The Royal College of Pathologists
Pathology: the science behind the cure

Standards and datasets for reporting cancers

Dataset for histopathology reports for prostatic carcinoma

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Comments	This document replaces the 3rd edition of the *Dataset for histopathology reports for prostatic carcinoma*, published in 2016. In accordance with the College's pre-publications policy, this document was on the Royal College of Pathologists' website for consultation from 15 August to 12 September. Responses and authors' comments are available to view on request. **Dr Brian Rous** **Clinical Lead for Guideline Review**

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Foreword

The cancer datasets published by the Royal College of Pathologists (RCPath) are a combination of textual guidance, educational information and reporting proformas. The datasets enable pathologists to report the most clinically relevant information on cancer specimens, including grade and stage, in a consistent manner, in compliance with international standards and provide prognostic information. This allows clinicians to provide a high standard of care for patients and appropriate management for specific clinical circumstances. This guideline has been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every pathological specimen type and clinical scenario. Occasional variation from the practice recommended in this guideline may therefore be required to report a specimen in a way that maximises benefit to the patient.

Each dataset contains core data items (see Appendices D–F) that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – previously the National Cancer Data Set) in England. Core data items are items that are supported by robust published evidence and are required for cancer staging, optimal patient management and prognosis. Core data items meet the requirements of professional standards (as defined by the Information Standards Board for Health and Social Care [ISB]) and it is recommended that at least 95% of reports on cancer resections should record a full set of core data items. Other non-core data items are described. These may be included to provide a comprehensive report or to meet local clinical or research requirements. All data items should be clearly defined to allow the unambiguous recording of data.

The following stakeholders were be contacted to consult on this document:

- British Association of Urological Surgeons (BAUS)/BAUS Section of Oncology
- British Uro-oncology Group
- British Association of Urological Pathologists (BAUP)
- UK and Ireland Association of Cancer Registries (UKIACR)
- National Prostate Cancer Audit.

The information used to develop this cancer dataset was obtained by undertaking a systematic search of PubMed. Key terms searched included ‘cribriform prostate cancer’, ‘intraductal carcinoma’, ‘percentage pattern 4’, ‘neuroendocrine carcinoma of the prostate’,

and ‘sampling in HoLEP’. The dates searched were between April 2016 and May 2024. Published evidence was evaluated using modified SIGN guidance (see Appendix G). Consensus of evidence in the guideline was achieved by expert review. Gaps in the evidence were identified by College members via feedback received during consultation.

Supporting evidence and recommendations in this dataset are based on:

- PubMed literature searches (up to April 2023)
- WHO classifications, 2022[1]
- NICE Improving Outcomes Guidance, 2002[2]
- NICE Prostate cancer diagnosis and treatment CG157[3]
- ICCR prostate dataset[4]
- TNM 8th edition staging classification, 2016.[5]

Most of the supporting evidence is level C or D at least or meets the good practice point (GPP) criteria (see explanation of levels of evidence in Appendix G). No major conflicts in the evidence have been identified and any minor discrepancies between evidence have been resolved by expert consensus.

No major organisational changes or cost implications have been identified that would hinder the implementation of the dataset.

A formal revision cycle for all cancer datasets takes place on a 3-yearly basis. However, each year, the College will ask the authors of the dataset, in conjunction with the relevant subspecialty adviser to the College, to consider whether the dataset needs to be revised. A full consultation process will be undertaken if major revisions are required, i.e. revisions to core data items (the only exception being changes to international tumour grading and staging schemes that have been approved by the Specialty Advisory Committee on Cellular Pathology and affiliated professional bodies; these changes will be implemented without further consultation). If minor revisions or changes to non-core data items are required, an abridged consultation process will be undertaken, whereby a short note of the proposed changes will be placed on the College website for 2 weeks for consultation with the membership. If members do not object to the changes, the changes will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

The dataset has been reviewed by the Professional Guidelines team, Working Group on Cancer Services and Lay Advisory Group and will be placed on the College website for consultation with the membership from 15 August to 12 September 2024. All comments received from the Working Group and membership will be addressed by the authors to the satisfaction of the Chair of the Working Group and the Clinical Lead for Guideline Review.

This dataset was developed without external funding to the writing group. The College requires the authors of datasets to provide a list of potential conflicts of interest; these are monitored by the Professional Guidelines team and are available on request. The authors of this document have declared that there are no conflicts of interest.

1 Introduction

In 2002, guidance from the National Institute for Health and Clinical Excellence (NICE), *Improving Outcomes in Urological Cancer*,[2] recommended the establishment of specialist multidisciplinary teams (MDTs) for radical pelvic surgery (prostatectomies and cystectomies), serving a catchment population of 1 million. It was estimated that such a population would produce more than 50 surgical procedures (combined total) per annum, regarded as a minimum to maintain specialist expertise and allow audit of outcomes. Since these guidelines were published, robotic prostatectomies have become increasingly common and NICE guidelines have recommended that robotic surgery should only be commissioned in centres performing more than 150 cases per year.[3] Patients with prostate cancer diagnosed by local urological multidisciplinary cancer teams should be referred to the specialist team and the diagnostic slides made available for review. In each hospital there should be a lead pathologist for uropathology and a deputy. It is expected that these pathologists should participate in the uropathology external quality assessment scheme (www.histopathologyeqa.org).

The diagnosis of prostate cancer was generally made on transrectal ultrasound (TRUS) guided prostatic biopsies, but there has been a steady rise in the numbers of transperineal biopsies. This move from TRUS to transperineal biopsies has accelerated owing to COVID and the ability to take the cores under local anaesthetic. Using a brachytherapy grid to guide sampling, known as template biopsies, has fallen out of favour as this requires multiple puncture sites and is not tolerated under local anaesthetic. Access to theatre time to perform these procedures has limited its use. Local anaesthetic transperineal biopsy (LATP) uses 2 puncture sites by a hollow sheath and the trucut needles are then passed through the sheath to sample the prostate. This procedure takes slightly longer than TRUS

biopsies, but it does enable sampling of the anterior prostate and, more importantly, has a lower sepsis rate. In the 2021 National Prostate Cancer Audit, 40% of biopsies were performed transperineally.[6] The technique for LATP biopsies requires training and it is at this point pathologists should give guidance as to the requirements that we need to enable standardisation of requests and biopsy numbers.

The role of pre-biopsy multiparametric MRI in the diagnosis of prostate cancer is now established in the UK following the results of the PROMIS trial[7] and the subsequent guidance from NICE. The PROMIS trial had suggested that there would be a decrease in the workload for pathologists as unnecessary biopsies would be avoided using MRI. This was true to a certain degree, but the numbers of biopsies increased as targeted cores of MRI-detected lesions were added to random systematic cores. Pre-biopsy MRI has led to a greater proportion of positive biopsies but, with ever-increasing demand, no pathology centre has seen a decrease in workload as a result of the implementation of pre-biopsy MRI. The implementation of LATP biopsies has also led to increase sampling as most centres use a Ginsburg approach – samples from anterior, mid and posterior bilaterally as opposed to TRUS biopsies sampling the right and left but not submitting different sites. This has led to more specimen samples and more blocks. Evidence from PROMIS study has shown that the more cores taken leads to more non-clinically significant cancers being detected. The Getting it Right First Time guidance recommends no more than 4 cores from the target lesion and systematic sampling of the background prostate following the RAPID approach. Patients should not be undergoing routine transperineal 5 mm or sector mapping.[8]

The NICE guidance used D'Amico classification of risk in prostate cancer (Table 1).[9] Although this system has drawbacks – not least with the continued drift of Gleason score – it is regularly utilised by urologists.[10] Furthermore, it does not differentiate between Gleason 3+4=7 and 4+3=7. The use of the Cambridge Prognostic Groups (Table 2) is becoming more widespread and this does differentiate between grade group (GG)2 and GG3.[11] The PREDICT prostate tool is also available and uses other pathological data points including the numbers of cores involved and the presence of intraductal or cribriform growth patterns.[12] For the numbers of cores involved, the tool considers target cores as a single core. Pathologists can give enormous amounts of data but there needs to be a balance between requirements for clinical management and resource implications. Some data is only useful in the setting of selecting patients for active surveillance,[13] but it is often not possible for the pathologist to know all the other parameters at the time of reporting the

prostate core biopsies. This dataset includes non-core data items that pathologists may want to record to validate these for future datasets.

Table 1: Risk stratification for men with localised prostate cancer used in NICE guidance.[3]

Level of risk	Prostate specific antigen		Gleason score		Clinical stage
Low	<10 ng/ml	and	≤6	and	T1–T2a
Intermediate	10–20 ng/ml	or	7	or	T2b
High	>20 ng/ml	or	8–10	or	≥T2c

Table 2: Cambridge prognostic groups.

Group	Prostate specific antigen		Grade group		Stage
1	<10 ng/ml	and	GG1	and	T1 or 2
2	10–20 ng/ml	or	GG2	and	T1 or 2
3	10–20 ng/ml	and	GG2 or GG3	and	T1 or 2
4	>20 ng/ml	or	GG4	or	T3
5 – 2 of these:	>20 ng/ml	and/ or	GG4	and /or	T3
or			GG5	or	T4

1.1 Target users and health benefits of this guideline

The target primary users of the dataset are trainee and consultant cellular pathologists and, on their behalf, the suppliers of IT products to laboratories. The secondary users are surgeons and oncologists, cancer registries and the National Cancer Intelligence Network. Standardised cancer reporting and MDT working reduce the risk of histological misdiagnosis or misinterpretation of histopathology reports and help to ensure that clinicians have all the relevant pathological information required for tumour staging, management and prognosis. Collection of standardised cancer-specific data also provides information for healthcare providers and epidemiologists and facilitates international benchmarking and research.

The most significant changes from the previous dataset are as follows:

- the dataset has been updated based on UICC TNM8, WHO 2022 classification of tumours of the prostate and ICCR recommendations
- specifying tumour length as a core item in the reporting of prostate cores and removing option of percentage tumour
- requiring percentage Gleason pattern 4 in core biopsies and presence of intraductal carcinoma (IDC)/ invasive cribriform carcinoma
- limit sampling of transurethral resections of the prostate.

2 Clinical information required on the specimen request form

This information includes the presenting prostate specific antigen (PSA), the clinical context and the type of specimen, and whether the specimen was taken by biopsy (systematic or targeted or transperineal), transurethral resection, radical prostatectomy (nerve sparing or not) or nodal dissection. The number and site (at least laterality) of prostatic biopsies taken must be recorded by the operator as this cannot be determined in the laboratory due to fragmentation of cores. Provision of this information avoids a situation where the number of positive cores exceeds the number of cores obtained. If targeted biopsies are taken from a radiologically identified lesion, these should be submitted in a separate container. Information of the MRI findings or, at the minimum, the PIRADS or Likert Score is now essential. The prostate volume, which allows the PSA density to be calculated, may be useful at the MDT. We have provided a request form in the appendices that can be adapted for use locally (Appendix C).

A standardised request form means that the specimens are submitted in a standardised order. Information about prior biopsies or resections, or prior treatment, helps in the interpretation of the microscopic findings within the appropriate clinical context (for instance, identifying low-volume, low-grade prostate cancer in needle biopsies is less important if the biopsies are performed as part of an active surveillance protocol). Anti-androgen therapy alters the cytology and architecture of both benign and malignant glands,[14–16] and may therefore alter the significance of Gleason grading.

The date of completion of radiotherapy is also important as, even if therapy is effective, tumour can persist for at least 2 years after external beam radiation and for up to 6 years

for brachytherapy.[17] It has been shown that 2-year post-radiotherapy biopsy results can be predictive of long-term, disease-free survival.[18] When the patient has undergone low-dose brachytherapy the seeds are permanently implanted.[19] There is a radiation risk until after the first 3–12 months (depending on the implant) but this is only really an issue at autopsy as the patients rarely undergo salvage surgery within this timeframe.[20,21] Obtaining the date of insertion of brachytherapy seeds is essential before the specimens are handled.

3 Preparation of specimens before dissection

Specimen types received from the prostate include the following:

- prostate biopsies
  - transrectal
  - transperineal
- transurethral resections (TURP)
- enucleations
- radical prostatectomies
- lymphadenectomies.

3.1 Transurethral resections and enucleations

Resections received as prostatic ‘chips’ do not require sectioning prior to fixation. Enucleations, or ‘open/simple’ prostatectomies, are generally restricted to large prostates in patients with lower urinary obstructive symptoms. Such specimens can benefit from a few incisions to allow formalin penetration. Inking of margins is not useful, even if carcinoma is detected incidentally, because these are not radical resections and, given the multifocality of prostatic cancer, demonstration of negative margins does not necessarily equate with absence of residual disease.

3.2 Radical prostatectomies

The prostate gland is covered by a very thin rim of connective tissue, which can easily be disrupted during surgery or in the pathology suite leading to ‘false-positive’ margins. Distinction between true and false surgical margins is easier when the specimen is fresh, because fixation changes the colour and appearance of the gland. In the fresh state, at the apex, intact Denonvilliers’ fascia should be identifiable posteriorly by its smooth, glistening

surface. Surgical dissection of the fascia normally causes it to retract up over a short distance exposing underlying tissues, and this area should not be regarded as a true surgical margin. A very small ring of sphincter muscle fibres is seen around the urethra. A small layer of connective tissue should also be present at the posterolateral edge to indicate the absence of capsular incision.[22]

Any surgical incision will expose underlying prostatic tissue, which is duller and more irregular than the covering fascia. Even small inadvertent incisions during the separation of the planes of dissection can result in relatively large areas of exposed glandular tissue if the prostate is under tension from hyperplasia and subsequently 'herniates' through the incision. An additional problem is the presence of clips or tight sutures required for haemostasis. The sutures in particular are easier to remove in the fresh state and are very difficult to identify if the specimen has been inked. For all these reasons, surgeons in some European centres remove clips and sutures in theatre and ink the true surgical margins themselves.

The specimen is fixed in formalin and this should cover the specimen entirely to ensure proper fixation. Injection of formalin into the specimen can help fixation and does not appear to affect tissue shrinkage and therefore tumour volume measurements.[23]

3.3 Lymphadenectomies

These are generally fixed en bloc in adequate volumes of formalin.

4 Specimen handling and block selection

4.1 Prostate biopsies

Cores may be sent to the laboratory as individual specimens, or several cores may be placed in 1 pot. At the very minimum, cores should be separated into right and left sides as the surgical approach may vary depending on side-specific tumour burden. The number of cores should be recorded and whether they are fragmented. Measuring individual core lengths is onerous but this is an area that can be audited (see below).

Most biopsies are taken with the 18-gauge biopsy gun under TRUS guidance. Handling of prostatic biopsies within the laboratory requires experienced staff and stringent quality control, as the aim is to produce the greatest surface area for examination in order to detect small foci of cancer.[24] Optimising pre-embedding and embedding techniques can reduce the number of levels required and the rate of equivocal diagnoses.[25]

The LUMEA biopsy chip was introduced to provide better tissue quality and the tool has proven to provide significant diagnostic efficiency.[26] Although an additional cost will be incurred in its introduction and usage, the standardisation of core quality and quantity will help improve cancer detection.

The prostate cores are thinner than biopsies of breast, for instance, and tend to curve and/or fragment. Care must be taken while straightening them for processing and embedding. Separation and flattening to subsequently optimise embedding of the cores are important to identify foci of cancer in individual cores, count the number of positive cores and assess the length of tumour. This can be achieved by using individual cassettes or by sandwiching the cores between 2 inserts, such as foam pads or nylon meshes,[25] depending on local practice. Cores can be laid out in a specific order to correlate with site of origin. The use of dyes such as haematoxylin to colour the cores is helpful in identifying them at the embedding stage. The numbers of cores per block is contentious and, although some advocate for multi-core embedding,[27] it is advisable that embedding more than 3 cores in a single cassette can make assessment of numbers of cores involved by tumour exceedingly difficult and should be avoided.[28,29]

Flat embedding is essential to optimise sectioning and representation of the full length of the core. At least 3 levels are taken: 1 from the top half, middle and lower portion of each core. Examining less than 3 levels may miss significant clinical findings, whether the diagnosis of cancer itself or prognostic features such as grade or perineural invasion.[30]

Small foci suspicious for carcinoma may only be present at specific levels. Retaining spare sections from each level allows the use of immunohistochemistry to make a definitive diagnosis in difficult cases. This is important to avoid unnecessary re-biopsy; firstly, because of the associated morbidity and, secondly, because subsequent biopsies will not necessarily sample the relevant area in the absence of clear anatomical landmarks on ultrasound. Immunostaining the original H&E section is a possibility, but there are technical difficulties related to sections lifting from non-charged slides.[31]

In addition to the costs of processing and sectioning additional blocks and workload implications, the value of retaining sections for immunohistochemistry makes embedding each core individually impractical in many laboratories. The disadvantages of combining multiple cores in 1 block are minimised if the techniques described above are employed.

The quality of the prostate cores should be audited. The operator performing the biopsies should compare the length of the core with the length of the needle notch to ensure each

core is adequate, and repeat the procedure if it is not and if the patient can tolerate it.[6] Nevertheless, there are wide, operator-dependent variations in the amount of prostatic tissue sampled, even if the same biopsy protocol is employed.[28] In the European Randomised Study of Screening for Prostate Cancer, there was a correlation between the average total amount of prostatic tissue sampled per centre and the cancer detection rate.[28] The length of single cores sampled can vary by more than 3.6-fold, and core length also correlated with the cancer detection rate in this study.[30] There is no accepted definition for an adequate core length but this can be critical in measuring the amount of tumour in a core.[32] Poor quality cores (e.g. extraprostatic tissue only) should be recorded to allow audit of operator technique. The request form example (Appendix C) asks for the operator's name so feedback can be given directly. During the learning curve of LATP biopsies, the anterior cores often consist of only extraprostatic tissue.

4.2 Transurethral resection of the prostate

The chips are weighed. In general, gross examination of chips for evidence of tumour, such as necrosis or induration, is unrewarding.

A proportion of these specimens will contain unsuspected foci of carcinoma, and the optimum sampling strategy is controversial. The TNM classification distinguishes between cases with over 5% of resected tissue involved (T1b) and those with smaller amounts of cancer (T1a). The p prefix is not used as there is insufficient tissue to assess the highest pT category.[5] The interpretation of this by pathologists has varied. Many assess the percentage number of chips involved, whereas others report the percentage of surface area involved. The latter is more difficult to report consistently, particularly in large resections, and the percentage of chips involved provides valuable information.[33] 'Eyeball' assessment is sufficient with these reported as <5%, 10% and then at 10% intervals, with particular care taken around the 5% cut-off.

32% of patients with T1b disease suffer clinical progression after 4 years,[34] whereas disease progression is slower for patients with T1a disease, with up to 16% progressing at 8 years.[34-36] More recent studies have shown that providing the percentage of chips involved gives more information.[33] Ideally, sampling protocols should identify all T1b patients and T1a patients with a life expectancy of 8 years or more. A common protocol is to embed the entire specimen up to 12 g (6 blocks) and a further 2 g (1 block) for every additional 5 g. Although these additional blocks may detect a higher proportion of tumours, they do not lead to upstaging or upgrading of T1a tumours if tumour was present in the first

6 blocks.[37] Holmium laser enucleation of the prostate (HoLEP) can generate very large volumes of chips and a recent paper found that the 96% of prostate cancers were detected by embedding 10 cassettes and all were detected by embedding 18.[38] Departments may want to review their current policy and move to embedding a maximum of 18 cassettes, although a consensus of whether this is excessive is required.

Examination of the entire specimen is justifiable for the small subset of patients who may benefit from radical treatment based on life expectancy or following discussion at the multidisciplinary meeting. Laser ablation prostatectomy leads to decreased amounts of tissue for histological examination and this tissue shows marked heat artifact but, as most incidental tumours found at TURP are low grade, this may not be significant.[39]

'Channel' TURPs are performed to relieve obstruction in men with known prostate cancer and pathological findings would have limited impact on patient management. Hence, a more limited sampling would be adequate in this setting. As with other TURP specimens, there are no good evidence-based recommendations on sampling protocols.

4.3 Enucleation specimens

These specimens should be weighed. There are no data on optimum block selection in enucleation specimens, and the most consistent approach is generally to sample according to weight, as for transurethral resections, again with the caveat discussed above.

4.4 Radical prostatectomy specimens

The prostate can be difficult to orientate because of distortion due to hyperplasia, in particular, and identification of several landmarks is helpful. The posterior aspect is flatter than the anterior surface and has a midline groove. The seminal vesicles arise from this aspect but are not necessarily removed en bloc (or at all), particularly during robotic surgery as excessive tension during dissection can shear the vesicles off the base of the prostate. The anterior surface is convex and shorter than the posterior. The base of the prostate (bladder neck) is flatter than the apex, which generally tapers to a more conical shape.

If the specimen has not been prepared in theatre or received fresh, following removal of the clips and sutures, it should be examined as described in section 3.2 and inked accordingly. The use of different colours to identify laterality is advised. The specimen should be weighed and can be measured in 3 dimensions. The International Society of Urological Pathologists (ISUP) consensus meeting recommended weighing the prostate after the seminal vesicles have been removed.[40]

The vas resection margins can be sampled and the seminal vesicles amputated close to the prostate base. The first section from the apex is perpendicular to the urethra. Precise depth will depend on the shape of the apex but is generally 5 mm thick and angled so that the prostate will be in the correct anatomical position when laid on the cutting board. The posterior aspect usually must be thicker than the anterior to achieve this. This section is then sectioned sagitally. Sections should be taken with the overall aim of demonstrating the margin as extensively as possible. The base margin is taken and sectioned in a similar fashion. So-called ‘shave’ resection margins are discouraged as the presence of tumour simply indicates that the tumour is close to, but not necessarily at, the inked resection margin.[40]

For those patients that opt for radical prostatectomy as the primary treatment, the pathologic findings in the resection specimen are critical for prognostication and 5-year disease-free recurrence.

Seminal vesicle invasion by prostatic adenocarcinoma (pT3b) has shown to be a predictor of poor prognosis after radical prostatectomy and is commonly seen in association with extraprostatic extension (EPE; pT3a). The literature relating to seminal vesicle sampling techniques are far and few. A comprehensive literature review[41] compared and showed large differences in published literature, in both the percentage involvement of seminal vesicles and in the 5-year disease-free recurrence.[42–44]

This further reiterated the need for conformity and a unified approach to seminal vesicle invasion in the analysis and comparison of future radical prostatectomy series, to provide meaningful statistical data for prognostication.

Based on the above studies and survey, it is recommended that a section from the junction of the seminal vesicle and the prostate should be sampled as this is most likely to detect contiguous spread of tumour. This should be considered the minimum necessary and the remaining blocks as random sections or suspicious for tumour may be analysed additionally. The entire submission of the seminal vesicles may not be considered pragmatic or necessary.[45]

Holding the remaining specimen as close as possible to the correct anatomical position, the prostate is then sliced into 4-mm sections, perpendicular to the urethra. A Perspex board with 4-mm edges or other guides can be used. Thinner sections may require the insertion of a foam pad or other device into cassettes to prevent the section from curling during processing, especially when megablocks are employed. It is important to avoid

applying too much pressure to the specimen or the sections will be too thick. Sections should be taken with a smooth sweep of the knife (rather than sawing backwards and forwards) to give a flat surface for embedding. If the knife deviates when slicing so that a particular margin is not represented, it is useful to make a note of this to avoid an unnecessary request for levels. Sections are laid out sequentially so that each face is also embedded sequentially. Prostatic adenocarcinomas are visible macroscopically in just over half of the cases and an identifiable gross lesion is correlated with increased tumour stage, grade and size.[46]

There are various methods for taking fresh samples from the specimen prior to fixation, but no agreement on the best method was reached at the ISUP consensus meeting.[40] The problems of distortion of the margins, as well as inability of visualising the tumour grossly, mean that this process can be extremely difficult and time consuming.[47]

Protocols based on series of fewer than 100 patients have detailed sampling strategies to detect the majority of prostatic tumours[48] and identify adverse pathological factors.[49] Nevertheless, complete embedding of the specimen is preferable for the following reasons:

- a high proportion of prostate cancers are not visible macroscopically and sampling would therefore be blind[46]
- in a large study of 1,383 patients, those with negative margins using step sectioning of the entire specimen had a lower risk of progression than similar patients whose specimens were partially sampled[50]
- although the location of positive margins is not relevant to immediate patient management, surgical margin status is one of the tools used to audit the quality of surgery.

The ISUP meeting could not reach consensus (defined as 65% agreement) on whether all tissue should be submitted,[40] whereas a European Network of Uropathology (ENUP) survey of uropathologists showed that 71% completely embedded these specimens.[51] Large block technology was used by 37.5% in the ENUP survey, but there was no consensus at the ISUP meeting on whether this was preferable.[40,51] Potential drawbacks include the additional fixation and processing required, which may alter the immunoreactivity of the tissues. However, immunocytochemistry is rarely required in routine practice.

The specimen is dissected as described and sequentially embedded to identify:

- right and left seminal vesicles
- the apex
- consecutive sections of the prostate
- the base.

4.5 Lymphadenectomy specimens

Specimens are measured in 3 dimensions. Lymph nodes are identified and described as either macroscopically normal or involved by tumour. However, the correlation between nodal size and the presence of metastasis is poor in the prostate, with 1 study demonstrating that the mean longitudinal length of negative nodes was 35 mm (range: 5–90 mm) compared with the smaller value of 16 mm (range: 2–65 mm) for positive nodes.[52] These are often impalpable. Submitting the whole specimen has been shown to increase the yield of lymph nodes, but whether these impalpable nodes are clinically significant is uncertain.[53]

5 Core data items

5.1 Clinical information

Recording the PSA level helps with future management and is deemed a required item. The clinician should provide this information if available. The MRI findings should be provided if available, to highlight any mismatch that can or cannot be explained. The clinical stage and any previous therapy are recommended. Recording the operative procedure is always required. The number of prostate cores taken and their location should be given.

[Level of evidence GPP – It is important to document the clinical information available to the reporting pathologist.]

5.2 Macroscopic data items

The number of prostate cores and their location should be recorded if not stated in the clinical information. The specimen weight for TURPs, enucleations and radical prostatectomies (without the seminal vesicles) should be recorded, as well as the presence or absence of the seminal vesicles in radical prostatectomies.

[Level of evidence GPP – It is important to document how much tissue was submitted for histopathological examination.]

5.3 Microscopic data items

5.3.1 Histological tumour type

>95% of tumours in the prostate are acinar adenocarcinomas.[1]Some other types of prostatic carcinomas, although rare, have a worse prognosis, e.g. small cell carcinoma.[1]

[Level of evidence D – Histological variants are important for cancer registration and prognosis.]

5.3.2 Histological grading

Gleason grading of prostatic biopsies remains one of the most crucial factors in deciding further therapy. However, Gleason grading has undergone considerable revision since its initial conception. ISUP has produced 2 guidance documents.[54] The 2005 guidance on scoring is now utilised by all pathologists in the UK.[55,56] The 2005 guidance changed 2 fundamental areas: 1 was the patterns in Gleason 3 and 4 and the other was tertiary scores in core biopsies. The subsequent ISUP 2014 guidance made recommendations about grading cribriform glands, glomeruloid glands, mucinous adenocarcinomas and IDC-P, as well as advising the use of a new grading system.[57,58]

Patterns

The main pattern of prostate cancer that remained in dispute was rounded cribriform glands, which some pathologists assigned to pattern 3 and others to pattern 4. It was proposed that cribriform glands should always be assigned pattern 4. There have been several independent papers suggesting that any form of cribriform architecture confers a poor prognosis.[56,59–61] A second pattern that has also been shown to confer a poorer prognosis is the glomeruloid pattern. It is recommended that both these patterns are considered Gleason pattern 4.[62]

It is important to recognise cribriform pattern in prostate cancer as it is well recognised to have an adverse prognosis in a biopsy setting and it is a strong predictor of metastasis and survival in a radical setting. Setting appropriate criteria with a morphological definition of cribriform tumour will aid exclusion of those patients from active surveillance as recommended by both societies, ISUP and Genitourinary Pathology Society (GUPS). The major urological societies, ISUP and GUPS, produced recommendations after their consensus meetings.[63,64]

A recent paper by the ISUP[64] helped define and facilitate the reproducible recognition and reporting of this clinically important growth pattern based on a consensus definition of its experts. The proposed definition is ‘a confluent sheet of contiguous malignant epithelial cells with multiple glandular lumina that are easily visible at low power (objective magnification x10)’. There should be no intervening stroma or mucin separating individual or fused glandular structures.

The reproducibility study by Shah and colleagues[65] showed the 3 features that achieved consensus: transluminal bridging or dense cellular proliferation of greater than 12 lumina, branching contour pattern with no intraglandular stroma, and small cribriform similar to the size of a benign acinus with less than 1 lumina.

Intracytoplasmic vacuoles should be ignored for grading purposes. It is assumed that cribriform, pseudo-rosette and solid patterns are a morphological continuum and, for this reason, borderline cases will occasionally occur that show patchy or few lumina. The prognostic significance of these borderline patterns is still unknown and debatable.

Rarely, mucinous carcinoma may show a true cribriform pattern,[66] but in most cases, these represent fused glands and or abundant intraglandular mucin. Grading of mucinous adenocarcinoma should be based on its underlying growth pattern as accepted and outlined by the 2014 ISUP consensus conference.

The label ‘complex fused’ glands for this pattern was adopted by Kweldam and colleagues[67] who demonstrated that this morphology was particularly prone to interobserver disagreement for the presence of a cribriform pattern. The prognostic impact of this pattern remains unclear in contrast to the voluminous evidence on cribriform pattern.

In the past there have been discussions regarding a minimum size of the cribriform sheet as a defining criterion, but there has been no clear consensus on its requirement per se, nor on specific size cut-off levels. Studies have shown that large gland cribriform morphology is aggressive in clinical behaviour.[60] The number of lumen spaces needed to qualify as cribriform cancer was set at >12 in the 2011 study by Iczkowski and colleagues,[61] based on consensus diagnoses of a subset of cases in the study. Other studies have also suggested 2-times the size of a typical benign gland and a cut-off of greater than 0.25 mm diameter.[68–71]

In a more recent study,[72] both large and small cribriform patterns in biopsies were associated with shorter time to metastasis and disease-free survival.

It has been well established that large cribriform pattern is invariably associated with small areas of cribriform pattern,[68] and it can be valuable to record this information during biopsies/TURP, given the low sensitivity of identifying cribriform patterns.[73,74]

The reporting of invasive cribriform growth pattern in radical prostatectomy specimens is considered a major predictive factor for distant metastasis, EPE and disease-specific death in Gleason 7 prostate cancer.[70,75]

The differential diagnoses of cribriform architecture can occasionally include benign lesions (normal central zone glands, clear cell cribriform hyperplasia, basal cell hyperplasia with cribriform pattern) and neoplastic (cribriform high-grade prostatic intraepithelial neoplasia [HGPIN] and intraductal carcinoma of the prostate [IDC-P]) lesions.

Histologically, the distinction between small cribriform prostate cancer and cribriform HGPIN may be difficult and is based on the absence or presence of basal cells investigated immunohistochemically. The WHO states “the existence of a cribriform pattern of HGPIN is now controversial and its diagnosis is not recommended on needle biopsy”.[1]When invasive cribriform carcinoma and IDC-P cannot be distinguished morphologically, immunohistochemistry for basal cell markers can be applied, especially if the tissue is a biopsy, but only when this would have clinical impact which is infrequent as PREDICT tool lumps these entities together.[12] The only scenario is when there is no invasive component and in which case IDC-P would not be graded. The presence of basal cells supports a diagnosis of IDC-P; however, it is worth noting that an occasional staining for basal cells does not preclude from making that distinction.

In particular, the prognostic importance of cribriform prostate cancer is an independent parameter for adverse outcome stressing the importance of recording this novel parameter in both biopsies and resections.

In a more recent study by Oufattole and colleagues,[76] the significance of different histologic patterns of Gleason 5 disease and cribriform components was assessed, including the prognostic significance of cribriform components of pattern 4 invasive carcinoma and/or IDC-P, with Gleason pattern 5 in radical prostatectomies. The analysis showed that the presence of cribriform components in radical prostatectomies with Gleason 5 is associated with adverse histopathologic findings and may represent an independent predictor of risk of biochemical recurrence. These cases demonstrated a

higher frequency of extraprostatic involvement and surgical margin positivity, as well as a higher risk of biochemical recurrence, attributed to the cribriform morphology.

Tertiary patterns

A modification to the method of reporting the sum score on biopsy material if a tertiary pattern was present was proposed. Although the evidence provided for making the change appeared to be scant, it is now recommended that tertiary grades are not used in prostate core biopsies and TURPs (unlike with the radical prostatectomy specimens).[54] The most predominant grade and the highest grade should be recorded in the Gleason score.

The 2005 ISUP guidance has resulted in a Gleason shift from Gleason score 3+3 to 3+4 in England over the decade.[10] This will have affected patient management, with fewer patients being offered active monitoring.

The ISUP consensus meeting (2005) recommended to continue using the most prevalent and second-most common grades to assign the Gleason sum score to radical prostatectomy specimens, and to mention the presence of a tertiary grade.[54] Some authors advocate that if a tertiary pattern is more than 5% then this is put as the second grade, but there is controversy in this area and ISUP did not reach agreement on this. A description as to which method used is advised.

Mucinous adenocarcinoma

The 2014 ISUP guidance recommends that the pattern should be based on its underlying growth pattern, rather than grading them all Gleason pattern 4.[58]

Intraductal carcinoma of the prostate

The 2014 ISUP guidance recommends that IDC-P without invasive carcinoma should not be assigned a Gleason grade,[58] but a comment as to its invariable association with aggressive prostate cancer should be made.

Percentage of pattern 4

ISUP[72] and GUPS[73] recommend reporting percentage pattern 4 in biopsies with Grade group 2 or 3 disease and it is now core in the ICCR dataset for tumours with a Gleason score of 7.[74] The relative percentage of pattern 4 tumour present at biopsy and resection may be of prognostic significance, although the evidence is conflicted on this.[63–67,75,76] It is worth remembering, however, that the Gleason grade is a biological continuum and is only estimated at biopsy. Therefore, indicating the percentage of pattern 4 tumour may also help clinicians understand this uncertainty, especially around the borders between

management critical grade groups. The methods of reporting percentage pattern 4 vary significantly in the literature and the reproducibility of these is uncertain, but we suggest a reasonable approach is indicating a range: <5%, 5–10%, 11–20%, 21–30%, 31–40%, 41–50%, 51–60%, 61–70%, 71–80%, 81–90% and >90%. This could be adapted to local preference.

[Level of evidence – C: Reporting IDC, cribriform and percentage of Gleason pattern 4 in biopsies.]

Prostate cancer grade group system

The 2014 ISUP guidance advised using a new grading system as previously published (Table 3).[57,58,77] This would be used in tangent with the Gleason score. The main reason is to stratify the Gleason score 7, which has been grouped in many studies but is clearly a dichotomous group. Although this was a novel system, it is easy to use and an online guide is available at https://pathology.jhu.edu/urologic/prostate-cancer-grading-system.

Table 3: Grade groups.[57,58]

Grade group	Gleason score equivalent	Description
1	≤6	Only individual discrete well-formed glands
2	3+4=7	Predominantly well-formed glands with a lesser component of poorly formed/fused/cribriform glands
3	4+3=7	Predominantly poorly formed/fused/cribriform glands with a lesser component of well-formed glands†
4	4+4	Only poorly formed/fused/cribriform glands
	3+5	Predominantly well-formed glands with a lesser component lacking glands††
	5+3	Predominantly lacking glands with a lesser component of well-formed glands††
5	9–10	Lacks gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands†

†For cases with >95% poorly formed/fused/cribriform glands or lack of glands on a core or at radical prostatectomy, the component of <5% well-formed glands is not factored into the grade.

††Poorly formed/fused/cribriform glands can be a more minor component.

Note: Tertiary grades – use only in radical prostatectomies; ignore this if less than 5% when determining the grade group.

It is not uncommon for a set of prostate biopsies to show different Gleason scores in individual cores, and it can be difficult to determine whether this variation reflects sampling from multiple tumours or intratumoural heterogeneity. The methodology of assigning Gleason scores to such cases is controversial. The previous version of this dataset recommended assigning a single 'composite' score to the whole series of biopsies, considering the series as a single specimen. However, it is common practice in other countries to assign a separate score for each biopsy and this approach was recommended by ISUP 2005.[54] The latter recognised that this approach is difficult if multiple biopsies are submitted in a single container and suggested assigning a score to each container in this scenario. A recent survey of practice in Europe showed great variation in methodology.[56]

The rationale behind ISUP 2005 recommendations is that a higher-grade tumour in a core/specimen is likely to be derived from a separate more aggressive tumour and, hence, would be most predictive of patient outcome. While appropriate in some cases, this approach risks significant over-grading in other scenarios. For example, if multiple cores show 3+4=7 and a single core contains a <1 mm focus of pure pattern 4 morphologically similar to that in other cores, it is very unlikely that this is derived from a separate 4+4 tumour. Providing information on tumour extent and grade in each core/specimen could enable the treating clinician to select the most appropriate Gleason score for patient management. However, a survey of 114 urologists and oncologists in the UK revealed that when presented with multiple Gleason scores for a set of prostate biopsies, 78% of clinicians would select the highest Gleason score in the report for patient management, even if it was in the core with the least amount of tumour.[78] Providing multiple scores in a report is also problematic for cancer registries and research databases that have to record a single score for each patient, as using the highest Gleason score may be misleading as in the example described above. If a separate Gleason score is assigned for each specimen container, the worst Gleason score may reflect biopsy submission protocol rather than tumour behaviour.

The authors believe it is too simplistic to advocate a simple ‘one-size-fits-all’ approach to prostate biopsy grading by recommending either the composite or worst score in all cases. As demonstrated in Figure 1, the composite score may be appropriate in some cases, while the worst score may be more appropriate in others.

In essence, a biopsy is a sample and an ‘estimate’ of the tumour grade that would be found in the radical prostatectomy. Both methodologies will be prone to error, however, it should be pointed out that when compared with outcome, there is data to suggest that both techniques are powerful at predicting the course of disease in large series.[79]

In most cases (including almost all cases of 3+3 and 3+4), the composite and worst scores would be the same. In the few cases where these are different, the pathologist should exercise judgment to determine which would be most appropriate for a particular case and record this as the ‘bottom line’ score. A text comment outlining the rationale of the decision would be appropriate in occasional cases. In some cases, it would be advisable to factor in tumour morphology when determining the Gleason score. If the morphology of pattern 4 in the 4+4 core is identical to that in other cores showing 3+4, it would favour all cores being derived from a single tumour. On the other hand, if the 4+4 core shows cribriform pattern 4 while other cores show only fused or poorly formed pattern 4, the 4+4 core is more likely to represent a separate, higher-grade tumour. While this approach may be subjective, subjectivity is also inherent in the diagnosis of prostate cancer and identification of Gleason grades.

The ICCR gives a choice of 2 methods of reporting prostate cores: specimen level, i.e. a Gleason score is given for each specimen, and case level where a Gleason score is given for the highest grade and a global score. We recommend that pathologists should use their judgement to determine which is the most appropriate score in an individual case and record this as the ‘bottom line’ score.

In radical prostatectomies, there is a high proportion of multifocal prostatic adenocarcinomas and there are 2 methods of grading. 1 method is to look at the totality of the different foci and assign a composite score by prevalence and mentioning the tertiary if present. This was the method used in the publications of the largest series investigating the significance of the tertiary grade.[80] The alternative method is to grade the dominant nodule, which is generally regarded as the tumour of highest stage, or of greatest size if all organ confined. Although there is no clear data to suggest which is superior, ISUP and

ICCR recommend giving the Gleason score of the dominant nodule,[54,81] an approach the authors of this dataset would recommend.

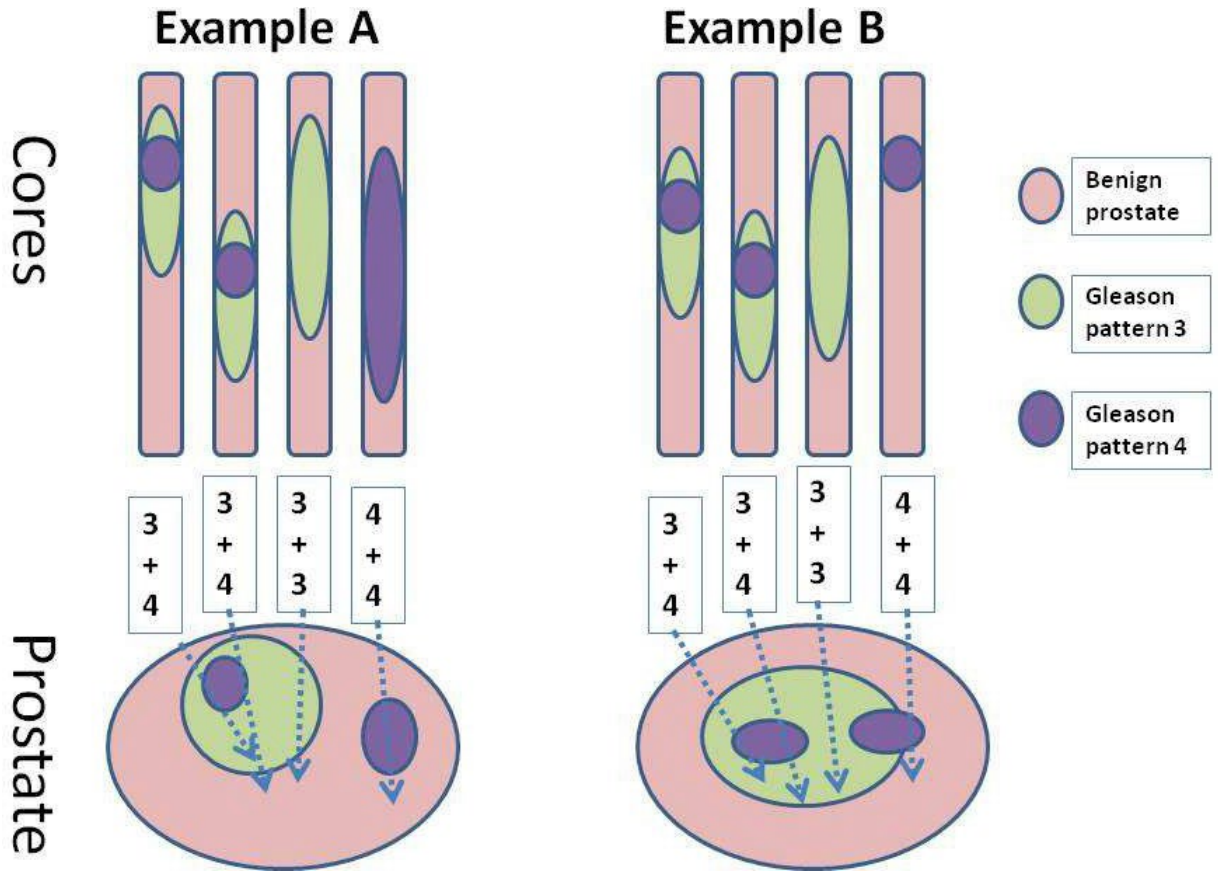

Figure 1: Grading in prostate biopsies. The worst Gleason score is most likely to be appropriate in example A and the 'composite' score appropriate in example B.

If there is a non-dominant nodule with a higher Gleason score, this should be commented on. As tertiary grades are not used in core biopsies, the following examples are specific to radical prostatectomies. The 5% cut-off used here is described by Epstein; it is not accepted by all published authors but we would advise this cut-off as the largest series to date uses this method and it is used in the WHO classification:[1, 57]

- example 1: 3+4=7 with <5% pattern 5 is called 3+4=7 with tertiary 5 (grade group 2 with minor high-grade pattern)
- example 2: 3+4=7 with >5% pattern 5 is called 3+5=8 (grade group 4)
- example 3: 4+3=7 with <5% pattern 5 is called 4+3=7 with tertiary 5 (grade group 3 with minor high-grade pattern)
- example 4: 4+3=7 with >5% pattern 5 is called 4+5=9 (grade group 5).

[Level of evidence C – Gleason score in core biopsies is of prognostic use.]

[Level of evidence C – Gleason score in radical prostatectomies is of prognostic use and the dominant nodule should be graded.]

[Level of evidence C – Grade group has been shown to add further information.]

5.3.3 Intraductal carcinoma

IDC-P is a neoplastic epithelial proliferation involving pre-existing ductal structures and characterised by architectural and cytological atypia beyond what is acceptable for HGPIN. In the vast majority of cases, it is associated with high-grade and high-stage prostate carcinoma but, in rare cases, may represent a precursor lesion,[4] or be associated with low-grade invasive carcinoma.[82] It is a significant diagnosis on core biopsy and any amount is associated with an increased risk of adverse findings, including lymph node metastases.[83]

IDC-P usually takes the form of a lumen-spanning proliferation of neoplastic cells with a dense cribriform or solid pattern of growth, often with comedonecrosis. The diagnosis of IDC-P can also be considered in cases where there is a loose cribriform or micropapillary architecture and marked cytological atypia with or without comedonecrosis. In all cases, there must be at least partial preservation of the basal layer demonstrated with immunohistochemistry.

The most significant differential diagnosis is with HGPIN as the subsequent management of these entities will be very different. The term atypical intraductal proliferation can be used for intraductal proliferations exceeding what is acceptable for HGPIN but not meeting the criteria for IDC-P.

An area of debate in the literature,[84] not settled in the 5th edition of the WHO classification of tumours, is whether IDC-P should be incorporated into the Gleason score when invasive carcinoma is present, i.e. Gleason 4 for cribriform and Gleason 5 for solid or comedonecrotic IDC-P. The recommendation of ISUP is that the grade of the IDC-P should be incorporated.[85] Conversely, GUPS recommend scoring the invasive component only, with a comment regarding the presence of IDC-P.[86]

The recommendation for this dataset is that the ISUP guidance be used, i.e. the IDC-P be incorporated into the Gleason score, as in the great majority of cases, IDC-P represents intraductal spread of high-grade prostate carcinoma.[87] If the GUPS guidance is used, this should be made clear in the report. These cases should be discussed at the MDT meeting.

[Level of evidence C – Reporting IDC-P in biopsies.]

5.3.4 Tumour extent in prostate core biopsies

Since the previous iteration of this dataset was published in 2016,[61,88] multiparametric MRI has become integral to the assessment of patients with suspected carcinoma of the prostate. The radiological identification of a suspicious lesion enables targeted biopsies to be performed; these may be submitted in isolation or with systematic biopsies. If several biopsies from a target site contain tumour, then giving a crude percentage of the number of positive cores will overestimate the extent of tumour, compared with if the tumour had been detected with systematic biopsies. It is therefore recommended that when giving a total number of positive cores that multiple positive biopsies from a targeted site be regarded as 1 positive core. This approach is taken in risk stratification assessments by both The National Comprehensive Cancer Network and Prostate Predict.[12,89,90]

The previous version[88] of this dataset included an estimate of linear tumour extent as a core data option with the recommendation that 1 of the following was included: greatest cancer length in any 1 core, greatest percentage of cancer in any 1 core or percentage of cancer in all cores. This led to a lack of consistency in the data items recorded in different laboratories. The quantification of tumour in biopsies has been widely discussed in the literature without a consensus as to which is the optimal method.[91–95] The fact that most of these studies are based on data series of systematic biopsies and subsequent radical prostatectomies makes the findings difficult to apply to biopsies taken in the current age of MRIs. Each of the 3 methods described above has its disadvantages.

Providing the longest focus of tumour is relatively straightforward and can be accomplished by marking each end of the focus with a dot and measuring between them with a ruler or using field diameters to give a measurement to the nearest millimetre. It is less straightforward when the cores are fragmented, or if there are foci of tumour separated by benign parenchyma. The limited literature on this subject suggests that discontinuous tumour foci are more likely to come from a single, irregular carcinoma than 2 smaller ones.[91] A recent paper reported that for men managed conservatively the exclusion or inclusion of stromal gaps (>2 mm) in measurements had no influence on tumour core length as a predictor of cancer death.[96]

Giving the greatest percentage of tumour in a single core may provide a misleading impression of tumour extent. For example, 70% of a 6-mm core is less than 30% of a 15-mm core. However, this method is used in some risk stratification tools.[96]

Calculating the overall percentage of cancer in all cores is the most time-consuming of the methods and, as with the total number of cores containing cancer, is likely to overestimate the actual percentage when targeted biopsies are included.

The role of prostate biopsy in predicting the size of the tumour has become less significant as this is often given in the MRI report. However, giving an estimate of extent of tumour can provide reassurance that the lesion has been biopsied. It is therefore recommended that a measurement, to the nearest millimetre, of the longest tumour focus is provided in the biopsy report. A comment should be added as to whether it is a continuous or discontinuous focus.

[Level of evidence C – Tumour extent in biopsies is prognostic.]

5.3.5 Perineural invasion in prostate core biopsies

A systematic review was undertaken to clarify the significance of perineural invasion in prostatic biopsies.[97] Perineural invasion is common in advanced disease and is not of prognostic significance. However, in clinically localised disease, the balance of evidence indicates that perineural invasion is independently significant, particularly if large or multiple nerves are involved. Active surveillance may be a less attractive option for these patients.[97]

Perineural invasion in radical prostatectomies is of less significance and is deemed a non-core item, although a recent meta-analysis looking at perineural invasion in both the core biopsies and radical prostatectomies found that it did predict biochemical recurrence.[98]

[Level of evidence B – Perineural invasion in core biopsies is important for cancer prognosis.]

5.3.6 Invasion into periprostatic tissue in core biopsies

Small groups of adipose cells are very rarely seen within the prostate,[99] therefore the presence of tumour in fat is generally indicative of EPE. Tumour within striated muscle is not deemed EPE as striated muscle merges with the prostatic stroma anteriorly and in the apex.[100] Tumour seen associated with a ganglion, which is not lying in adipose tissue, is also not EPE as intraprostatic ganglia are common. These ganglia lie within the capsule, and this would suggest that the patient is at high risk of EPE, although there are no studies examining this.

[Level of evidence C – EPE invasion in cores is important for cancer prognosis.]

5.3.7 Location of tumour and staging radical prostatectomies

The location of the dominant tumour within the prostate does not appear to be an independent prognostic variable.[101] This is a relatively easy parameter to record and will provide feedback to radiologists, as there are an increasing number of MRI staging procedures being undertaken. A standardised approach for describing the location is advised (Figure 4).

Staging using the TNM8 criteria[5] is mandatory. Subdividing the category of organ-confined tumours (pT2) does not appear to provide useful independent prognostic information and is no longer required.

It should be noted that the T1 category is limited to biopsies and transurethral material, and does not apply to radical prostatectomies, even if unsuspected prostatic carcinoma is identified in cystoprostatectomy specimens for bladder cancer.

The major decision in radical prostatectomy specimens is to distinguish between tumours limited to the prostate (organ confined, pT2) or involving extraprostatic tissues (pT3). While invasion into seminal vesicles (pT3b) is generally easier to assess, identification of EPE (pT3a), defined as tumour extending beyond the normal confines of the prostate gland,[102,103] can be problematic.

The prostatic capsule is not a well-defined structure.[104] In the lateral and posterior parts of the gland, it consists of a band of fibromuscular connective tissue that blends imperceptibly with the prostatic stroma. In other areas, such as the apex and the bladder neck, the capsule is not present so definitions of EPE have to be carefully defined. Although there are rare instances of fat within the prostate (usually only 1 or 2 adipose cells),[99] involvement of peri-prostatic fat by the tumour indicates EPE and, thus, spread beyond the gland.[105] Tumour involving large nerve bundles in the region of the neurovascular bundles, even in the absence of fat involvement is considered EPE, as long as these are outside the normal contour of the gland as intraprostatic ganglia do occur. In addition, tumour that is beyond the normal contour of the prostatic edge involving connective tissue that is typically looser than prostatic stroma is an indicator of EPE.[103] In some instances, bulging tumours are associated with desmoplastic stromal response, and generally this is an indication of EPE. This is particularly important in looking at the anterior region, where the anterior fibromuscular stroma blends into the extraprostatic connective tissue. In this location, tumour that extends beyond the confines of the normal glandular portion of the prostate is considered EPE.[106]

The assessment of EPE at the apex is controversial, with no agreement at the ISUP consensus meeting on a reliable method for determining this.[106] Because of the common presence of benign glands within skeletal muscle bundles from the urogenital diaphragm, some pathologists contend that EPE cannot be assessed at this site. Others consider the presence of tumour beyond the level of normal prostatic acini or involvement of the inked perpendicular (radial) apical margin if benign glands are not present at that site[101] as indicative of EPE. However, EPE is most commonly seen in peripheral zone tumours posterolaterally.

[Level of evidence C – Location of tumour is not of prognostic use but provides measure for auditing of biopsies and MRI.]

[Level of evidence C – Staging in radical prostatectomies is of prognostic use.]

5.3.8 Extent of EPE in radical prostatectomies

The degree of EPE can be subdivided into focal or established (non-focal or extensive).[107] In focal EPE, neoplastic glands occupy no more than 1 high-power field in no more than 2 sections, whereas established EPE represents more than this.[108] Other methods such as measuring the distance of extension from the capsule have been shown to have prognostic use,[109] but there are practical problems with measuring from the capsule, which as previously mentioned is often difficult to define. Despite the variation in methods, most studies have shown it to be prognostically significant.[107,110]

[Level of evidence C – Extent of EPE in radical prostatectomies is of prognostic use.]

5.3.9 Seminal vesicle involvement

Seminal vesicle invasion in core biopsies cannot be reliably stated, as the epithelium of the ejaculatory duct (i.e. the intraprostatic portion) resembles that of the seminal vesicle.

Seminal vesicle involvement (SVI; pT3b) is a poor prognostic factor after radical prostatectomy[42,44,111,112] and is commonly associated with EPE. There is much variation in the amount of seminal vesicle type epithelium that is within the prostate gland and invasion of the intraprostatic portion is viewed as ejaculatory duct involvement and not SVI (Figure 2). Carcinoma can invade the extra-prostatic seminal vesicles by spreading along the ejaculatory duct, by direct invasion at the base of the prostate, by extending into peri-seminal vesicle soft tissue and then into the wall of the seminal vesicle or, rarely, via discontinuous metastases.[113] The pattern of spread into the seminal vesicle has been shown to be significant, with invasion of the mucosa having a higher risk than invasion of

the muscle wall alone.[114] Intraepithelial spread into the seminal vesicles has been described but this is extremely rare and it doesn't appear to be a poor prognostic factor.[115] It should be noted that invasion of soft tissues around the seminal vesicles is still classified as EPE (pT3a) unless there is invasion into the muscular stroma of the seminal vesicle (Figure 3).[45]

[Level of evidence C – SVI in radical prostatectomies is of prognostic use.]

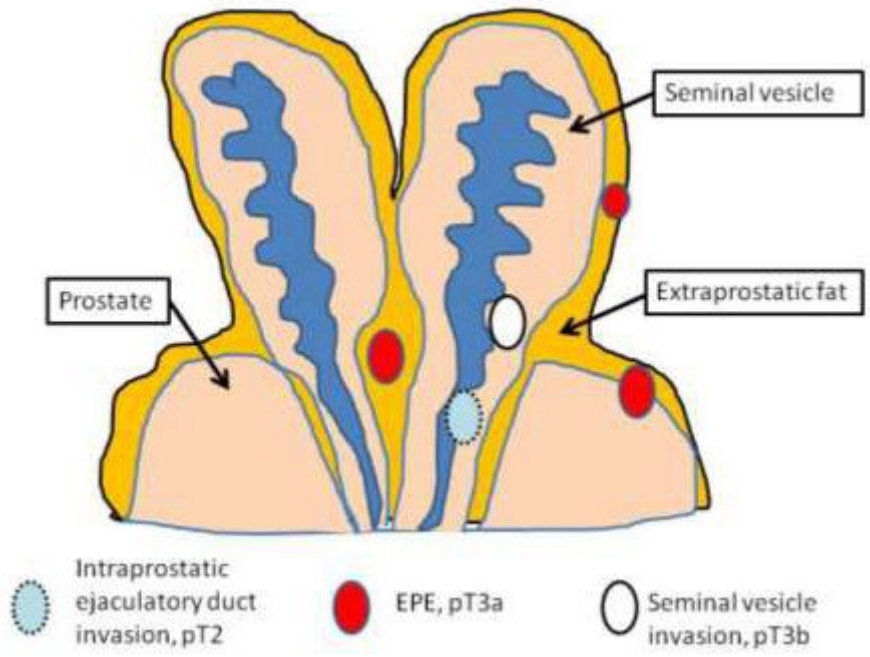

Figure 2: Definition of seminal vesicle invasion. EPE: Extraprostatic extension.

5.3.10 Bladder neck involvement

Invasion into the bladder neck (identified most readily when there is invasion of detrusor muscle) was classified as pT4 disease in the 2002 TNM system, which would indicate that prognosis is worse than for EPE (pT3a) or seminal vesicle invasion (pT3b).[116] Although 1 prospective study of 364 patients concluded that bladder neck invasion, controlling for pathological classification, margin status and Gleason score, was an independent predictor of early PSA recurrence,[117] larger, retrospective studies have not confirmed this.[118,119] Outcomes have been reported as better than those of patients with seminal vesicle invasion and similar to those of patients with EPE.[120,121] TNM7 recognised this and this is now staged as pT3a.[5,122] It can be difficult to assess what is bladder neck due to the median lobe extending into the bladder. If neoplastic glands are seen in thick muscle bundles beyond the level of benign glands, this should be considered as bladder neck invasion (Figure 3). This can be identified in TURP specimens, although this can be extremely difficult. If the tumour is seen lying in thick bundles of smooth muscle with no

associated benign glands, this should be highlighted in the report and the possibility of T3a disease raised.

[Level of evidence C – Microscopic bladder neck involvement in radical prostatectomies is staged as pT3a not pT4.]

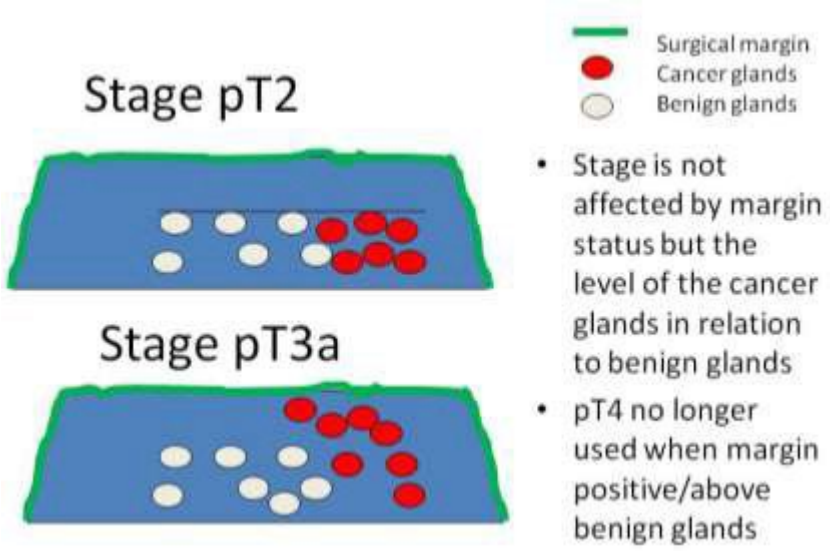

Figure 3: Bladder neck invasion. Definition of bladder neck invasion: the neoplastic glands must be above the level of benign glands and in thick muscle bundles in the sections taken from the base of the radical prostatectomy to be staged as pT3a.

5.3.11 Margin status in radical prostatectomies

Many studies have reported on the prognostic significance of involved margins.[123–131] A positive margin is identified when the tumour is in contact with an inked surface of the specimen. As the radical prostatectomy specimen is surrounded by a tiny amount of periprostatic connective tissue, the tumour has to involve the inked surface, and a closely approaching margin should be considered negative.[132]

As detailed in section 3.2, tumour at an inked margin can be difficult to interpret because of disruption of the specimen either during surgery or subsequent specimen handling. When prostatic cancer at the inked margin is intraprostatic, the designation of stage pT2+ disease has been used, indicating that the tumour is essentially organ confined elsewhere, but EPE in the region of the capsular incision cannot be assessed.[124,133] The location of positive margins is required for audit purposes, as a consistent pattern would indicate that changes to surgical technique are required (Figure 4).

There is some indication that the extent of margin positivity is important. Extensive or multifocal positive margins demonstrate a higher risk of relapse than solitary or focal positive margins.[111,112,133] There is evidence that the 5-year PSA recurrence risk appears to be significantly greater when the length of the involved margin is ≥3 mm (53% versus 14%).[134–136]

It has been suggested that extent of margin positivity is useful only in organ-confined tumours.[137] The ISUP consensus recommended giving the location and the measurement in millmetres of the involved margin, but the ICCR dataset required this as a non-core data element.[80,138] A recent study looking at robotic radical prostatectomies found that a ≥3 mm cut-off for a single positive margin was associated with an increased risk of biochemical recurrence; multiple positive margins were less predictive.[136] The updated ICCR dataset only recommends this, but as it is used in the BAUS dataset as a surgical outcome, it is a core item in this dataset. For ease, a combined margin length with a cut-off of 3 mm should be used; a more detailed breakdown of location can be included in the comments. The length should be measured in cross-section, i.e. if 1 mm in a single section and 1 mm in the next section, then combine to give 2 mm rather than assuming block thickness being 3 mm and counting as 6 mm.

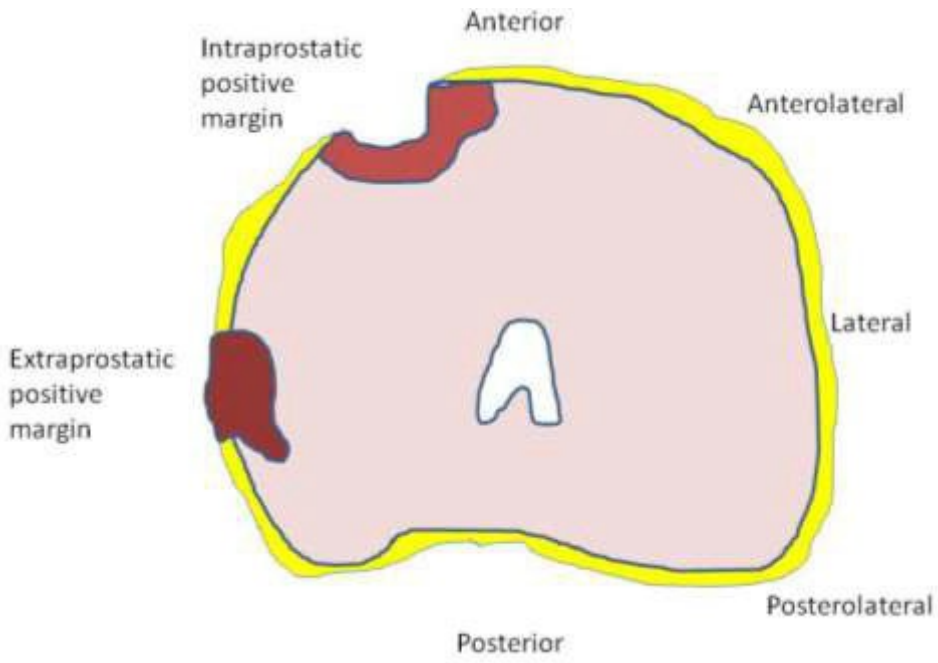

Figure 4: The location and whether intraprostatic or extraprostatic margin should be recorded.

The Gleason grade at the surgical margin has been shown to predict recurrence,[139–141] with studies finding that having a positive margin with low-grade cancer was similar to having negative margins. There is some practical difficulty in how to do this – with some using the Gleason score and others the Gleason pattern at the margin. Combining this with possible diathermy artifact makes this difficult. As a result we would recommend that this is reported but it is not a core item.

[Level of evidence C – Margin status in radical prostatectomies is of prognostic use. The use of a ≥3 mm cut-off to measure extent has been used to predict biochemical recurrence.]

5.3.12 Vascular invasion

This is extremely rare and, although it is likely to have prognostic significance, it is considered a non-core item in core biopsies.

Vascular invasion is rarely seen in radical prostatectomy specimens and is usually associated with high-volume, high-grade and high-stage tumours. However, the presence of vascular invasion has been consistently identified as an independent predictor of biochemical recurrence following radical prostatectomy and is thus considered a core item in these specimens.[63,134,142–149]

[Level of evidence B – Vascular invasion in radical prostatectomies is of prognostic use.]

5.3.13 Nodal status

Few published data exist on the pathological examination of pelvic lymphadenectomies in patients undergoing radical prostatectomy, but the number of lymph nodes obtained in a lymphadenectomy dissection varies widely. 1 study reported that a median of 16 nodes (range: 5–40) could be detected, and that the rate of cancer detection increased with the number of nodes present, suggesting that a minimum of 13 nodes was required.[53,150] Such high yields are not the norm in UK practice and the ISUP consensus conference found that <10% of respondents detected >10 lymph nodes.[45] The diameter of the largest metastasis appears to be more predictive of cancer-specific survival than the number of positive nodes alone,[102,142] whereas the presence of extranodal extension was not predictive.[151]

[Level of evidence C – Tumour volume in lymph nodes and number of lymph nodes involved at radical prostatectomies is of prognostic use.]

5.3.14 Representative block for molecular studies

With the advent of personalised cancer therapy in prostate cancer, it is essential now to comment in the report on a representative tumour block. This enables rapid selection of a block for genetic studies at a later date, without having to review the slides. Stating percentage of tumour nuclei is also essential.

6 Summary of core data items

6.1 Prostate biopsies

Clinical data:

- PSA
- MRI findings
- number and site of prostatic biopsies
- type of biopsy.

Macroscopic pathology data:

- number of cores or fragments (if not stated in clinical information)
- location.

Microscopic pathology data:

- histological type of prostate cancer
- the number of cores positive per side (right/left) or other (e.g midline, targeted) and total
- longest length of tumour in any 1 core
- Invasive cribriform or IDC
- perineural invasion, not identified/present
- Extraprostatic extension, not identified/present
- Gleason sum score
  - if only 1 grade is present, it is doubled (e.g. 3+3)
  - if 2 grades are present, both are included by order of prevalence

  - if more than 2 grades are present, the 3rd is included in the sum score if it is of higher grade – no tertiary grade
- grade group
- percentage pattern 4
- representative block for molecular studies (tumour content: 0–20%, 20–30%, 31–40%, 41–50%, 51–60%, 61–70%, 71–80%, 81–90%, 91–100%).

6.2 Core data items – TURPs

Clinical data:

- PSA
- type of specimen.

Macroscopic pathology data:

- specimen weight.

Microscopic pathology data:

- histological type of prostate cancer
- Gleason score
- grade group
- percentage Gleason pattern 4
- intraductal or invasive cribriform carcinoma
- prostatic tissue involved by tumour
- representative block for molecular studies (tumour content: 0–20%, 20–30%, 31–40%, 41–50%, 51–60%, 61–70%, 71–80%, 81–90%, 91–100%)
- TNM stage classification (requires percentage of chips with cancer for TURP specimens).

6.3 Core data items – radical prostatectomies

Clinical data:

- PSA
- type of specimen.

Macroscopic pathology data:

- specimen weight (without seminal vesicles)
- lymph nodes.

Microscopic pathology data:

- histological type of prostate cancer
- Gleason score (by dominant nodule) and the presence/absence of a higher tertiary grade
- grade group
- TNM stage classification
- absence or extent of EPE (focal or established)
- bladder neck status
- seminal vesicle invasion
- margin status and, if positive, their location and extent with cut-off at ≥3 mm (<3 mm or ≥3 mm)
- presence or absence of vascular invasion
- IDC and / or invasive cribriform carcinomarepresentative block for molecular studies (tumour content: 0–20%, 20–30%, 31–40%, 41–50%, 51–60%, 61–70%, 71–80%, 81–90%, 91–100%).

If lymphadenectomy performed:

- number of nodes present on each side
- number of positive nodes on each side
- diameter of largest tumour deposit in a positive node.

7 Non-core data items

7.1 Prostate biopsy length

Measuring the core length can be extremely onerous especially in a set of template cores. The amount of tissue received is known to relate to the cancer detection rate. We would

advise audits in this area if there is a clear difference between operators, rather than recommending measuring all cores as part of the dataset.

[Level of evidence C – Core length should only be recorded if a perceived difference in samples is noted.]

7.2 Vascular invasion in core biopsies

This is not commonly seen in localised disease. Given that the presence of vascular invasion in radical prostatectomy specimens is reported as an independent predictor of biochemical recurrence,[55–62,134,142–149,152] it is likely to be of significance in biopsies, although specific data are scant. Owing to the rarity of its occurrence and its normal association with extensive disease, we believe this should be considered as non-core in the current dataset.

[Level of evidence C – Vascular invasion is important for prognosis but is extremely rare in core biopsies.]

7.3 Co-existent pathology

Although there has been controversy about the significance of PIN in prostatic cores, there is evidence that it is a risk factor for subsequent positive cores in future biopsies. Multifocal PIN has been shown to be a stronger risk factor than a single focus and as a result the number of cores with PIN should be recorded if no tumour is present.[153–155] More important is the presence of atypical glands lacking a basal layer adjacent to a focus of PIN – so-called PINATYP – which has a higher risk of cancer detection in subsequent biopsies than PIN alone.[156]

If a tumour is detected, there is no definite significance of PIN in the cores away from this tumour and so there is no requirement to report this.

Foci suspicious for malignancy should be reported as the risk for subsequent positive cores is higher than for PIN. If tumour is present, then suspicious foci are only of any importance if there is a low tumour volume on the other side or the patient is considered suitable for active surveillance. The number of cores and their location should be recorded as this will enable further targeted cores or correlation with MRI images if available.

If no carcinoma is present, any features that should lead to consideration of re-biopsy should be reported, these include:

- PIN to include the number of cores and location

- PINATYP to include the number of cores and location
- foci suspicious for but not diagnostic of carcinoma, the number of cores and location
- intraductal cancer, to include the number of cores and location with comment regarding likelihood of aggressive tumour elsewhere but not graded.

7.4 Macroscopic incisions in prostate capsule

The presence of incisions in the prostate capsule noted macroscopically may be helpful for feedback to the surgeon as well as interpreting positive margins.

7.5 Tumour quantification and location in radical prostatectomies

Studies on the significance of tumour volume as an independent, prognostically useful factor are conflicting. Volume correlates with Gleason score, pathologic stage and margin status. Although the percentage of the radical prostatectomy specimen involved by cancer has been reported to provide predictive information in a multivariate model by some authors,[157,158] this has been disputed by others,[159–161] including a study focusing on Gleason 6 score tumours.[161] Difficulties are compounded by the fact that some centres do not process the entire specimen[51] and, given the multifocal nature of the disease, there are questions about whether all tumours or merely the index tumour should be assessed.[162,163]

The assessment of studies of tumour volume is complicated by the numerous methodologies in use. These include visual extent of tumour,[162] the percentage of carcinoma relative to the overall prostatic volume,[158] more complex grid based estimates[164] and maximum tumour diameter.[165] The ISUP consensus meeting recommended that a volume of tumour was given, but there was no agreement on the methodology.[166] Maximum tumour diameter (in any of the 3 dimensions) is an easy measurement and has shown to be useful in a specific subset of cases.[167] This measurement has also been shown to be a surrogate of tumour volume.[163,167,168] If only a small, organ-confined tumour is present, the urologist may advise the patient that they are likely to be cured of their disease.

[Level of evidence C – Tumour volume in radical prostatectomies is of uncertain prognostic use.]

7.6 Perineural invasion and high-grade PIN in radical prostatectomies

Perineural invasion is commonly observed in radical prostatectomy specimens, recorded in 90% of cases when immunocytochemistry is used to increase the detection of nerves.[169]

Studies correlating its presence with biochemical recurrence have generally found that it is not independently significant when analysed with other predictive factors such as seminal vesicle or lymphovascular invasion.[169–172] When analysis was restricted to only large diameter nerves (>0.25 mm), perineural invasion was independently predictive of worse outcome in a cohort of 640 patients after a median follow-up period of 48 months.[173] A subsequent study that included the diameter and location of the nerves involved did not confirm this, but only 105 patients were included and the median follow-up period was significantly shorter, at 26 months.[169] Further difficulties in interpreting the literature include the retrospective nature of most studies and the absence of information regarding the surgical procedure. For instance, removal of the neurovascular bundle may improve cancer control in patients with perineural invasion, but indications for a nerve-sparing procedure can vary between and within studies.

The reporting of high-grade PIN in radical prostatectomy specimens is of no clinical use.

[Level of evidence C – Reporting of perineural invasion and PIN in radical prostatectomies is of uncertain prognostic use.]

8 Diagnostic coding

The 8th edition of TNM[5] is recommended for tumour staging (see Appendix A). The main SNOMED codes relating to prostatic disease are summarised in Appendix B.

9 Reporting of frozen sections

Frozen sections were regularly performed to assess nodal status during radical prostatectomy in the 1990s, until it became clear that the false-negative rate could be as high as 33%.[174] In parallel, the refinement of predictive tables for the risk of lymph node metastasis relative to biopsy Gleason score and presenting PSA reduced the necessity for pre- or peri-operative nodal examination.[175]

The NeuroSafe technique is currently being evaluated in a trial in the UK, although it is widely employed in Europe. Multiple frozen sections of the posterolateral aspects of the radical prostate specimen are taken to evaluate tumour penetrating the capsule. If tumour is present at the margin, the neurovascular bundle can be removed. This is very labour intensive for laboratories as most prostates require at least 10 frozen sections. Until the

results of the trial are known and NICE assesses this technique for cost–effectiveness, this should be discouraged in the setting of the NHS.

[Level of evidence C – Frozen sections not routinely useful. NeuroSafe awaiting further clinical evaluation.]

10 Adjuncts to diagnosis: immunohistochemistry

Immunochemistry is an important adjunct to accurate prostatic cancer diagnosis in the differentiation of prostate cancer from another tumour, the investigation of differentiation patterns within a prostatic cancer and the examination of suspicious acini.[176]

10.1 Differentiation of prostate cancer from another tumour type

Identification of the prostatic origin of a poorly differentiated primary or metastatic carcinoma is important because prostate cancer, even in advanced stages, may respond to hormonal manipulation. Serum PSA may help to establish the prostatic origin of poorly differentiated carcinomas. However, some tumours, although expressing PSA immunohistochemically, may secrete only small amounts into the blood. Furthermore, because PSA production and mitotic activity can be mutually exclusive, high-grade tumours may not be associated with high serum PSA levels. Finally, urothelial carcinomas extending into the prostate gland are often associated with raised serum PSA.

Previously, immunohistochemistry for PSA and prostate specific acid phosphatase (PSAP) have been the definitive method for establishing the diagnosis in morphologically difficult cases, but the use of NKX3.1 is now more widespread and has slightly better sensitivity and specificity.[177] The distinction of prostate cancer from other tumours, such as urothelial carcinoma, has important therapeutic implications, therefore an immunohistochemical panel including both markers is generally recommended. GATA3 is useful to distinguish urothelial carcinomas from prostatic adenocarcinoma.[176]

10.2 Neuroendocrine differentiation in prostatic cancer

Most prostatic malignancies are adenocarcinomas. Rarely, sarcomas may arise requiring immunohistochemistry. More common is neuroendocrine differentiation. Some degree of neuroendocrine differentiation in untreated prostatic adenocarcinoma is not clinically relevant and so routine immunohistochemistry in all adenocarcinomas is not necessary.[1,178] If the tumour is morphologically a neuroendocrine carcinoma with no adenocarcinoma component, the possibility that this is from the bladder or a metastasis

should be considered. PSA and NKX3.1 are lost in neuroendocrine carcinomas, and these cannot be used to identify the origin. Fluorescence in situ hybridisation analysis of ERG has been used.[179] Tumours that express neuroendocrine markers and express NKX3.1 or PSA have been classified as amphicrine prostate cancer. This subtype is poorly understood and differs from neuroendocrine carcinomas clinically.[180] There is evidence that neuroendocrine carcinomas in the prostate arise from transformation of adenocarcinomas rather than from neuroendocrine cells themselves. This lineage plasticity leads to resistance to androgen-targeted therapy. The majority of neuroendocrine carcinomas in the prostate are as a result of treatment. When the tumour has gone through this process, the mean survival time is 12 months.[181] As a result, it is important to identify these changes in tumours. A common scenario is a channel TURP in a patient with known treated prostate cancer. Neuroendocrine carcinomas are not Gleason graded.

10.3 The examination of suspicious acini

While the absence of basal cells is an established diagnostic criterion for prostatic adenocarcinoma, identification of basal cells in H&E-stained sections is unreliable as stromal fibroblasts and flattened tumour cells may be indistinguishable from basal cells. Hence, in morphologically equivocal cases, immunostaining using basal cell markers, high-molecular-weight cytokeratin (HMWCK) and/or p63 is recommended.

Prostate adenocarcinoma, especially when high grade, may show patchy positivity for basal cell markers, particularly HMWCK, but diffuse positivity as generally seen in high-grade urothelial carcinoma, has not been reported in prostate carcinoma. By contrast, a ‘basal cell pattern’ of immunostaining is almost never seen in prostatic adenocarcinoma.[182] Aberrant expression of p63 has been shown in a subset of prostate carcinomas and this may cause confusion.[183] Although the diagnosis of prostate cancer is confirmed by negative staining for basal markers, the converse is not true as fragmented or even absent immunoreactivity is not uncommonly seen in high-grade PIN and a plethora of benign mimickers such as adenosis, partial atrophy and post-atrophic hyperplasia.

Basal cell markers should be considered as positive markers for benign prostate glands rather than negative markers for prostate cancer as prostate glands showing a basal cell pattern of immunoreactivity should almost never be interpreted as malignant. Foci consisting of an admixture of basal markers positive and negative acini should be interpreted with caution and a diagnosis of carcinoma rendered only if the negative acini are unequivocally morphologically distinct from those that show a basal cell pattern of

immunoreactivity. Immunohistochemistry must always be interpreted with close morphological correlation that is facilitated by slightly stronger haematoxylin counterstaining. Morphological correlation is also facilitated by performing immunohistochemistry on the H&E-stained level, as opposed to the intervening or deeper level. When performing immunohistochemistry on TURP specimens, it is good practice to request an H&E-stained section from the deeper immunostained level and to examine the entire immunostained section to avoid missing high-grade carcinoma in a chip that was not represented in the original H&E-stained level.

A number of prostatic basal cell markers are currently available and there is no clear evidence that any of these is superior to the others. In the UK, the most widely used basal cell marker is the HMWCK clone 34βE12, but other HMWCK antibodies such as CK5 and CK5/6 are also used. p63 is now commonly used in the UK. We recommend that pathologists use markers that work best in their laboratories but maintain careful quality assurance by routinely evaluating the immunostaining in background benign glands in the biopsies. If these show weak basal cell staining, the staining technique should be scrutinised and use of a different marker considered.

In contrast to basal cell markers, alpha methylacyl coenzyme A racemase (AMACR) is overexpressed in prostate cancer compared with benign prostate and is widely used to help establish a diagnosis of prostate carcinoma in morphologically equivocal cases.[184,185] Since benign glands do express AMACR, albeit at a lower level, sensitivity of immunostaining has to be carefully adjusted so that staining is not seen in benign glands. AMACR immmunoreactivity is often heterogeneous with weaker staining in pseudohyperplastic and foamy gland variants of prostate cancer, so AMACR negativity does not exclude carcinoma. AMACR should be used with caution as it is generally strongly positive in high-grade PIN and nephrogenic adenoma as well as in a smaller but significant proportion of adenosis. Several benign mimickers of carcinoma also express AMACR, although generally more weakly.

ERG antibody detects truncated ERG resulting from TMPRSS2-ERG fusion, which appears to be specific for prostate carcinoma. However, it is expressed by only 40–50% of prostate cancers and is often expressed by PIN. Some authors have used the expression of ERG as a discriminator between small cell carcinomas of the prostate and the bladder – with 40% of prostate-derived small cell carcinomas being positive, as opposed to bladder small cell being negative.[179] Endothelial cells express ERG and can be used as an internal control. The clinical utility of ERG immunohistochemistry remains to be established.

Routine immunostaining of prostate biopsies is not recommended. While this practice could reduce the risk of missing cancers, it is expensive and would have a significant impact on the laboratory and the pathologist's workload. There is also the risk of over-interpreting benign glands immunonegative for basal markers as suspicious or even malignant. Instead, a low threshold for performing immunohistochemistry in morphologically suspect glands is favoured.

The number and choice of markers should depend on the morphological differential diagnosis, the degree of uncertainty and the clinical relevance. AMACR has little diagnostic utility if the morphological differential diagnosis includes PIN or nephrogenic adenoma. Glands of nephrogenic adenoma are also often basal markers negative, but are also prostatic markers (PSA, PSAP) negative, while PAX2 and PAX8 are positive. In morphologically difficult cases in which the diagnosis of prostate carcinoma is established by basal marker immunonegativity, use of an immunopanel composed of an HMWCK antibody (34βE12, CK5 or CK5/6) is recommended as benign glands may not express either HMWCK or p63. Absence of immunoreactivity with 2 markers, preferably on separate sections, would reduce the risk of false-negative immunostaining. However, a single marker may be sufficient to confirm the benign nature of an atypical lesion that is favoured to be benign on morphology. The rare p63-positive prostate cancer is a potential pitfall if p63 is used as sole basal cell marker to distinguish atrophy from atrophic prostate carcinoma.[186] Use of 34βE12, CK5 and CK5/6 in combination is not recommended as all these HMWCK markers stain CK5.

Use of antibody cocktails would be more economical and particularly useful in the work-up of minute lesions that may not be represented in serial sections or deeper levels. The main drawback, however, of using ready-made commercially available antibody cocktails is that the individual antibody concentrations cannot be adjusted to compensate for variations in in-house tissue processing and immunostaining methodology. If a single colour detection system is used, AMACR may mask focal basal cell marker positivity and the granular cytoplasmic immunostaining sometimes seen with p63 may mimic AMACR positivity. On the other hand, a dual-colour detection system provides an easy method of assessing difficult foci.

Immunohistochemistry should always be interpreted in the context of morphology. The diagnosis of prostate cancer must be based on morphology supported, if necessary, by immunohistochemical examination.

Less commonly immunohistochemistry is used to confirm the diagnosis of Gleason pattern 5 prostate carcinoma, where the main differential diagnosis is a histiocytic proliferation. In this scenario, use of cytokeratins such as AE1/AE3 and Cam 5.2 and histiocytic markers such as CD68 is recommended. Prostatic markers (PSA and PSAP) should be used with caution as these may not be expressed by high-grade prostate carcinoma.[138]

11 Criteria for audit

The following are recommended by the RCPath as key assurance indicators (see Key assurance indicators for pathology services, November 2019) and key performance indicators (see Key performance indicators – proposals for implementation, July 2013):

- cancer resections should be reported using a template or proforma, including items listed in the English COSD, which are, by definition, core data items in RCPath cancer datasets. English trusts were required to implement the structured recording of core pathology data in the COSD.
  - standard: 95% of reports must contain structured data
- histopathology cases must be reported, confirmed and authorised within 7 and 10 calendar days of the procedure
  - standard: 80% of cases must be reported within 7 calendar days and 90% within 10 calendar days.

Audits of the availability of pathology reports and data at MDT meetings (national cancer standards) are as follows:

- standard: 90% of cases discussed at MDT meetings where biopsies or resections have been taken should have pathology reports/core data available for discussion at the time of the meeting
- standard: 90% of cases where pathology has been reviewed for the MDT meeting should have the process of review recorded.

The following criteria may be assessed in periodic reviews of histological reports on prostate core biopsies and radical prostatectomies:

- surgical margin status of radical prostatectomy specimens
- correlation of prostate biopsies and MRI findings

- correlation of target cores versus systematic cores in detection of significant prostate cancer
- correlation of presence of invasive cribriform/IDC in cores versus radical prostatectomies.

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Appendix A TNM (8th edition, UICC)[5]

The major change in the 8th edition compared with the 7th edition is the removal of the substaging of pT2.

T – Primary tumour

Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
*T1	Clinically inapparent tumour not palpable or visible by imaging
*T1a	Tumour incidental histological finding in 5% or less of tissue resected
*T1b	Tumour incidental histological finding in more than 5% of tissue resected
*T1c	Tumour identified by needle biopsy (e.g. because of elevated PSA)
T2	Tumour confined within prostate
T3	Tumour extends through the prostate capsule
T3a	Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles external sphincter, rectum, levator muscles, or pelvic wall

Notes

1. Tumour found in 1 or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.
2. Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.
3. *The pT and pN categories correspond to the T and N categories. However, there is no pT1 category because there is insufficient tissue to assess the highest pT category.

N – Regional lymph nodes

Nx Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

M – Distant metastasis

M0 No distant metastasis

M1 Distant metastasis

M1a Non-regional lymph node(s)

M1b Bone(s)

M1c Other site(s)

Stage grouping

Stage I	T1, T2a	N0	M0
Stage II	T2b, T2c	N0	M0
Stage III	T3	N0	M0
Stage IV	T4	N0	M0
	Any T	N1	M0
	Any T	Any N	M1

Appendix B SNOMED codes

Topographical codes (T) and morphological codes (M)

Topographical codes are used in SNOMED 2 and SNOMED 3 to indicate the site of lesions and morphological codes (M) are used to indicate the morphological diagnosis. Common topography and morphology codes are given in Table 3 below, although the list is not exhaustive.

SNOMED versions

Different versions of SNOMED are in use and are compared in Table 3 below. For the sites and disease entities applicable to the current dataset, the older coding systems known as SNOMED 2 and SNOMED 3 (including version 3.5, its most recent update released in 1998) use slightly different codes (shown in the 2 left-hand columns of the table). SNOMED CT, also known as SNOMED International, is the newer SNOMED system. This was first introduced in 2002 with multiple updates (shown in the 2 right-hand columns) and uses different codes from SNOMED 2 and SNOMED 3 (numerical code only is used for SNOMED CT, rather than T and M codes followed by a number).

Table 3: A comparison of SNOMED 2 or 3 with SNOMED CT codes.

Topographical codes	**SNOMED 2**	**SNOMED 3**	**SNOMED CT terminology**	**SNOMED CT code**
Prostate	T-77100	T-92000	Prostatic structure (body structure)	41216001
Lymph node		T-C4600	Pelvic lymph node structure (body structure)	54268001

Morphological codes	**SNOMED 2 or 3**	**SNOMED CT terminology**	**SNOMED CT code**
Normal tissue	M-00100	Normal tissue (finding)	30389008
High-grade prostatic intraepithelial neoplasia (PIN)	M-74003	High-grade prostatic intraepithelial neoplasia (disorder)	446711009

Suspicious for malignancy	M-67060	Atypia suspicious for malignancy (morphologic abnormality)	44085002
Adenocarcinoma	M-81403	Adenocarcinoma, no subtype (morphologic abnormality)	35917007
Small cell carcinoma	M-80413	Small cell carcinoma of prostate (disorder)	396198006
Prostatic ductal carcinoma	M-85003	Infiltrating duct carcinoma (morphologic abnormality)	82711006
Adenosquamous carcinoma	M-85603	Adenosquamous carcinoma (morphologic abnormality)	59367005
Sarcomatoid adenocarcinoma	M-85723	Adenocarcinoma with spindle cell metaplasia (morphologic abnormality)	68358000
Undifferentiated carcinoma	M-80203	Carcinoma, undifferentiated (morphologic abnormality)	38549000

Procedure codes (P)

These are used in SNOMED 2 and SNOMED 3 to distinguish biopsies, partial resections and radical resections to indicate the nature of the procedure.

Local P codes should be recorded. At present, P codes vary according to the SNOMED system in use in different institutions.

Appendix C Transperineal clinical request form

Clinical information		Name:	
PSA:		D.O.B	
DRE:		Hospital number	
Clinical stage:			
Volume:			
MRI findings: PIRADS LIKERT			
Other details:			
Operator performing biopsy: *PRINT NAME*			
SPECIMEN TYPE – TRANSPERINEAL PROSTATE BIOPSY			

		Location	Number of cores taken		
1	A	Right anterior			
2	B	Right mid			
3	C	Right posterior			
4	D	Left anterior			
5	E	Left mid			
6	F	Left posterior			
7	I	Targeted Site (Please specify):			
8	J				

Appendix D Reporting proforma for prostatic biopsies in list format

Element name	Values	Implementation comments	COSD
Pre-biopsy PSA	Numerical value in ng/nml		
Pre-biopsy PSA availability	Single selection value list: • Not available • Not applicable	Not applicable if a value is given for 'Pre-biopsy PSA'	
Pre-biopsy MRI	Free text		
Type of specimen	Multiple selection value list: • TRUS biopsy • Transperineal • Targeted • Other		
Type of specimen, other (specify)	Free text	Only applicable if 'Type of specimen – Other' selected	
Systematic Right side, location [n]	Free text	Repeating data item n value increases as required	
Systematic Right side, number taken [n]	Integer		
Systematic Right side, number received [n]	Integer		

Element name	Values	Implementation comments	COSD
Systematic Left side, location [n]	Free text	Repeating data item n value increases as required	
Systematic Left side, number taken [n]	Integer		
Systematic Left side, number received [n]	Integer		
Target, location [n]	Free text	Repeating data item n value increases as required	
Target, number taken [n]	Integer		
Target, number received [n]	Integer		
Histological tumour type	Multiple selection value list: • Acinar adenocarcinoma • Prostatic ductal adenocarcinoma • Small cell neuroendocrine carcinoma • Other		
Histological tumour type, Other specify	Free text	Only applicable if 'Histological tumour type – Other' selected	
Total number of right cores	Integer	May be calculated from Right side, number received [n]	

Element name	Values	Implementation comments	COSD
Number of right cores involved	Integer	Only applicable if total number of cores >0	
Location of involved right cores	Free text		
Total number of left cores	Integer	May be calculated from Left side, number received [n]	
Number of left cores involved	Integer	Only applicable if total number of cores >0	
Location of involved left cores	Free text		
Total number of other cores	Integer	May be calculated from Other, number received [n]	
Number of other cores involved	Integer	Only applicable if total number of cores >0	
Location of involved other cores	Free text		
Total number of systematic cores	Integer	May be calculated from sum of ‘Total number of left cores’, ‘Total number of right cores’	

Element name	Values	Implementation comments	COSD
Total number of systematic cores involved	Integer	May be calculated from sum of 'Total number of left cores involved', 'Total number of right cores involved'	
Total number of targeted cores	Integer	May be calculated from sum of targeted cores	
Total number of targeted cores involved	Integer	May be calculated from sum of 'Total number of targeted involved'	
Longest length of cancer in 1 core	Distance in mm		
Location of longest length of cancer in 1 core	Free text		
Perineural invasion	Single selection value list: • Not identified • Present		pUR15240 Not identified = N Present = Y
Extraprostatic extension	Single selection value list: • Not identified • Present		
Gleason score, applicable	Single selection value list: • Applicable • Not applicable		

Element name	Values	Implementation comments	COSD
Gleason score, primary Gleason grade	Single selection value list: • 3 • 4 • 5 • Not applicable		pUR15210
Gleason score, secondary Gleason grade	Single selection value list: • 3 • 4 • 5 • Not applicable		pUR15220
Gleason score, total	Single selection value list • 6 • 7 • 8 • 9 • 10 • Not applicable		
Grade group	Single selection value list: • 1 • 2 • 3 • 4 • 5 • Not applicable		

Element name	Values	Implementation comments	COSD
Percentage Gleason pattern 4	Single selection value list: • <5% • 5–<10% • 10–<20% • 20–<30% • 30–<40% • 40–<50% • 50–<60% • 60–<70% • 70–<80% • 80–<90% • 90–100% • Not applicable		
Invasive cribriform and/or intraductal carcinoma	Single selection value list: • Not present • Present		
Representative block for molecular studies	Free text Single selection value list: • 0–20% • 20–30% • 31–40% • 41–50% • 51–60% • 61–70% • 71–80% • 91–100% • Not applicable		

Element name	Values	Implementation comments	COSD
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables		pCR6410
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables		pCR6420

Appendix E Reporting proforma for transurethral resections or enucleations of the prostate in list format

Element name	Values	Implementation comments	COSD
Pre-biopsy PSA	Numerical value in ng/nml		
Pre-biopsy PSA availability	Single selection value list: • Not available • Not applicable	Not applicable if a value is given for 'Pre-biopsy PSA'	
Type of specimen	Single selection value list: • TURP • Enucleation		
Histological tumour type	Multiple selection value list: • Acinar adenocarcinoma • Prostatic ductal adenocarcinoma • Small cell neuroendocrine carcinoma • Other		
Histological tumour type, other specify	Free text	Only applicable if 'Histological tumour type – Other' is selected.	
Percentage of prostate tissue involved based on area	Numerical value (0–100)		

Element name	Values	Implementation comments	COSD
Percentage of prostate tissue involved based on area, availability	Single selection value list: • Not used • Not applicable	Not applicable if 'Percentage of prostate tissue involved based on area' is completed	
Percentage of prostate tissue involved based on number of chips	Numerical value (0–100)		
Percentage of prostate tissue involved based on number of chips, availability	Single selection value list: • Not used • Not applicable	Not applicable if 'Percentage of prostate tissue involved based on number of chips' is completed	
Gleason score, applicable	Single selection value list: • Applicable • Not applicable		
Primary Gleason grade	Single selection value list: • 2 • 3 • 4 • 5 • Not applicable		pUR15210

Element name	Values	Implementation comments	COSD
Secondary Gleason grade	Single selection value list: • 2 • 3 • 4 • 5 • Not applicable		pUR15220
Gleason score, total	Single selection value list • 4 • 5 • 6 • 7 • 8 • 9 • 10 • Not applicable		
Grade group	Single selection value list: • 1 • 2 • 3 • 4 • 5 • Not applicable		

Element name	Values	Implementation comments	COSD
Percentage Gleason pattern 4	Single selection value list: • <5% • 5–<10% • 10–<20% • 20–<30% • 30–<40% • 40–<50% • 50–<60% • 60–<70% • 70–<80% • 80–<90% • 90–100% • Not applicable		
Invasive cribriform and/or intraductal carcinoma	Single selection value list: • Not present • Present		
Representative block for molecular studies	Free text Single selection value list: • 0–20% • 20–30% • 31–40% • 41–50% • 51–60% • 61–70% • 71–80% • 91–100% • Not applicable		

Element name	Values	Implementation comments	COSD
T category	Single selection value list: • T1a • T1b • T3a		pCR0910
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables		pCR6410
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables		pCR6420

Appendix F Reporting proforma for radical prostatectomies in list format

Element name	Values	Implementation comments	COSD
Pre-biopsy PSA	Numerical value in ng/nml		
Pre-biopsy PSA availability	Single selection value list: • Not available • Not applicable	Not applicable if a value is given for 'Pre-biopsy PSA'	
Specimen weight	Weight in g		
Seminal vesicles	Single selection value list: • Present • Absent		
Seminal vesicle, laterality	Single selection value list: • Left • Right • Bilateral • Not applicable	Not applicable if 'Seminal vesicles – absent' is selected	
Lymph nodes	Single selection value list: • Present • Absent		
Lymph nodes, laterality	Single selection value list: • Left • Right • Pre-prostatic • Not applicable	Not applicable if 'Lymph nodes – absent' is selected	

Element name	Values	Implementation comments	COSD
Histological tumour type	Multiple selection value list: • Acinar adenocarcinoma • Prostatic ductal adenocarcinoma • Small cell neuroendocrine carcinoma • No tumour • Other		
Histological tumour type, other specify	Free text	Only applicable if 'Histological tumour type – Other' selected	
Gleason score, applicable	Single selection value list: • Applicable • Not applicable		
Primary Gleason grade	Single selection value list: • 2 • 3 • 4 • 5 • Not applicable		pUR15210
Secondary Gleason grade	Single selection value list: • 2 • 3 • 4 • 5 • Not applicable		pUR15220

Element name	Values	Implementation comments	COSD
Tertiary Gleason grade	Single selection value list: • 3 • 4 • 5 • Not applicable		pUR15230
Gleason score, total	Single selection value list • 4 • 5 • 6 • 7 • 8 • 9 • 10 • Not applicable		
Grade group	Single selection value list: • 1 • 2 • 3 • 4 • 5 • Not applicable		
Location of dominant tumour	Free text		
Extraprostatic extension	Single selection value list: • Not identified • Present • Indeterminate		

Element name	Values	Implementation comments	COSD
Location of extraprostatic extension	Free text	Not applicable if not identified	
Extent of extraprostatic extension	Single selection value list: • Focal • Established • Not applicable	Not applicable if 'Extraprostatic extension' is 'Not identified'	
Bladder neck involvement	Single selection value list: • Involved • Not involved • Not applicable		
Seminal vesicle involvement	Single selection value list: • Involved • Not involved • Not applicable		
Margin status	Single selection value list: • Involved • Not involved • Indeterminate		pCR0880 Involved = 05 Not involved = 01 Indeterminate = 06
Margin extent	Single selection value list: • <3 mm • ≥3 mm • Not applicable	Not applicable if 'Margin status' is 'Not applicable'	

Element name	Values	Implementation comments	COSD
Margin location	Multiple selection value list: • Apical • Bladder neck • Circumferential • Not applicable	Not applicable if 'Margin status' is 'Not applicable'	
Circumferential margin, type	Multiple selection value list: • Intraprostatic • Extraprostatic • Not applicable	Not applicable if 'Margin location – Circumferential' is not selected	
Circumferential margin, location	Free text		
Lymphovascular invasion	Single selection value list: • Not identified • Present		pCR0870 Not identified = NU Present = YU
Invasive cribriform and/or intraductal carcinoma	Single selection value list: • Not Present • Present		

Element name	Values	Implementation comments	COSD
Representative block for molecular studies	Free text Not applicable Single selection value list: • 0–20% • 20–30% • 31–40% • 41–50% • 51–60% • 61–70% • 71–80% • 91–100%		
Number of lymph nodes examined	Integer		
Number of positive lymph nodes	Integer		
Maximum dimension of largest deposit	Size in mm		
T category	Single selection value list: • pT0 • pT2 • pT3a • pT3b • pT4	pCR0910	
N category	Single selection value list: • pNx • pN0 • pN1	pCR0920	

Element name	Values	Implementation comments	COSD
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables	pCR6410	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables	pCR6420	

Appendix G Summary table – Explanation of levels of evidence

(modified from Palmer K *et al. BMJ* 2008;337:1832)

Level of evidence	Nature of evidence
Level A	At least 1 high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target cancer type or A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target cancer type.
Level B	A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in A.
Level C	A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high-quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in B.
Level D	Non-analytic studies such as case reports, case series or expert opinion or

	Extrapolation evidence from studies described in C.
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group.

Appendix H AGREE II guideline monitoring sheet

The cancer datasets of the Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of this dataset that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	Introduction
2 The health question(s) covered by the guideline is (are) specifically described	Introduction
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	Foreword
6 The target users of the guideline are clearly defined	Introduction
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Foreword
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword and Introduction

12 There is an explicit link between the recommendations and the supporting evidence	All sections
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	2–10
16 The different options for management of the condition or health issue are clearly presented	2–10
17 Key recommendations are easily identifiable	2–10
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	Appendices
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	11
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interest of guideline development group members have been recorded and addressed	Foreword