which includes periprostatic tissue). A minor limitation of the results may be the fact that the question covered the choice of method for both single and multiple foci, so the somewhat low response rate for the single-focus options (Figure 4B) may not be representative of this type of case. However, the greatest differences between the two groups surveyed here were in the management of intervening benign and extraprostatic soft tissue, with the former only being an issue in a multiple focus scenario. Reporting of discontinuous carcinomas infiltrates has long been a matter of research. Without imaging information, it remains unclear whether two distinct tumour foci in a biopsy represent two different tumours or spurs of the same tumour. Due to the largely non-destructive infiltrative growth of prostate cancer, most authors agree that intervening benign tissue is probably intratumourally located, and hence ought to be included in the measurement.[27] Approximately 20% of tumours, however, represent distinct tumour foci, so that it should be stated clearly in the report if a discontinuous measurement is provided.[28]

Determining tumour extent in absolute measures offers fewer options. The most common approach involved measuring tumour infiltrates end-to-end, including benign tissue (52.0%), followed by subtracting intervening benign tissue (33.8%). ISUP members favoured including benign tissue, whereas DGP members preferred not to.

The practical element of this study, to analyse 10 haematoxylin and eosin slides, was taken by approximately 40% of participants. First, the data confirm that they largely (78.3%) adhere to their stated preferred procedure of evaluation (mm versus percentage). Secondly, the expected interobserver variability of tumour grades demonstrated very good reporting consistency, with a weighted Fleiss' kappa of 0.769. Finally, the variability of tumour extent reported was remarkable. Interobserver variability in histopathology has long been recognised as a relevant confounder in cancer treatment planning. The observer-dependent variation in Gleason grading has received the most attention.[29,30] Interobserver variability extends to tumour staging, margin diagnosis and the identification of perineural invasion—categories typically considered more robust.[31,32] This study identifies the reporting of tumour extent in prostate biopsies as a previously underestimated source of variability, noting a lower variability when reporting lengths. The strength of this study is the voluntary contribution of ISUP and DGP members who participated in this survey and who signed out 10 real prostate biopsy cases. Weaknesses of the study are the small number analysed (n = 10) that necessitated a selection of cases and the lack of immunohistochemistry and follow-up data.

Conclusion

The significant interobserver variability observed in reporting tumour content from prostate biopsies urges us to reconsider the methodology to determine tumour content, which ought to be defined more clearly in the future. Concluding from the data presented, providing absolute measures (in mm) of tumour length in core biopsies, measured end-to-end including intervening benign tissue, seems to be a rational choice. If percentages are required, we suggest they should also be based on exactly these measurements and calculated in relation to the prostate biopsy as measured under the microscope, excluding periprostatic tissue.

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supplement 1. Invitation letter and Survey questions.

Supplement 2. Survey, practical part: links to the whole slide images of 10 biopsy cases of prostate cancer.

Supplement 3. Survey results in detail.

