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REVIEW AND PERSPECTIVES

Dataset for the reporting of prostate carcinoma in radical prostatectomy specimens: updated recommendations from the International Collaboration on Cancer Reporting

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Abstract

The International Collaboration on Cancer Reporting (ICCR) was formed in 2011 to harmonise the datasets, protocols and checklists for pathological reporting of various cancers and develop internationally agreed upon, evidence-based datasets. A dataset for prostate cancer in radical prostatectomy specimens was developed in 2011–2012 as part of a pilot project; however, it required substantial revision following the ISUP Consensus Conference on Gleason Grading in 2014, the publication of the World Health Organisation (WHO) Classification of Tumours of the Urinary System and Male Genital Organs in 2016, and the 8th edition of the Tumour-Node-Metastasis (TNM) staging system in late 2016. This article presents the up-to-date, evidence-based ICCR dataset and associated commentary for reporting prostate cancer in radical prostatectomy specimens. PubMed and Google search engines were used to review the published literature on the subject, and the dataset was developed in line with the previously published ICCR framework for the development of cancer datasets. Substantial changes have been incorporated into the second edition of the ICCR prostate cancer (radical prostatectomy) dataset. These include revisions to prostate cancer grading, reporting of intraductal carcinoma of prostate and surgical margins, among others. Up-to-date cancer datasets underpin structured reporting and facilitate the production of consistent and accurate pathological data for patient care as well as comparisons between different cohorts and populations internationally.

Keywords Prostate cancer · Datasets · Protocols · Pathology

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Introduction

Prostate cancer (PC) is the most commonly diagnosed cancer in men in developed countries and the third most common cause of cancer-related death: in 2018, in the USA, there are projected to be 164,690 new cases and 29,430 deaths from prostate cancer [1], while in the UK, there were 46,690 new cases and 11,287 deaths in 2014 [2]. Following radical prostatectomy for localised PC, assessments of the histological parameters of the tumour are important predictors of outcome and strongly influence subsequent clinical decision making. Studies in several organs, including breast, colon, pancreas and prostate among others, have demonstrated the superiority of structured (synoptic) pathology reporting of cancer over traditional narrative or free text reports with regard to the completeness and quality of the pathological data included for accurate cancer classification, prognostication and management [3–6]. In addition, structured reports have been shown to be superior to narrative reports with respect to readability and access to information and are well accepted by clinicians [7, 8].

Over the last two decades, professional bodies in several countries have produced datasets for histopathology reporting of a variety of cancers and, unsurprisingly, there are broad similarities between the protocols, checklists or proformas developed in different jurisdictions since they are all largely based on the published scientific evidence. However, there are significant differences in the terminology, definitions, methods of measurement and expression of the results for the key pathological data elements; limiting local, national and international benchmarking, epidemiological studies and comparisons of clinical trials or practice. Moreover, the development of similar protocols in different countries represents a significant duplication of effort, which is magnified by the need to regularly update the datasets to incorporate new evidence and ensure they reflect contemporary practice. To address these issues, three professional bodies that were already developing their own structured reporting protocols or checklists for cancer, i.e. the College of American Pathologists (CAP), the Royal College of Pathologists (RCPath) and the Royal College of Pathologists of Australasia (RCPA), combined with the Canadian Association of Pathologists and Canadian Partnership Against Cancer to collaborate in the development of standardised datasets. Initially, a quadripartite group, the International Collaboration on Cancer Reporting (ICCR), was formed in 2011 with the European Society of Pathology (ESP) joining in 2013. Since then, other pathology bodies including the American Society of Clinical Pathology (ASCP) and the Faculty of Pathology of the Royal College of Physicians of Ireland (RCPI) have joined the ICCR, which has become incorporated as a not-for-profit organisation. Strategic alliances have been formed with other international cancer organisations, including the International Agency for Research on Cancer (IARC), Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC).

As a pilot project in 2011–2012 to demonstrate the potential synergies and to test the feasibility of this initiative, the ICCR developed internationally agreed upon, evidence-based datasets for four common malignancies, comprising prostate, lung and endometrial carcinoma and melanoma. Each of these datasets was produced by a panel of internationally recognised expert pathologists and one clinician, included feedback from international open consultation and was published in peer-reviewed journals [9–12]. The successful pilot project highlighted the interdependence of the ICCR datasets with the World Health Organisation (WHO) Classifications of Tumours (or 'blue books'), and the decision was made to develop further datasets in synchrony with updates to these classifications for each organ system. An ICCR suite of 12 datasets for genitourinary cancers was instigated when the WHO Classification of Tumours of the Urinary System and Male Genital Organs was published in 2016. Publication was delayed to ensure that the final versions of the datasets were aligned with the 8th edition of the Tumour-Node-Metastasis (TNM) staging system published in late 2016. Although an ICCR prostate cancer dataset for radical prostatectomy specimens had been previously developed in 2011–2012 as part of the pilot project [11], key data elements required substantial updating following the 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma, the new WHO Classification and other recent publications. Hence, the ICCR initiated a substantial revision of this dataset with the aim of developing an up-to-date, evidence-based dataset and associated commentary that would facilitate the production of consistent and accurate pathological data for patient management as well as comparisons between different cohorts and populations internationally.

Methods

The previously published ICCR framework for the development of cancer datasets (Guidelines for the Development of ICCR Datasets [13], http://www.iccr-cancer.org/datasets/dataset-development) that have been described in detail in previous publications were followed [14–16]. In summary, the process was initiated by the ICCR Dataset Steering Committee (DSC) who selected two co-Chairs (JGK and LE) to lead the development process for the prostate cancer datasets. The chairs assisted the DSC with identifying and recruiting ten further genitourinary pathologists for the expert panel that forms the Dataset Authoring Committee (DAC), ensuring that, in addition to having internationally recognised expertise in prostate cancer, the members also covered a wide geographical and linguistic diversity. In addition, a clinician (urologist KR), project manager and the ICCR genitourinary series champion (JRS) were added to the committee, the latter

to provide guidance and support to the co-Chairs of the DAC regarding ICCR standards and to ensure harmonisation across all the various genitourinary datasets under development.

The prostate cancer DAC held four web/teleconferences, each with accompanying email dialogue, to discuss proposed elements for prostate cancer datasets, and the resulting draft prostate cancer (radical prostatectomy) dataset with associated commentary was then submitted to a 6-week period of open international consultation. The dataset was further refined following the open consultation feedback, updated to include the recently published TNM 8, reviewed and ratified by the DSC, and then published on the open access ICCR website (http://www.iccr-cancer.org/datasets/published-datasets/urinary-male-genital/prostate-cancer-radical-prostatectomy-specimen).

Like all ICCR datasets, the prostate cancer (radical prostatectomy) dataset includes both required (core) and recommended (non-core) elements. Required elements are mandatory and defined as those that are unanimously agreed by the expert panel to be essential for histological diagnosis, clinical management, staging and/or prognosis. Recommended (non-core) elements were defined as those that the panel agreed should be included in the dataset but not as mandatory items. These non-core elements may be clinically important, and their inclusion in reports represents good clinical practice, but these items currently lack sufficient validation. Evidentiary support at Level III-2 or above [based on prognostic factors in the NHMRC (National Health and Medical Research Council) levels of evidence document and defined as 'Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial' [17]] is required to support required (mandatory) elements. Rarely, where Level III-2 evidence is not available, an element can be categorised as required with unanimous agreement of the expert panel. Value lists or permitted responses, are defined for each element. Commentary, i.e., explanatory text, diagrams or tables, is added where necessary to clarify the elements and to define the way in which an item should be reported, to foster reproducibility; explain why an element is included (e.g. how does the item assist with clinical management or prognosis of the specific cancer); cite published evidence in support of the element and to state any exceptions or issues that may be encountered by the reporting pathologist.

Results

Scope

Since there are significant differences in the required and recommended elements, permitted responses and commentaries between radical prostatectomy, needle biopsy and transurethral resection specimens, the co-Chairs of the prostate cancer DAC, in consultation with the ICCR DSC, decided to develop separate datasets for these three specimen types to maximise clarity and useability. The elements and associated commentaries presented below are for radical prostatectomy specimens.

Required data elements

Table 1 lists the required data elements.

Specimen weight

The prostate gland should be weighed without the seminal vesicles since their size can vary markedly, and their inclusion would introduce error into the measurement of the prostate gland weight and distort comparisons with the radiologically estimated weight. Given this, a working group at the 2009 International Society of Urological Pathology (ISUP) Consensus Conference in Boston recommended that the prostate should be weighed following removal of the seminal vesicles [18].

Seminal vesicles

A record of all organs/tissues received is a standard and required item in gross/macroscopic pathology reports.

Lymph nodes

The recording of the presence or absence of lymph nodes is a required element while recording of the laterality of the nodes is recommended see Tables 1 and 4. If present, the laterality of the lymph nodes submitted may be recorded as left, right or bilateral.

Table 1 Required data elements for pathological reporting of radical prostatectomy specimens

Macroscopic	Microscopic
Specimen weight	Histological tumour type
Seminal vesicles	Histological grade
Lymph nodes	• Gleason score
• Absence or presence	• International Society of Urological Pathology (ISUP) Grade (Grade group)
	Extraprostatic extension
	• Present/not identified
	Extent of extraprostatic extension
	Seminal vesicle invasion
	Urinary bladder neck invasion
	Margin status
	• Involved/not involved
	• Location of positive margins
	Lymph node status
	• Number of lymph nodes examined
	• Number of involved nodes
	Pathological staging

Histological tumour type (Table 2)

The vast majority (> 95%) of prostate cancers are acinar adenocarcinomas [19]. Other types of carcinoma, while rarer, must be recorded if present as some subtypes, such as ductal adenocarcinoma, small-cell carcinoma, sarcomatoid carcinoma and urothelial-type adenocarcinoma, have a significantly poorer prognosis [19–25]. The tumour type should conform with the 2016 World Health Organisation (WHO) classification and, if present, combinations of different types of carcinoma should be indicated [19]. Subtypes of prostate carcinoma are often identified in association with acinar adenocarcinoma, and in such cases, the tumour type should be classified according to the subtype.

Table 2 WHO classification of tumours of the prostate

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

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

Histological grade

The recording of Gleason score and the ISUP grade (Grade group) are required elements, while recording of the Percentage Gleason pattern 4/5 is recommended (see Tables 1 and 4).

The Gleason score of radical prostatectomy specimens is obtained by adding the two most commonly observed Gleason patterns/grades or doubling the pattern in cases without a secondary pattern. In the 2005 ISUP revision, it was recommended that this be done for each dominant tumour nodule(s) [26]. The rationale was that additional separate tumours of lower grade (e.g. transition zone cancers) would not be expected to mitigate the prognostic impact of the main tumour and, thus, their grades should not be included in the overall Gleason score. Unlike in needle biopsies where inclusion of highest grade regardless of extent in the Gleason score was recommended, the issue of how to deal with a minor (< 5%) secondary pattern of higher grade cancer in radical prostatectomy specimens was not specifically addressed in the 2005 consensus conference, i.e. a carcinoma with 95% pattern 3 and < 5% pattern 4 could be reported as either 3 + 4 = 7 or 3 + 3 = 6 with tertiary pattern 4. However, it was agreed that in radical prostatectomy specimens, where the Gleason score was composed of two predominant patterns/grades, a minor (< 5%) tertiary grade should be mentioned separately in the report. The grading practices for radical prostatectomy specimens currently vary, and some pathologists would include a tertiary component of Gleason pattern 5 in the Gleason score, if comprising 5% or more of the tumour volume [27].

At the 2014 ISUP Consensus Conference on Gleason grading, a grouping of the Gleason scores into five categories was proposed for several reasons; over the past decades Gleason scores below 6 have become less commonly assigned. There is also an understanding that Gleason score 7 tumours have a worse outcome if there is a predominant pattern 4 (4 + 3) rather than if pattern 3 dominates (3 + 4) [28]. Following the 2014 conference, a recommendation has been made advocating the reporting of the percentage of Gleason pattern 4 in cases with a Gleason score of 7 (ISUP grades 2 or 3). In radical prostatectomy specimens, this is recommended principally to aid clinical decision making regarding adjuvant therapy in cases on the borderline between 3 + 4 = 7 and 4 + 3 = 7 (i.e. near 50% pattern 4). Indeed, many pathologists have been recording the percentage of Gleason pattern 4/5 based on studies published over the last two decades showing that this parameter is a reproducible, independent predictor of prognosis following radical prostatectomy [29–32].

The groupings and associated definitions are outlined in Table 3. Both the Gleason score and the ISUP grade (Grade group) should always be reported for the sake of clarity. At the 2014 ISUP expert consultation meeting, there was no decision as to how tertiary patterns of higher grade should be

Table 3 ISUP grading system, radical prostatectomy 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 (*) of poorly-formed/fused/cribriform glands
Grade 3	4 + 3 = 7	Predominantly poorly-formed/fused/cribriform glands with lesser component (**) 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 (*) lacking glands
	5 + 3 = 8	Predominantly lacking glands and lesser component (**) of well-formed glands
Grade 5	9–10	Lack gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands

*A high-grade pattern is included in the grade only if it is at least 5%. If less than 5%, it should be mentioned separately in the report

**The low-grade pattern is included in the grade only if it is at least 5%

incorporated into the ISUP grades, but it was agreed that the Gleason score and tertiary Gleason patterns of higher grade should be reported and that this information be included in the ICCR dataset.

Extraprostatic extension

The recording of the presence or absence and extent of extraprostatic extension (EPE) are required elements, while recording of its location is recommended (see Tables 1 and 4).

EPE, defined as the extension of tumour beyond the confines of the gland into the periprostatic soft tissue, is a significant predictor of recurrence in node-negative patients [33, 34]. EPE replaced earlier, less clearly defined terms, such capsular penetration, perforation or invasion, following the recommendations from a 1996 Consensus Conference [35]. The assessment of EPE can be difficult, as the prostate is not surrounded by a discrete, well defined fibrous capsule [36], but rather by a band of concentrically placed fibromuscular tissue that is an inseparable component of the prostatic stroma [37]. EPE can be recognised in several different settings: (i) the presence of neoplastic glands abutting on or within periprostatic fat or beyond the adjacent fat plane in situations where no fat is present in the immediate area of interest (most useful at the lateral, posterolateral and posterior aspects of the prostate), (ii) neoplastic glands surrounding nerves in the neurovascular bundle (posterolaterally) beyond the boundary of the normal prostatic glandular tissue, and (iii) the presence of a nodular extension of tumour bulging beyond the periphery of the prostate or beyond the compressed fibromuscular prostatic stroma at the outer edge of the gland. There is often a desmoplastic reaction in the vicinity of EPE, and the neoplastic extraprostatic glands may then be seen in fibrous tissue, rather than in fat [37, 38]. Extraprostatic tumour in fibrous tissue is best identified initially at low-power magnification, but should then be confirmed at high-power magnification, verifying that the neoplastic glands are in fibrous stroma beyond the condensed smooth muscle of the prostate [34, 38]. The presence of cancer within fibrous stroma that is in the same tissue plane as adipose tissue on either side is a helpful indicator of EPE.

The boundary of the prostate gland cannot be readily identified anteriorly and at the base or apex of the prostate. Moreover, benign glands at the apex are frequently admixed with skeletal muscle, and the presence of neoplastic glands

Table 4 Recommended data elements for pathological reporting of radical rostatectomy specimens

Clinical	Macroscopic	Microscopic
Clinical information	Specimen dimensions	Histological grade
Pre-biopsy serum PSA	Lymph nodes	• Percentage Gleason pattern 4 or 4/5
	• Laterality	Intraglandular extent
	Block identification key	Intraductal carcinoma of prostate
		Margin status
		• Type of margin positivity
		• Extent of margin positivity
		• Gleason pattern of tumour present at positive margin
		Lymphovascular invasion
		Lymph node status
		• Laterality
		• Maximum dimension of largest deposit

within skeletal muscle does not necessarily constitute EPE. Similarly, the assessment of EPE at the anterior aspect of the prostate may be difficult as the prostatic stroma blends in with extraprostatic fibromuscular tissue, but in this location, EPE can be diagnosed (in the manner described above) when the carcinoma appears to bulge beyond the boundary of the normal prostate gland [38, 39].

Extent of EPE

Categorisation of the extent of EPE as focal or non-focal (also referred to as 'extensive' or 'established') is a required (core) item in the ICCR dataset. Focal EPE was originally defined as no more than 'a few' neoplastic glands just outside the prostate, then subsequently, in a more semi-quantified manner, as extraprostatic glands which occupy no more than one high-power field in no more than two sections, with extensive EPE representing anything more than this [33, 34]. More rigorous quantification of the extent of EPE by measuring the maximum distance that the tumour bulges beyond the outer edge of the fibromuscular prostatic stroma radially has been proposed by some investigators [40]. However, the practical value of such parameters is limited by the difficulty in precisely defining the outer limit of the prostate gland, especially when the tumour is associated with a desmoplastic reaction. The identification of any EPE is important, as both focal and non-focal EPE are associated with a significantly higher risk of recurrence at both 5 and 10 years [33, 34]. Following radical prostatectomy, the 10-year progression-free probability for node negative patients with uninvolved seminal vesicles is 85–89% for organ confined disease, falling to 67–69% for focal EPE and to 36–58% for extensive EPE [33, 34].

Seminal vesicle invasion

The expert panel included seminal vesicle invasion (SVI) as a required (core) element of the ICCR dataset as SVI is a well-established, independent, adverse prognostic factor [39, 41–43] and an integral component of TNM staging as well as commonly used nomograms and tables that predict risk of post prostatectomy cancer recurrence [44–46]. SVI is defined as tumour involving the muscular wall of the extraprostatic seminal vesicle. Only extraprostatic seminal vesicle is included in this definition of SVI, since it is difficult differentiating between intraprostatic seminal vesicle and ejaculatory duct invasion as these structures merge without a clear histological cut off [47]. The finding of SVI at the time of radical prostatectomy is associated with a significantly increased risk of PSA recurrence [41, 42, 48], and the presence of SVI and a positive surgical margin may also influence the response to adjuvant radiotherapy [49, 50]. Bilaterality and extent of extraprostatic SVI are not independently predictive of prognosis and were not included as required or recommended items in the ICCR dataset [51].

Urinary bladder neck invasion

Urinary bladder neck invasion is a required data item which can be identified microscopically when there are neoplastic glands within the thick smooth muscle bundles of the bladder neck in sections from the base of the prostate, in the absence of associated benign prostatic glandular tissue [52]. Microscopic bladder neck involvement is a significant predictor of PSA-recurrence in univariate analysis, although not in multivariate modelling in most studies [53–55]. Neoplastic glands intermixed with benign prostatic glands at the bladder neck margin is equivalent to prostatic incision rather than true bladder neck invasion [53, 56, 57]. In the 7th and 8th editions of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) Cancer Staging Manuals, microscopic bladder neck invasion is classified as stage pT3a disease as it has a similar biochemical recurrence-free survival and cancer-specific survival to patients with EPE [52, 58–61].

Margin status

The recording of the involvement and location of positive margins are required elements, while recording of the type and extent of margin positivity as well as the Gleason pattern of tumour present at positive margin are recommended (see Tables 1 and 4).

A positive surgical margin (PSM) has a significant adverse impact on the likelihood of PSA recurrence-free survival and local recurrence-free survival, and also increases the risk of development of metastases after radical prostatectomy in multivariate analysis [39, 62–66]. Moreover, positive margins are associated with a 2.6-fold increased risk of prostate cancer specific mortality [67]. Careful inking of the outer surface of the radical prostatectomy specimen before macroscopic dissection (grossing) greatly facilitates the determination of margin status. A PSM can then be defined as cancer extending to the inked surface of the specimen, representing a site where the urologist has cut through cancer [39, 68]. PSMs are reported from 10 to 48% of patients treated by radical prostatectomy for both organ-confined and non-organ-confined prostate cancer, with the rates in the lower range typically being found in more modern cohorts [66, 69–71].

The presence of prostate carcinoma close to, but not touching the inked margin, should not be labelled as a PSM as this finding has been shown to have little, if any, prognostic significance [72–75]. Close surgical margins are most commonly seen posterolaterally in cases where neurovascular bundle preservation leaves virtually no extraprostatic tissue. Studies on such nerve sparing cases

have shown that additional tissue removed from these sites did not contain any carcinoma and a close margin was not associated with a worse prognosis [72, 74].

Stating the location of the PSM is useful information for the urologist who can then modify future operations to avoid iatrogenic margin positivity and increase the likelihood of curative surgery. The site of the PSM and the number of positive margins have been shown to influence biochemical recurrence and risk of progression [71, 76–78]. For instance, a margin involving the bladder neck or the posterolateral surface of the prostate has a more significant adverse impact on prognosis than an involved apical or anterior margin [71, 76].

Lymph node status

The recordings of the number of lymph nodes examined and involved are required elements while recordings of the laterality of the nodes examined and maximum dimension of largest deposit are recommended (see Tables 1 and 4).

Lymph node involvement is a well-established independent adverse prognostic factor [39, 43] and is an integral component of TNM staging and the commonly used nomograms that predict the risk of post prostatectomy disease recurrence [44, 58, 59]. There are little published data on the prognostic significance of isolated tumour cells (clusters less than < 200 μm in greatest dimension) in prostate cancer, and insufficient evidence exists at present to support the routine use of immunohistochemistry as an ancillary technique in identifying lymph node involvement.

Pathologic staging

The pathological primary tumour (T), regional lymph node (N) and distant metastasis (M) categories are considered as generic required (core) elements for all ICCR cancer datasets. Staging data should be assessed according to the most recent edition of the AJCC Staging Manual (8th Edition) [58, 59].

Recommended data elements

Table 4 lists the recommended data elements.

Clinical information

It is the responsibility of the clinician requesting the pathological examination of a specimen to provide information that will have an impact on the diagnostic process or affect its interpretation. The use of a standard pathology requisition/request form including a checklist of important clinical information is strongly encouraged to help ensure that important clinical data is provided by the clinicians. Providing information about prior biopsies or treatment aids interpretation of the microscopic findings and accurate pathological diagnosis. Radiation and/or endocrine therapy for prostate cancer have a profound effect on the morphology of both the cancer and the benign prostatic tissue [79–85] For this reason, information about any previous therapy is important for the accurate assessment of radical prostatectomy specimens.

Pre-biopsy serum PSA

The clinician requesting the pathological examination should provide information on the pre-biopsy serum prostate-specific antigen (PSA) level. Pre-biopsy serum PSA is a key parameter in some nomograms widely used to estimate the risk of recurrence postoperatively and guide clinical decision making on adjuvant therapy [44–46]. 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 [86–89].

Specimen dimensions

Although the shape of the prostate changes somewhat once removed from the pelvis, measurements of specimen size are generally considered part of a standard pathology report. In addition, measurements for apex to base, right to left and anterior to posterior enable comparison with clinical and imaging estimates of volume.

Block identification key

The origin/designation of all tissue blocks should be recorded, and it is preferable to document this information in the final pathology report. This information greatly assists review of the case findings by another pathologist. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to any reviewing pathologist.

Recording the origin/designation of tissue blocks also facilitates retrieval of blocks, for example for further immunohistochemical or molecular analysis, research studies or clinical trials.

Intraglandular extent

Some measurement of the size or extent of the tumour is typically given in histopathology reports for most sites, and this parameter forms part of the generic International Collaboration on Cancer Reporting (ICCR) dataset for all tumour types. However, in prostate, while cancer volume is a prognostic factor on univariate analysis, it is significantly correlated with other clinicopathological features, including Gleason score, EPE, surgical margin status and pathological TNM stage, and the majority of studies have not demonstrated

independent prognostic significance on multivariate analysis [90–94]. Hence, the ICCR expert panel regarded this factor as a recommended (non-core) rather than a required item.

The irregular distribution and often multifocal nature of prostate cancer makes accurate calculation of tumour volume challenging for the pathologist in routine diagnostic practice; a situation where precise methods, such as computerised planimetry or image analysis, are too time and labour intensive to be practical. However, there was consensus at the 2009 ISUP Conference that some quantitative measure of the extent of the tumour in a prostatectomy specimen should be recorded [95]. This can be done either as a visual estimate of intraglandular percentage of cancer [96, 97] or by measuring the maximum dimension of the dominant tumour nodule(s) [98, 99]. The latter has been shown to correlate with tumour volume and has also been recommended as a readily assessed surrogate for tumour volume in some studies and protocols [94, 98, 99].

Location of EPE

Since it was considered a generic element forming part of a comprehensive pathology report, the location of any EPE present has been included in the recommended (non-core) dataset, despite the lack of published evidence for its influence on staging, prognosis or treatment [38]. Localising EPE does provide potentially useful information to the urologist, enabling correlation with clinical findings and any preoperative imaging studies performed.

Intraductal carcinoma of prostate

Intraductal carcinoma of the prostate (IDC-P) is found in approximately 17% of radical prostatectomy specimens and is usually associated with invasive prostate cancer [100]. However, isolated IDC-P is occasionally found without invasive carcinoma. This latter situation is very rare and beyond the scope of this dataset.

IDC-P has been well characterised at the histological and molecular level over the past decade, and its clinical significance is now also better understood [101]. The diagnosis of IDC-P is based on morphology and the key criteria include (i) large calibre glands that are more than twice the diameter of normal non-neoplastic peripheral glands; (ii) preserved (at least focally) basal cells identified on H&E 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, rather than mandatory, for the diagnosis of IDC-P); (iii) significant nuclear atypia including enlargement and anisonucleosis; and (iv) comedonecrosis, which is often, but not always present [102, 103]. It is important to distinguish IDC-P from high-grade prostatic intraepithelial neoplasia (HGPIN), and compared to IDC-P, HGPIN has less architectural and cytological atypia, the glands are often smaller in size and cribriform HGPIN is rare.

When present in combination with invasive carcinoma in radical prostatectomy specimens, IDC-P is strongly associated with high-volume, high-grade and -stage (EPE or SVI positive) carcinoma [104]. Moreover, the presence of IDC-P is independently associated with biochemical recurrence, regional lymph node metastasis and cancer-specific survival [100, 105, 106]. Hence, in radical prostatectomy specimens, the presence of IDC-P, in association with invasive carcinoma, should be recorded.

There was a strong consensus (82% of respondents) at the Chicago 2014 ISUP consensus meeting that IDC-P without invasive carcinoma should not be assigned an ISUP grade or Gleason score [28]. It is also unnecessary to measure the extent of the IDC-P.

Type of margin positivity

Intraprostatic margin involvement or prostatic incision (also known as capsular incision) occurs when the urologist inadvertently develops the resection margin within the plane of the prostate rather than in periprostatic tissue. Prostatic incision with a positive surgical margin is diagnosed when malignant glands are cut across adjacent to benign prostatic glands [37]. In these cases, the edge of the prostate in this region remains in the patient. Data on the prognostic significance of prostatic incision vary among studies [107–109]. According to the largest series published, a significantly higher recurrence rate is found in patients with intraprostatic margin involvement than in patients with organ-confined disease with negative margins, or focal EPE with negative margins, although prostatic incision has a significantly better outcome than that associated with non-focal EPE and positive true margins [110].

Margin involvement associated with EPE is diagnosed when malignant glands in extraprostatic tissue are transected at the resection margin. This can be difficult to distinguish from capsular incision in some cases, particularly posteriorly and posterolaterally, if there is a desmoplastic reaction. Cancer extending to a margin which is beyond the normal contour of the prostate gland, or beyond the compressed fibromuscular prostatic stroma at the outer edge of the prostate, can be diagnosed as a positive surgical margin with EPE. This is similar to margin involvement when there is cancer in adipose tissue [108]. At the apex, the histological boundaries of the prostate gland can be difficult to define, and there is usually a paucity of periprostatic fat so EPE with a positive margin can be difficult to differentiate from prostatic incision/intraprostatic margin involvement. Hence, if carcinoma extends to an inked margin at the apex where benign glands are not transected, this is considered a positive margin in an area of EPE by some authors [39, 108]. In contrast, other authors, and the majority of survey

participants at the 2009 ISUP Consensus Conference, believe there is no reliable method to diagnose EPE in sections from the prostatic apex [38].

Extent of margin involvement

Although a PSM has a significant adverse impact on the overall likelihood of progression-free survival, in most published series, only about a third of individual patients with a PSM will experience biochemical recurrence [62, 63, 69, 111]. The expert panel considered that there is sufficient evidence to include measurement of the length of margin involved by carcinoma as a recommended element in the ICCR dataset [51, 72, 74, 110–114]. In particular, the 5-year PSA recurrence risk appears to be significantly greater when the length of the involved margin is 3 mm or more, (53% versus 14%) [51, 77, 78, 110, 115]. However, in one series, Cao et al. [113] found that the linear length of a positive margin was an independent prognostic factor for organ-confined tumours only, i.e. pT2 not pT3. Another investigation found that the impact of a positive surgical margin after radical prostatectomy was greater in intermediate and high-risk groups (based on Gleason score and pre-biopsy PSA) than in low-risk patients [65]. Further studies of such factors potentially affecting the impact of PSMs are required before there is sufficient evidence justifying their inclusion as required (mandatory) data elements. The optimal method of assessing the extent of margin involvement when multiple positive margins are present is currently uncertain, but, until more evidence is available, it is suggested that extent is measured as the linear cumulative length of all positive margins [116].

Gleason pattern at the margin

Four recently published studies have shown that Gleason pattern/grade or score of the tumour at the positive surgical margin is an independent predictor of biochemical recurrence and may aid optimal selection of patients for adjuvant therapy [111, 117–119]. In one of these studies patients with Gleason pattern 4 or 5 carcinoma (Gleason score 3 + 4, 4 + 3, 4 + 4 or 4 + 5) at a PSM had double the risk of PSA relapse when compared to those with only Gleason grade 3 (score 3 + 3) tumour at the margin [111]. Moreover, men with Gleason pattern/grade 3 tumour at the PSM had a similar 5-year biochemical relapse-free survival rate to those with negative margins [111]. Another study, restricted to men with dominant nodule Gleason score 7 and non-focal EPE, also found that the grade of cancer at the site of a PSM was associated with biochemical recurrence [117]. The largest series, including 405 cases with a PSM, confirmed that a lower Gleason score at the margin was independently associated with a decreased risk of early biochemical recurrence [119].

In each of the published studies, the potential problem of cautery/thermal artefact was considered. Each group noted that in slides where the cancer at the margin was distorted by cautery/thermal or crush artefact and could not be reliably assessed, the margin pattern, or score, was designated as that of the closest, well preserved carcinoma in direct continuity with the distorted neoplastic glands; hence, due to these considerations, this element was categorised as recommended rather than required in the dataset [111, 117–119]. Limiting assessment to only the highest pattern present at the PSM may simplify measurement of this parameter; however, it should be noted that in most of the published studies, Gleason score could be reported [117–119]. When there are multiple positive margins, with differently scored cancers present, the highest pattern or score should be recorded.

Lymphovascular invasion

Lymphovascular invasion (LVI) is defined as the unequivocal presence of tumour cells within endothelial-lined spaces with no or only thin underlying muscular walls [120, 121]. Lymphatic and venous invasion should be assessed together due to the difficulties in distinguishing between the two by routine light microscopy, and it is important that artefacts, such as retraction or mechanical displacement of tumour cells into vessels, are excluded. Immunohistochemistry for endothelial markers, e.g. CD31, CD34 or D2–40, may aid in the assessment of equivocal cases, but is not recommended for routine use at present.

LVI has been reported to be associated with decreased time to biochemical progression, distant metastases and overall survival after radical prostatectomy [120–125]. Multivariate analysis, controlling for other pathological variables known to affect clinical outcome, showed that LVI is an independent predictor of disease recurrence in some studies [120, 121, 123, 125, 126]. However, the independent prognostic value of LVI is uncertain as definitions of LVI have varied between studies. A further problem is that some studies include a substantial number of patients with lymph node metastases or SVI, and thus fail to stratify patients into clinically meaningful categories. Additional well-designed studies, with standardised definitions, are necessary to confirm the independent prognostic significance of LVI and hence this element is categorised as recommended rather than required.

Maximum dimension of largest nodal deposit

The diameter of the largest metastatic deposit was found to correlate with the development of distant metastasis and cancer-specific survival in two of three studies [127–129]. In view of this, this factor has been included in the recommended (non-core) dataset rather than as a required (core) item. There was consensus (81% of respondents) at the 2009 ISUP

Conference that the diameter of the largest lymph node metastasis should be included in pathology reports on radical prostatectomy specimens [43].

Discussion

Studies on various organs, including the prostate gland, have demonstrated that structured (synoptic) reporting improves the completeness of the pathology data available to clinicians for patient management. Structured reporting also facilitates comparison of clinical trials, benchmarking and other studies [5]. In one study of prostate cancer cases in Ontario, Canada, the completeness rate in structured reports was 96.2% versus 50.8% in the traditional narrative reports [5]. Structured reports also have been shown to be superior to narrative reports with respect to readability and accessibility to information [7, 8]. However, structured reports require regular revision to ensure that they remain relevant to contemporary practice and incorporate changes in classification, grading and other important prognostic and predictive indicators. Indeed, dataset development and maintenance is one of the key objectives behind the decision of CAP, RCPath (UK), RCPA and Canadian Association of Pathologists to pool resources and form the ICCR as part of an initiative to reduce the global burden of cancer. With this objective in mind, the ICCR have refined their processes since the initial pilot studies and have synchronised their schedule for dataset development and revision to align with updates to the World Health Organisation (WHO) Classifications of Tumours (or 'blue books').

The prostate cancer (radical prostatectomy) dataset was one of the original four ICCR pilot datasets developed in 2011–12 [11, 130]; however, since then, there have been significant changes in classification, grading and reporting of prostate cancer. These changes have arisen, not only from the fourth edition of the WHO Classification of Tumours of the Urinary System and Male Genital Organs [19], published in 2016, and the 2014 ISUP Consensus Conference on Gleason Grading of Prostatic Carcinoma, but also from studies on prognostic factors in radical prostatectomy specimens published since 2011 [19, 28]. In response to these changes, reporting of intraductal carcinoma of the prostate (IDC-P) has been added as a recommended element to the second edition ICCR dataset, based on its inclusion in the 2016 WHO Classification and the results of studies that have clarified its clinical significance in radical prostatectomy specimens. IDC-P is associated with high-volume, -grade and -stage invasive carcinoma, and is an independent predictor of biochemical recurrence, regional lymph node metastasis and cancer-specific survival [100, 104–106]. Therefore, the expert panel recommended that the presence of IDC-P, in association with invasive carcinoma, should be recorded. It was also noted that the 2014 ISUP Consensus Conference meeting decided that IDC-P should not be considered when the Gleason score of a case is assigned [28].

The 2014 ISUP Consensus Conference on Gleason Grading of Prostatic Carcinoma, like the 2005 conference before it, proposed some major changes to the practice of prostate cancer grading, most notably endorsing a proposal that Gleason scores could be grouped into five categories [28]. This consensus decision was based on the observations over the past decades that (i) some Gleason scores [2–5] were only rarely reported; while (ii) others have a similar biochemical recurrence rates (the latter being an imperfect surrogate for clinical recurrence and survival endpoints); and (iii) that Gleason score 7 tumours have different prognoses depending whether pattern 3 or 4 tumour predominates. Somewhat ironically, a lack of consensus over the nomenclature of this grouping system has led at times to fierce debate in the international urological pathology community over the last few years. In this climate, it has been the aim of the ICCR expert panel to be inclusive by offering pathologists the choice of using either terminology, i.e. ISUP grades or Grade groups.

Although there is strong evidence from several studies involving radical prostatectomy specimens, that tertiary-grade patterns are an important prognostic factor, a consensus on the ideal way to incorporate tertiary patterns (minor high-grade patterns) into the Gleason Grading system and ISUP grade (Grade groups) could not be achieved, either at the 2014 ISUP meeting or subsequently [28]. There have been a variety of suggestions: for instance, it was proposed that a minor high-grade pattern could be indicated in the ISUP grade (Grade group) system by the addition of a '+' symbol after the numeral, e.g 1+, 2+ etc. [27]. Additionally, after the 2014 meeting, some authors have advocated that when there is tertiary pattern 5 comprising ≥ 5% of a Gleason score 7 tumour (i.e. either 3 + 4 = 7 or 4 + 3 = 7), it would be assigned as the secondary pattern to replace the second most prevalent pattern, so, in this example, the Gleason score of the tumour would become either 8 or 9 (3 + 5 = 8 or 4 + 5 = 9) [19, 27]. However, neither of the above two proposals are universally accepted since they add a level of complexity to prostate cancer grading with only limited supporting evidence available at present [131, 132]. In these circumstances, the ICCR expert panel agreed that a minor tertiary pattern (< 5%) should be mentioned separately in the report, while a more extensive tertiary component could either be incorporated into the Gleason score or not, depending on local practice. However, it should be clearly indicated in the report when the tertiary pattern has been incorporated into the Gleason score.

In the discussions leading to publication of the first edition of the ICCR Prostate Cancer (Radical Prostatectomy) dataset in 2012, the Gleason grade or score of the prostatic carcinoma present at a positive surgical margin in radical prostatectomy specimens was identified as a potential prognostic factor [9]. Although there were three retrospective studies in moderate-

sized cohorts published at that time [111, 117, 118], it was decided by the expert panel that there was insufficient evidence to justify adding this element to the dataset. We have now included this item in the second edition of the dataset, based on additional evidence from a larger series of 405 men with a PSM after radical prostatectomy, which confirmed that a lower Gleason score at the margin was independently associated with a decreased risk of early BCR [119]. However, given that there are no prospective studies of this prognostic factor, and that it is sometimes difficult to determine the grade or score of the tumour at the PSM when there is crush or diathermy artefact present, the ICCR expert panel determined that this should be a recommended, rather than required element of the dataset.

In conclusion, structured pathology reports improve the completeness and quality of the data available for patient management, clinical trials and epidemiological studies. However, it is essential that the datasets underpinning structured pathology reporting are regularly revised to reflect advances in our understanding of cancer classification and prognostication, as well as changes in contemporary clinical practice. We hope that the second edition of the ICCR Prostate Cancer (Radical Prostatectomy) dataset meets these needs and promotes international best practice in prostate cancer reporting.

Contribution statement James Kench, Meagan Judge, John Srigley and Lars Egevad conceived and designed the dataset, edited and reviewed the manuscript. Brett Delahunt, Peter Humphrey, Glen Kristiansen, John Oxley, Krishan Rasiah, Hiroyuki Takahashi, Kirol Trpkov, Murali Varma, Thomas Wheeler and Ming Zhou provided analysis of the published literature, edited and reviewed the manuscript. All authors gave final approval for publication. James Kench and Lars Egevad take full responsibility for the work as a whole, including the dataset design and the decision to submit and publish the manuscript.

Compliance with ethical standards

Review type article - No ethics committee/institutional review board approval required.

Conflict of interest The authors declare that they have no conflict of interest.

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