Prostate Cancer Histopathology Reporting Guide
Radical Prostatectomy Specimen

International Collaboration on Cancer Reporting (ICCR)

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

Given name(s)

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

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

Pre-biopsy serum PSA (Note 1)

Not available ◯ or ng/mL

Specimen weight (ie Prostate without seminal vesicles)

g

Specimen dimensions (prostate)

length mm x width mm x depth mm

Seminal vesicles

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

Lymph nodes

Present ◯ Absent ◯

Laterality

Left ◯ Right ◯ Bilateral ◯

Block identification key

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

Histological tumour type (Note 2)

(Value list from the World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs (2004))

- ☐ Adenocarcinoma (Acinar, usual type)
- ☐ Adenocarcinoma (Acinar variant eg. Foamy, Pseudohyperplastic) (specify type)
- ☐ Prostatic ductal adenocarcinoma
- ☐ Adenosquamous carcinoma
- ☐ Small cell carcinoma
- ☐ Sarcomatoid carcinoma
- ☐ Undifferentiated carcinoma, not otherwise specified
- ☐ Other

HISTOLOGICAL GRADE (Note 3)

Primary Gleason grade

1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯

Secondary Gleason grade

1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯

Tertiary Gleason grade

3 ◯ 4 ◯ 5 ◯ Not applicable ◯

Gleason Score

Intraglandular extent (Note 4) %

Maximum size of dominant nodule mm

Extraprostatic extension (Note 5)

Not identified ◯ Present ◯ Indeterminate ◯

Location(s) (Select all that apply)

- ☐ Apical
- ☐ Bladder neck
- ☐ Anterior
- ☐ Lateral
- ☐ Postero-lateral
- ☐ Posterior
- ☐ Other

Extent (Note 6)

Non-focal ◯ Focal ◯

Seminal vesicles (Note 7)

Involved ◯ Not involved ◯ Not applicable ◯

Bladder neck (Note 8)

Involved ◯ Not involved ◯ Not applicable ◯

Margin status (Note 9)

Involved ◯ Not involved ◯ Indeterminate ◯

⇩

Location(s) (Select all that apply)

Apical ☐ Lateral ☐
Bladder neck ☐ Postero-lateral ☐
Anterior ☐ Posterior ☐
Other ☐

Extent (total) (If more than 1 positive margin, record the cummulative length) _____ mm

Gleason score at margin (If more than 1 positive margin, record the higest score) _____

Type of margin positivity

☐ EPE
☐ Intraprostatic (capsular incision)

Lymphovascular invasion (Note 10)

Not identified ◯ Present ◯ Indeterminate ◯

LYMPH NODES STATUS (Note 11)

Number of lymph nodes examined _____

Number of positive lymph nodes _____

⇩

Laterality

Left ◯ Right ◯ Bilateral ◯

Maximum dimension of largest deposit _____ mm

Pathological staging (AJCC 7th edition)## (Note 12)

☐ m multiple primary tumours
☐ r recurrent
☐ y posttreatment

Primary tumour (T)*

◯ TX Primary tumour cannot be assessed.
◯ T0 No evidence of primary tumour
◯ T2 Organ confined
◯ T2a Unilateral, one-half of one side or less
◯ T2b Unilateral, involving more than one-half of side but not both sides
◯ T2c Bilateral disease
◯ T3 Extraprostatic extension
◯ T3a Extraprostatic extension or microscopic invasion of bladder neck**
◯ T3b Seminal vesicle invasion
◯ T4 Invasion of rectum, levator muscles and/or pelvic wall.

Notes:

1. Invasion into the prostate apex or into (but not beyond) the prostate capsule is not classified as T3, but as T2.

* Note: There is no pathologic T1 classification

** Note: Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease)

Regional lymph nodes (N)

◯ NX Regional lymph nodes not sampled
◯ N0 No positive regional nodes
◯ N1 Metastasis in regional node(s)

Distant metastasis (M)

◯ Not applicable
◯ M0 No distant metastasis
◯ 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 one site of metastasis is present, the most advanced category is used. pM1c is most advanced.

American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springerlink.com. Update: 1st July 2011. Copyright permission pending.

Note 1 – Pre-biopsy serum PSA

Reason/Evidentiary Support:

Pre-biopsy serum PSA is essential for stage grouping in the 7th Edition of the AJCC/UICC TNM staging system.[1] In addition, 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.[2-4]

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Note 2- Histological tumour type

Reason/Evidentiary Support:

The large majority (>95%) of prostate cancers are acinar adenocarcinomas.[5] 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.[5-11] The tumour type should be assigned in line with the 2004 WHO classification[5] and mixtures of different types should be indicated.

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Note 3 - Histological grade

Reason/Evidentiary Support:

The 2005 ISUP modified Gleason score is a required (core) element for all radical prostatectomy specimens containing adenocarcinoma, except for those showing morphological changes consistent with androgen withdrawal or significant radiation therapy changes. The Gleason grading system has been in use for over 40 years and is the current, internationally accepted grading system for prostate cancer.[12] It has undergone several significant modifications over time, with an updated version developed at the 2005 ISUP Consensus Conference on Gleason Grading of Prostatic Carcinoma.[13] The Gleason score is an important, independent predictor of tumour behaviour and is a key parameter in the tables and nomograms commonly used to guide decisions on clinical treatment.[2-4]

The method for Gleason scoring is described in the 2005 ISUP Consensus Conference recommendations.[13] Gleason grading is based solely on the architectural patterns of the tumour, best assessed at low power magnification, using a 4x or 10x objectives, and is not influenced by nuclear or cytoplasmic features. Following the ISUP recommendations, the Gleason score for radical prostatectomy specimens is based on assessment of the dominant tumour nodule (the largest nodule) and derived by adding the primary grade (defined as that occupying the greatest area) to

the secondary grade (that occupying the second largest area). In general, the dominant nodule has the highest Gleason score; however, in the unusual situation where there is a smaller nodule (non-dominant nodule) that is composed of higher Gleason grade patterns, the Gleason score of that nodule must also be reported.

In radical prostatectomy specimens the dominant or highest grade tumour nodule may show more than two Gleason grades. The grade that is the third most prevalent (i.e., occupies the third largest area in the tumour nodule) is referred to as the tertiary grade.[14] In a radical prostatectomy specimen, where the tertiary grade (usually grade 5) is higher than the primary or secondary grades the tertiary grade is also recorded.[13] There is strong evidence, including a 2007 meta-analysis, that small volumes of tertiary grade 5 patterns (See Fig. 1 below) are associated with aggressive pathological features and a higher risk of biochemical recurrence.[15-20] Moreover, a recently published study in a retrospective cohort showed an association between the presence of a tertiary Gleason grade of 4 or 5 in the radical prostatectomy specimen and clinical progression, defined as either local failure or metastasis.[21]

The question of how extensive clusters of individual cells, strands or nests without lumina need to be to qualify as tertiary grade 5 is unresolved (for example, whether tertiary grade 5 should exceed 5% of the tumour overall or not).[22] One survey of the current grading practises among genitourinary pathologists found the large majority required identification of such clusters at less than x40 magnification.[23] Another investigation, while reporting under diagnosis of Gleason grade/pattern 5 in prostatic needle biopsies specimens, stressed that pathologists should have a high threshold before diagnosing Gleason pattern 5, and not assign this grade on the basis of a few individual cells or solid nests that could represent tangential sectioning of poorly formed Gleason pattern 4 glands.[24]

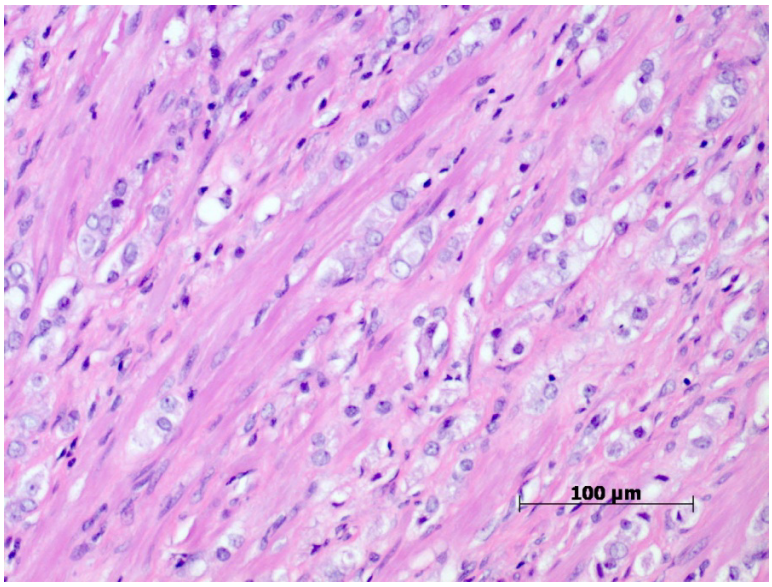

Figure 1. Gleason grade 5 carcinoma.

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Note 4 - Intraglandular extent

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 ICCR dataset for all tumour types. However in prostate, while cancer volume is a prognostic factor on univariate analysis, it is significantly correlated with other clinicopathological features, including Gleason score, EPE, surgical margin status and pathological TNM stage, and the majority of studies have not demonstrated independent prognostic significance on multivariate analysis.[25-30] Hence, the ICCR expert panel regarded this factor as a recommended (non-core) rather that 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 [31-32] or by measuring the maximum size of dominant tumour nodule.[33-34] 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.[30,33-34]

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Note 5 - Extraprostatic extension

Reason/Evidentiary Support:

Extraprostatic extension (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.[25,35] EPE replaced earlier, less clearly defined terms, such capsular penetration, perforation or invasion, following a 1996 Consensus Conference.[36] The assessment of EPE can be difficult, as the prostate is not surrounded by a discrete, well defined fibrous capsule,[37] but rather of a band of concentrically placed fibromuscular tissue that is an inseparable component of the prostatic stroma.[38] 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) (See Fig. 2A below); (2) neoplastic glands surrounding nerves in the neurovascular bundle (posterolaterally); (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—as 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.[38-39] 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 (See Fig. 2B below).[25,39] The presence of cancer within fibrous stroma that is in the same tissue plane as adipose tissue on either side is a helpful indictor 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 prostatic glandular tissue.[39-40]

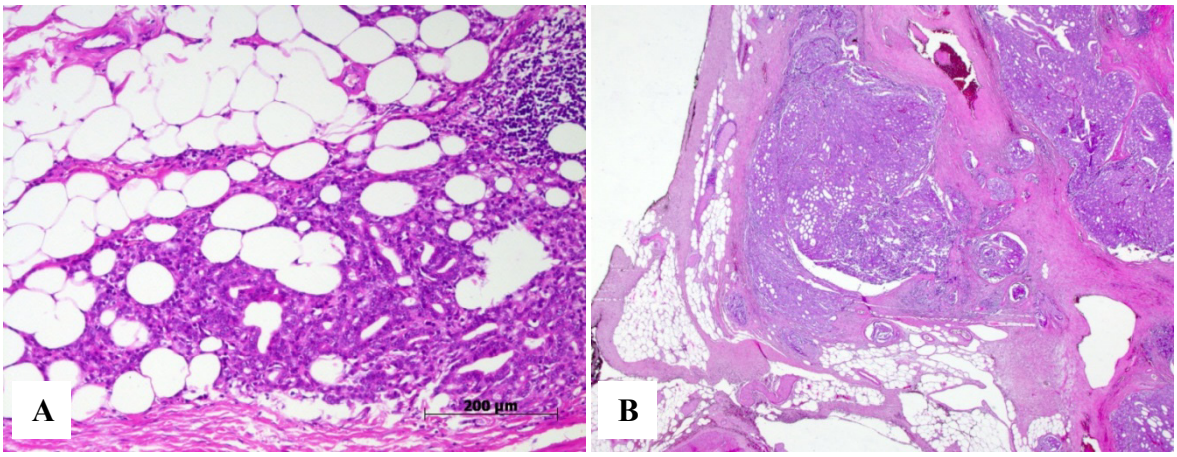

Figure 2A&B. Extraprostatic extension (EPE). A. Carcinoma infiltrating extraprostatic adipose and fibrous tissue. B. A nodular extension of tumour bulging beyond the normal contour of the prostate gland.

Location of EPE

Since it was considered a generic element forming part of a comprehensive pathology report, the location of any extraprostatic extension present has been included in the recommended (non-core) dataset, despite the lack of published evidence for its influence on staging, prognosis or treatment.[39] 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 6 - Extent of extraprostatic extension

Reason/Evidentiary Support:

Categorisation of the extent of EPE as focal or non-focal (also referred to as 'established' or 'extensive') 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.[25] 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.[41] 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 extensive EPE are associated with a significantly higher risk of recurrence at both 5 and 10 years.[25,35] 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.[25,35]

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Note 7 - Seminal vesicles

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[40,42-43] and an integral component of the commonly used nomograms and tables that predict risk of post prostatectomy cancer recurrence.[2-4] The finding of SVI at the time of radical prostatectomy is associated with a significantly increased risk of PSA recurrence[42-44] and the presence of SVI and a positive surgical margin may also influence the response to adjuvant radiotherapy.[45-46] 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.[47]

Different definitions of seminal vesicle invasion have been used over the years complicating comparison of the published survival analyses.[45,48] 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.[49-50] 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 (See Fig.3 below). [48] 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.[51] It was concluded that older definitions that include invasion of the adipose tissue around the seminal vesicle are imprecise and should be discarded.[45,48]

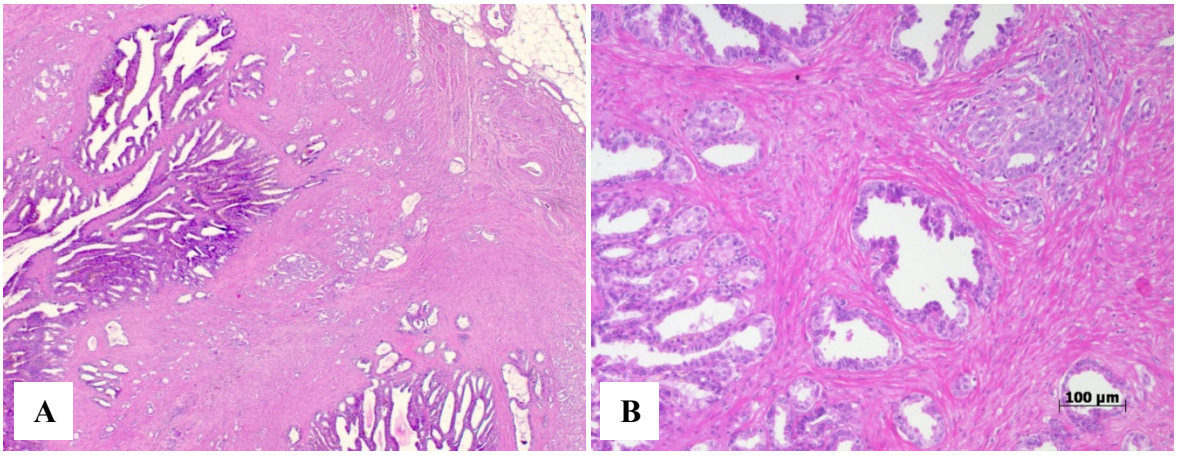

Figure 3A&B. Seminal vesicle invasion (SVI). A. Low power view showing carcinoma centre and seminal vesicle lumen on left. B. Medium power view of seminal vesicle invasion by prostatic adenocarcinoma (top right)

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Note 8 - Bladder neck

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 (Fig. 4).[52] Microscopic bladder neck involvement is a significant predictor of PSA-recurrence in univariate analysis, although not in multivariate modelling in most studies.[53-55] Neoplastic glands intermixed with benign prostatic glands at the bladder neck margin is equivalent to capsular incision rather than true bladder neck invasion.[53,56-57] In the 7th Edition of the AJCC Cancer Staging Manual microscopic bladder neck invasion is classified as stage pT3a disease since it has a similar biochemical recurrence free survival and cancer specific survival to patients with SVI or EPE.[1,52]

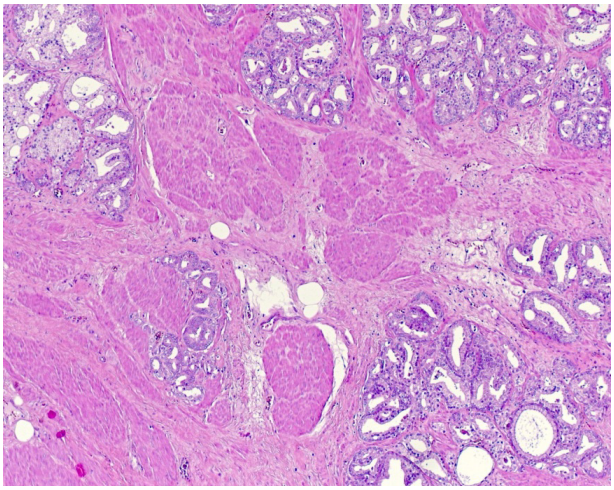

Figure 4. Neoplastic glands within the thick smooth muscle bundles of the bladder neck.

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Note 9 - Margin status

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.[40,58-62] Moreover, positive margins are associated with a 2.6-fold increased risk of prostate cancer specific mortality.[63] 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[40,64] (See Fig. 5 below). 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.[62,65-67]

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.[68-70] 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.[68,70]

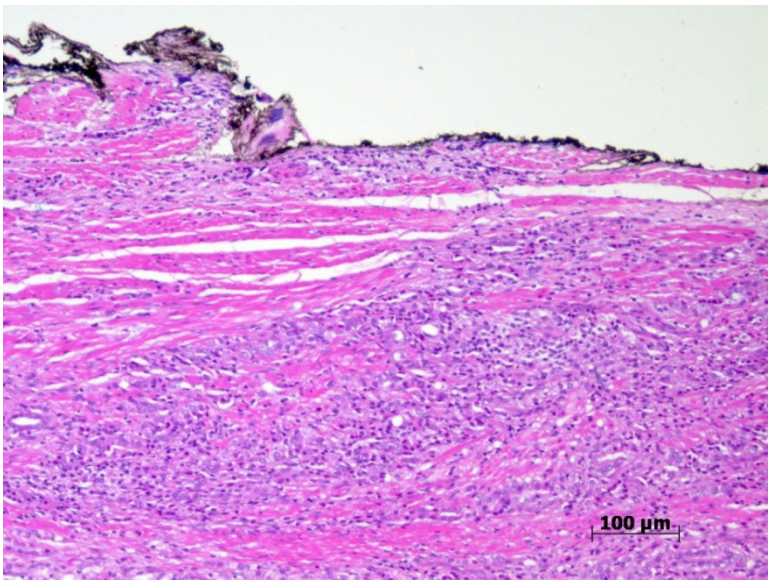

Figure 5. Positive surgical margin (PSM). Prostatic adenocarcinoma extending to black inked margin (top)

Extent (total) of margin involvement

Extent is measured as the linear cumulative length of all positive margins.[71]

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.[58-59,65,72] Studies aiming to better quantify the risk associated with a PSM have focussed on a number of factors such as number, location and extent of positive margins. However, the published data relating to these parameters are somewhat contradictory, and the expert panel considered that there is only sufficient evidence to include measurement of the length of margin involved by carcinoma as an element in the ICCR dataset at present.[47,68,70,72-76] In particular, the 5 year PSA recurrence risk appears to be significantly greater when the length of the involved margin is 3mm or more, (53% versus 14%).[47,74] However, in one series, Cao *et al*[75] 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.[61] 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.

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.[38] 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.[77-79] 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 nonfocal EPE and positive margins.[74]

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.[78] 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.[40,78] 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.[39]

Gleason score at the margin

Following review of feedback on the draft prostate cancer (radical prostatectomy) dataset and commentary, the expert panel has included the Gleason score of the tumour at the positive surgical margin as a recommended (non-core) element of the ICCR dataset. Three recently published papers have found that Gleason score or grade 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.[72,80-81] In one of these studies patients with Gleason grade 4 or 5 carcinoma (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 score 3 at the PSM had a similar 5-year biochemical relapse-free survival rate to those with negative margins.[72] 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.[80]

In the event there are multiple positive margins with differently scored cancers present, the highest score should be recorded.

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Note 10 - Lymphovascular invasion

Reason/Evidentiary Support:

Lymphovascular invasion is defined as the unequivocal presence of tumour cells within endothelial-lined spaces with no underlying muscular walls.[82-83] 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.

Lymphovascular (LVI) invasion has been reported to be associated with decreased time to biochemical progression, distant metastases and overall survival after radical prostatectomy.[82-87] 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.[82-83,85,87-88] 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 11 - Lymph nodes status

Reason/Evidentiary Support:

Lymph node involvement is a well established independent adverse prognostic factor[40,48] and is an integral component of the commonly used nomograms that predict the risk of post prostatectomy disease recurrence.[2] 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[89-91] 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.[48]

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Note 12 - Pathological staging (AJCC 7th edition)

Reason/Evidentiary Support:

The pathological tumour (T) and lymph node (N) categories were 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/UICC Staging Manuals (7th Edition)[1] except pT2 subcategorization should be considered optional in line with ISUP recommendations as it lacks additional prognostic significance.[92]

The reference document: TNM Supplement: A commentary on uniform use, 4th Edition (C. Wittekind editor) may be of assistance when staging.[93]

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