

Sponsored by



Prostate Core Needle Biopsy Histopathology Reporting Guide Part 2 - Specimen Level Reporting



Family/Last name

Date of birth

Given name(s)

Patient identifiers

Date of request

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

FOR EACH SPECIMEN - COMPLETE THE FOLLOWING

SPECIMEN ID AND LOCATION (Note 1)

HISTOLOGICAL TUMOUR TYPE (select all that apply) (Note 2)

- No evidence of primary tumour
- Adenocarcinoma (Acinar, usual type)
- Other, *specify*

HISTOLOGICAL TUMOUR GRADE (Note 3)

Gleason score

Primary pattern/grade
 3 4 5

Highest remaining pattern/grade
 3 4 5

Indeterminate, *specify reason*

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*

Percentage Gleason pattern 4

(Applicable for Gleason score 3+4=7 or WHO/ISUP Grade 2)

- 1-5%
- 6-10%
- 11-20%
- 21-30%
- 31-40%
- 41-50%

Percentage Gleason pattern 4

(Applicable for WHO/ISUP Grade ≥3)

Percentage Gleason pattern 5

(Applicable for WHO/ISUP Grade ≥4)

 %

TUMOUR GROWTH PATTERNS (Note 4)

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

(Applicable for Gleason score 7 or 8)

- Not identified
- Present

^a Use of immunohistochemistry is optional.

TUMOUR EXTENT (Note 5)

Number of positive cores/total number of cores

 /

AND

Linear extent of prostatic tissue involved by carcinoma

- 1% - 5%
- 6% - 10%
- 11% - 20%
- 21% - 30%
- 31% - 40%
- 41% - 50%
- 51% - 60%
- 61% - 70%
- 71% - 80%
- 81% - 90%
- >90%

AND/OR

Length of tissue involved by carcinoma mm

EXTRAPROSTATIC EXTENSION (Note 6)

- Indeterminate
- Not identified
- Present

SEMINAL VESICLE/EJACULATORY DUCT INVASION (Note 7)

- Not identified
- Present

LYMPHOVASCULAR INVASION (Note 8)

- Not identified
- Present

PERINEURAL INVASION (Note 9)

- Not identified
- Present

COEXISTENT PATHOLOGY (Note 10)

- None identified
- Present, *specify*

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 evidence¹). In rare circumstances, where level III-2 evidence is not available an element may be made a CORE element where there is unanimous agreement by the Dataset Authoring Committee (DAC).

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.

 **Back**

Scope

The dataset has been developed for the examination of prostate core needle biopsies. The dataset applies to invasive carcinomas of the prostate gland. Transurethral resection and enucleation specimens and radical prostatectomy specimens are dealt with in separate ICCR datasets.^{2,3} Urothelial carcinomas arising in the bladder or urethra are dealt with in separate datasets.^{4,5} Rare urothelial carcinomas arising within the prostate are included in a separate ICCR dataset.⁵

The second 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, 2022.⁶ The ICCR dataset includes 5th edition Corrigenda, July 2024.⁷ In development of this dataset, the DAC considered evidence up until July 2024.

The prostate biopsy reports can be done using *Specimen level reporting* or *Case level reporting*. The following commentary applies to both specimen level and case level reporting of prostate core needle biopsies. Reporting by either specimen level or case level will be sufficient or users may also use both.

Choosing which reporting to use will depend on your local practice or institutional preference, as well as regional or national recommendations.

A list of changes in this dataset edition can be accessed [here](#).

The authors of this dataset can be accessed [here](#).

 [Back](#)

Note 1 – Specimen identification and location (Core)

Biopsy cores are generally taken in a systematic way from multiple sites mapped in the prostate.⁸⁻¹¹ Systematic biopsies are now widely performed either by transperineal or transrectal approach, the former having the advantage of lesser infectious complications. If a lesion in prostate is identified on imaging, a magnetic resonance imaging (MRI)-targeted biopsy is additionally performed.¹²⁻¹⁴ The targeted biopsy has a greater chance of detecting clinically significant cancer and has a lower risk of sampling clinically insignificant cancer. A usual prostate biopsy has 12 to 14 specimens from the systematic biopsy plus the additional specimens from the targeted biopsy.

The prostate biopsy reports can be done using *Specimen level reporting* or *Case level reporting*. Specimen level reporting can be used for every positive specimen site generating multiple reports. Case level reporting summarises all positive specimen sites generating a single report. For example, a 12-site systematic biopsy with 5 sites positive for cancer will have 5 specimen level reports or 1 case level report. Reporting by either specimen level or case level will be sufficient or users may also use both. Choosing which reporting to use will depend on your local practice or institutional preference, as well as regional or national recommendations.

In specimen level reporting, individual reports are specific for each positive specimen site and the specimen identification and location must be documented. When using a case level reporting, the location of all positive specimen sites should be documented. Targeted biopsies must be distinguished from the systematic biopsies.

 [Back](#)

Note 2 – Histological tumour type (Core)

The vast majority (>95%) of prostate cancers are acinar adenocarcinomas.^{6,15} 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 carcinoma, have a significantly poorer prognosis. The tumour type should be assigned in line with the 2022 WHO Classification and mixtures of different types should be indicated (Table 1).¹⁶ Some prostate carcinoma subtypes, such as ductal and signet-ring cell-like, require full examination of the resected tumour with percent cut-offs to make the diagnosis. Thus, using descriptive diagnosis, for example ‘adenocarcinoma with ductal features’, is recommended in biopsy. Subtypes of prostate carcinoma (under acinar adenocarcinoma in Table 1) are often identified in combination with acinar type adenocarcinoma, and in such cases the tumour type should be classified according to the subtype(s) present.

Information on histological tumour type may be recorded at a specimen level or at a case level depending on local practice. The response type 'No evidence of primary tumour' should only be used if specimen level reporting is utilised.

Table 1: World Health Organization classification of epithelial tumours of the prostate.¹⁶

Descriptor	ICD-O codes ^a
Epithelial tumours of the prostate	
<i>Glandular neoplasms of the prostate</i>	
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 carcinoma	8140/3
Ductal adenocarcinoma	8500/3
Adenocarcinoma with neuroendocrine differentiation	8574/3
<i>Squamous neoplasms of the prostate</i>	
Adenosquamous carcinoma	8560/3
Squamous cell carcinoma	8070/3
Adenoid cystic (basal cell) carcinoma [†]	8147/3
Mesenchymal tumours unique to the prostate	
<i>Stromal tumours of the prostate</i>	
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-O-3.2).¹⁷ 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 2024.⁷

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

© World Health Organization/International Agency for Research on Cancer (IARC). Reproduced with permission.

 **Back**

Note 3 – Histological tumour grade (Core and Non-core)

The Gleason grading system is the foundation of grading for prostatic adenocarcinoma.^{15,18-21} The Gleason score is traditionally obtained by adding the two predominant Gleason patterns or doubling the pattern in cases with uniform grade. This was modified in the International Society of Urological Pathology (ISUP) 2005 revision by always including the highest grade in the Gleason score of needle biopsies, regardless of its

amount.²² At the 2014 ISUP Consensus Conference, the Gleason system was further modified that mainly focused on the Gleason patterns.²³ It was decided that Gleason pattern 4 should include fused or poorly formed glands, glomerulations and all cribriform patterns of acinar adenocarcinoma. Additional refinements were made in the 2019 ISUP Consensus Conference and the 2019 Genitourinary Pathology Society (GUPS) 'White paper' mainly on reporting of Gleason scores and its components.^{24,25} Many of these changes have been incorporated into the 4th and 5th editions of the WHO Classification.^{6,26}

Over the past decades, Gleason scores below 6 have become less commonly used, especially on needle biopsies.²⁷ There is also an understanding that Gleason score 7 tumours have a worse prognosis if there is a predominant pattern 4 (4+3) than if pattern 3 dominates (3+4).²⁸ Grouping of the Gleason scores (6 or less, 3+4, 4+3, 8 and 9-10) into 5 grade categories (1 to 5) that was endorsed by ISUP is now recommended in the WHO Classification (WHO/ISUP Grade or Grade Group).²⁹⁻³³

The WHO/ISUP grades and associated definitions are outlined in Table 2.

Both the Gleason score and the WHO/ISUP Grade should always be reported for the sake of clarity. For specimen level reporting, separate grade is rendered on every positive specimen site. In targeted biopsies, grade should be rendered on every positive lesion. Occasionally, multiple cores are taken from one target lesion and is rendered an overall (global) grade.

For case level reporting, the highest (or worst) grade and overall (global) grade should be documented. Studies have shown that the highest and overall grades are good predictors of prostate cancer and adding a case level overall score showed comparable or slightly improved concordance with radical prostatectomy grade.^{34,35} There are also worldwide geographic variations in the use of highest grade and/or overall (global) grade, and thus, both are required for case level reporting.

The highest grade and overall (global) grade can be derived from the systematic or targeted biopsies, or both. The overall (global) grade is the aggregate grade of multiple positive sites and can be *global* or *composite* grade. Global grade considers all positive sites whereas composite grade takes into consideration the location of the positive sites that may represent the dominant nodule.³⁶ Because of the challenges in deriving the composite grade, recording the global grade will be sufficient as the overall grade.

In the presence of significant treatment effects, prostate cancer may not be gradable. In rare instances, grading may not be feasible in very small tumour (tumour microfocus) or in tissues showing processing artifacts. In such challenging cases, grade can be documented as indeterminate.

The 2019 ISUP Consensus Conference and 2019 GUPS 'White paper' also recommended that the percentage of Gleason pattern 4 be reported in cases with WHO/ISUP Grades 2 or 3.³⁷⁻³⁹ The rationale for this is to indicate if the tumour is bordering on the lower or higher ends of Gleason score 7. In some protocols, Gleason score 7 tumours with low or ≤10% pattern 4 are considered for active surveillance.^{40,41} Since clinical use of this information has been mainly for active surveillance, reporting of percentage Gleason pattern 4 is currently required only for Gleason 3+4 tumours. The percentage of Gleason pattern 4 and 5 is reported by some pathologists for Gleason score 4+3 and higher tumours,^{42,43} but this information is not widely used in clinical decision making. This element is therefore optional (non-core).

Table 2: World Health Organization (WHO)/International Society of Urological Pathology (ISUP) grading system, core needle biopsies and transurethral resection of the prostate (TURP) specimens.^{16,23}

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 (or with necrosis)
	5+3=8	Predominantly lacking glands (or with necrosis) 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

* Any component of the high grade pattern (i.e., even if less than 5%) is included in the grade.

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

↑ Back

Note 4 – Tumour growth patterns (Core and Non-core)

Several studies have shown the importance of invasive cribriform carcinoma (ICC) and intraductal carcinoma of prostate (IDC-P) as independent adverse prognosticators.⁴⁴⁻⁴⁷ Both the 2019 ISUP Consensus Conference and 2019 GUPS ‘White paper’ recommended reporting of these two elements in biopsies with prostate cancer. Presence of either of these growth patterns would make the patients suboptimal for active surveillance.^{48,49}

Invasive cribriform carcinoma (ICC) is one of the basic architectures for Gleason pattern 4. Presence of luminal necrosis upgrades the cribriform gland to Gleason pattern 5. Among the Gleason pattern 4 architectures, cribriform morphology has been shown to be associated with higher biochemical recurrence rate or poorer survival after radical prostatectomy or radiotherapy. Many of these findings were shown in Gleason score 7 prostate cancers.⁵⁰⁻⁵⁴ Several studies have shown that cribriform pattern can also be prognostic in Gleason score 9-10 cancers.^{49,55} However, because of the lack of clinical actionability on the presence of cribriform in Gleason score 9-10 cancers, reporting is only required for Gleason score 7 or 8 prostate cancers.

Both small and large cribriform glands are associated with poorer outcome, although the definition of small or large cribriform is still under debate.⁵⁶⁻⁵⁸ To improve interobserver agreement, ISUP has proposed a definition for cribriform pattern as a confluent sheet of contiguous malignant epithelial cells with multiple glandular lumina that are easily visible at low power (objective magnification X10) and that there should be no intervening stroma or mucin separating individual or fused glandular structures.⁵⁹

Intraductal carcinoma of prostate (IDC-P) is seen usually associated with invasive prostate cancer. However rarely, isolated IDC-P is found without invasive carcinoma.^{60,61}

Intraductal carcinoma of prostate (IDC-P) has been well characterised at the histological and molecular levels over the past decade and its clinical significance is now better understood.⁶² 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.¹⁶ Desirable diagnostic criteria include immunohistochemistry demonstrating at least partial basal cell retention.^{63,64}

Intraductal carcinoma of prostate (IDC-P) is strongly associated with high volume, high grade invasive prostate carcinoma and metastatic disease.^{49,51,65,66} Hence, the presence of IDC-P in a biopsy, even if invasive carcinoma cannot be identified, mandates immediate repeat biopsy or definitive therapy (depending on the clinical situation). In patients treated with radiation with or without androgen deprivation therapy, the presence of IDC-P in the needle biopsy was an independent predictor of early biochemical recurrence, survival and metastasis.^{53,67}

Presence of IDC-P in biopsy should be documented regardless of the grade. In terms of grading, it is recommended that pure IDC-P without invasive should not be graded. However, there is controversy in terms of grading IDC-P with invasive cancer.^{68,69} ISUP recommended incorporating IDC-P into grade, whereas GUPS recommended excluding IDC-P from grading of invasive cancer. The prostate biopsy dataset allows either manner of grading invasive cancer with IDC-P, however, the approach should be documented in the report.

Distinction between ICC and IDC-P should be made based on morphology. Use of immunohistochemistry for basal cell markers to distinguish these two growth patterns is not recommended. If the grading approach is to exclude IDC-P in invasive carcinoma grade, it was recommended by GUPS to perform immunohistochemistry when biopsy shows Gleason score 6 cancer and cribriform glands that include a differential diagnosis of IDC-P versus Gleason pattern 4 cancer, or if the results would change the highest Gleason score of the case. Such approach can be opted in regions of the world with adequate resources available to support performing immunohistochemistry.

It is important to distinguish IDC-P from atypical intraductal proliferation (AIP) and high grade prostatic intraepithelial neoplasia (HGPIN).⁷⁰ AIP when present suggests an undersampled or concomitant IDC-P.^{6,71-73} Compared to IDC-P, AIP and HGPIN have less architectural and cytological atypia.

↑ Back

Note 5 – Tumour extent (Core)

Number of biopsy cores positive for cancer and linear extent of cancer in the cores correlate with tumour volume, postoperative stage and outcome.⁷⁴⁻⁷⁶ Number of positive cores should be reported but may be difficult to determine because of fragmentation when multiple cores have been submitted together. The number of positive cores should not be greater than the number of cores taken (as specified in **Part 1 Clinical Information/Specimen Receipt Reporting Guide**). Site specific labelling and single core submission facilitates the assessment of cancer extent.⁷⁷

Linear extent is a core data element and may be recorded either as percentage of cancer or millimetres (mm) cancer length in each core or as a composite measure of linear extent (mm or percentage) in multiple or fragmented cores in a specimen.^{78,79} One approach to calculate percentage of cancer is to measure the length of cancer and divide by the entire length of prostatic tissue. The methods for reporting of discontinuous cancer remain controversial. Most (78%) discontinuous tumour foci in biopsy corresponded to a single tumour focus on radical prostatectomy and can be measured including the intervening stroma as one continuous tumour. However, this approach will also result to overestimating the tumour extent in a minority of cases. Whether intervening benign tissue is included or subtracted from the extent measurement may determine eligibility for active surveillance. A patient with WHO/ISUP Grade 1 cancer in no more than three cores may be a candidate for active surveillance. In some protocols, if a positive core is greater than 50% involved by tumour, a patient would be ineligible for active surveillance. In such a case it is recommended that the tumour extent of a discontinuous cancer should be reported by both including and subtracting the intervening benign tissue, e.g., in a 20 mm core there are two 1 mm discontinuous foci of cancer WHO/ISUP Grade 1 cancer spanning a distance of 12 mm (60% linear extent) and measuring 1+1 mm (10% linear extent).⁷⁸

Since most active surveillance protocols use a cut-off determined by the greatest extent of core involvement, documenting the greatest linear extent and/or length of tissue involved by carcinoma will be sufficient for case level reporting.

 [Back](#)

Note 6 – Extraprostatic extension (Core and Non-core)

Extraprostatic extension (EPE) is now the accepted terminology and replaces earlier ambiguous terms such as capsular penetration, perforation, or invasion.^{6,80} In radical prostatectomy specimens EPE is an independent prognostic indicator of increased risk of recurrence post radical prostatectomy and is important in assignment of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) T category.⁸¹⁻⁸⁴ There is limited data specifically on the significance of EPE in core needle biopsies given that it is relatively uncommon; however, it may be occasionally be seen and should be reported when.⁸⁵⁻⁸⁷ One study showed that EPE in biopsy is strongly correlated with aggressive disease features.⁸⁵ In core needle biopsies, EPE is defined as tumour admixed with adipocytes, usually at the end of a biopsy core. 'Indeterminate' should be used sparingly but may be applicable to cases where the tumour involves fibrous tissue without directly involving adipocytes.

It is recommended that the site of any EPE present is recorded since this information is useful for correlation with MRI results and may assist the urologist or radiation oncologist with the technical aspects of treatment planning.

'Indeterminate' should be used sparingly but may be applicable to cases where the tumour involves fibrous tissue without directly involving adipocytes.

 [Back](#)

Note 7 – Seminal vesicle/ejaculatory duct invasion (Non-core)

Seminal vesicle invasion (SVI) is rarely identified in core needle biopsies, hence its absence does not need to be explicitly stated.⁸⁸ However, if seminal vesicle/ejaculatory duct invasion is present it should be recorded and the following comments apply.

Seminal vesicle invasion (SVI) is defined as involvement of the muscular wall of the extraprostatic portion of the seminal vesicle.⁸⁹ If possible seminal vesicle tissue is present (either unintentionally or intentionally, as in a targeted biopsy) and involved by carcinoma, this may be significant since it indicates that the tumour could be T3b in the UICC/AJCC staging system.^{81,82} However, assessment of SVI is problematic in needle biopsy specimens since it is impossible to reliably distinguish between extraprostatic seminal vesicle and intraprostatic seminal vesicle or ejaculatory duct tissue, therefore it is important not to over interpret invasion of the latter two structures as SVI since their involvement by tumour does not constitute T3b disease. Unless one is dealing with a targeted seminal vesicle biopsy, it is recommended to report tumour involvement of such structures in a core needle biopsy as ‘seminal vesicle/ejaculatory duct invasion’ rather than as SVI.

 [Back](#)

Note 8 – Lymphovascular invasion (Non-core)

Lymphovascular invasion (LVI) is rarely identified in core needle biopsies, hence its absence does not need to be explicitly stated. However, if LVI is present it should be recorded.

Invasion of lymphatic or blood vessels (i.e., thin-walled endothelial-lined spaces) is uncommonly identified in core needle biopsy specimens and there is little published data on its significance specifically relating to prostate core biopsies. However, there is good evidence that LVI identified at radical prostatectomy is an independent prognosticator associated with adverse pathology, increased recurrence, metastasis and poorer outcome including those receiving radiotherapy.⁹⁰⁻⁹⁴ Therefore, if LVI is identified in a core needle biopsy it may well be significant and its presence should be recorded. The presence of LVI does not affect assignment of the UICC/AJCC T category.^{81,82}

 [Back](#)

Note 9 – Perineural invasion (Non-core)

The significance of perineural invasion in prostate core biopsy specimens is uncertain.⁹⁵ Some studies show a correlation with EPE in the corresponding radical prostatectomy specimens or an association with adverse outcome in patients treated with radical prostatectomy or radiotherapy.⁹⁶⁻¹⁰¹ Other investigators have questioned prognostic value of biopsy perineural invasion in univariate or multivariate analyses.¹⁰²⁻¹⁰⁵ The weight of evidence suggested that in clinically localised disease perineural invasion was a significant prognostic factor for EPE and subsequent local recurrence.^{106,107} In advanced disease perineural invasion is common and probably not of prognostic significance. It should also be noted that nerves are not necessarily present in biopsy material, therefore it is not always possible to assess the possibility of perineural invasion.

 [Back](#)

Note 10 – Coexistent pathology (Non-core)

In some cases clinical management decisions may be aided by knowledge of coexisting pathology, such as HGPIN, glandular atypia suspicious for malignancy (atypical small acinar proliferation (ASAP)), AIP, granulomatous prostatitis, etc.¹⁵

If there is carcinoma present, the presence of HGPIN is generally not clinically meaningful. Even if no cancer is identified in the specimen, the significance of finding HGPIN in core needle biopsies has been controversial with some studies finding an increased risk for detection of prostatic adenocarcinoma in subsequent biopsies, while others did not.¹⁰⁸ Studies, including one analysing data from a large Canadian cohort, found that this risk was related to the extent of HGPIN, i.e., the number of involved sites; only patients with multifocal HGPIN had a significantly increased risk of prostate cancer.^{109,110} Low grade prostatic intraepithelial neoplasia (PIN) should not be reported.

Likewise, if there is carcinoma present in a specimen, the presence of ASAP is generally not significant, except occasionally in the situation where the carcinoma is bordering the criteria for active surveillance. In this situation, thorough evaluation, and reclassification of glandular atypia to carcinoma may influence the management decision. In specimens where there is no cancer identified but glandular atypia is present, the risk of carcinoma being present in subsequent biopsies is approximately 35%, a high proportion of these are clinically insignificant cancer.¹¹¹⁻¹¹⁵

Atypical intraductal proliferation (AIP) is the preferred term to describe intraductal neoplasm that has complexity or atypia greater than HGPIN but falls short for the diagnosis of IDC-P.^{6,71-73} AIP is characterised by loose cribriform proliferation and/or nuclear atypia falling short for IDC-P and encompasses what was previously known as cribriform HGPIN. Because of the association of AIP with IDC-P, documenting their presence in biopsy is recommended especially in lower grade prostate cancers. Presence of AIP alone in biopsy specimens is uncommon and is managed with repeat follow-up biopsy.

Active prostatitis and granulomatous prostatitis may cause a rise in serum prostate-specific antigen (PSA), although inflammatory lesions may coexist with carcinoma and it is important not to assume that their presence always accounts for an unexplained or disproportional increase in a patient's PSA.¹¹⁶⁻¹¹⁸

In negative targeted biopsy, it is recommended by ISUP to report the presence of non-cancerous lesions that may explain the radiologic abnormality.²⁴

 **Back**

References

- 1 Merlin T, Weston A and Tooher R (2009). Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Med Res Methodol* 9:34.
- 2 International Collaboration on Cancer Reporting (2024). *Prostate Cancer, Transurethral Resection and Enucleation Histopathology Reporting Guide. 2nd edition*. Available from: <https://www.iccr-cancer.org/datasets/published-datasets/urinary-male-genital/prostate-tr/> (Accessed 30th November 2024).
- 3 International Collaboration on Cancer Reporting (2024). *Prostate Cancer Radical Prostatectomy Histopathology Reporting Guide*. Available from: <https://www.iccr-cancer.org/datasets/published-datasets/urinary-male-genital/prostate-rad-pros/> (Accessed 30th November 2024).

- 4 International Collaboration on Cancer Reporting (2024). *Carcinoma of the bladder - cystectomy, cystoprostatectomy and diverticulectomy specimen Histopathology Reporting Guide. 2nd edition*. Available from: <https://www.iccr-cancer.org/datasets/published-datasets/urinary-male-genital/bladder/> (Accessed 2nd July 2024).
- 5 International Collaboration on Cancer Reporting (2018). *Carcinoma of the urethra - urethrectomy specimen Histopathology Reporting Guide. 1st edition*. Available from: <https://www.iccr-cancer.org/datasets/published-datasets/urinary-male-genital/urethra-urethrectomy/> (Accessed 2nd July 2024).
- 6 WHO Classification of Tumours Editorial Board (2022). *Urinary and Male Genital Tumours, WHO Classification of Tumours, 5th edition, Volume 8*, IARC Publications, Lyon.
- 7 WHO Classification of Tumours Editorial Board (2022). *Urinary and Male Genital Tumours, WHO Classification of Tumours, 5th edition, Volume 8 - Corrigenda July 2024*. Available from: [file:///C:/Users/fleurw/Downloads/Uro5%20Corrigenda%20doc_2024-07-08%20\(1\).pdf](file:///C:/Users/fleurw/Downloads/Uro5%20Corrigenda%20doc_2024-07-08%20(1).pdf) (Accessed 2nd August 2024).
- 8 Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, Fanti S, Fossati N, Gandaglia G, Gillessen S, Grivas N, Grummet J, Henry AM, van der Kwast TH, Lam TB, Lardas M, Liew M, Mason MD, Moris L, Oprea-Lager DE, van der Poel HG, Rouvière O, Schoots IG, Tilki D, Wiegel T, Willemsse PM and Cornford P (2021). EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol* 79(2):243-262.
- 9 Wei JT, Barocas D, Carlsson S, Coakley F, Eggener S, Etzioni R, Fine SW, Han M, Kim SK, Kirkby E, Konety BR, Miner M, Moses K, Nissenberg MG, Pinto PA, Salami SS, Souter L, Thompson IM and Lin DW (2023). Early Detection of Prostate Cancer: AUA/SUO Guideline Part II: Considerations for a Prostate Biopsy. *J Urol* 210(1):54-63.
- 10 Connor MJ, Gorin MA, Eldred-Evans D, Bass EJ, Desai A, Dudderidge T, Winkler M and Ahmed HU (2023). Landmarks in the evolution of prostate biopsy. *Nat Rev Urol* 20(4):241-258.
- 11 Bjurlin MA, Carter HB, Schellhammer P, Cookson MS, Gomella LG, Troyer D, Wheeler TM, Schlossberg S, Penson DF and Taneja SS (2013). Optimization of initial prostate biopsy in clinical practice: sampling, labeling and specimen processing. *J Urol* 189(6):2039-2046.
- 12 Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, Briganti A, Budäus L, Hellawell G, Hindley RG, Roobol MJ, Eggener S, Ghei M, Villers A, Bladou F, Villeirs GM, Viridi J, Boxler S, Robert G, Singh PB, Venderink W, Hadaschik BA, Ruffion A, Hu JC, Margolis D, Crouzet S, Klotz L, Taneja SS, Pinto P, Gill I, Allen C, Giganti F, Freeman A, Morris S, Punwani S, Williams NR, Brew-Graves C, Deeks J, Takwoingi Y, Emberton M and Moore CM (2018). MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *N Engl J Med* 378(19):1767-1777.
- 13 Drost FH, Osses D, Nieboer D, Bangma CH, Steyerberg EW, Roobol MJ and Schoots IG (2020). Prostate Magnetic Resonance Imaging, with or Without Magnetic Resonance Imaging-targeted Biopsy, and Systematic Biopsy for Detecting Prostate Cancer: A Cochrane Systematic Review and Meta-analysis. *Eur Urol* 77(1):78-94.

- 14 Eklund M, Jäderling F, Discacciati A, Bergman M, Annerstedt M, Aly M, Glaessgen A, Carlsson S, Grönberg H and Nordström T (2021). MRI-Targeted or Standard Biopsy in Prostate Cancer Screening. *N Engl J Med* 385(10):908-920.
- 15 Paner GP, Magi-Galluzzi C, Amin MB, Srigley JR: Adenocarcinoma of the prostate. In: Amin MB, Grignon DJ, Srigley JR, Eble JN, eds. *Urological Pathology*. Philadelphia, PA: Lippincott William & Wilkins; 2014:559-673.
- 16 Kench JG, Berney DM, De Marzo A, et al. Prostatic acinar adenocarcinoma. In: *Urinary and Male Genital Tumours, WHO Classification of Tumours, 5th edition, Volume 8*, IARC Publications, Lyon; 2022; 203-219.
- 17 Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM and Whelan S (eds) (2020). *International Classification of Diseases for Oncology, Third edition, Second revision ICD-O-3.2*. Available from: http://www.iacr.com.fr/index.php?option=com_content&view=category&layout=blog&id=100&Itemid=577 (Accessed 2nd July 2024).
- 18 Srigley JR, Delahunt B, Samaratunga H, Billis A, Cheng L, Clouston D, Evans A, Furusato B, Kench J, Leite K, MacLennan G, Moch H, Pan CC, Rioux-Leclercq N, Ro J, Shanks J, Shen S, Tsuzuki T, Varma M, Wheeler T, Yaxley J and Egevad L (2019). Controversial issues in Gleason and International Society of Urological Pathology (ISUP) prostate cancer grading: proposed recommendations for international implementation. *Pathology* 51(5):463-473.
- 19 Paner GP, Gandhi J, Choy B and Amin MB (2019). Essential Updates in Grading, Morphotyping, Reporting, and Staging of Prostate Carcinoma for General Surgical Pathologists. *Arch Pathol Lab Med* 143(5):550-564.
- 20 Epstein JI (2018). Prostate cancer grading: a decade after the 2005 modified system. *Mod Pathol* 31(S1):S47-63.
- 21 Kweldam CF, van Leenders GJ and van der Kwast T (2019). Grading of prostate cancer: a work in progress. *Histopathology* 74(1):146-160.
- 22 Epstein JI, Allsbrook WC, Jr., Amin MB and Egevad LL (2005). The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *Am J Surg Pathol* 29(9):1228-1242.
- 23 Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR and Humphrey PA (2016). The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. *Am J Surg Pathol* 40(2):244-252.
- 24 van Leenders G, van der Kwast TH, Grignon DJ, Evans AJ, Kristiansen G, Kweldam CF, Litjens G, McKenney JK, Melamed J, Mottet N, Paner GP, Samaratunga H, Schoots IG, Simko JP, Tsuzuki T, Varma M, Warren AY, Wheeler TM, Williamson SR and Iczkowski KA (2020). The 2019 International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma. *Am J Surg Pathol* 44(8):e87-e99.

- 25 Epstein JI, Amin MB, Fine SW, Algaba F, Aron M, Baydar DE, Beltran AL, Brimo F, Cheville JC, Coicchia M, Comperat E, da Cunha IW, Delprado W, DeMarzo AM, Giannico GA, Gordetsky JB, Guo CC, Hansel DE, Hirsch MS, Huang J, Humphrey PA, Jimenez RE, Khani F, Kong Q, Kryvenko ON, Kunju LP, Lal P, Latour M, Lotan T, Maclean F, Magi-Galluzzi C, Mehra R, Menon S, Miyamoto H, Montironi R, Netto GJ, Nguyen JK, Osunkoya AO, Parwani A, Robinson BD, Rubin MA, Shah RB, So JS, Takahashi H, Tavora F, Tretiakova MS, True L, Wobker SE, Yang XJ, Zhou M, Zynger DL and Trpkov K (2021). The 2019 Genitourinary Pathology Society (GUPS) White Paper on Contemporary Grading of Prostate Cancer. *Arch Pathol Lab Med* 145(4):461-493.
- 26 WHO (World Health Organization) (2016). *Classification of tumours. Pathology and genetics of the urinary system and male genital organs, 4th edition*. Moch H, Humphrey PA, Ulbright TM and Reuter VE (eds). IARC Press, Lyon.
- 27 Berney DM (2007). Low Gleason score prostatic adenocarcinomas are no longer viable entities. *Histopathology* 50(6):683-690.
- 28 Stark JR, Perner S, Stampfer MJ, Sinnott JA, Finn S, Eisenstein AS, Ma J, Fiorentino M, Kurth T, Loda M, Giovannucci EL, Rubin MA and Mucci LA (2009). Gleason score and lethal prostate cancer: does $3 + 4 = 4 + 3$? *J Clin Oncol* 27(21):3459-3464.
- 29 Pierorazio PM, Walsh PC, Partin AW and Epstein JI (2013). Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. *BJU Int* 111(5):753-760.
- 30 Samaratunga H, Delahunt B, Gianduzzo T, Coughlin G, Duffy D, LeFevre I, Johannsen S, Egevad L and Yaxley J (2015). The prognostic significance of the 2014 International Society of Urological Pathology (ISUP) grading system for prostate cancer. *Pathology* 47(6):515-519.
- 31 Epstein JI, Zelefsky MJ, Sjoberg DD, Nelson JB, Egevad L, Magi-Galluzzi C, Vickers AJ, Parwani AV, Reuter VE, Fine SW, Eastham JA, Wiklund P, Han M, Reddy CA, Ciezki JP, Nyberg T and Klein EA (2016). A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score. *Eur Urol* 69(3):428-435.
- 32 Leapman MS, Cowan JE, Simko J, Roberge G, Stohr BA, Carroll PR and Cooperberg MR (2017). Application of a Prognostic Gleason Grade Grouping System to Assess Distant Prostate Cancer Outcomes. *Eur Urol* 71(5):750-759.
- 33 Berney DM, Beltran L, Fisher G, North BV, Greenberg D, Møller H, Soosay G, Scardino P and Cuzick J (2016). Validation of a contemporary prostate cancer grading system using prostate cancer death as outcome. *Br J Cancer* 114(10):1078-1083.
- 34 Trpkov K, Sangkhamanon S, Yilmaz A, Medlicott SAC, Donnelly B, Gotto G and Shea-Budgell M (2018). Concordance of "Case Level" Global, Highest, and Largest Volume Cancer Grade Group on Needle Biopsy Versus Grade Group on Radical Prostatectomy. *Am J Surg Pathol* 42(11):1522-1529.
- 35 Tolonen TT, Kujala PM, Tammela TL, Tuominen VJ, Isola JJ and Visakorpi T (2011). Overall and worst gleason scores are equally good predictors of prostate cancer progression. *BMC Urol* 11:21.
- 36 Arias-Stella JA, 3rd, Shah AB, Montoya-Cerrillo D, Williamson SR and Gupta NS (2015). Prostate biopsy and radical prostatectomy Gleason score correlation in heterogenous tumors: proposal for a composite Gleason score. *Am J Surg Pathol* 39(9):1213-1218.

- 37 Sauter G, Steurer S, Clauditz TS, Krech T, Wittmer C, Lutz F, Lennartz M, Janssen T, Hakimi N, Simon R, von Petersdorff-Campen M, Jacobsen F, von Loga K, Wilczak W, Minner S, Tsourlakis MC, Chirico V, Haese A, Heinzer H, Beyer B, Graefen M, Michl U, Salomon G, Steuber T, Budäus LH, Hekeler E, Malsy-Mink J, Kutzera S, Fraune C, Göbel C, Huland H and Schlomm T (2016). Clinical Utility of Quantitative Gleason Grading in Prostate Biopsies and Prostatectomy Specimens. *Eur Urol* 69(4):592-598.
- 38 Cole AI, Morgan TM, Spratt DE, Palapattu GS, He C, Tomlins SA, Weizer AZ, Feng FY, Wu A, Siddiqui J, Chinnaiyan AM, Montgomery JS, Kunju LP, Miller DC, Hollenbeck BK, Wei JT and Mehra R (2016). Prognostic Value of Percent Gleason Grade 4 at Prostate Biopsy in Predicting Prostatectomy Pathology and Recurrence. *J Urol* 196(2):405-411.
- 39 Choy B, Pearce SM, Anderson BB, Shalhav AL, Zagaja G, Eggener SE and Paner GP (2016). Prognostic Significance of Percentage and Architectural Types of Contemporary Gleason Pattern 4 Prostate Cancer in Radical Prostatectomy. *Am J Surg Pathol* 40(10):1400-1406.
- 40 Morash C, Tey R, Agbassi C, Klotz L, McGowan T, Srigley J and Evans A (2015). Active surveillance for the management of localized prostate cancer: Guideline recommendations. *Can Urol Assoc J* 9(5-6):171-178.
- 41 Eastham JA, Auffenberg GB, Barocas DA, Chou R, Crispino T, Davis JW, Eggener S, Horwitz EM, Kane CJ, Kirkby E, Lin DW, McBride SM, Morgans AK, Pierorazio PM, Rodrigues G, Wong WW and Boorjian SA (2022). Clinically Localized Prostate Cancer: AUA/ASTRO Guideline, Part I: Introduction, Risk Assessment, Staging, and Risk-Based Management. *J Urol* 208(1):10-18.
- 42 Egevad L, Delahunt B, Samaratunga H and Srigley JR (2016). Utility of Reporting the Percentage of High-grade Prostate Cancer. *Eur Urol* 69(4):599-600.
- 43 Berney DM, Beltran L, Sandu H, Soosay G, Møller H, Scardino P, Murphy J, Ahmad A and Cuzick J (2019). The percentage of high-grade prostatic adenocarcinoma in prostate biopsies significantly improves on Grade Groups in the prediction of prostate cancer death. *Histopathology* 75(4):589-597.
- 44 Iczkowski KA, Paner GP and Van der Kwast T (2018). The New Realization About Cribriform Prostate Cancer. *Adv Anat Pathol* 25(1):31-37.
- 45 Gandhi JS, Smith SC, Paner GP, McKenney JK, Sekhri R, Osunkoya AO, Baras AS, DeMarzo AM, Cheville JC, Jimenez RE, Trpkov K, Colecchia M, Ro JY, Montironi R, Menon S, Hes O, Williamson SR, Hirsch MS, Netto GJ, Fine SW, Sirohi D, Kaushal S, Sangoi A, Robinson BD, Kweldam CF, Humphrey PA, Hansel DE, Schultz L, Magi-Galluzzi C, Przybycin CG, Shah RB, Mehra R, Kunju LP, Aron M, Kryvenko ON, Kench JG, Kuroda N, Tavora F, van der Kwast T, Grignon DJ, Epstein JI, Reuter VE and Amin MB (2020). Reporting Practices and Resource Utilization in the Era of Intraductal Carcinoma of the Prostate: A Survey of Genitourinary Subspecialists. *Am J Surg Pathol* 44(5):673-680.
- 46 Kweldam CF, van der Kwast T and van Leenders GJ (2018). On cribriform prostate cancer. *Transl Androl Urol* 7(1):145-154.
- 47 Varma M (2021). Intraductal Carcinoma of the Prostate: A Guide for the Practicing Pathologist. *Adv Anat Pathol* 28(4):276-287.

- 48 Lam TBL, MacLennan S, Willemse PM, Mason MD, Plass K, Shepherd R, Baanders R, Bangma CH, Bjartell A, Bossi A, Briers E, Briganti A, Buddingh KT, Catto JWF, Colecchia M, Cox BW, Cumberbatch MG, Davies J, Davis NF, De Santis M, Dell'Oglio P, Deschamps A, Donaldson JF, Egawa S, Fankhauser CD, Fanti S, Fossati N, Gandaglia G, Gillessen S, Grivas N, Gross T, Grummet JP, Henry AM, Ingels A, Irani J, Lardas M, Liew M, Lin DW, Moris L, Omar MI, Pang KH, Paterson CC, Renard-Penna R, Ribal MJ, Roobol MJ, Rouprêt M, Rouvière O, Sancho Pardo G, Richenberg J, Schoots IG, Sedelaar JPM, Stricker P, Tilki D, Vahr Lauridsen S, van den Bergh RCN, Van den Broeck T, van der Kwast TH, van der Poel HG, van Leenders G, Varma M, Violette PD, Wallis CJD, Wiegel T, Wilkinson K, Zattoni F, N'Dow JMO, Van Poppel H, Cornford P and Mottet N (2019). EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel Consensus Statements for Deferred Treatment with Curative Intent for Localised Prostate Cancer from an International Collaborative Study (DETECTIVE Study). *Eur Urol* 76(6):790-813.
- 49 Kweldam CF, Kümmerlin IP, Nieboer D, Verhoef EI, Steyerberg EW, van der Kwast TH, Roobol MJ and van Leenders GJ (2016). Disease-specific survival of patients with invasive cribriform and intraductal prostate cancer at diagnostic biopsy. *Mod Pathol* 29(6):630-636.
- 50 Kweldam CF, Wildhagen MF, Steyerberg EW, Bangma CH, van der Kwast TH and van Leenders GJ (2015). Cribriform growth is highly predictive for postoperative metastasis and disease-specific death in Gleason score 7 prostate cancer. *Mod Pathol* 28(3):457-464.
- 51 Kweldam CF, Kümmerlin IP, Nieboer D, Steyerberg EW, Bangma CH, Incrocci L, van der Kwast TH, Roobol MJ and van Leenders GJ (2017). Presence of invasive cribriform or intraductal growth at biopsy outperforms percentage grade 4 in predicting outcome of Gleason score 3+4=7 prostate cancer. *Mod Pathol* 30(8):1126-1132.
- 52 Kweldam CF, Kümmerlin IP, Nieboer D, Verhoef EI, Steyerberg EW, Incrocci L, Bangma CH, van der Kwast TH, Roobol MJ and van Leenders GJ (2016). Prostate cancer outcomes of men with biopsy Gleason score 6 and 7 without cribriform or intraductal carcinoma. *Eur J Cancer* 66:26-33.
- 53 Tom MC, Nguyen JK, Lucianò R, Mian OY, Stephans KL, Ciezki JP, Smile TD, Wei W, McKenney JK, Magi-Galluzzi C and Tendulkar RD (2019). Impact of Cribriform Pattern and Intraductal Carcinoma on Gleason 7 Prostate Cancer Treated with External Beam Radiotherapy. *J Urol* 202(4):710-716.
- 54 Keefe DT, Schieda N, El Hallani S, Breau RH, Morash C, Robertson SJ, Mai KT, Belanger EC and Flood TA (2015). Cribriform morphology predicts upstaging after radical prostatectomy in patients with Gleason score 3 + 4 = 7 prostate cancer at transrectal ultrasound (TRUS)-guided needle biopsy. *Virchows Arch* 467(4):437-442.
- 55 Oufattole J, Dey T, D'Amico AV, van Leenders G and Acosta AM (2023). Cribriform morphology is associated with higher risk of biochemical recurrence after radical prostatectomy in patients with Grade Group 5 prostate cancer. *Histopathology* 82(7):1089-1097.
- 56 Rijstenberg LL, Hansum T, Kweldam CF, Kümmerlin IP, Remmers S, Roobol MJ and van Leenders G (2022). Large and small cribriform architecture have similar adverse clinical outcome on prostate cancer biopsies. *Histopathology* 80(7):1041-1049.
- 57 Iczkowski KA, Torkko KC, Kotnis GR, Wilson RS, Huang W, Wheeler TM, Abeyta AM, La Rosa FG, Cook S, Werahera PN and Lucia MS (2011). Digital quantification of five high-grade prostate cancer patterns, including the cribriform pattern, and their association with adverse outcome. *Am J Clin Pathol* 136(1):98-107.

- 58 Greenland NY, Cowan JE, Stohr BA, Simko JP, Carroll PR and Chan E (2024). Large cribriform glands (> 0.25 mm diameter) as a predictor of adverse pathology in men with Grade Group 2 prostate cancer. *Histopathology* 84(4):614-623.
- 59 van der Kwast TH, van Leenders GJ, Berney DM, Delahunt B, Evans AJ, Iczkowski KA, McKenney JK, Ro JY, Samaratunga H, Srigley JR, Tsuzuki T, Varma M, Wheeler TM and Egevad L (2021). ISUP Consensus Definition of Cribriform Pattern Prostate Cancer. *Am J Surg Pathol* 45(8):1118-1126.
- 60 Robinson BD and Epstein JI (2010). Intraductal carcinoma of the prostate without invasive carcinoma on needle biopsy: emphasis on radical prostatectomy findings. *J Urol* 184(4):1328-1333.
- 61 Grypari IM, Logotheti S, Lazaris AC, Kallidonis P, Fokaefs E, Melachrinou M, Zolota V and Tzelepi V (2020). Isolated Intraductal Carcinoma of the Prostate in Prostatectomy Specimens: Report of 2 Cases and Review of the Literature. *Int J Surg Pathol* 28(8):918-924.
- 62 Zong Y, Montironi R, Massari F, Jiang Z, Lopez-Beltran A, Wheeler TM, Scarpelli M, Santoni M, Cimadamore A and Cheng L (2021). Intraductal Carcinoma of the Prostate: Pathogenesis and Molecular Perspectives. *Eur Urol Focus* 7(5):955-963.
- 63 Guo CC and Epstein JI (2006). Intraductal carcinoma of the prostate on needle biopsy: Histologic features and clinical significance. *Mod Pathol* 19(12):1528-1535.
- 64 Cohen RJ, Wheeler TM, Bonkhoff H and Rubin MA (2007). A proposal on the identification, histologic reporting, and implications of intraductal prostatic carcinoma. *Arch Pathol Lab Med* 131(7):1103-1109.
- 65 Zhao T, Liao B, Yao J, Liu J, Huang R, Shen P, Peng Z, Gui H, Chen X, Zhang P, Zhu Y, Li X, Wei Q, Zhou Q, Zeng H and Chen N (2015). Is there any prognostic impact of intraductal carcinoma of prostate in initial diagnosed aggressively metastatic prostate cancer? *Prostate* 75(3):225-232.
- 66 Kato M, Tsuzuki T, Kimura K, Hirakawa A, Kinoshita F, Sassa N, Ishida R, Fukatsu A, Kimura T, Funahashi Y, Matsukawa Y, Hattori R and Gotoh M (2016). The presence of intraductal carcinoma of the prostate in needle biopsy is a significant prognostic factor for prostate cancer patients with distant metastasis at initial presentation. *Mod Pathol* 29(2):166-173.
- 67 Van der Kwast T, Al Daoud N, Collette L, Sykes J, Thoms J, Milosevic M, Bristow RG, Van Tienhoven G, Warde P, Mirimanoff RO and Bolla M (2012). Biopsy diagnosis of intraductal carcinoma is prognostic in intermediate and high risk prostate cancer patients treated by radiotherapy. *Eur J Cancer* 48(9):1318-1325.
- 68 Varma M and Epstein JI (2021). Head to head: should the intraductal component of invasive prostate cancer be graded? *Histopathology* 78(2):231-239.
- 69 Smith SC, Gandhi JS, Moch H, Aron M, Comp erat E, Paner GP, McKenney JK and Amin MB (2021). Similarities and Differences in the 2019 ISUP and GUPS Recommendations on Prostate Cancer Grading: A Guide for Practicing Pathologists. *Adv Anat Pathol* 28(1):1-7.
- 70 Cai Q and Shah RB (2022). Cribriform Lesions of the Prostate Gland. *Surg Pathol Clin* 15(4):591-608.

- 71 Shah RB, Nguyen JK, Przybycin CG, Reynolds JP, Cox R, Myles J, Klein E and McKenney JK (2019). Atypical intraductal proliferation detected in prostate needle biopsy is a marker of unsampled intraductal carcinoma and other adverse pathological features: a prospective clinicopathological study of 62 cases with emphasis on pathological outcomes. *Histopathology* 75(3):346-353.
- 72 Shah RB, Yoon J, Liu G and Tian W (2017). Atypical intraductal proliferation and intraductal carcinoma of the prostate on core needle biopsy: a comparative clinicopathological and molecular study with a proposal to expand the morphological spectrum of intraductal carcinoma. *Histopathology* 71(5):693-702.
- 73 Tremont G, Davis JD, Ott BR, Galioto R, Crook C, Papandonatos GD, Fortinsky RH, Gozalo P and Bishop DS (2017). Randomized Trial of the Family Intervention: Telephone Tracking-Caregiver for Dementia Caregivers: Use of Community and Healthcare Resources. *J Am Geriatr Soc* 65(5):924-930.
- 74 Harnden P, Shelley MD, Naylor B, Coles B and Mason MD (2008). Does the extent of carcinoma in prostatic biopsies predict prostate-specific antigen recurrence? A systematic review. *Eur Urol* 54(4):728-739.
- 75 Epstein JI (2011). Prognostic significance of tumor volume in radical prostatectomy and needle biopsy specimens. *J Urol* 186(3):790-797.
- 76 Ochiai A, Troncoso P, Chen ME, Lloreta J and Babaian RJ (2005). The relationship between tumor volume and the number of positive cores in men undergoing multisite extended biopsy: implication for expectant management. *J Urol* 174(6):2164-2168, discussion 2168.
- 77 Srigley JR, Delahunt B, Egevad L, Samaratunga H and Evans AJ (2014). Optimising pre-analytical factors affecting quality of prostate biopsies: the case for site specific labelling and single core submission. *Pathology* 46(7):579-580.
- 78 Amin MB, Lin DW, Gore JL, Srigley JR, Samaratunga H, Egevad L, Rubin M, Nacey J, Carter HB, Klotz L, Sandler H, Zietman AL, Holden S, Montironi R, Humphrey PA, Evans AJ, Epstein JI, Delahunt B, McKenney JK, Berney D, Wheeler TM, Chinnaiyan AM, True L, Knudsen B and Hammond ME (2014). The critical role of the pathologist in determining eligibility for active surveillance as a management option in patients with prostate cancer: consensus statement with recommendations supported by the College of American Pathologists, International Society of Urological Pathology, Association of Directors of Anatomic and Surgical Pathology, the New Zealand Society of Pathologists, and the Prostate Cancer Foundation. *Arch Pathol Lab Med* 138(10):1387-1405.
- 79 Srigley JR, Humphrey PA, Amin MB, Chang SS, Egevad L, Epstein JI, Grignon DJ, McKiernan JM, Montironi R, Renshaw AA, Reuter VE and Wheeler TM (2009). Protocol for the examination of specimens from patients with carcinoma of the prostate gland. *Arch Pathol Lab Med* 133(10):1568-1576.
- 80 Magi-Galluzzi C, Evans AJ, Delahunt B, Epstein JI, Griffiths DF, van der Kwast TH, Montironi R, Wheeler TM, Srigley JR, Egevad LL and Humphrey PA (2011). International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens. Working group 3: extraprostatic extension, lymphovascular invasion and locally advanced disease. *Mod Pathol* 24(1):26-38.
- 81 Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *TNM Classification of Malignant Tumours, 8th Edition*, Wiley, USA.

- 82 Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM and Meyer LR (eds) (2017). *AJCC Cancer Staging Manual. 8th ed.*, Springer, New York.
- 83 Wheeler TM, Dilliogluligil O, Kattan MW, Arakawa A, Soh S, Suyama K, Ohori M and Scardino PT (1998). Clinical and pathological significance of the level and extent of capsular invasion in clinical stage T1-2 prostate cancer. *Hum Pathol* 29(8):856-862.
- 84 Epstein JI, Partin AW, Sauvageot J and Walsh PC (1996). Prediction of progression following radical prostatectomy. A multivariate analysis of 721 men with long-term follow-up. *Am J Surg Pathol* 20(3):286–292.
- 85 Miller JS, Chen Y, Ye H, Robinson BD, Brimo F and Epstein JI (2010). Extraprostatic extension of prostatic adenocarcinoma on needle core biopsy: report of 72 cases with clinical follow-up. *BJU Int* 106(3):330-333.
- 86 Zhao J and Epstein J (2023). Significance of extraprostatic extension by Grade Groups 1-3 prostatic carcinoma on needle biopsy. *Prostate* 83(8):809-813.
- 87 Tolonen TT, Riikonen J, Tammela TLJ, Koivusalo L, Haapasalo H, Kujala P and Kaipia A (2018). Extraprostatic extension (pT3a) in prostate biopsy is an under-recognized feature indicating high risk disease. *Ann Diagn Pathol* 35:80-84.
- 88 Arista-Nasr J, Trolle-Silva A, Aguilar-Ayala E and Martínez-Benítez B (2016). Seminal epithelium in prostate biopsy can mimic malignant and premalignant prostatic lesions. *Actas Urol Esp* 40(1):17-22.
- 89 Berney DM, Wheeler TM, Grignon DJ, Epstein JI, Griffiths DF, Humphrey PA, van der Kwast T, Montironi R, Delahunt B, Egevad L and Srigley JR (2011). International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens. Working group 4: seminal vesicles and lymph nodes. *Mod Pathol* 24(1):39-47.
- 90 Sathianathen NJ, Furrer MA, Mulholland CJ, Katsios A, Soliman C, Lawrentschuk N, Peters JS, Zargar H, Costello AJ, Hovens CM, Bishop C, Rao R, Tong R, Steiner D, Moon D, Thomas BC, Dundee P, Calero JAR, Thalmann GN and Corcoran NM (2023). Lymphovascular Invasion at the Time of Radical Prostatectomy Adversely Impacts Oncological Outcomes. *Cancers (Basel)* 16(1):123.
- 91 Kawase M, Ebara S, Tatenuma T, Sasaki T, Ikehata Y, Nakayama A, Toide M, Yoneda T, Sakaguchi K, Teishima J, Makiyama K, Inoue T, Kitamura H, Saito K, Koga F, Urakami S and Koie T (2024). Prognostic Importance of Lymphovascular Invasion for Specific Subgroup of Patients with Prostate Cancer After Robot-Assisted Radical Prostatectomy (The MSUG94 Group). *Ann Surg Oncol* 31(3):2154-2162.
- 92 Jamil M, Rakic N, Sood A, Keeley J, Modonutti D, Novara G, Jeong W, Menon M, Rogers CG and Abdollah F (2021). Impact of Lymphovascular Invasion on Overall Survival in Patients With Prostate Cancer Following Radical Prostatectomy: Stage-per-Stage Analysis. *Clin Genitourin Cancer* 19(5):e319-e325.
- 93 Jeong JU, Nam TK, Song JY, Yoon MS, Ahn SJ, Chung WK, Cho IJ, Kim YH, Cho SH, Jung SI and Kwon DD (2019). Prognostic significance of lymphovascular invasion in patients with prostate cancer treated with postoperative radiotherapy. *Radiat Oncol J* 37(3):215-223.

- 94 Kang YJ, Kim HS, Jang WS, Kwon JK, Yoon CY, Lee JY, Cho KS, Ham WS and Choi YD (2017). Impact of lymphovascular invasion on lymph node metastasis for patients undergoing radical prostatectomy with negative resection margin. *BMC Cancer* 17(1):321.
- 95 Niu Y, Förster S and Muders M (2022). The Role of Perineural Invasion in Prostate Cancer and Its Prognostic Significance. *Cancers (Basel)* 14(17):4065.
- 96 Stankovic M, Wolff L, Wieder T, Mendes J and Schumacher B (2022). Perineural invasion as predictor of biochemical recurrence in prostate cancer following open radical prostatectomy: a single-center experience. *World J Urol* 40(11):2695-2700.
- 97 Delahunt B, Murray JD, Steigler A, Atkinson C, Christie D, Duchesne G, Egevad L, Joseph D, Matthews J, Oldmeadow C, Samaratunga H, Spry NA, Srigley JR, Hondermarck H and Denham JW (2020). Perineural invasion by prostate adenocarcinoma in needle biopsies predicts bone metastasis: Ten year data from the TROG 03.04 RADAR Trial. *Histopathology* 77(2):284-292.
- 98 Peng LC, Narang AK, Gergis C, Radwan NA, Han P, Marciscano AE, Robertson SP, He P, Trieu J, Ram AN, McNutt TR, Griffith E, DeWeese TA, Honig S, Singh H, Greco SC, Tran PT, Deville C, DeWeese TL and Song DY (2018). Effects of perineural invasion on biochemical recurrence and prostate cancer-specific survival in patients treated with definitive external beam radiotherapy. *Urol Oncol* 36(6):309.e307-309.e314.
- 99 DeLancey JO, Wood DP, Jr., He C, Montgomery JS, Weizer AZ, Miller DC, Jacobs BL, Montie JE, Hollenbeck BK and Skolarus TA (2013). Evidence of perineural invasion on prostate biopsy specimen and survival after radical prostatectomy. *Urology* 81(2):354-357.
- 100 Loeb S, Epstein JI, Humphreys EB and Walsh PC (2010). Does perineural invasion on prostate biopsy predict adverse prostatectomy outcomes? *BJU Int* 105(11):1510-1513.
- 101 Zhang LJ, Wu B, Zha ZL, Qu W, Zhao H, Yuan J and Feng YJ (2018). Perineural invasion as an independent predictor of biochemical recurrence in prostate cancer following radical prostatectomy or radiotherapy: a systematic review and meta-analysis. *BMC Urol* 18(1):5.
- 102 Barsky AR, Kraus RD, Carmona R, Santos PMG, Li C, Schwartz LE, Ballas LK and Vapiwala N (2020). Investigating association of perineural invasion on prostate biopsy with Gleason score upgrading at prostatectomy: A multi-institutional analysis. *Cancer Med* 9(10):3383-3389.
- 103 Kraus RD, Barsky A, Ji L, Garcia Santos PM, Cheng N, Groshen S, Vapiwala N and Ballas LK (2019). The Perineural Invasion Paradox: Is Perineural Invasion an Independent Prognostic Indicator of Biochemical Recurrence Risk in Patients With pT2N0R0 Prostate Cancer? A Multi-Institutional Study. *Adv Radiat Oncol* 4(1):96-102.
- 104 Lian Z, Zhang H, He Z, Ma S, Wang X and Liu R (2020). Impact of positive surgical margin location and perineural invasion on biochemical recurrence in patients undergoing radical prostatectomy. *World J Surg Oncol* 18(1):201.
- 105 Elharram M, Margel D, Finelli A, Trachtenberg J, Evans A, van der Kwast TH, Sweet JM and Fleshner N (2012). Perineural invasion on prostate biopsy does not predict adverse pathological outcome. *Can J Urol* 19(6):6567-6572.

- 106 Harnden P, Shelley MD, Clements H, Coles B, Tyndale-Biscoe RS, Naylor B and Mason MD (2007). The prognostic significance of perineural invasion in prostatic cancer biopsies: a systematic review. *Cancer* 109(1):13-24.
- 107 Wu S, Lin X, Lin SX, Lu M, Deng T, Wang Z, Olumi AF, Dahl DM, Wang D, Blute ML and Wu CL (2019). Impact of biopsy perineural invasion on the outcomes of patients who underwent radical prostatectomy: a systematic review and meta-analysis. *Scand J Urol* 53(5):287-294.
- 108 Epstein JI and Herawi M (2006). Prostate needle biopsies containing prostatic intraepithelial neoplasia or atypical foci suspicious for carcinoma: implications for patient care. *J Urol* 175(3 Pt 1):820-834.
- 109 Srigley JR, Merrimen JL, Jones G and Jamal M (2010). Multifocal high-grade prostatic intraepithelial neoplasia is still a significant risk factor for adenocarcinoma. *Can Urol Assoc J* 4(6):434.
- 110 Merrimen JL, Jones G and Srigley JR (2010). Is high grade prostatic intraepithelial neoplasia still a risk factor for adenocarcinoma in the era of extended biopsy sampling? *Pathology* 42(4):325-329.
- 111 Ericson KJ, Wenger HC, Rosen AM, Kiriluk KJ, Gerber GS, Paner GP and Eggner SE (2017). Prostate cancer detection following diagnosis of atypical small acinar proliferation. *Can J Urol* 24(2):8714-8720.
- 112 Leone A, Gershman B, Rotker K, Butler C, Fantasia J, Miller A, Afiadata A, Amin A, Zhou A, Jiang Z, Sebo T, Mega A, Schiff S, Pareek G, Golijanin D, Yates J, Karnes RJ and Renzulli J (2016). Atypical small acinar proliferation (ASAP): Is a repeat biopsy necessary ASAP? A multi-institutional review. *Prostate Cancer Prostatic Dis* 19(1):68-71.
- 113 Mancuso PA, Chabert C, Chin P, Kovac P, Skyring T, Watt WH and Napaki S (2007). Prostate cancer detection in men with an initial diagnosis of atypical small acinar proliferation. *BJU Int* 99(1):49-52.
- 114 Ynalvez LA, Kosarek CD, Kerr PS, Mahmoud AM, Eyzaguirre EJ, Orihuela E, Sonstein JN and Williams SB (2018). Atypical small acinar proliferation at index prostate biopsy: rethinking the re-biopsy paradigm. *Int Urol Nephrol* 50(1):1-6.
- 115 Warlick C, Feia K, Tomasini J, Iwamoto C, Lindgren B and Risk M (2015). Rate of Gleason 7 or higher prostate cancer on repeat biopsy after a diagnosis of atypical small acinar proliferation. *Prostate Cancer Prostatic Dis* 18(3):255-259.
- 116 Vasavada SR, Dobbs RW, Kajdacsy-Balla AA, Abern MR and Moreira DM (2018). Inflammation on Prostate Needle Biopsy is Associated with Lower Prostate Cancer Risk: A Meta-Analysis. *J Urol* 199(5):1174-1181.
- 117 Moreira DM, Nickel JC, Andriole GL, Castro-Santamaria R and Freedland SJ (2016). Greater extent of prostate inflammation in negative biopsies is associated with lower risk of prostate cancer on repeat biopsy: results from the REDUCE study. *Prostate Cancer Prostatic Dis* 19(2):180-184.
- 118 Moreira DM, Nickel JC, Gerber L, Muller RL, Andriole GL, Castro-Santamaria R and Freedland SJ (2014). Baseline prostate inflammation is associated with a reduced risk of prostate cancer in men undergoing repeat prostate biopsy: results from the REDUCE study. *Cancer* 120(2):190-196.