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ANATOMICAL PATHOLOGY

Dataset for the reporting of prostate carcinoma in core needle biopsy and transurethral resection and enucleation specimens: recommendations from the International Collaboration on Cancer Reporting (ICCR)

Lars Egevad[1], Meagan Judge[2], Brett Delahunt[3], Peter A. Humphrey[4], Glen Kristiansen[5], Jon Oxley[6], Krishan Rasiah[7], Hiroyuki Takahashi[8], Kiril Trpkov[9], Murali Varma[10], Thomas M. Wheeler[11], Ming Zhou[12], John R. Srigley[13], James G. Kench[14]

[1]Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; [2]Royal College of Pathologists of Australasia, Sydney, NSW, Australia; [3]Department of Pathology and Molecular Medicine, Wellington School of Medicine and Health Sciences, University of Otago, Wellington, New Zealand; [4]Department of Pathology, Yale University School of Medicine, New Haven, CT, USA; [5]Institute of Pathology, University Hospital Bonn, Bonn, Germany; [6]Department of Cellular Pathology, Southmead Hospital, Bristol, UK; [7]Department of Urology, Royal North Shore Hospital, St Leonards, NSW, Australia; [8]Department of Pathology, The Jikei University School of Medicine, Tokyo, Japan; [9]Department of Pathology and Laboratory Medicine, University of Calgary and Calgary Laboratory Services, Alberta, Canada; [10]Department of Cellular Pathology, University Hospital of Wales, Cardiff, UK; [11]Department of Pathology & Immunology, Baylor College of Medicine, Houston, TX, USA; [12]Department of Pathology, UT Southwestern Medical Center, Dallas, TX, USA; [13]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada; [14]Department of Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Camperdown, NSW, Australia

Summary

The International Collaboration on Cancer Reporting (ICCR) is a project which issues datasets and guidelines for international standardisation of cancer reporting. This review summarises the required and recommended elements of the datasets for prostate core needle biopsies and transurethral resection (TURP) and enucleation specimens of the prostate. To obtain as much information as possible from needle biopsies there should be only one core in each specimen jar with the exception of saturation biopsies. The gross description of the specimens should include core lengths of needle biopsies and weight of resection specimens. The tumours should be classified according to the 4th World Health Organization (WHO) classification and graded both by Gleason scores and the grouping of these in International Society of Urological Pathology (ISUP) grades (Grade groups). Percent high-grade cancer is an optional component of the report. Tumour extent in needle biopsies should be reported both by number of cores positive for cancer and the linear extent measured in either millimetre or percent core involvement by tumour. In needle biopsies where low-grade cancer is discontinuous and seen in few cores, it is recommended that the tumour extent should be reported both by including and subtracting intervening benign tissue. For resection specimens, the percentage of the tissue area (or percentage of number of TURP chips) involved with cancer should be estimated. Extraprostatic extension should be reported when seen, while the reporting of perineural, seminal vesicle/ejaculatory duct and lymphovascular invasion is only recommended. Intraductal carcinoma of the prostate (IDC-P) should be reported when present, because of its strong link with aggressive cancer. The current recommendation is that the IDC-P component should not be graded. The structured and standardised reporting of prostate cancer contributes to safer and more efficient patient care and facilitates the compilation and understanding of multiparametric diagnostic and prognostic data.

Key words: Prostate; TURP; needle biopsy; cancer; datasets; protocols; tumour classification; grading.

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INTRODUCTION

Over recent years, datasets for the pathology reporting of cancer have been published by many organisations around the world, at national and institutional levels. In the United States of America the College of American Pathologists (CAP) currently publishes more than 80 'checklists' for synoptic reporting of all major cancers.[1] In the United Kingdom the Royal College of Pathology (RCPath) publishes cancer datasets,[2] and in Australia the Royal Australasian College of Pathologists (RCPA) has published

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structured reporting protocols for cancer reporting.[3] Moreover, a number of European countries have active programs of a similar nature. These protocols define the detailed pathology and staging data essential for patient management and prognostication, with the intention that the documentation is complete, concise, reproducible and in line with international standards and current knowledge. Since all evidence-based cancer protocols are necessarily derived from international peer-reviewed literature, it is inevitable that cancer protocols produced by these various organisations will contain similar data elements, although with minor variations.

Recognising that standardised cancer datasets are a prerequisite for national and international benchmarking in cancer monitoring and management, the quadripartite alliance of CAP, RCPath UK, the Canadian Association of Pathologists in association with the Canadian Partnership Against Cancer (Canada) and the RCPA signed an agreement in 2011 to pilot the development of four cancer datasets: prostate (radical prostatectomy), endometrium, melanoma, and lung cancer. This pilot was established to examine the practicability of developing international, evidence informed pathology datasets for all major cancers and has proved to be very successful. In 2013 the initial quadripartite collaboration was joined by the European Society of Pathology and these five parties became the foundation members of the International Collaboration on Cancer Reporting (ICCR) when it was incorporated as a not-for-profit organisation in 2014.

The International Agency on Cancer Research (IARC) is responsible for the development and publication of the World Health Organization (WHO) Classification of Tumours blue book series which is an essential inclusion in all ICCR datasets. In 2013, the ICCR agreed to synchronise its schedule of dataset development with the publication of the WHO blue book series. In 2016, the IARC released the 4th edition of the WHO Classification of Tumours of the Urinary System and Male Genital Organs;[4] as a result, the ICCR initiated the development of genitourinary datasets to align with this publication.

As prostate cancer is one of the most commonly diagnosed cancers worldwide, the development of internationally agreed evidence-based datasets for prostate cancer specimens was of high priority. The ICCR has already published a radical prostatectomy dataset which was developed in 2011 as part of a pilot project and this has subsequently been revised and updated.[5] Datasets for core needle biopsies and transurethral resection of the prostate (TURP), and enucleation specimens were developed in conjunction with the revised protocol for radical prostatectomy specimens and incorporates recent developments in the literature. All ICCR Datasets are freely available from the website (www.ICCR-Cancer.org).

METHODS

In the development of the previous datasets a variety of processes were established for review of the literature and agreement on consensus recommendations. This process has been extensively refined and is now documented in the Guidelines for the Development of ICCR Datasets.[6] This guideline provides a framework both for the process of development of each dataset as well as for its format and content.

Each dataset is developed by a Dataset Authoring Committee (DAC), being led by chairs appointed by the ICCR Dataset Steering Committee (DSC). The co-chairs appointed for the development of datasets for prostate cancer were James Kench (Australia) and Lars Egevad (Sweden). The co-chairs assisted the DSC in identifying suitable candidates for the DAC, as did the International Society of Urological Pathology (ISUP).

The DAC convened for prostate cancer consisted of 12 expert pathologists, which included the co-chairs, a urologist, an ICCR project manager to assist in the development process and an ICCR DSC representative. The DSC representative's role was to provide guidance and support to the chairs of the DAC regarding ICCR standards and to monitor quality assurance. The development of datasets for genitourinary specimens prompted the ICCR to consider an additional role of 'Series Champion' to oversee harmonisation across the suite and in this case the ICCR DSC representative was also appointed to this role.

The members of the DAC were tasked with the development of three datasets: an update of the published radical prostatectomy dataset[5] and two additional datasets to support core needle biopsies and TURP and enucleation specimens which are the focus of this review.

Each dataset is comprised of elements with value lists and a commentary. Elements may be either required or recommended. Required (Core) elements are essential for the clinical management, staging or prognosis of the cancer. For inclusion in this category evidentiary support at Level III-2 or above (based on prognostic factors in the NHMRC levels of evidence document[7]) was sought. Recommended (Non-Core) elements may be clinically important and appropriate to good practice, but are not yet fully validated or universally required for patient management.

Other components of the dataset are the Value Lists (Responses) and Commentary. The Value Lists for the data elements were defined for each of the data elements to reduce ambiguity and to provide consistency in the dataset. The Commentary consists of explanatory text, diagrams, or tables. These aim to clarify the elements, define the way an item should be reported, ensure clarity and conformity and explain why an item is included (e.g., how an item assists clinical management or informs of prognosis). The Commentary cites published evidence in support of the element and states any exceptions or issues that may be encountered by the reporting pathologist.

For core needle biopsies, TURP and enucleation specimen datasets initial working drafts were developed by the Project Manager, edited by the chairs and distributed to the DAC. Feedback from the DAC was compiled and provided the basis for discussion at a series of web/teleconferences. Based on these discussions, the chairs edited the documents and re-circulated them to the DAC for a second review and comment. After final endorsement by the DAC, the dataset was formatted and posted to the ICCR website for a period of 6 weeks for public comment. Following this feedback, the dataset was reviewed and final changes made by the DAC. After final review by the DAC, the dataset was approved for publication and submitted to the ICCR DSC for ratification.

RESULTS

The elements and associated commentary in these two datasets apply to invasive carcinomas of the prostate gland. Urothelial carcinomas arising in the bladder or urethra are dealt with in separate datasets,[8,9] while urothelial carcinomas arising in the prostate are included in this dataset. Tables 1 and 2 list the required data elements and Tables 3 and 4 the recommended data elements for pathological reporting of TURP and enucleation specimens. Table 5 summarises the WHO classification of tumours of the prostate and Table 6 the ISUP grading system.

Required elements (Tables 1 and 2)

Specimens submitted (core needle biopsy specimens)

Information on submitted needle biopsies should include the number and length of cores, and the sites of the biopsy.[6] The core lengths should be assessed by measuring the wet specimens before tissue processing and paraffin embedding. To obtain as much information as possible from needle biopsies there should be only one core in each specimen jar.[10] If two or

Table 1 Required data elements for pathological reporting of core needle biopsies

Macroscopic	Microscopic
Specimens submitted • Specimen/container identity • Biopsy location • Total number of cores • Length of core(s)	Histological tumour type Histological grade • Gleason score • International Society of Urological Pathology (ISUP) grade (Grade group) Tumour extent • Number of positive cores/total number of cores AND • Length of tissue involved by carcinoma by millimetre OR • Linear extent of prostatic tissue involved by carcinoma by % Extraprostatic extension

more cores are submitted in a single container, it may not be possible to determine the number of involved cores because of biopsy fragmentation. If more than one core is submitted per container the number of cores present should be stated by the submitting urologist as this may assist interpretation. However, this would not be an issue if cores are submitted individually.[11] If more than five cores are submitted in a specimen jar, e.g., with saturation/template biopsies, the range of core lengths may be reported rather than measuring each core.

Operative procedure (TURP/enucleation specimens)

Information regarding the nature of the surgical procedure undertaken is generally a required item in ICCR datasets. Thus, specifying that a specimen is obtained by TURP or enucleation is mandatory.

Specimen weight (TURP/enucleation specimens)

The total specimen weight is the best estimate of the amount of tissue resected at TURP or enucleation.[12] The specimen may be weighed either in the operation room or in the pathology laboratory.

Histological tumour type (core/needle biopsy and TURP/enucleation specimens) (Table 5)

Greater than 95% of prostate cancers are acinar adenocarcinomas.[4] Other types of carcinoma must be recorded if present, since some subtypes, such as ductal adenocarcinoma, small cell carcinoma, sarcomatoid carcinoma and urothelial carcinoma, have a poor prognosis.[4,13–18] The tumour type should be assigned according to the 2016 WHO classification.[4] Subtypes of prostate carcinoma are often combined with acinar adenocarcinoma, and in such cases the tumour type should be classified according to the non-acinar subtype.

As noted earlier, urothelial carcinomas arising within the prostate are included in this dataset, while urothelial carcinomas arising in the bladder or urethra are dealt with in separate datasets. Information on histological tumour type may be recorded at either specimen or case level. The response type 'No evidence of primary tumour' can only be used in specimen level reporting since the datasets are only applicable to prostate cancer specimens.

Histological grade (core/needle biopsy and TURP/enucleation specimens)

The Gleason grading system is the foundation of prostatic adenocarcinoma grading. The Gleason score was traditionally obtained by adding the two predominant Gleason patterns, or doubling the pattern in cases with uniform grade. This was modified in the ISUP 2005 revision by always including the highest grade in the Gleason score of needle biopsies, regardless of its amount.[19] At a subsequent ISUP consensus conference in 2014, the Gleason system was further modified and this version was adopted in the 4th edition of the WHO classification. It was decided that Gleason pattern 4 should include fused or poorly formed glands, glomerulations and all cribriform patterns of acinar adenocarcinoma. A grouping of the Gleason scores into 5 grade categories (ISUP grades) was

Table 2 Required data elements for pathological reporting of TURP and enucleation specimens

Clinical	Macroscopic	Microscopic
Operative procedure	Specimen weight	Histological tumour type Histological grade • Gleason score • International Society of Urological Pathology (ISUP) grade (Grade group) Prostatic tissue involved by tumour • Prostatic tissue involved by tumour measured as % of tissue area (TURP or enucleation/suprapubic prostatectomy specimens) OR • Prostatic tissue involved by tumour measured as % of number of prostatic chips (TURP specimens only)

Table 3 Recommended data elements for pathological reporting of core needle biopsies

Clinical	Macroscopic	Microscopic
Clinical information • Previous history of prostate cancer • Previous biopsy Pre-biopsy serum PSA Clinical stage	Block identification key	Histological grade – Percentage Gleason pattern 4/5 Perineural invasion Seminal vesicle ejaculatory duct invasion Lymphovascular invasion Extraprostatic extension – location Intraductal carcinoma of prostate Coexistent pathology

Table 4 Recommended data elements for pathological reporting of TURP and enucleation specimens

Clinical	Macroscopic	Microscopic
Clinical information • Previous history of prostate cancer • Previous biopsy • Previous therapy • Other Pre-procedure serum PSA Clinical stage	Specimen dimensions Block identification key	Histological grade – Percentage Gleason pattern 4 or 4/5 Perineural invasion Seminal vesicle invasion Lymphovascular invasion Extraprostatic extension Intraductal carcinoma of prostate Coexistent pathology

proposed and later formally endorsed by the ISUP Council in March 2015.

Over recent decades Gleason scores below 6 are less commonly reported, especially on needle biopsies. There is also an understanding that score 7 tumours have a less favourable prognosis if Gleason pattern 4 predominates over pattern 3 (i.e., 4+3 v 3+4).[20] The ISUP grading system and associated definitions are outlined in Table 6. Both the Gleason score and the ISUP grade (also known as Grade group) should always be reported together for the sake of clarity.

Table 5 World Health Organization (WHO) classification of tumours of the prostate[a]

Descriptor	ICD-O codes
Epithelial tumours	
Glandular neoplasms	
Acinar adenocarcinoma	8140/3
Atrophic	
Pseudohyperplastic	
Microcystic	
Foamy gland	
Mucinous (colloid)	8480/3
Signet ring-like cell	8490/3
Pleomorphic giant cell	
Sarcomatoid	8572/3
Prostatic intraepithelial neoplasia, high-grade	8148/2
Intraductal carcinoma	8500/2
Ductal adenocarcinoma	8500/3
Cribiform	8201/3
Papillary	8260/3
Solid	8230/3
Urothelial carcinoma	8120/3
Squamous neoplasms	
Adenosquamous carcinoma	8560/3
Squamous cell carcinoma	8070/3
Basal cell carcinoma	8147/3
Neuroendocrine tumours	
Adenocarcinoma with neuroendocrine differentiation	8574/3
Well-differentiated neuroendocrine tumour	8240/3
Small cell neuroendocrine carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3

[a] The morphology codes are from the International Classification of Diseases for Oncology (ICD-O). Behaviour is coded/0 for benign tumours;/1 for unspecified, borderline, or uncertain behaviour;/2 for carcinoma *in situ* and grade III intraepithelial neoplasia; and/3 for malignant tumours.

Depending on local practice, the different elements of grade data on needle biopsy may be reported at either specimen (core) level or as a composite (global) grade based on all cancer present in the biopsy cores, or a combination of both. However, it has recently been shown that global ISUP grade correlates better with radical prostatectomy ISUP grade than core level reporting.[21]

Prostate cancer in TURP specimens is graded according to similar principles as for needle core biopsies, since resections do not sample the entire tumour. A TURP mainly harvests tissue from the transition zone and cancers arising in this part of the prostate are thus over-represented in TURP specimens. However, peripheral zone tissue is sometimes also resected and large peripheral zone cancers may involve the transition zone. Thus, TURP specimens include the same spectrum of cancers as needle biopsies, albeit with a different distribution. For example, small low-grade transition zone cancers are more often detected by TURP than by needle biopsies. It has been demonstrated that the Gleason score of cancer detected at TURP predicts cancer-specific survival[22,23] and local progression.[24] Grading of cancer in TURP specimens was not specifically addressed in the ISUP 2005 revision. One study based on TURP specimens showed that conventional Gleason score and modified Gleason score including the highest Gleason grade were independent predictors of cancer-specific survival on watchful waiting, but conventional Gleason score showed a slightly stronger correlation with outcome.[22]

TURP is sometimes undertaken for palliative reasons in patients with locally advanced prostate cancer. These cancers have usually been treated with androgen deprivation and a common indication for TURP is that the tumour has become hormone refractory. It is important that information about the hormonal treatment is given on the request form. Prostate

Table 6 International Society of Urological Pathology (ISUP) grading system, core needle biopsies, transurethral resection of the prostate (TURP) and enucleation specimens

ISUP grade (Grade group)	Gleason score	Definition
Grade 1	2–6	Only individual discrete well-formed glands
Grade 2	3+4=7	Predominantly well-formed glands with lesser component[a] of poorly-formed/fused/cribriform glands
Grade 3	4+3=7	Predominantly poorly-formed/fused/cribriform glands with lesser component[b] of well-formed glands
Grade 4	4+4=8	Only poorly-formed/fused/cribriform glands
	3+5=8	Predominantly well-formed glands and lesser component[a] lacking glands (or with necrosis)
	5+3=8	Predominantly lacking glands (or with necrosis) and lesser component[b] of well-formed glands
Grade 5	9–10	Lack gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands

[a] Any component of the high-grade pattern (i.e., even if less than 5%) is included in the grade.
[b] The low-grade pattern is included in the grade only if it is at least 5%.

cancer showing morphological signs of hormonal treatment should not be graded as the treatment effect can mimic a higher grade. Cancers in patients who are treated with finasteride because of prostatic hyperplasia can be graded as there is no evidence that finasteride has a significant effect on cancer morphology. Small cell carcinoma that is encountered most commonly in the setting of hormone resistance should not be graded in any specimen type.

Tumour extent (core/needle biopsy specimens)

The extent of carcinoma should be reported by number of positive cores over the total number of cores and an estimate of the linear cancer extent in the cores. Both the number of biopsy cores positive for cancer and the linear extent of cancer in the cores correlate with tumour volume, post-operative stage and outcome.[25–29] The number of positive cores present should be reported; however, this may be difficult to determine in cases where core fragmentation occurs when multiple cores have been submitted together. Site specific labelling and single core submission facilitates the assessment of cancer extent.[10] Linear extent should be reported and may be recorded either as millimetres cancer length or % cancer in each core, or as a composite measure of cancer involvement in all cores.[30]

The methods for reporting of discontinuous cancer remain controversial. Whether intervening benign tissue is included or subtracted from the measurement of tumour extent may determine treatment. In some protocols the patient would be ineligible for active surveillance, if more than 50% of a core is involved by tumour.[31] For example, a biopsy core may be reported to have 12 mm (or 60%) discontinuous cancer with two foci 1 mm each 10 mm apart or 2 mm (5%+5%=10%) linear extent.[31] In cases where low-grade cancer is discontinuous and in only a few cores, it is recommended that the tumour extent should be reported by both methods, i.e., by providing values in which the intervening benign tissue is either included or subtracted.

Prostatic tissue involved by tumour (TURP/enucleation specimens)

In the American Joint Committee on Cancer (AJCC)/Union of International Cancer Control (UICC) TNM classification, incidentally detected cancer is substaged as cT1a (≤5% cancer) and cT1b (>5% cancer) based on the involvement of resected tissue.[32,33] Although stage is primarily a measure of tumour extent, stage category cT1a is restricted to cancer of ISUP grade 1 while tumours of grades 2–5 are included in cT1b regardless of their extent. This substaging predicts cancer progression[34] and disease-specific survival.[35,36] The TNM classification does not specify how tumour extent should be measured, but the reported percentage of extent is commonly assumed to be calculated as the fraction of total tissue area in the sections.

It has recently been proposed that the percentage of number of chips positive for cancer over the total number of chips be reported. With this method 10% involvement was found to be a more useful cut-off for prediction of outcome than 5%.[36] This should be expected as the percentage of tumour involvement increases when a chip is considered positive, regardless of the extent of cancer involvement. The advantage of this method is its simplicity, but there is also a risk of overestimation when only minute foci of cancer are present in several chips. The report should specify which of these methods (% of positive chips or % cancer) was used. Percentage of positive chips cannot be used for enucleation specimens.

For practical purposes it is only necessary to estimate the extent of tumour involvement to the nearest 10%, or for small tumours to state if the tumour comprises ≤5% of the specimen.

Extraprostatic extension (core/needle biopsy specimens)

Extraprostatic extension (EPE) is the accepted terminology for prostatic carcinoma extending beyond the prostate and replaces earlier nomenclature such as capsular penetration, perforation, or invasion.[37] In radical prostatectomy specimens EPE is an independent indicator of risk of recurrence and an important component of staging.[38,39]

EPE may occasionally be seen in needle biopsies and should be reported as it indicates that the tumour is at least pT3a in the TNM system.[40] In needle cores it is defined as tumour admixed with adipocytes, usually at the end of a biopsy core.

Recommended elements (Tables 3 and 4)

Clinical information (core/needle biopsy and TURP/enucleation specimens)

The clinician submitting the specimen is responsible for providing information that may affect the diagnostic process.

The use of standardised pathology requisition forms with checklists are strongly encouraged to ensure that relevant clinical data are provided. When submitting prostate biopsies, indicating the number of needle cores taken from each site facilitates the assessment of the number of involved cores.

Information relating to prior biopsy or treatment facilitates histopathological evaluation. Radiation and/or endocrine therapy for prostate cancer has a profound effect on the morphology of prostatic tissue and it is very important that such information be provided. Following irradiation, benign acinar epithelium may mimic cancer by showing nuclear enlargement and nucleolar prominence.[41] There may also be increased stromal fibrosis, which may resemble tumour-induced desmoplasia. Radiation may be associated with apparent upgrading of prostate cancer in prostatectomy specimens.[42] Similarly, neoadjuvant androgen deprivation therapy (ADT) may induce morphological changes in both prostate cancer and benign tissue. Neoadjuvant ADT may increase the risk of overlooking acinar adenocarcinoma on low power microscopic examination due to collapse of glandular lumina, cytoplasmic pallor and shrinkage of nuclei.[43–45] The effect of androgen blockage on prostate cancer is variable and an apparent upgrading of the cancer has been reported in a number of studies.[42,46] Hence, it has been suggested that following radiotherapy or androgen deprivation therapy, tumours that show significant treatment effect should not be graded.[47]

The Gleason score of prostate cancer in any previously submitted specimen should be provided by the clinician as this allows assessment of any progression of the tumour towards a higher grade, which itself may be of prognostic significance. If the patient is on active surveillance this should also be mentioned.

Pre-biopsy/procedure serum PSA (core/needle biopsy and TURP/enucleation specimens)

The clinician requesting the pathological examination should provide information on the pre-biopsy/procedure serum prostate-specific antigen (PSA) level, if this has been measured. Serum PSA is a key parameter in some nomograms that are widely used to predict the AJCC/UICC pathological T category of prostate cancer preoperatively, assess the risk of recurrence following radical prostatectomy and to guide clinical decision making with respect to patient management.[48]

If the patient is on 5-alpha-reductase inhibitor medications, such as finasteride or dutasteride, this should be recorded as it may lower serum PSA levels and affect interpretation of serum PSA values for detecting prostate cancer.[49–52]

Clinical stage (core/needle biopsy and TURP/enucleation specimens)

The clinician requesting the pathological examination should provide information relating to clinical stage. Along with pre-biopsy serum PSA, clinical stage is a key parameter in some nomograms that are widely used predict the pathological T category of prostate cancer pre-operatively and to guide clinical decision making with respect to patient management.[48]

Transurethral resections are usually performed for the relief of benign prostatic hyperplasia when it is not anticipated that there will be cancer present. If cancer is found on microscopic examination in this situation it will be assigned to staging category T1. In men with a known cancer, transurethral resection may be performed to relieve an obstruction caused by the cancer.

Specimen dimensions (TURP/enucleation specimens)

Information relating to the size of the submitted specimen documents the tissue received by the pathology laboratory. For practical reasons the amount of tissue removed at TURP is better estimated by documenting the total weight of the specimen. Enucleation specimens are often received in pieces and these need to be weighed, while only the largest piece or pieces need to be measured.

Block identification key (core/needle biopsy and TURP/enucleation specimens)

The origin and designation of all tissue blocks should be recorded and should be included in the pathology report. If this information is not presented in the report, it should be available to the reviewing pathologist in the laboratory computer system.[6] In needle core biopsy cases, this may be helpful when interpreting the histology and also for providing information to the clinician regarding tumour location and extent.

Although a reviewer does not require information relating to the origin of each block in a transurethral resection specimen in order to provide an informed specialist opinion, such data may be more useful in enucleation specimens for assessment of multifocality and tumour extent. Recording the origin/nature of tissue blocks also facilitates retrieval of blocks and, therefore, is important when further immunohistochemical investigations are contemplated or for molecular analysis, research studies or clinical trials.

Percent Gleason grade 4/5 (core/needle biopsy and TURP/enucleation specimens)

In addition to the development of ISUP grade and the modification of Gleason scoring, the 2014 ISUP consensus conference also recommended that the percentage of Gleason pattern 4 be reported in cases with ISUP grades 2 or 3. The rationale for this is to indicate if the tumour is bordering on the lower or higher ends of Gleason score 7. In some treatment guidelines, Gleason score 7 tumours with $\leq$10% pattern 4 are eligible for active surveillance.[53] The percentage of Gleason pattern 4 and 5 is reported by some pathologists[54] and has been found to predict cancer-specific survival independently of Gleason score.[22] Despite this, reporting of % high-grade cancer remains optional.

Perineural invasion (core/needle biopsy and TURP/enucleation specimens)

The significance of perineural invasion in prostate core biopsy, TURP or enucleation specimens is uncertain and there is little published literature specific to these particular specimen types. Some studies have shown a correlation with EPE in the corresponding radical prostatectomy specimens or an association with adverse outcome in patients treated with radical prostatectomy or external beam radiation.[55–60] Other investigators have questioned the prognostic value of

perineural invasion in biopsies using univariate or multivariate analyses.[61–64] In needle core biopsies a systematic review of the literature concluded that in clinically localised disease perineural invasion was a significant prognostic factor for EPE and subsequent local recurrence.[65] Hence, it is recommended that perineural invasion be recorded when present in needle biopsies, TURP and enucleation specimens.

Seminal vesicle/ejaculatory duct invasion (core/needle biopsy and TURP/enucleation specimens)

Seminal vesicle invasion (SVI) is rarely identified in needle biopsies or TURP specimens, and as a consequence its absence does not need to be explicitly stated. However, if seminal vesicle/ejaculatory duct invasion is present the reporting of this is recommended.

SVI is defined as involvement of the muscular wall of the extraprostatic portion of the seminal vesicle.[66] If seminal vesicle tissue is present and involved by carcinoma, this indicates that the tumour could be pT3b in the AJCC/UICC staging system.[32,40] However, assessment of SVI is problematic in needle biopsy, TURP and enucleation specimens since it is difficult to reliably distinguish between extraprostatic seminal vesicle and intraprostatic seminal vesicle or ejaculatory duct tissue,[67] and invasion of the latter two structures does not constitute pT3b disease. Unless one is dealing with a targeted seminal vesicle biopsy, if there is doubt as to whether the involved tissue represents the extraprostatic seminal vesicle or the intraprostatic seminal vesicle/ejaculatory duct, this should be reported as 'seminal vesicle/ejaculatory duct invasion' rather than as SVI.

Lymphovascular invasion (core/needle biopsy and TURP/enucleation specimens)

Lymphovascular invasion (LVI) is rarely identified in needle biopsies cores and TURP specimens, and its absence does not need to be explicitly stated; however, if LVI is present it should be recorded.

Invasion of lymphatic or blood vessels (i.e., thin-walled endothelial-lined spaces) is uncommonly identified in needle core biopsy, TURP or enucleation specimens and there are little published data on its significance specifically relating to these specimen types. However, there is good evidence that LVI is a significant independent prognostic indicator of increased risk of recurrence post radical prostatectomy.[68–71] As a consequence, if LVI is identified in a needle core or TURP/enucleation specimens it may well be significant and reporting is recommended. The presence of LVI does not affect assignment of the AJCC/UICC T staging category.

Extraprostatic extension (TURP/enucleation specimens)

In radical prostatectomy specimens EPE is an independent prognostic indicator of increased risk of recurrence post radical prostatectomy and is important in the assignment of AJCC/UICC T staging category.[38,39] There are little data specifically on the significance of EPE in TURP or enucleation specimens, which is not surprising as it is rarely identified. If EPE is present this should be reported as it indicates that the tumour is at least category pT3a in the TNM staging system.[40] In TURP specimens it is defined as tumour admixed with adipocytes.

For core needle biopsies it is recommended that the site of any EPE present is recorded since this information is useful for correlation with magnetic resonance imaging (MRI) results and may assist technical aspects of treatment planning.

Intraductal carcinoma of prostate (core/needle biopsy and TURP/enucleation specimens)

Intraductal carcinoma of the prostate (IDC-P) is an uncommon finding in needle biopsies cores and TURP specimens, hence its absence does not need to be explicitly stated. However, if IDC-P is present its reporting is recommended. IDC-P is usually associated with invasive prostate cancer, but may occasionally be found in isolation, although this is a rare finding the discussion of which is beyond the scope of this dataset.

IDC-P has been characterised at histological and molecular levels over the past decade and its clinical significance is now better understood.[72] The diagnosis of IDC-P is based on morphology and the key criteria include: (1) large calibre glands that are more than twice the diameter of normal non-neoplastic peripheral glands; (2) preserved (at least focally) basal cells identified on haematoxylin and eosin staining (or with basal cell markers, such as p63, keratin 34βE12 and keratin 5/6, however, the use of immunohistochemistry to identify basal cells is optional for the diagnosis of IDC-P); (3) significant nuclear atypia including enlargement and anisonucleosis; and (4) comedonecrosis, which is usually, but not always, present.[73,74] It is important to distinguish IDC-P from high grade prostatic intraepithelial neoplasia (HGPIN). Compared to IDC-P, HGPIN has less architectural and cytological atypia, and cribriform HGPIN is rare.

IDC-P is strongly associated with high volume, high grade invasive prostate carcinoma and metastatic disease. Hence the presence of IDC-P in a biopsy or TURP specimen without invasive carcinoma mandates immediate further investigation such as repeat biopsy or even definitive therapy.[75–78] In a cohort treated with radiation and/or androgen deprivation therapy, the presence of IDC-P in the needle biopsy was an independent predictor of early biochemical recurrence and metastasis.[79] There was consensus at the 2014 ISUP conference on grading that IDC-P should not be assigned an ISUP grade or Gleason score,[80] although this has more recently been questioned for cases with concomitant invasive carcinoma.[67,81]

Co-existent pathology (core/needle biopsy and TURP/enucleation specimens)

In the presence of invasive carcinoma, the finding of HGPIN is generally not significant. When no cancer is identified in the specimen, HGPIN in needle core biopsies has been associated with an increased risk for prostatic adenocarcinoma in subsequent biopsies in some studies, but not in others.[82,83] The risk may be related to the extent of HGPIN, as patients with involvement in multiple cores have been reported to have a significantly increased risk of prostate cancer.[84–86] Low grade prostatic intraepithelial neoplasia (PIN) should not be reported.

Likewise, if there is carcinoma in a specimen, an additional focus of glandular atypia suspicious for malignancy is generally not significant. In core biopsies where there is no cancer identified, the finding of glandular atypia suspicious

for malignancy indicates a risk of carcinoma in subsequent specimens of approximately 50%.[86–90]

Active prostatitis and granulomatous prostatitis may cause a rise in serum PSA; however, inflammatory lesions may coexist with carcinoma and it is important not to assume that their presence always accounts for an increase in a patient's PSA.

DISCUSSION

Surveys have shown a considerable variation in practice in the reporting of prostate needle biopsies, even among pathologists with an interest in uropathology.[87,88] To some extent this is caused by disagreements as to the optimal reporting of prostate specimens, but sometimes there is also a lack of compliance with current recommendations. The purpose of guidelines and checklists is to standardise the format and contents of pathology reports. This is important as uniform information about diagnostic and prognostic data facilitates treatment decisions.

Numerous regional and national guidelines have been issued on prostate pathology. The information in these largely agrees, but there are also some conflicting recommendations. In order to achieve international standardisation, the ICCR aims to issue datasets with minimum requirements for the reporting that can be followed by pathologists practising under different jurisdictions. It is important to understand that there may be economic constraints that limit what can be done routinely in some countries. For example, health insurance policies may restrict the practice of pathology. The individual pathologist has the freedom to report in greater detail than advised by the ICCR datasets and may undertake more extensive special studies than those recommended here.

One of the challenges in prostate biopsy pathology is that it is rarely known if lesions identified in multiple cores are part of the same tumour focus or if they represent different foci. Therefore, reporting of the findings can be undertaken at specimen level (assuming that there may be separate lesions) or case level (assuming that there may a single lesion). A combination of these two reporting methods is often used. The datasets for core needle biopsies have allowed for this complexity by offering separate datasheets for specimen (core) or case level reporting. The individual pathologist can thus choose the preferred dataset.

The practice of prostatic biopsy is currently undergoing a rapid change. Over the past two decades, routine practise has been to take a set of biopsies with standardised positions under transrectal ultrasound guidance, sometimes combined with additional biopsies directed at ultrasound-detected lesions. The number of biopsy cores submitted has gradually increased from sextant biopsies to 10–12 cores or more. In recent years template biopsies have been introduced with the aim of detecting cancers that have gone undetected by standard biopsies, because of their small size or anterior localisation. More recently MRI guided biopsies or fusion biopsies have become more common. Here biopsies are directed against MRI detected lesions and this has been reported to increase the cancer detection rate and also grading accuracy.[89] This may influence how data are interpreted relating to the reporting of the number of positive biopsy cores and tumour extent.

One of the major changes in prostate pathology reporting over the past one and a half decades relates to grading practice. The ISUP has organised two consensus conferences on grading in 2005 and 2014.[19,80] The resulting ISUP consensus guidelines have had a significant impact on the interpretation of morphological patterns and reporting routines. The current update of ICCR datasets has taken these ISUP recommendations into account. Some areas remain contentious. It has become obvious that some Gleason scores are no longer used while others have a similar outcome and may be grouped together. It is also a well known observation that Gleason score 7 tumours have differing prognosis depending on whether pattern 3 or 4 predominates. It was recommended at the 2014 ISUP consensus conference that Gleason scores be grouped in five categories. The terminology for this grouping has caused a heated debate in the international pathology community in recent years.[90] The WHO blue book editorial meeting chose not to issue a recommendation on grading nomenclature but decided to use a descriptive terminology and allow the pathology community freedom to use its preferred terminology. This has led to a plethora of alternative terms. It has been the wish of the DAC expert panel to accommodate for this by offering pathologists the ability to use either ISUP grades or Grade groups (or both) in their reports.

The practice of pathology is now rapidly evolving. Novel imaging techniques influence biopsy routines and have provided for the interpretation of novel information relating to sampled lesions. Moreover, an array of molecular techniques is increasingly being used for the extraction of diagnostic and prognostic information. These developments will alter the way pathology is reported and will increase the demands on pathologists to present and summarise complex data. In these developments the ICCR datasets will continue to play a key role in defining how reports are structured in order to provide the clinician with comprehensive yet relevant information.

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Address for correspondence: Prof Lars Egevad, Department of Pathology, Karolinska University Hospital, Radiumhemmet P1:02, 171 76 Stockholm, Sweden. E-mail: Lars.Egevad@ki.se

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