Prostate Cancer Histopathology Reporting Guide
Radical Prostatectomy Specimen

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are REQUIRED. Elements in **grey text** are RECOMMENDED.

CLINICAL INFORMATION (select all that apply) (Note 1)

- ◯ Not provided
- ☐ Previous history of prostate cancer *(including the Gleason grade and score of previous specimens if known)*
- ☐ Previous biopsy, *specify date and where performed*
- ☐ Previous therapy, *specify*
- ☐ Other, *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 NODES (Note 6)

- ◯ Absent
- ◯ Present (partially or completely resected)

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 GRADE (Note 9)

Gleason score

Indicate how *Gleason score* is being reported:

__ *Largest tumour nodule present*

__ *Highest score tumour (if it is smaller than the largest)*

__ *Composite (global) score*

Primary pattern/grade

◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5

Secondary pattern/grade

◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5

Tertiary pattern/grade (if present and higher than primary and secondary grade)

◯ 3 ◯ 4 ◯ 5 ◯ Not applicable

◯ Indeterminate, *specify reason*

International Society of Urological Pathology (ISUP) Grade (Grade Group)

Indicate how *ISUP grade* is being reported:

__ *Largest tumour nodule present*

__ *Highest grade tumour (if it is smaller than the largest)*

__ *Composite (global) grade*

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

Percentage Gleason pattern 4/5 *(applicable for Gleason scores ≥7)*

Indicate how *Gleason pattern 4/5* is being reported:

__ *Largest tumour nodule present*

__ *Highest score tumour (if it is smaller than the largest)*

__ *Carcinoma as a whole*

% ◯ Not identified

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INTRAGLANDULAR EXTENT (Note 10)

◯ Tumour identified

__% __ mm __mL(cc)

__Other units *(specify)*

◯ No tumour identified

EXTRAPROSTATIC EXTENSION (Note 11)

◯ Not identified ◯ Present ◯ Indeterminate

⇩

Location(s)

Extent

◯ Focal ◯ Non-focal

SEMINAL VESICLE INVASION (Note 12)

◯ Not identified ◯ Present ◯ Not applicable*

**Refers to rare cases where seminal vesicles are not included in specimen.*

URINARY BLADDER NECK INVASION (Note 13)

◯ Not identified ◯ Present ◯ Not applicable*

**Refers to cases where bladder neck is not included in specimen.*

INTRADUCTAL CARCINOMA OF PROSTATE (Note 14)

◯ Not identified ◯ Present

MARGIN STATUS (Note 15)

◯ Not involved ◯ Involved ◯ Indeterminate

⇩

Location of positive margin(s)

Type of margin positivity

◯ Indeterminate

☐ Extraprostatic (EPE)

☐ Intraprostatic (capsular incision)

Extent of margin positivity*

◯ <3 mm linear extent

◯ ≥3 mm linear extent

**If more than 1 positive margin, the extent should reflect the cumulative length.*

Gleason pattern of tumour present at positive margin*

**If more than 1 pattern at margin select highest.*

◯ Gleason pattern 3

◯ Gleason pattern 4/5

LYMPHOVASCULAR INVASION (Note 16)

◯ Not identified ◯ Present ◯ Indeterminate

LYMPH NODE STATUS (Note 17)

Number of lymph nodes examined

Number of involved nodes

⇩

Laterality

◯ Left ◯ Right ◯ Bilateral ◯ Other

Maximum dimension of largest deposit mm

PATHOLOGICAL STAGING (AJCC TNM 8th edition)## (Note 18)

☐ m - multiple primary tumours

☐ r - recurrent

☐ y - post neoadjuvant therapy

Primary tumour (pT)

◯ TX Primary tumour cannot be assessed

◯ T0 No evidence of primary tumour

◯ T2 Organ confined

◯ T3 Extraprostatic extension

◯ T3a Extracapsular extension (unilateral or bilateral) or microscopic invasion of bladder neck

◯ T3b Tumour invades seminal vesicle(s)

◯ T4 Tumour is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, levator muscles, and/or pelvic wall

Regional lymph nodes (pN)

◯ NX Regional nodes were not assessed

◯ N0 No positive regional nodes

◯ N1 Metastases in regional node(s)

Distant metastasis (pM)*

◯ Not applicable

◯ M1 Distant metastasis

◯ M1a Non-regional lymph node(s)

◯ M1b Bone(s)

◯ M1c Other site(s) with or without bone disease

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

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Scope

This dataset has been developed for radical prostatectomy specimens for prostate carcinoma. Core biopsies and transurethral resection (TUR) and enucleation specimens are dealt with in separate datasets.

Note 1 - Clinical information (Recommended)

Reason/Evidentiary Support

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,[1] while basal cells may show cytological atypia, nuclear enlargement and nuclear smudging.[2] 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.[2,3] It is important to document any previous radiotherapy to help the pathologist to interpret changes accurately. Radiation may be associated with apparent upgrading of prostate cancer in prostatectomy specimens.[4]

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.[5] 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.[6-8] 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.[4,5] Hence, it has been suggested that in prostate glands resected following either radiotherapy or androgen deprivation therapy, tumours that show significant treatment effect should not be graded.[9]

The Gleason grade and score of prostate cancer in any previously submitted specimen should also be provided by the clinician as this allows assessment of any progression of the tumour towards a higher grade/more undifferentiated state, which itself may be of prognostic significance.

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Note 2 - Pre-biopsy serum PSA (Recommended)

Reason/Evidentiary Support

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. Despite criticisms about the utility of PSA-based prostate cancer screening, most prostate cancers are detected in asymptomatic men on the basis of PSA testing. Although PSA levels provide some indication of the likelihood of discovering cancer within a biopsy of the prostate, a diagnosis of malignancy should be based on histological findings and should not be influenced by PSA levels.

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.[10-12]

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.[13-16]

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Note 3 - Specimen weight (Required)

Reason/Evidentiary Support

The prostate gland should be weighed without the seminal vesicles since the seminal vesicles can vary markedly in size; hence, if only a combined weight is recorded, this will introduce error into the measurement of the prostate gland weight and distort comparisons with the radiologically estimated weight. Given this, a working group at the 2009 International Society of Urological Pathology (ISUP) Consensus Conference in Boston recommended that the prostate should be weighed following removal of the seminal vesicles.[17]

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Note 4 - Specimen dimensions (Recommended)

Reason/Evidentiary Support

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.

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Note 5 - Seminal vesicles (Required)

Reason/Evidentiary Support

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

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Note 6 - Lymph nodes (Required and Recommended)

Reason/Evidentiary Support

A record of all organs/tissues received is typically a standard item in gross/macroscopic pathology reports. If present, the laterality of the lymph nodes submitted may be recorded as left, right or bilateral.

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Note 7 - Block identification key (Recommended)

Reason/Evidentiary Support

The origin/designation of all tissue blocks should be recorded and it is preferable to document this information in the final pathology report. This information greatly assists review of the case findings by another pathologist. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist.[18]

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

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Note 8 - Histological tumour type (Required)

Reason/Evidentiary Support

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

WHO classification of tumours of the prostate[a][19]

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

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

Urothelial carcinomas arising in the bladder or urethra are dealt with in separate datasets; however, those rare urothelial carcinomas arising within the prostate are included in this dataset.

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Note 9 - Histological grade (Required and Recommended)

Reason/Evidentiary Support

The Gleason score of radical prostatectomy specimens is usually obtained by adding the two predominant Gleason patterns/grades or doubling the pattern in cases with uniform grade. In the 2005 ISUP revision it was recommended that this is done for each dominant tumour nodule(s).[26] The rationale was that additional separate tumours of lower grade (e.g. transition zone cancers) would not be expected to mitigate the prognostic impact of the main tumour and, thus, their grades should not be included in the overall Gleason score. 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 ISUP 2005 Gleason grading modified the definitions for Gleason scoring of needle biopsies to always include the highest grade, regardless of its amount. It was recommended that minor (<5%) secondary or tertiary patterns of higher grade be included in the Gleason scores of biopsy specimens where there are 2 or 3 different patterns, respectively. The rationale behind this recommendation was that biopsies only sample a minor fraction of the tumour and reporting of small components of higher grade would indicate to the clinician that there might be more extensive involvement of high-grade disease elsewhere in the tumour. The issue of how to deal with a minor (<5%) secondary pattern of higher grade in radical prostatectomy specimens was not specifically addressed in the 2005 consensus conference. However, it was agreed that in radical prostatectomy specimens, where the Gleason score was composed of two most predominant grades, a minor (<5%) tertiary grade should be mentioned separately in the report. The grading practices for radical prostatectomy specimens currently vary and some pathologists would include a tertiary component of Gleason pattern 5 in the Gleason score, at least if more than 5%.

At the 2014 ISUP expert consultation meeting on Gleason grading, a grouping of the Gleason scores into 5 grade categories was proposed. Over the past decades Gleason scores below 6 have become less commonly used, especially on needle biopsies. There is also an understanding that Gleason score 7 tumours have a worse outcome if there is a predominant pattern 4 (4+3) than if pattern 3 dominates (3+4). In line with this, a recommendation has been issued to report the percentage of Gleason pattern 4 in cases with a Gleason score of 7 (ISUP grades 2 or 3). Some pathologists also report the percentage of Gleason pattern 4/5.

The grade groups and associated definitions are outlined in Table 1.

Both the Gleason score and the ISUP grade (Grade group) should always be reported for the sake of clarity.

At the 2014 ISUP expert consultation meeting it was not decided how tertiary patterns of higher grade be reported in radical prostatectomy specimens when applying the ISUP grading. By also reporting the Gleason score and tertiary Gleason patterns of higher grade this information is included.

Table 1: ISUP grading system, radical prostatectomy specimens

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

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

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Note 10 - Intraglandular extent (Recommended)

Reason/Evidentiary Support

Some measurement of the size or extent of the tumour is typically given in histopathology reports for most sites and this parameter forms part of the generic International Collaboration on Cancer Reporting (ICCR) dataset for all tumour types. However in prostate, while cancer volume is a prognostic factor on univariate analysis, it is significantly correlated with other clinicopathological features, including Gleason score, extraprostatic extension (EPE), surgical margin status and pathological TNM stage, and the majority of studies have not demonstrated independent prognostic significance on multivariate analysis.[27-32] Hence, the ICCR expert panel regarded this factor as a recommended (non-core) rather than a required item.

The irregular distribution and often multifocal nature of prostate cancer makes accurate calculation of tumour volume challenging for the pathologist in routine diagnostic practice; a situation where precise methods, such as computerised planimetry or image analysis, are too time and labour intensive to be practical. However, there was consensus at the 2009 ISUP Conference that some quantitative measure of the extent of the tumour in a prostatectomy specimen should be recorded. This can be done either as a visual estimate of intraglandular percentage of cancer[33,34] or by measuring the maximum size of dominant tumour nodule.[35,36] 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.[32,35,36]

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Note 11 - Extraprostatic extension (Required and Recommended)

Reason/Evidentiary Support

EPE, defined as the extension of tumour beyond the confines of the gland into the periprostatic soft tissue, is a required (core) element of the ICCR dataset as it is a significant predictor of recurrence in node negative patients.[27,37] EPE replaced earlier, less clearly defined terms, such capsular penetration, perforation or invasion, following a 1996 Consensus Conference.[38] The assessment of EPE can be difficult, as the prostate is not surrounded by a discrete, well defined fibrous capsule,[39] but rather by a band of concentrically placed fibromuscular tissue that is an inseparable component of the prostatic stroma.[40] 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; (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.[40,41] 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.[27,41] 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.[41,42]

Extent of EPE

Categorisation of the extent of EPE as focal or non-focal (also referred to as 'extensive' or 'established') is a required (core) item in the ICCR dataset. Focal EPE was originally defined no more than 'a few' neoplastic glands just outside the prostate, then subsequently, in a more semi-quantified manner, as extraprostatic glands which occupy no more than one high power field in no more than two sections, with extensive EPE representing anything more than this.[27] 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.[43] However, the practical value of such parameters is limited by the difficulty in precisely defining the outer limit of the prostate gland, especially when the tumour is associated with a desmoplastic reaction. The identification of any EPE is important, as both focal and non-focal EPE are associated with a significantly higher risk of recurrence at both 5 and 10 years.[27,37] Following radical prostatectomy, the progression-free probability for node negative patients with uninvolved seminal vesicles at 10 years for organ confined disease is 85–89%, falling to 67–69% for focal EPE and to 36–58% for extensive EPE.[27,37]

Location of EPE

Since it was considered a generic element forming part of a comprehensive pathology report, the location of any EPE present has been included in the recommended (non-core) dataset, despite the lack of published evidence for its influence on staging, prognosis or treatment.[41] It provides potentially useful information to the urologist, enabling correlation with clinical findings and any pre-operative imaging studies performed.

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Note 12 - Seminal vesicle invasion (Required)

Reason/Evidentiary Support

The expert panel included seminal vesicle invasion (SVI) as a required (core) element of the ICCR dataset as SVI is a well-established, independent, adverse prognostic factor[42,44,45] and an integral component of the commonly used nomograms and tables that predict risk of post prostatectomy cancer recurrence.[10-12] The finding of SVI at the time of radical prostatectomy is associated with a significantly increased risk of PSA recurrence[44-46] and the presence of SVI and a positive surgical margin may also influence the response to adjuvant radiotherapy.[47,48] Bilaterality and extent of extraprostatic SVI are not independently predictive of prognosis and were not included as required or recommended items in the ICCR dataset.[49]

Different definitions of seminal vesicle invasion have been used over the years complicating comparison of the published survival analyses.[47,50] Older definitions including involvement of the adipose tissue or adventitia around the seminal vesicle are problematic with regard to distinction from EPE; while in other studies a distinction between intraprostatic and extraprostatic seminal vesicle invasion has not always been made, impeding comparisons between series.[51,52] 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.[50] Only extraprostatic seminal

vesicle is included in this definition of SVI, since it is difficult differentiating between intraprostatic seminal vesicle and ejaculatory duct invasion as these structures merge without a clear histological cut off.[53] It was concluded that older definitions that include invasion of the adipose tissue around the seminal vesicle are imprecise and should be discarded.[47,50]

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Note 13 - Urinary bladder neck invasion (Required)

Reason/Evidentiary Support

Microscopically, 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.[54] Microscopic bladder neck involvement is a significant predictor of PSA-recurrence in univariate analysis, although not in multivariate modelling in most studies.[55-57] Neoplastic glands intermixed with benign prostatic glands at the bladder neck margin is equivalent to capsular incision rather than true bladder neck invasion.[55,58,59] In the 7th and 8th Editions of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) 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.[54,60-63]

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Note 14 - Intraductal carcinoma of prostate (Recommended)

Intraductal carcinoma of the prostate (IDC-P) is found in approximately 17% of radical prostatectomy specimens and is usually associated with invasive prostate cancer.[64] However, occasionally isolated IDC-P is found without invasive carcinoma; this latter situation is very rare and beyond the scope of this dataset.

IDC-P has been well characterised at the histological and molecular levels over the past decade and its clinical significance is now also better understood.[65] The diagnosis of IDC-P is based on morphology and the key criteria include: 1) large calibre glands that are more than twice the diameter of normal non-neoplastic peripheral glands; 2) preserved (at least focally) basal cells identified on H&E staining (or with basal cell markers, such as p63, keratin 34βE12 and keratin 5/6, however, the use of immunohistochemistry to identify basal cells is optional, rather than mandatory, for the diagnosis of IDC-P); 3) significant nuclear atypia including enlargement and anisonucleosis; and 4) comedonecrosis, which is often but not always present.[66,67] It is important to distinguish IDC-P from high grade prostatic intraepithelial neoplasia (HGPIN): compared to IDC-P, HGPIN has less architectural and cytological atypia, and cribriform HGPIN is rare.

When present in combination with invasive carcinoma in radical prostatectomy specimens, IDC-P is strongly associated with high volume, high grade and stage (EPE or SVI positive) carcinoma.[68]

Moreover the presence of IDC-P is independently associated with biochemical recurrence, regional lymph node metastasis and cancer specific survival.[64,69,70] Hence, in radical prostatectomy specimens, the presence of IDC-P in association with invasive carcinoma should be recorded.

There was a strong consensus (82%) at the recent ISUP consensus meeting (Chicago 2014) that IDC-P should not be assigned an ISUP or Gleason grade.[71] It is also unnecessary to measure the extent of the IDC-P.

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Note 15 - Margin status (Required and Recommended)

Reason/Evidentiary Support

A positive surgical margin (PSM) 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 multivariate analysis.[42,72-76] Moreover, positive margins are associated with a 2.6-fold increased risk of prostate cancer specific mortality.[77] 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.[42,78] PSMs are reported in between 10–48% of patients treated by radical prostatectomy for both organ confined and non-organ confined prostate cancer with the rates in the lower range typically found in more modern cohorts.[76,79-81]

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.[82-84] 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.[82,84]

Stating the location of the PSM is useful information for the urologist who can then modify future operations to avoid iatrogenic margin positivity and increase the likelihood of curative surgery. The site of the PSM and the number of positive margins have been shown to influence biochemical recurrence and risk of progression. 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.[81,85]

Type of margin positivity

Intraprostatic margin involvement or capsular incision (CI) occurs when the urologist inadvertently develops the resection margin within the plane of the prostate rather than outside the capsule. CI with a positive surgical margin is diagnosed when malignant glands are cut across adjacent to benign prostatic glands.[40] 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.[86-88] According to the largest series published, 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.[89]

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 capsular incision in some cases, particularly posteriorly and posterolaterally if there is a desmoplastic reaction. Cancer extending to a margin which is beyond the normal contour of the prostate gland, or beyond the compressed fibromuscular prostatic stroma at the outer edge of the prostate, can be diagnosed as a positive surgical margin with EPE, similarly to margin involvement when there is cancer in adipose tissue.[87] 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.[42,87] 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.[41]

Extent (total) of margin involvement

Although a positive surgical marginal (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.[72,73,79,90] The expert panel considered that there is sufficient evidence to include measurement of the length of margin involved by carcinoma as an element in the ICCR dataset.[49,82,84,89-93] In particular, the 5 year PSA recurrence risk appears to be significantly greater when the length of the involved margin is 3 mm or more, (53% versus 14%).[49,89,94-96] However, in one series, Cao et al[92] 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 positive surgical margin after radical prostatectomy was greater in intermediate and high risk groups (based on Gleason score and pre-biopsy PSA) than in low risk patients.[75] Further studies of such factors potentially affecting the impact of PSMs are required before there is sufficient evidence justifying their inclusion as required (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.[97]

Gleason pattern at the margin

Four recently published papers have found that Gleason pattern/grade or score of the tumour at the positive surgical margin is an independent predictor of biochemical recurrence and may aid optimal selection of patients for adjuvant therapy.[90,98-100] In one of these studies patients with Gleason pattern 4 or 5 carcinoma (Gleason score 3+4, 4+3, 4+4 or 4+5) at a PSM had double the risk of PSA relapse compared to those with only Gleason grade 3 (score 3+3) at the margin. Moreover, men with Gleason pattern/grade 3 at the PSM had a similar 5-year biochemical relapse-free survival rate to those with negative margins.[90] Another study, restricted to men with dominant nodule Gleason score 7 and non-focal EPE, also found that the grade of cancer at the site of a PSM was associated with biochemical recurrence.[98] The largest series, including 405 cases with a PSM, confirmed that a

lower Gleason score at the margin was independently associated with a decreased risk of early biochemical recurrence.[100]

In each of the published studies, the potential problem of cautery/thermal artefact was considered - each group noted that in slides where the cancer at the margin was distorted by cautery/thermal or crush 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.[90,98-100] Limiting assessment to only the highest pattern present at the PSM may simplify measurement of this parameter, however, it should be noted that in most of the published studies Gleason score could be reported.[98-100] 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 16 - Lymphovascular invasion (Recommended)

Reason/Evidentiary Support

Lymphovascular invasion (LVI) is defined as the unequivocal presence of tumour cells within endothelial-lined spaces with no or only thin underlying muscular walls.[101,102] Lymphatic and venous invasion should be assessed together due to the difficulties in distinguishing between the two by routine light microscopy and it is important that artefacts, such as retraction or mechanical displacement of tumour cells into vessels, are excluded. Immunohistochemistry for endothelial markers, e.g. CD31, CD34 or D2-40, may aid in the assessment of equivocal cases but is not recommended for routine use at present.

LVI has been reported to be associated with decreased time to biochemical progression, distant metastases and overall survival after radical prostatectomy.[101-106] 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.[101,102,104,106,107] However, the independent prognostic value of LVI is uncertain as definitions of LVI have varied between studies and most included a substantial number of patients with lymph node metastases or SVI, failing to stratify patients into clinical meaningful categories. Further well designed studies with standardised definitions are necessary to confirm the independent prognostic significance of LVI.

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Note 17 - Lymph node status (Required and Recommended)

Reason/Evidentiary Support

Lymph node involvement is a well established independent adverse prognostic factor[42,50] and is an integral component of the commonly used nomograms that predict the risk of post prostatectomy disease recurrence.[10] There is little published data on the prognostic significance of isolated tumour cells (clusters less than <200 µm in greatest dimension) in prostate cancer and insufficient evidence at present to support the routine use of immunohistochemistry as an ancillary technique in the identification of lymph node involvement.

Maximum dimension of largest deposit
The diameter of the largest metastatic deposit correlated with distant metastasis and cancer-specific survival in two studies but not in another[108-110] and this factor has been included in the recommended (non-core) dataset rather than as a required (core) item. There was consensus (81% respondents) at the 2009 ISUP Conference that that the diameter of the largest lymph node metastasis should be included in the pathology reports on radical prostatectomy specimens.[50]

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Note 18 - Pathological staging (Required and Recommended)

Reason/Evidentiary Support

The pathological primary tumour (T), regional lymph node (N) and distant metastasis (M) categories are considered as generic required (core) elements for all ICCR cancer datasets. Staging data should be assessed according to the most recent edition of the AJCC Staging Manual (8th Edition).[61] However, it should be noted that the implementation of AJCC TNM 8th edition has been deferred until January 2018 in some jurisdictions. UICC or AJCC 7th editions may be used in the interim. If TNM 7th edition is used pT2 subcategorization should be considered optional in line with ISUP recommendations as it lacks additional prognostic significance.[111]

It should also be noted that that the UICC 8th Edition Stage Grouping differs from the AJCC Prognostic Stage Groups.[61,62]

The reference document *TNM Supplement: A commentary on uniform use, 4th Edition* (C. Wittekind editor) may be of assistance when staging.[112]

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References

1 Cheng L, Cheville JC and Bostwick DG (1999). Diagnosis of prostate cancer in needle biopsies after radiation therapy. *Am J Surg Pathol* 23(10):1173–1183.

2 Magi-Galluzzi C, Sanderson HBS and Epstein JI (2003). Atypia in non-neoplastic prostate glands after radiotherapy for prostate cancer: duration of atypia and relation to type of radiotherapy. *Am J Surg Pathol* 27:206–212.

3 Herr HW and Whitmore WF, Jr (1982). Significance of prostatic biopsies after radiation therapy for carcinoma of the prostate. *Prostate* 3(4):339–350.

4 Grignon DJ and Sakr WA (1995). Histologic effects of radiation therapy and total androgen blockage on prostate cancer. *Cancer* 75:1837–1841.

5 Vailancourt L, Ttu B, Fradet Y, Dupont A, Gomez J, Cusan L, Suburu ER, Diamond P, Candas B and Labrie F (1996). Effect of neoadjuvant endocrine therapy (combined androgen blockade) on normal prostate and prostatic carcinoma. A randomized study. *Am J Surg Pathol* 20(1):86-93.

6 Montironi R, Magi-Galluzzi C, Muzzonigro G, Prete E, Polito M and Fabris G (1994). Effects of combination endocrine treatment on normal prostate, prostatic intraepithelial neoplasia, and prostatic adenocarcinoma. *J Clin Pathol* 47(10):906-913.

7 Civantos F, Marcial MA, Banks ER, Ho CK, Speights VO, Drew PA, Murphy WM and Soloway MS (1995). Pathology of androgen deprivation therapy in prostate carcinoma. A comparative study of 173 patients. *Cancer* 75(7):1634-1641.

8 Bostwick DG and Meiers I (2007). Diagnosis of prostatic carcinoma after therapy. *Arch Pathol Lab Med* 131(3):360-371.

9 Epstein JI and Yang XJ (2002). Benign and malignant prostate following treatment. In: *Prostate Biopsy Interpretation*, Lippincott Williams and Wilkins, Philadelphia, Pennsylvania, 209–225.

10 Kattan MW, Wheeler TM and Scardino PT (1999). Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer. *J Clin Oncol* 17(5):1499-1507.

11 Partin AW, Piantadosi S, Sanda MG, Epstein JI, Marshall FF, Mohler JL, Brendler CB, Walsh PC and Simons JW (1995). Selection of men at high risk for disease recurrence for experimental adjuvant therapy following radical prostatectomy. *Urology* 45(5):831-838.

12 Han M, Partin AW, Zahurak M, Piantadosi S, Epstein JI and Walsh PC (2003). Biochemical (prostate specific antigen) recurrence probablity following radical prostatectomy for clinically localised prostate cancer. *J Urol* 169:517-523.

13 Guess HA, Gormley GJ, Stoner E and Oesterling JE (1996). The effect of finasteride on prostate specific antigen: review of available data. *J Urol* 155(1):3-9.

14 Oesterling JE, Roy J, Agha A, Shown T, Krarup T, Johansen T, Lagerkvist M, Gormley G, Bach M and Waldstreicher J (1997). Biologic variability of prostate-specific antigen and its usefulness as a marker for prostate cancer: effects of finasteride. The Finasteride PSA Study Group. *Urology* 50(1):13-18.

15 Marberger M, Freedland SJ, Andriole GL, Emberton M, Pettaway C, Montorsi F, Teloken C, Rittmaster RS, Somerville MC and Castro R (2012). Usefulness of prostate-specific antigen (PSA) rise as a marker of prostate cancer in men treated with dutasteride: lessons from the REDUCE study. *BJU Int* 109(8):1162-1169.

16 Andriole GL, Humphrey P, Ray P, Gleave ME, Trachtenberg J, Thomas LN, Lazier CB and Rittmaster RS (2004). Effect of the dual 5alpha-reductase inhibitor dutasteride on markers of tumor regression in prostate cancer. *J Urol* 172(3):915-919.

17 Samaratunga H, Montironi R, True L, Epstein JI, Griffiths DF, Humphrey PA, van der Kwast T, Wheeler TM, Srigley JR, Delahunt B, Egevad L and The ISUP Prostate Cancer Group (2011). International Society of Urological Pathology (ISUP) consensus conference on handling and staging of radical prostatectomy specimens. Working group 1: specimen handling. *Mod Pathol* 24:6-15.

18 ICCR (International Collaboration on Cancer Reporting) (2017). Guidelines for the development of ICCR datasets. Available from: *http://www.iccr-cancer.org/datasets/dataset-development* (Accessed Accessed 1st March 2017).

19 World Health Organization (2016). *World Health Organization (WHO) Classification of tumours. Pathology and genetics of the urinary system and male genital organs*. Humphrey PA, Moch H, Reuter VE, Ulbright TM, editors. IARC Press, Lyon, France.

20 Christensen WN, Steinberg G, Walsh PC and Epstein JI (1991). Prostatic duct adenocarcinoma. Findings at radical prostatectomy. *Cancer* 67(8):2118-2124.

21 Rubenstein JH, Katin MJ, Mangano MM, Dauphin J, Salenius SA, Dosoretz DE and Blitzer PH (1997). Small cell anaplastic carcinoma of the prostate: seven new cases, review of the literature, and discussion of a therapeutic strategy. *Am J Clin Oncol* 20:376-380.

22 Dundore PA, Cheville JC, Nascimento AG, Farrow GM and Bostwick DG (1995). Carcinosarcoma of the prostate. Report of 21 cases. *Cancer* 76:1035-1042.

23 Hansel DE and Epstein JI (2006). Sarcomatoid carcinoma of the prostate. A study of 42 cases. *Am J Surg Pathol* 30:1316-1321.

24 Osunkoya AO and Epstein JI (2007). Primary mucin-producing urothelial-type adenocarcinoma of prostate: report of 15 cases. *Am J Surg Pathol* 31:1323-1329.

25 Curtis MW, Evans AJ and Srigley J (2005). Mucin-producing urothelial-type adenocarcinoma of prostate: report of two cases of a rare and diagnostically challenging entity. *Mod Pathol* 18:585-590.

26 Epstein JI, Allsbrook WCJ, 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.

27 Wheeler TM, Dillioglugil 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.

28 Epstein JI, Carmichael M, Partin AW and Walsh PC (1993). Is tumor volume an independent predictor of progression following radical prostatectomy? A multivariate analysis of 185 clinical stage B adenocarcinomas of the prostate with 5 years of followup. *J Urol* 149(6):1478–1481.

29 Kikuchi E, Scardino PT, Wheeler TM, Slawin KM and Ohori M (2004). Is tumor volume an independent prognostic factor in clinically localized prostate cancer? *J Urol* 172:508-511.

30 Van Oort IM, Witjes JA, Kok DE, Kiemeney LALM and Hulsbergen-vandeKaa CA (2008). Maximum tumor diameter is not an independent prognostic factor in high-risk localised prostate cancer. *World J Urol* 26:237-241.

31 Wolters T, Roobol MJ, van Leeuwen PJ, van den Bergh RC, Hoedemaeker RF, van Leenders GJ, Schröder FH and van der Kwast TH (2010). Should pathologist routinely report prostate tumor volume? The prognostic value of tumor volume in prostate cancer. *Eur Urol* 57(5):735-920.

32 Dvorak T, Chen MH, Renshaw AA, Loffredo M, Richie JP and D'Amico AV (2005). Maximal tumor diameter and the risk of PSA failure in men with specimen-confined prostate cancer. *Urology* 66:1024-1028.

33 Epstein JI, Oesterling JE and Walsh PC (1988). Tumor volume versus percentage of specimen involved by tumor correlated with progression in stage A prostatic cancer. *J Urol* 139:980-984.

34 Partin AW, Epstein JI, Cho KR, Gittelsohn AM and Walsh PC (1989). Morphometric measurement of tumor volume and per cent of gland involvement as predictors of pathological stage in clinical stage B prostate cancer. *J Urol* 141:341-345.

35 Wise AM, Stamey TA, McNeal JE and Clayton JL (2002). Morphologic and clinical significance of multifocal prostate cancers in radical prostatectomy specimens. *Urology* 60(2):264–269.

36 Renshaw AA, Richie JP, Loughlin KR, Jiroutek M, Chung A and D'Amico AV (1999). Maximum diameter of prostatic carcinoma is a simple, inexpensive, and independent predictor of prostate-specific antigen failure in radical prostatectomy specimens. Validation in a cohort of 434 patients. *Am J Clin Pathol* 111(5):641–644.

37 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.

38 Sakr WA, Wheeler TM, Blute M, Bodo M, Calle-Rodrigue R, Henson DE, Mostofi FK, Seiffert J, Wojno K and Zincke H (1996). Staging and reporting of prostate cancer-sampling of the radical prostatectomy specimen. *Cancer* 78(2):366–368.

39 Ayala AG, Ro JY, Babaian R, Troncoso P and Grignon DJ (1989). The prostatic capsule: does it exist? Its importance in the staging and treatment of prostatic carcinoma. *Am J Surg Pathol* 13:21-27.

40 Chuang AY and Epstein JI (2008). Positive surgical margins in areas of capsular incision in otherwise organ-confined disease at radical prostatectomy: histologic features and pitfalls. *Am J Surg Pathol* 32(8):1201–1206.

41 Magi-Galluzzi C, Evans AJ, Delahunt B, Epstein JI, Griffiths DF, van der Kwast TH, Montironi R, Wheeler TM, Srigley JR, Egevad LL, Humphrey PA and ISUP Prostate Cancer Group (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* 24:26-38.

42 Epstein JI, Amin M, Boccon-Gibod L, Egevad L, Humphrey PA, Mikuz G, Newling D, Nilsson S, Sakr W, Srigley JR, Wheeler TM and Montironi R (2005). Prognostic factors and reporting of prostate carcinoma in radical prostatectomy and pelvic lymphadenectomy specimens. *Scand J Urol Nephrol Suppl* 216:34–63.

43 Sung MT, Lin H, Koch MO, Davidson DD and Cheng L (2007). Radial distance of extraprostatic extension measured by ocular micrometer is an independent predictor of prostate specific antigen recurrence: a new protocol for the substaging of pT3a prostate cancer. *Am J Surg Pathol* 31:311-318.

44 Debras B, Guillonneau B, Bougaran J, Chambon E and Vallancien G (1998). Prognostic significance of seminal vesicle invasion on the radical prostatectomy specimen. Rationale for seminal vesicle biopsies. *Eur Urol* 33(3):271–277.

45 Tefilli MV, Gheiler EL, Tiguert R, Banerjee M, Sakr W, Grignon DJ, Pontes JE and Wood Jr DP (1998). Prognostic indicators in patients with seminal vesicle involvement following radical prostatectomy for clinically localized prostate cancer. *J Urol* 160(3):802–806.

46 Epstein JI, Partin AW, Potter SR and Walsh PC (2000). Adenocarcinoma of the prostate invading the seminal vesicle: prognostic stratification based on pathologic parameters. *Urology* 56(2):283–288.

47 Potter SR, Epstein JI and Partin AW (2000). Seminal vesicle invasion by prostate cancer: prognostic significance and therapeutic implications. *Rev Urol* 2(3):190–195.

48 Swanson GP, Goldman B, Tangen CM, Chin J, Messing E, Canby-Hagino E, Forman JD, Thompson IM and Crawford ED (2008). The prognostic impact of seminal vesicle involvement found at prostatectomy and the effects of adjuvant radiation: data from Southwest Oncology Group 8794. *J Urol* 180(6):2453–2457.

49 Babaian RJ, Troncoso P, Bhadkamkar VA and Johnston DA (2001). Analysis of clinicopathologic factors predicting outcome after radical prostatectomy. *Cancer* 91:1414-1422.

50 Berney DM, Wheeler TM, Grignon DJ, Epstein JI, Griffiths DF, Humphrey PA, van der Kwast T, Montironi R, Delahunt B, Egevad L, Srigley JR and ISUP Prostate Cancer Group (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* 24:39-47.

51 Jewett HJ, Eggleston JC and Yawn DH (1972). Radical prostatectomy in the management of carcinoma of the prostate: probables causes of some therapeutic failures. *J Urol* 107:1034-1040.

52 Soh S, Arakawa A and Suyama K et al (1998). The prognosis of patients with seminal vesicle involvement depends upon the level of extraprostatic extension. *J Urol* 159:296A.

53 Ohori M, Scardino PT, Lapin SL, Seale-Hawkins C, Link J and Wheeler TM (1993). The mechanisms and prognostic significance of seminal vesicle involvement by prostate cancer. *Am J Surg Pathol* 17:1252-1261.

54 Pierorazio PM, Epstein JI, Humphreys E, Han M, Walsh PC and Partin AW (2010). The significance of a positive bladder neck margin after radical prostatectomy: the American Joint Committee on Cancer Pathological Stage T4 designation is not warranted. *J Urol* 183:151-157.

55 Zhou M, Reuther AM, Levin HS, Falzarano SM, Kodjoe E, Myles J, Klein E and Magi-Galluzzi C (2009). Microscopic bladder neck involvement by prostate carcinoma in radical prostatectomy specimens is not a significant independent prognostic factor. *Mod Pathol* 22(3):385–392.

56 Dash A, Sanda MG, Yu M, Taylor JM, Fecko A and Rubin MA (2002). Prostate cancer involving the bladder neck: recurrence-free survival and implications for AJCC staging modification. American Joint Committee on Cancer. *Urology* 60(2):276–280.

57 Yossepowitch O, Engelstein D, Konichezky M, Sella A, Livne PM and Baniel J (2000). Bladder neck involvement at radical prostatectomy: positive margins or advanced T4 disease? *Urology* 56(3):448–452.

58 Poulos CK, Koch MO, Eble JN, Daggy JK and Cheng L (2004). Bladder neck invasion is an independent predictor of prostate-specific antigen recurrence. *Cancer* 101(7):1563–1568.

59 Rodriguez-Covarrubias F, Larre S, Dahan M, De La Taille A, Allory Y, Yiou R, Vordos D, Hoznek A, Abbou CC and Salomon L (2009). Prognostic significance of microscopic bladder neck invasion in prostate cancer. *BJU Int* 103(6):758–761.

60 Edge SE, Byrd DR, Compton CC, Fritz AG, Greene FL and Trotti A (eds) (2010). *AJCC Cancer Staging Manual 7th ed.*, New York, NY.: Springer.

61 Amin M.B., Edge, S., Greene, F.L., Byrd, D.R., Brookland, R.K., Washington, M.K., Gershenwald, J.E., Compton, C.C., Hess, K.R., Sullivan, D.C., Jessup, J.M., Brierley, J.D., Gaspar, L.E., Schilsky, R.L., Balch, C.M., Winchester, D.P., Asare, E.A., Madera, M., Gress, D.M., Meyer, L.R. (Eds.) (2017). *AJCC Cancer Staging Manual 8th ed.* Springer, New York.

62 Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *UICC TNM Classification of Malignant Tumours, 8th Edition*, Wiley-Blackwell.

63 International Union against Cancer (UICC) (2009). *TNM Classification of Malignant Tumours (7th edition)*. Sobin L, Gospodarowicz M and Wittekind C (Eds). Wiley-Blackwell, Chichester, UK and Hoboken, New Jersey.

64 Miyai K, Divatia MK, Shen SS, Miles BJ, Ayala AG and Ro JY (2014). Heterogeneous clinicopathological features of intraductal carcinoma of the prostate: a comparison between "precursor-like" and "regular type" lesions. *Int J Clin Exp Pathol* 7(5):2518-2526.

65 Zhou M (2013). Intraductal carcinoma of the prostate: the whole story. *Pathology* 45(6):533-539.

66 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.

67 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.

68 McNeal JE and Yemoto CE (1996). Spread of adenocarcinoma within prostatic ducts and acini. Morphologic and clinical correlations. *Am J Surg Pathol* 20(7):802-814.

69 Kimura K, Tsuzuki T, Kato M, Saito AM, Sassa N, Ishida R, Hirabayashi H, Yoshino Y, Hattori R and Gotoh M (2014). Prognostic value of intraductal carcinoma of the prostate in radical prostatectomy specimens. *Prostate* 74(6):680-687.

70 Kryvenko ON, Gupta NS, Virani N, Schultz D, Gomez J, Amin A, Lane Z and Epstein JI (2013). Gleason score 7 adenocarcinoma of the prostate with lymph node metastases: analysis of 184 radical prostatectomy specimens. *Arch Pathol Lab Med* 137(5):610-617.

71 Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR and Humphrey PA (2015). 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): 244-52.

72 Blute ML, Bostwick DG, Bergstralh EJ, Slezak JM, Martin SK, Amling CL and Zincke H (1997). Anatomic site-specific positive margins in organ-confined prostate cancer and its impact on outcome after radical prostatectomy. *Urology* 50:733-739.

73 Swindle P, Eastham JA, Ohori M, Kattan MW, Wheeler T, Maru N, Slawin K and Scardino PT (2005). Do margins matter? The prognostic significance of positive surgical margins in radical prostatectomy specimens. *J Urol* 174(3):903–907.

74 Pfitzenmaier J, Pahernik S, Tremmel T, Haferkamp A, Buse S and Hohenfellner M (2008). Positive surgical margins after radical prostatectomy: do they have an impact on biochemical or clinical progression? *BJU Int* 102(10):1413–1418.

75 Alkhateeb S, Alibhai S, Fleshner N, Finelli A, Jewett M, Zlotta A, Nesbitt M, Lockwood G and Trachtenberg J (2010). Impact of a positive surgical margin after radical prostatectomy differs by disease risk group. *J Urol* 183:145-150.

76 Ploussard G, Agamy MA, Alenda O, Allory Y, Mouracade P, Vordos D, Hoznek A, Abbou CC, de la Taille A and Salomon L (2011). Impact of positive surgical margins on prostate-specific antigen failure after radical prostatectomy in adjuvant treatment-naïve patients. *BJU Int* 107:1748-1754.

77 Wright JL, Dalkin BL, True LD, Ellis WJ, Stanford JL, Lange PH and Lin DW (2010). Positive surgical margins at radical prostatectomy predict prostate cancer specific mortality. *J Urol* 183:2213-2218.

78 Tan PH, Cheng L, Srigley JRS, Griffiths D, Humphrey PA, van der Kwast, Montironi R, Wheeler TM, Delahunt B, Egevad L, Epstein JI and ISUP Prostate Cancer Group (2011). International Society of Urological Pathology (ISUP) consensus conference on handling and staging of radical prostatectomy specimens. Working group 5: surgical margins. *Mod Pathol* 24:48-57.

79 Simon MA, Kim S and Soloway MS (2006). Prostate specific antigen recurrence rates are low after radical retropubic prostatectomy and positive margins. *J Urol* 175:140-145.

80 Eastham JA, Kattan MW, Riedel E, Begg CB, Wheeler TM, Gerigk C, Gonen M, Reuter V and Scardino PT (2003). Variation among individual surgeons in the rate of positive surgical margins in radical prostatectomy specimens. *J Urol* 170:2292-2295.

81 Eastham JA, Kuroiwa K, Ohori M, Serio AM, Gorbonos A, Maru N, Vickers AJ, Slawin KM, Wheeler TM, Reuter VE and Scardino PT (2007). Prognostic significance of location of positive margins in radical prostatectomy specimens. *Urology* 70(5):965–969.

82 Epstein JI and Sauvageot J (1997). Do close but negative margins in radical prostatectomy specimens increase the risk of postoperative progression? *J Urol* 157(1):241–243.

83 Emerson RE, Koch MO, Daggy JK and Cheng L (2005). Closest distance between tumor and resection margin in radical prostatectomy specimens: lack of prognostic significance. *Am J Surg Pathol* 29(2):225–229.

84 Epstein JI (1990). Evaluation of radical prostatectomy capsular margins of resection. The significance of margins designated as negative, closely approaching, and positive. *Am J Surg Pathol* 14(7):626–632.

85 Obek C, Sadek S, Lai S, Civantos F, Rubinowicz D and Soloway MS (1999). Positive surgical margins with radical retropubic prostatectomy: anatomic site-specific pathologic analysis and impact on prognosis. *Urology* 4(54):682–688.

86 Barocas DA, Han M, Epstein JI, Chan DY, Trock BJ, Walsh PC and Partin AW (2001). Does capsular incision at radical retropubic prostatectomy affect disease-free survival in otherwise organ-confined prostate cancer? *Urology* 58(5):746–751.

87 Kumano M, Miyake H, Muramaki M, Kurahashi T, Takenaka A and Fujisawa M (2009). Adverse prognostic impact of capsular incision at radical prostatectomy for Japanese men with clinically localized prostate cancer. *Int Urol Nephrol* 41(3):581–586.

88 Shuford MD, Cookson MS, Chang SS, Shintani AK, Tsiatis A, Smith JA, Jr. and Shappell SB (2004). Adverse prognostic significance of capsular incision with radical retropubic prostatectomy. *J Urol* 172(1):119–123.

89 Chuang AY, Nielsen ME, Hernandez DJ, Walsh PC and Epstein JI (2007). The significance of positive surgical margin in areas of capsular incision in otherwise organ confined disease at radical prostatectomy. *J Urol* 178(4 pt. 1):1306–1310.

90 Savdie R, Horvath LG, Benito RP, Rasiah KK, Haynes AM, Chatfield M, Stricker PD, Turner JJ, Delprado W, Henshall SM, Sutherland RL and Kench JG (2012). High Gleason grade carcinoma at a positive surgical margin predicts biochemical failure after radical prostatectomy and may guide adjuvant radiotherapy. *BJU Int* 109:1794-1800.

91 Watson RB, Civantos F and Soloway MS (1996). Positive surgical margins with radical prostatectomy: detailed pathological analysis and prognosis. *Urology* 48(1):80–90.

92 Cao D, Humphrey PA, Gao F, Tao Y and Kibel AS (2011). Ability of length of positive margin in radical prostatectomy specimens to predict biochemical recurrence. *Urology* 77:1409-1414.

93 Marks RA, Koch MO, Lopez-Beltran A, Montironi R, Juliar BE and Cheng L (2007). The relationship between the extent of the surgical margin positivity and prostate specific antigen recurrence in radical prostatectomy specimens. *Hum Pathol* 38:1207-1211.

94 Shikanov S, Song J, Royce C, Al-Ahmadie H, Zorn K, Steinberg G, Zagaja G, Shalhav A and Eggener S (2009). Length of positive surgical margin after radical prostatectomy as a predictor of biochemical recurrence. *J Urol* 182(1):139-144.

95 Dev HS, Wiklund P, Patel V, Parashar D, Palmer K, Nyberg T, Skarecky D, Neal DE, Ahlering T and Sooriakumaran P (2015). Surgical margin length and location affect recurrence rates after robotic prostatectomy. *Urol Oncol* 33(3):109.e107-113.

96 Sooriakumaran P, Ploumidis A, Nyberg T, Olsson M, Akre O, Haendler L, Egevad L, Nilsson A, Carlsson S, Jonsson M, Adding C, Hosseini A, Steineck G and Wiklund P (2015). The impact of length and location of positive margins in predicting biochemical recurrence after robot-assisted radical prostatectomy with a minimum follow-up of 5 years. *BJU Int* 115(1):106-113.

97 van Oort IM, Bruins HM, Kiemeney LA, Knipscheer BC, Witjes JA and Hulsbergen-van de Kaa CA (2010). The length of positive surgical margins correlates with biochemical recurrence after radical prostatectomy. *Histopathology* 56:464-471.

98 Brimo F, Partin AW and Epstein JI (2010). Tumor grade at margins of resection in radical prostatectomy specimens is an independent predictor of prognosis. *Urology* 76:1206-1209.

99 Cao D, Kibel AS, Gao F, Tao Y and Humphrey PA (2010). The Gleason score of tumor at the margin in radical prostatectomy specimens is predictive of biochemical recurrence. *Am J Surg Pathol* 34:994-1001.

100 Kates M, Sopko NA, Han M, Partin AW and Epstein JI (2015). Importance of Reporting The Gleason Score at the Positive Surgical Margin Site: An Analysis of 4,082 Consecutive Radical Prostatectomy Cases. *J Urol* 195(2):337-42.

101 Herman CM, Wilcox GE, Kattan MW, Scardino PT and Wheeler TM (2000). Lymphovascular invasion as a predictor of disease progression in prostate cancer. *Am J Surg Pathol* 24(6):859-863.

102 Cheng L, Jones TD, Lin H, Eble JN, Zeng G, Carr MD and Koch MO (2005). Lymphovascular invasion is an independent prognostic factor in prostatic adenocarcinoma. *J Urol* 174(6):2181–2185.

103 van den Ouden D, Hop WCJ, Kranse R and Schroder FH (1997). Tumour control according to pathological variables in patients treated by radical prostatectomy for clinically localized carcinoma of the prostate. *Brit J Urol* 79:203-211.

104 Van den Ouden D, Kranse R, Hop WC, van der Kwast TH and Schroder FH (1998). Microvascular invasion in prostate cancer: prognostic significance in patients treated by radical prostatectomy for clinically localized carcinoma. *Urol Int* 60:17-24.

105 Loeb S, Roehl KA, Yu X, Antenor JA, Han M, Gashti SN, Yang XJ and Catalona WJ (2006). Lymphovascular invasion in radical prostatectomy specimens: prediction of adverse prognostic features and biochemical progression. *Urology* 68:99-103.

106 Yee DS, Shariat SF, Lowrance WT, Maschino AC, Savage CJ, Cronin AM, Scardino PT and Eastham JA (2011). Prognostic significance of lymphovascular invasion in radical prostatectomy specimens. *BJU Int* 108:502-507.

107 May M, Kaufmann O, Hammermann F and Siegsmund M (2007). Prognostic impact of lymphovascular invasion in radical prostatectomy specimens. *BJU Int* 99:539-544.

108 Cheng L, Bergstralh EJ, Cheville JC, Slezak J, Corica FA, Zincke H, Blute ML and Bostwick DG (1998). Cancer volume of lymph node metastasis predicts progression in prostate cancer. *Am J Surg Pathol* 22(12):1491-1500.

109 Boormans JL, Wildhagen MF, Bangma CH, Verhagen PC and van Leenders GJ (2008). Histopathological characteristics of lymph node metastases predict cancer-specific survival in node-positive prostate cancer. *BJU Int* 102:1589-1593.

110 Sgrignoli AR, Walsh PC, Steinberg GD, Steiner MS and Epstein JI (1994). Prognostic factors in men with stage D1 prostate cancer: identification of patients less likely to have prolonged survival after radical prostatectomy. *J Urol* 152:1077-1081.

111 Van der Kwast TH, Amin MB, Billis A, Epstein JI, Griffiths D, Humphrey PA, Montironi R, Wheeler TM, Srigley JR, Egevad L, Delahunt B and ISUP Prostate Cancer Group (2011). International Society of Urological Pathology (ISUP) consensus conference on handling and staging of radical prostatectomy specimens. Working group 2: T2 substaging and prostate cancer volume. *Mod Pathol* 24:16-25.

112 Wittekind C (ed) (2012). *TNM Supplement : A Commentary on Uniform Use*, The Union for International Cancer Control (UICC), Wiley-Blackwell.