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Prostate Cancer Histopathology Reporting Guide Radical Prostatectomy Specimen

ICCR

Family/Last name | Date of birth DD – MM – YYYY

Given name(s)

Patient identifiers | Date of request DD – MM – YYYY | Accession/Laboratory number

Elements in **black text** are CORE. Elements in **grey text** are NON-CORE.

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

CLINICAL INFORMATION (Note 1)

◯ Information not provided
◯ Information provided (select all that apply)

- ☐ Previous history of prostate cancer (including the Gleason score or WHO/ISUP Grade/Grade Group of previous specimens if known), *specify*
- ☐ Previous biopsy, *specify date and where performed*
- ☐ Previous therapy, *specify*
- ☐ Other clinical information, *specify*

PRE-BIOPSY SERUM PSA (Note 2)

ng/mL

SPECIMEN WEIGHT (Note 3)

(Weight of the prostate gland without the seminal vesicles)

g

SPECIMEN DIMENSIONS (Note 4)

(Of the prostate gland)

length mm x width mm x depth mm

SEMINAL VESICLES (Note 5)

◯ Absent
◯ Present (partially or completely resected)

LYMPH NODE DISSECTION SPECIMEN(S) (Note 6)

◯ Not submitted
◯ Present (partially or completely resected)

Site(s), *specify*

Laterality

◯ Left ◯ Right ◯ Bilateral ◯ Other

BLOCK IDENTIFICATION KEY (Note 7)

(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

HISTOLOGICAL TUMOUR TYPE (select all that apply) (Note 8)

☐ Adenocarcinoma (Acinar, usual type)
☐ Other, *specify*

HISTOLOGICAL TUMOUR GRADE (Note 9)

Gleason score

Indicate how Gleason score is being reported

◯ Largest tumour nodule
◯ Highest score tumour nodule
◯ Highest pT category tumour nodule
◯ Global score (summation of Gleason patterns in all nodules)

Primary pattern

◯ ≤3 ◯ 4 ◯ 5

Secondary pattern

◯ ≤3 ◯ 4 ◯ 5

◯ Indeterminate, *specify reason*

Minor tertiary pattern (if present and higher than primary and secondary grade)

◯ 4 ◯ 5 ◯ Not applicable

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HISTOLOGICAL TUMOUR GRADE (Note 9) **continued**

WHO/ISUP Grade (Grade Group)

- ◯ WHO/ISUP Grade (Grade Group) 1 (Gleason score ≤6)
- ◯ WHO/ISUP Grade (Grade Group) 2 (Gleason score 3+4=7)
- ◯ WHO/ISUP Grade (Grade Group) 3 (Gleason score 4+3=7)
- ◯ WHO/ISUP Grade (Grade Group) 4 (Gleason score 8)
- ◯ WHO/ISUP Grade (Grade Group) 5 (Gleason score 9-10)
- ◯ Indeterminate, *specify reason*

TUMOUR GROWTH PATTERNS (Note 10)

Intraductal carcinoma of the prostate (IDC-P) AND/OR Invasive cribriform carcinoma (ICC)

- ◯ Indeterminate
- ◯ Not identified
- ◯ Present

If present, specify the tumour growth pattern (if apparent on H&E staining[a])

IDC-P

- ◯ Not identified
- ◯ Present
  - ◯ IDC-P incorporated into Gleason score
  - ◯ IDC-P not incorporated into Gleason score

Invasive cribriform carcinoma

- ◯ Not identified
- ◯ Present

[a] *Use of immunohistochemistry is optional.*

TUMOUR QUANTIFICATION (Note 11)
(Amount of tumour identified)

Percentage of prostate involved by tumour

- ◯ ≤5%
- ◯ 6-10%
- ◯ 11-20%
- ◯ 21-50%
- ◯ 51-80%
- ◯ ≥80%

OR

Diameter of largest nodule

mm

EXTRAPROSTATIC EXTENSION (Note 12)

- ◯ Indeterminate
- ◯ Not identified
- ◯ Present

Specify location(s)

Extent

- ◯ Focal
- ◯ Non-focal (established)

MICROSCOPIC URINARY BLADDER NECK INVASION (Note 13)

- ◯ Not applicable[b]
- ◯ Not identified
- ◯ Present

[b] *Refers to cases where bladder neck is not included in the specimen.*

MARGIN STATUS (Note 14)

- ◯ Cannot be assessed
- ◯ Not involved
- ◯ Involved, *specify margin(s) and their location, if possible*

Type of margin positivity (select all that apply)

- ◯ Indeterminate
- ☐ Extraprostatic (EPE)
- ☐ Intraprostatic (capsular incision)

Length of margin involved by carcinoma[c]

mm

Gleason pattern of tumour present at positive margin[d]

- ◯ Gleason pattern 3
- ◯ Gleason pattern 4 or/and 5

[c] *If more than 1 positive margin the extent should reflect the cumulative length.*

[d] *If more than 1 pattern at margin select the highest.*

SEMINAL VESICLE INVASION (Note 15)

- ◯ Not applicable[e]
- ◯ Not identified
- ◯ Present

[e] *Refers to rare cases where seminal vesicles are not included in the specimen.*

LYMPHOVASCULAR INVASION (Note 16)

- ◯ Indeterminate
- ◯ Not identified
- ◯ Present

LYMPH NODE STATUS (Note 17)

- ◯ No nodes submitted or found

Number of lymph nodes examined

- ◯ Not involved
- ◯ Involved

Number of involved lymph nodes

- ◯ Number cannot be determined

Maximum dimension of largest deposit

mm

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PATHOLOGICAL STAGING (UICC TNM 8th edition)[f] (Note 18)

TNM Descriptors (only if applicable) (select all that apply)

- ☐ m - multiple primary tumours
- ☐ r - recurrent
- ☐ y - post neoadjuvant therapy

Primary tumour (pT)

- ◯ TX[g] Primary tumour cannot be assessed
- ◯ T0 No evidence of primary tumour
- ◯ T2 Tumour confined within prostate
- ◯ T3 Tumour extends through the prostatic capsule[h,i]
  - ◯ T3a Extracapsular extension[h] (unilateral or bilateral) including microscopic bladder neck involvement
  - ◯ T3b Tumour invades seminal vesicle(s)
- ◯ T4 Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles and/or pelvic wall

Regional lymph nodes (pN)

- ◯ NX[g] Regional nodes cannot be assessed
- ◯ N0 No regional lymph node metastasis
- ◯ N1 Regional lymph node metastasis

Distant metastasis (pM)[j]

- ◯ Not applicable[k]
- ◯ M1 Distant metastasis
  - ◯ M1a Non-regional lymph node(s)
  - ◯ M1b Bone(s)
  - ◯ M1c Other site(s)

[f] *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley. (incorporating any errata published up until 12th July 2024).*

[g] *TX and NX should be used only if absolutely necessary.*

[h] *The consensus of the dataset authors is that the term extraprostatic extension is preferred.*

[i] *Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.*

[j] *Note: When more than 1 site of metastasis is present, the most advanced category is used. pM1c is the most advanced category.*

[k] *No clinical and radiological correlation available.*

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Definitions

CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council (NHMRC) levels of evidence[1]). In rare circumstances, where level III-2 evidence is not available an element may be made a CORE element where there is unanimous agreement in the Dataset Authoring Committee (DAC). An appropriate staging system e.g., Pathological TNM staging would normally be included as a CORE element.

Molecular and immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world this type of testing is limited by the available resources. In order to encourage the global adoption of ancillary tests for patient benefit, International Collaboration on Cancer Reporting (ICCR) includes the most relevant ancillary testing in ICCR Datasets as CORE elements, especially when they are necessary for the diagnosis. Where the technical capability does not yet exist, laboratories may consider temporarily using these data elements as NON-CORE items.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of the DAC.

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Scope

The dataset has been developed for radical prostatectomy specimens for prostate carcinoma. Core biopsies and transurethral resection and enucleation specimens are dealt with in separate ICCR datasets.[2,3] Rare urothelial carcinomas arising within the prostate are included in a separate ICCR dataset.[4]

The third edition of this dataset includes changes to align the dataset with the World Health Organization (WHO) Classification of Tumours, Urinary and Male Genital Tumours, 5th edition, 2022.[5] The ICCR dataset includes 5th edition Corrigenda, July 2024.[6] In development of this dataset, the DAC considered evidence up until August 2024.

A list of changes in this dataset edition can be accessed here.

The authors of this dataset can be accessed here.

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Note 1 – Clinical information (Core and Non-core)

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 with the specimen. 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. For this reason, information about any previous therapy is important for the accurate assessment of radical prostatectomy specimens.

Following irradiation, benign acinar epithelium shows nuclear enlargement and nucleolar prominence,[7] while basal cells may show cytological atypia, nuclear enlargement and nuclear smudging.[8] There may also be increased stromal fibrosis, which may resemble tumour-induced desmoplasia. These changes may persist for a considerable period, having been reported up to 72 months after treatment, and are more pronounced in patients who have undergone brachytherapy compared to those who have received external beam radiation therapy.[8,9] Radiation may be associated with apparent upgrading of prostate cancer in prostatectomy specimens.[10]

Likewise, neoadjuvant androgen deprivation therapy (ADT) may induce morphological changes in both prostate cancer and benign tissue. Androgen blockade induces basal cell hyperplasia and cytoplasmic vacuolation in benign prostatic tissue, although this is unlikely to be confused with malignancy.[11] More significantly from a diagnostic point of view, neoadjuvant ADT may increase the risk of overlooking acinar adenocarcinoma on low power microscopic examination due to collapse of glandular lumina, cytoplasmic pallor and shrinking of nuclei.[12-14] 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.[10,11] Hence, it has been suggested that in prostate glands resected following either radiotherapy or ADT, tumours that show significant treatment effect should not be graded.[15]

The Gleason score (GS) or International Society of Urological Pathology (ISUP)/WHO Grade (Grade Group) of prostate cancer in any previously submitted specimen should also be provided by the clinician.

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Note 2 – Pre-biopsy serum PSA (Non-core)

The clinician requesting the pathological examination should provide information on the pre-biopsy serum prostate-specific antigen (PSA) level. 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 with the specimen.

Pre-biopsy serum PSA is a key parameter in some nomograms widely used to estimate the risk of recurrence post-operatively and guide clinical decision making on adjuvant therapy.[16-18]

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.[19-22]

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Note 3 – Specimen weight (Non-core)

The prostate gland should be weighed (ideally in the unfixed condition) without the seminal vesicles since the seminal vesicles can vary markedly in size. If only a combined weight is recorded, this will introduce error into the measurement of the prostate gland weight and distort comparisons, hence a working group at the 2009 ISUP Consensus Conference recommended that the prostate should be weighed following removal of the seminal vesicles.[23]

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Note 4 – Specimen dimensions (Non-core)

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. Recording the volume of the prostate also allows comparisons with the pre-operative assessments of PSA density.

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Note 5 – Seminal vesicles (Core)

A record of all organs/tissues received is typically a standard (core) item in gross/macroscopic pathology reports and assessment of invasion of the seminal vesicles is required for staging.

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Note 6 – Lymph node dissection specimen(s) (Core and Non-core)

A record of all organs/tissues received is typically a standard (core) item in gross/macroscopic pathology reports and assessment of nodal metastasis is required for staging.

If present, the laterality of the pelvic lymph nodes submitted may be recorded as left, right, bilateral or other (as non-core).

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Note 7 – Block identification key (Non-core)

The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important should the need for internal or external review arise. The reviewer needs to be clear about the origin of each block in order to provide an informed specialist opinion. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. It may be useful to have a digital image of the specimen and record of the origin of the tumour blocks in some cases.

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

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Note 8 – Histological tumour type (Core)

The vast majority (>95%) of prostate cancers are acinar adenocarcinomas.[5] Other types and subtypes of carcinoma are rarer but must be recorded if present, since some, such as ductal adenocarcinoma, sarcomatoid carcinoma and pleomorphic giant cell adenocarcinoma, have a significantly poorer prognosis.[24-28] The tumour type should be assigned in line with the 2022 WHO classification of epithelial tumours of the prostate, and mixtures of different types should be indicated (Table 1).[24]

Table 1: World Health Organization classification of tumours of the prostate.[24]

Descriptor	ICD-O codes[a]
Epithelial tumours of the prostate	
Glandular neoplasms of the prostate	
Cystadenoma	8440/0
Prostatic intraepithelial neoplasia, high grade	8148/2
Intraductal carcinoma	8500/2
Acinar adenocarcinoma	8140/3
Signet-ring cell-like acinar adenocarcinoma	8490/3
Pleomorphic giant cell acinar adenocarcinoma	8140/3
Sarcomatoid acinar adenocarcinoma	8572/3
Prostatic intraepithelial neoplasia-like carcinorna	8140/3
Ductal adenocarcinoma	8500/3
Adenocarcinoma with neuroendocrine differentiation	8574/3
Squamous neoplasms of the prostate	
Adenosquamous carcinoma	8560/3
Squamous cell carcinoma	8070/3
Adenoid cystic (basal cell) carcinoma†	8147/3
Mesenchymal tumours unique to the prostate	
Stromal tumours of the prostate	
Stromal tumour of uncertain malignant potential	8935/1
Stromal sarcoma	8935/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-0-3.2).[29] Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Behaviour code /6 is not generally used by cancer registries. Subtype labels are indented. Incorporates all relevant changes from the 5th edition Corrigenda, July 2024.[6]

† Labels marked with a dagger have undergone a change in terminology of a previous code.

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Note 9 – Histological tumour grade (Core)

The Gleason system has been the worldwide standard for prostate cancer grading over several decades with its contemporary application outlined in detail in the 5th edition of the WHO Classification of Urinary and Male Genital Tumours, 2019 ISUP Consensus Conference, and 2019 Genitourinary Pathology Society (GUPS) 'White paper'.[24,30,31] It is regarded as a core element since validation studies over the years have demonstrated that Gleason scoring is a robust independent predictor of biochemical recurrence, metastasis, and prostate cancer specific mortality.[32-35]

In summary, the GS of radical prostatectomy specimens is usually obtained by adding the two predominant Gleason patterns or doubling the pattern in cases of uniform pattern. In the 2005 ISUP revision it was recommended that a separate GS should be assigned for each dominant tumour nodule(s).[36] 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 patterns should not be included in the global GS. Reporting of separate tumours may, however, be difficult in practice if the prostatectomy specimen is not totally embedded and multifocal tumour nodules may merge into a single large tumour mass. The 2019 ISUP Consensus Conference on the grading of prostate carcinoma recommended that the GS of the (a) largest, (b) highest stage, and (c) highest grade tumour nodules should be recorded, if these are not one in the same. In the large majority of cases (approximately 90%) the highest GS, tumour volume, and stage are all seen in the one nodule.[30,37]

Not uncommonly in radical prostatectomy specimens there are more than two Gleason patterns present and if there is a minor component of pattern 5 comprising the smallest volume it is referred to as a tertiary high grade pattern or minor tertiary pattern 5. If the tertiary pattern 5 carcinoma constitutes >5% of the estimated volume of the dominant tumour nodule(s) it used as the secondary pattern in Gleason scoring (and associated WHO/ISUP Grade or Grade Group). If there is <5% tertiary pattern 5 carcinoma present the GS remains unchanged but the presence of a minor or tertiary high grade pattern should be noted in the pathology report.[24,30,31] This 5% cut-off point is somewhat arbitrary, but acknowledges that higher tertiary pattern 5 volumes are associated with a worse prognosis. Gleason scoring in radical prostatectomy specimens is summarised in the WHO Classification of Urinary and Male Genital Tumours, 5th edition.[24]

At the 2014 ISUP expert consultation meeting on Gleason grading, a grouping of the GS into 5 grade categories was proposed (variously termed Grade Groups, ISUP Grade or WHO Grade).[38] The grade groupings and associated definitions are outlined in Table 2. Over the past decades GS below 6 have become less commonly used. There is also evidence that GS 7 (Grade Groups 2 and 3) tumours have a worse outcome if there is a predominant pattern 4 (4+3) than if pattern 3 dominates (3+4). However, more precise quantification of the proportion of Gleason patterns 4 and 5 in radical prostatectomy specimens is currently considered a non-core element since the evidence for its significance is mixed.[30,31]

Both the GS and the WHO Grade/ISUP Grade/Grade Group must always be reported for the sake of clarity. It should also be stated whether or not any intraductal carcinoma of prostate (IDC-P) component, if present, has been included in the assignment of the tumour grade. If an IDC-P component has not been included in the assessment of prostate carcinoma grade, immunohistochemistry (IHC) may be necessary to differentiate IDC-P from invasive cribriform carcinoma (ICC), invasive solid carcinoma and/or invasive carcinoma with comedonecrosis.[24,39,40]

Table 2: Gleason scoring in radical prostatectomy and core needle biopsy specimens.[22]

Gleason score	Grade Group	Needle biopsy scoring[a]	Prostatectomy scoring[b]
≤3 + 3 = 6	1	Only pattern 3 present	Usually only pattern 3 present Very rarely lower grade patterns seen Minor higher grade pattern (International Society of Urological Pathology (ISUP) only)[c]
3 + 4 = 7	2	2 grade patterns present Most prevalent (primary) 3 Highest grade pattern (secondary) 4	2 or 3 grade patterns present Most prevalent (primary) 3 Second most prevalent (secondary) 4 Can have minor tertiary pattern 5 (≤5% tumour volume)[d]
4 + 3 = 7	3	2 grade patterns present Most prevalent (primary) 4 Highest grade pattern (secondary) 3	2 or 3 grade patterns present Most prevalent (primary) 4 Second most prevalent (secondary) 3 Can have minor tertiary pattern 5 (≤5% tumour volume)[d]
4 + 4 = 8 3 + 5 = 8 5 + 3 = 8	4	1, 2 or 3 grade patterns present Only pattern 4 present OR Most prevalent (primary) 3 Highest grade pattern (secondary) 5 OR Most prevalent (primary) 5 Highest grade pattern (secondary) 3	1, 2 or 3 grade patterns present Pattern 4 ≥95% tumour volume[e] Pattern 3 ignored if third most prevalent or ≤5% tumour OR Most prevalent (primary) 3 Second most prevalent (secondary) 5 OR Most prevalent (primary) 3 Third most prevalent (>5% tumour) 5 OR Most prevalent (primary) 5 Second most prevalent (secondary) 3
4 + 5 = 9 5 + 4 = 9	5	1, 2 or 3 grade patterns present Most prevalent (primary) 4 Highest grade pattern (secondary) 5 OR Most prevalent (primary) 5 Highest grade pattern (secondary) 4	1, 2 or 3 grade patterns present Most prevalent (primary) 4 Second most prevalent (secondary) 5[e] OR Most prevalent (primary) 4 Third most prevalent pattern 5 (>5% tumour) OR Most prevalent (primary) 5 Second most prevalent (secondary) 4

5 + 5 = 10[f]		OR ≥95% pattern 5 present	OR ≥95% pattern 5 present

[a] For needle core biopsies with multiples specimens there is uncertainty on whether the highest specimen score or the global (overall) Gleason score is superior in predicting the radical prostatectomy score and clinical outcome. ISUP recommends reporting a separate Gleason score for each biopsy site. Global scores should be assigned for each magnetic resonance imaging (MRI)-targeted lesion.[30,31]

[b] Most radical prostatectomy specimens show multifocal carcinoma[41] and ISUP recommends that the Gleason score of the largest, highest grade and highest stage nodules are recorded.

[c] ISUP 2019 recommendations would allow assignment of a minor Gleason pattern 4 or 5 in a 3 + 3 = 6 (Grade Group (GG) 1) carcinoma provided that the pattern 4 or 5 represents ≤5% of the tumour volume. If this grading approach is followed it is recommended that a comment is made on the presence of the higher grade pattern. Genitourinary Pathology Society (GUPS) 2020 defines minor tertiary pattern as requiring the presence of 3 different patterns, and confines its use to GG 2 or 3 cancers. Hence, in the GUPS system, a carcinoma with 96% pattern 3 and 4% pattern 4 would be scored as 3 + 4 = 7.

[d] Minor tertiary grade patterns should be mentioned in report. However, if tertiary pattern 5 comprises >5% tumour volume it becomes the secondary pattern in the Gleason score (i.e., either 3 + 5 = 8 or 4 + 5 = 9).

[e] Can have a minor component of Gleason pattern 5 (≤5% pattern 5 and >95% pattern 4) in a cancer scored as 4 + 4 = 8 (GG 4) under ISUP 2019 recommendations. In contrast, according to the GUPS guidelines such a tumour would be scored 4 + 5 = 9 (GG 5).

[f] May have minor Gleason pattern 3 or 4 component comprising <5% of the tumour volume.

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Note 10 – Tumour growth patterns (Core and Non-core)

Presence of either intraductal carcinoma of the prostate (IDC-P) and/or invasive cribriform carcinoma (ICC) (Core)

The presence or absence of either IDC-P or ICC is a core item in pathology reporting since several studies have demonstrated that the presence of cribriform growth patterns has a significant prognostic impact.[30,31,42-51] However, it is not critically important to distinguish between these entities as there is currently little impact on post-surgical management.

Immunohistochemistry (IHC) may be required to differentiate intraductal cribriform patterns seen in IDC-P from ICC when standard morphological criteria are equivocal.[42,52,53] Hence, the differentiation between IDC-P and ICC is recommended as a non-core element (see below) to mitigate the risk of overuse of IHC in distinguishing intraductal from ICC.

Intraductal carcinoma of the prostate (IDC-P) (Non-core)

The WHO 2022 Classification defines intraductal carcinoma as "a neoplastic epithelial proliferation involving pre-existing, generally expanded, duct-acinar structures and characterised by architectural and cytological atypia beyond what is acceptable for high grade prostatic intraepithelial neoplasia".[24] IDC-P is found in 15-30% of radical prostatectomy specimens and is usually associated with invasive prostate cancer.[54] Occasionally isolated IDC-P ('precursor-type' IDC-P) is found without invasive carcinoma; this latter situation is very rare and beyond the scope of this dataset and IDC-P without an associated invasive carcinoma should not be assigned an GS or Grade Group.[55]

Intraductal carcinoma of the prostate (IDC-P) has been well characterised at the histological and molecular levels over the past decade and its clinical significance is now also better understood.[56] In the 5th edition of the WHO Classification of Tumours the essential diagnostic criteria for IDC-P are: 1) expansile epithelial proliferation in the pre-existing duct-acinar system; 2) lumen spanning solid, cribriform and/or comedo patterns; 3) loose cribriform or micropapillary patterns with enlarged pleomorphic nuclei; and 4) residual basal cells.[24] Desirable diagnostic criteria include IHC demonstrating at least partial basal cell retention.

It is important to distinguish IDC-P from high grade prostatic intraepithelial neoplasia (HGPIN). Compared to IDC-P, HGPIN does not have necrosis, marked nuclear pleomorphism or brisk mitotic activity. Cribriform HGPIN is a controversial entity and it has been proposed that such lesions which do not meet the threshold for diagnosis of IDC-P should instead be referred to as 'atypical intraductal proliferation' (AIP) or 'atypical proliferation suspicious for intraductal carcinoma' (ASID).[24,31,39]

When present in combination with invasive carcinoma in radical prostatectomy specimens, IDC-P is strongly associated with high volume, high grade and stage (extraprostatic extension (EPE) or seminal vesicle invasion (SVI) positive) carcinoma.[57] Moreover the presence of IDC-P is independently associated with biochemical recurrence, regional lymph node metastasis and cancer specific survival.[48,49,58] Hence, in radical prostatectomy specimens, the presence of IDC-P in association with invasive carcinoma should be recorded. It is unnecessary to measure the extent of the IDC-P.

Invasive cribriform carcinoma (ICC) (Non-core)

The presence of ICC should be recorded in the pathology report. In 2021, ISUP proposed a consensus definition of cribriform pattern in prostate carcinoma, namely 'A confluent sheet of contiguous malignant epithelial cells with multiple glandular lumina that are easily visible at low power (objective magnification x10).[59] There should be no intervening stroma or mucin separating individual or fused glandular structures.' Additional criteria have also been proposed based on an interobserver reproducibility study among urological pathologists which found that transluminal bridging and a clear luminal space along the periphery of gland occupying <50% of gland circumference were reliable diagnostic features of cribriform adenocarcinoma.[60]

Several studies in radical prostatectomy specimens have shown that the presence of cribriform pattern 4 carcinoma in GS 7, 8 and 9 (WHO/ISUP Grades or Grade Groups 2-5) tumours confers a worse prognosis, including biochemical-free, metastasis-free and disease specific survival.[30,31,39,44-47,61-63] Differentiating between large and small cribriform glands is not currently recommended due to the varying definitions used and findings in the published studies.

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Note 11 – Tumour quantification (Non-core)

Some measurement of the size or extent of the tumour forms part of the generic 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 GS, EPE, surgical margin status and pathological TNM stage, and the majority of studies have not demonstrated independent prognostic significance on multivariate analysis.[64-69] Hence, the DAC regarded this element as non-core.

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 Consensus Conference that some quantitative

measure of the extent of the tumour in a prostatectomy specimen should be recorded.[70] This can be done either as a visual estimate of intraglandular percentage of cancer,[71,72] or by measuring the maximum size of dominant tumour nodule.[73,74] 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.[69,73,74] In the future more widespread utilisation of artificial intelligence based methods may make precise tumour quantification more feasible in routine practice.

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Note 12 – Extraprostatic extension (Core and Non-core)

Extraprostatic extension (EPE), defined as the extension of tumour beyond the confines of the gland into the periprostatic soft tissue, is a core element as it is a significant predictor of recurrence in node negative patients.[64,75] EPE replaced earlier, less clearly defined terms such as capsular penetration, perforation or invasion, following a 1996 Consensus Conference.[76]

The assessment of EPE can be difficult, as the prostate is not surrounded by a discrete, well defined fibrous capsule,[77] but rather by a band of concentrically placed fibromuscular tissue that is an inseparable component of the prostatic stroma.[78] EPE can be recognised in several different settings: 1) 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); 2) neoplastic glands surrounding nerves in the neurovascular bundle (posterolaterally) beyond the boundary of the normal prostatic glandular tissue; and 3) 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—since 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.[78,79] Extraprostatic tumour in fibrous tissue is best identified initially at low power magnification, but should be then confirmed by high power magnification examination verifying that the neoplastic glands are in stroma that is fibrous and beyond the condensed smooth muscle of the prostate.[64,79] 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, at the apex benign glands are frequently admixed with skeletal muscle and the presence of neoplastic glands within skeletal muscle does not necessarily constitute EPE. Hence, in this region it is more important to accurately assess the completeness of surgical resection. 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 in the previous paragraph) when the carcinoma appears to bulge beyond the boundary of the normal prostate gland.[79,80]

Location of extraprostatic extension (EPE) (Non-core)

Since it was considered a generic element forming part of a comprehensive pathology report, the location of any EPE has been included as a non-core item based on the consensus of the DAC, despite the lack of published evidence for its influence on staging, prognosis or treatment.[79] It provides potentially useful information to the urologist, enabling correlation with clinical findings and any pre-operative imaging studies performed.

Extent of extraprostatic extension (EPE) (Non-core)

Categorisation of the extent of EPE as focal or non-focal (also referred to as 'extensive' or 'established') is a non-core item. Focal EPE was originally defined as no more than 'a few' neoplastic glands just outside the prostate which is now interpreted in a more semi-quantified manner as extraprostatic glands which occupy no more than one high power field (HPF) in no more than two sections, with extensive EPE representing anything more than this.[64] 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.[81] 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. Studies of the extent of EPE and outcome have yielded mixed results and a 2024 comprehensive meta-analysis has found no significant difference between focal and established EPE.[64,75,82-85]

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Note 13 – Microscopic urinary bladder neck invasion (Core)

Microscopic invasion of the urinary bladder neck can be identified 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.[86] Microscopic bladder neck involvement is a significant predictor of PSA-recurrence in univariate analysis, although not in multivariate modelling in most studies.[87-89] Neoplastic glands intermixed with benign prostatic glands at the bladder neck margin is equivalent to capsular incision (CI) rather than true bladder neck invasion.[87,90,91] In the 8th edition of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) Cancer Staging Manual microscopic bladder neck invasion is classified as stage pT3a disease since it has a similar biochemical recurrence-free survival and cancer specific survival to patients with SVI or EPE.[92,93] Macroscopic invasion of the bladder wall is categorised as pT4.

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Note 14 – Margin status (Core and Non-core)

A positive surgical margin (PSM) is regarded as a core element since it significantly reduces the likelihood of progression-free survival, including PSA recurrence-free survival, local recurrence-free survival and development of metastases after radical prostatectomy in some multivariate analyses.[80,94-98] In some studies positive margins are associated with an increased risk of prostate cancer specific mortality.[99-101] 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.[80,102]

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.[103-106] 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.[103,105]

Stating the location of the PSM is useful information for the urologist. The site of the PSM and the number of positive margins have been shown to influence biochemical recurrence and risk of progression. 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.[107,108]

Type of margin positivity (Non-core)

The type of margin positivity is regarded as a non-core item. Intraprostatic margin involvement or CI occurs when the urologist inadvertently develops the resection margin within the plane of the prostate rather than outside the capsule. CI with a PSM is diagnosed when malignant glands are cut across adjacent to benign prostatic glands.[78] In these cases, the edge of the prostate in this region is left in the patient. Data on the prognostic significance of CI vary among studies.[109-111] In one large series, a significantly higher recurrence rate is found in patients with CI/intraprostatic margin involvement than in patients with organ confined disease with negative margins, or focal EPE with negative margins, although CI has a significantly better outcome than that associated with non-focal EPE and positive margins.[112]

Margin involvement associated with EPE is diagnosed when malignant glands in extraprostatic tissue are transected by the resection margin. This can be difficult to distinguish from CI 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 PSM with EPE, similarly to margin involvement when there is cancer in adipose tissue.[110] At the apex, the histological boundaries of the prostate gland can be difficult to define and again EPE with a positive margin can be difficult to differentiate from CI/ 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.[80,110] 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.[79]

Extent (total) of margin involvement (Non-core)

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.[94,95,113,114] The DAC considered that there is sufficient evidence to include measurement of the length of margin involved by carcinoma as an element in the dataset (as non-core).[103,105,112,114-120] However, in one series, Cao et al (2011)[117] found that the linear length of a positive margin was an independent prognostic factor for organ confined tumours only, i.e., pT2 not pT3, while, another investigation found that the impact of a PSM after radical prostatectomy was greater in intermediate and high risk groups (based on GS and pre-biopsy PSA) than in low risk patients.[97] Further studies of such factors potentially affecting the impact of PSMs are required before there is sufficient evidence justifying their inclusion as core 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.[121]

Gleason pattern at the margin (Non-core)

Gleason pattern at the surgical margin is classified as a non-core item since some studies have found that Gleason pattern or score of the tumour at the PSM is an independent predictor of biochemical recurrence and may aid optimal selection of patients for adjuvant therapy.[114,122-128] In one of these studies patients with Gleason pattern 4 or 5 carcinoma (GS 3+4, 4+3, 4+4 or 4+5) at a PSM had double the risk of PSA relapse compared to those with only Gleason pattern 3 (score 3+3) at the margin. Moreover, men with Gleason pattern 3 at the PSM had a similar 5 year biochemical relapse-free survival rate to those with negative margins.[114] Another study, restricted to men with dominant nodule GS 7 and non-focal EPE, also found that the grade of cancer at the site of a PSM was associated with biochemical recurrence.[122] A meta-analysis of 10

eligible studies also demonstrated that GS, primary Gleason pattern and Grade Group at the PSM were significantly associated with increased risk of biochemical recurrence (BCR).[125]

In these studies, the potential problem of cautery/thermal artefact was considered — in slides where the cancer at the margin was distorted by cautery/thermal or crush artifact 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.[114,122-124] Limiting assessment to only the highest pattern present at the PSM may simplify measurement of this parameter,[126] however, it should be noted that in most of the published studies GS could be reported.[122-124] In the event there are multiple positive margins with differently scored cancers present, the highest pattern or score should be recorded.

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Note 15 – Seminal vesicle invasion (Core)

The DAC included SVI as a core element as SVI is a well-established, independent, adverse prognostic factor,[80,129,130] is required for staging, and constitutes an integral component of the commonly used nomograms and tables that predict risk of post prostatectomy cancer recurrence.[16-18] The finding of SVI at the time of radical prostatectomy is associated with a significantly increased risk of PSA recurrence,[129-131] and the presence of SVI and a PSM may also influence the response to adjuvant radiotherapy.[132,133] Bilaterality and extent of extraprostatic SVI are not independently predictive of prognosis and were not included in the ICCR dataset.[115]

Different definitions of SVI complicate comparison of the published survival analyses.[132,134] Older definitions including involvement of the adipose tissue or adventitia around the seminal vesicle are problematic with regard to distinction from EPE. In other studies a distinction between intraprostatic and extraprostatic SVI has not always been made, impeding comparisons between series.[135,136] At the 2009 ISUP meeting, the proposal that SVI should be defined as carcinomatous invasion of the muscular wall of the seminal vesicle exterior to the prostate was endorsed.[134] Only extraprostatic seminal vesicle is included in this definition of SVI, since it is difficult to differentiate between intraprostatic seminal vesicle and ejaculatory duct invasion as these structures merge without a clear histological cut off.[137] It was concluded that older definitions that include invasion of the adipose tissue around the seminal vesicle are imprecise and should be discarded.[132,134]

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Note 16 – Lymphovascular invasion (Core)

Lymphovascular invasion (LVI) is defined as the unequivocal presence of tumour cells within endothelial-lined spaces with no or only thin underlying muscular walls.[138,139] 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. IHC 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.

Lymphovascular invasion (LVI) has been reported to be associated with decreased time to biochemical progression, distant metastases and overall survival after radical prostatectomy.[138-146] 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.[138,139,141,143-147]

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Note 17 – Lymph node status (Core and Non-core)

Lymph node involvement is a well-established independent adverse prognostic factor,[80,134] and is an integral component of the commonly used nomograms that predict the risk of post prostatectomy disease recurrence.[16] Stating the number of examined lymph nodes and the number of involved nodes is a useful quality indicator for urologists and pathologists.

There is little published data on the prognostic significance of isolated tumour cells (clusters less than <200 micrometre (µm) in greatest dimension) in prostate cancer and insufficient evidence at present to support the routine use of IHC as an ancillary technique in the identification of lymph node involvement.

Maximum dimension of largest deposit (Non-core)

As the diameter of the largest metastatic deposit correlated with distant metastasis and cancer-specific survival in two studies but not in another,[148-150] maximum dimension of largest deposit has been included as a non-core item rather than as a core item. There was consensus (81% of respondents) at the 2009 ISUP Consensus Conference that that the diameter of the largest lymph node metastasis should be included in the pathology reports on radical prostatectomy specimens.[134]

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Note 18 – Pathological staging (Core and Non-core)

Staging data must be assessed according to the 8th edition of the UICC/AJCC Cancer Staging Manual.[92,93]

It should also be noted that that the UICC 8th edition Stage Grouping differs from the AJCC 8th edition Prognostic Stage Groups.[92,93]

Reporting of pathological staging categories (pT,pN,pM) is based on the evidence available to the pathologist at the time of reporting. As indicated in UICC/AJCC TNM8,[92,93] the final stage grouping of a patient's tumour is based on a combination of pathological staging and other clinical and imaging information.

The reference document TNM Supplement: A commentary on uniform use, 5th edition (C Wittekind et al. editors) may be of assistance when staging.[151]

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