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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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 grade and stage cancers in an accurate, consistent manner in compliance with international standards and provide prognostic information, thereby allowing clinicians to provide a high standard of care for patients and appropriate management for specific clinical circumstances. It may rarely be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. The clinical risk of departing from the guidelines should be assessed by the relevant multidisciplinary team (MDT); just as adherence to the guidelines may not constitute defence against a claim of negligence, so deviation from them should not necessarily be deemed negligent.

Each dataset contains core data items 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 90% 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 stakeholder organisations have been consulted during the preparation of the dataset:

- British Association of Urological Surgeons (BAUS)/BAUS Section of Oncology
- British Uro-oncology Group
- National Cancer Research Institute (NCRI) Prostate Cancer Clinical Studies Group
- British Association of Urological Pathologists (BAUP)
- UK and Ireland Association of Cancer Registries (UKIACR)
- National Cancer Intelligence Network (NCIN) Urology Clinical Reference Group.

Supporting evidence and recommendations in this dataset are based on:

- PubMed literature searches (up to September 2015)
- WHO classifications, 2016[1]
- NICE *Improving Outcomes Guidance*, 2002[2]
- NICE *Prostate cancer diagnosis and treatment* CG157[3]
- ICCR prostate dataset[4]
- TNM 7th *edition staging classification*, 2009.[5]

Most of the supporting evidence is level C or D at least or meets the GPP (good practice point) criteria (see explanation of levels of evidence in Appendix I). 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 have been identified that would hinder the implementation of the dataset and there are no new major financial or work implications arising from the implementation, compared to the 2009 dataset.

A formal revision cycle for all cancer datasets takes place on a three-yearly basis. However, each year, the College will ask the authors of the dataset, in conjunction with the relevant sub-specialty adviser to the College, to consider whether or not 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 two weeks for Fellows' attention. If Fellows do not object to the changes, the short notice of change will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

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 Director of the Professional Standards Unit 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* (www.nice.org.uk), recommended the establishment of specialist multidisciplinary teams for radical pelvic surgery (prostatectomies and cystectomies) serving a catchment population of one million. It was estimated that such a population would produce well in excess of the 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 the most recent 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 (EQA) Scheme (www.histopathologyeqa.org).

The diagnosis of prostate cancer is generally made on transrectal ultrasound (TRUS) guided prostatic biopsies, but there has been a steady rise in the numbers of template perineal biopsies (Figure 1). Biopsy procedures have varied widely, both in terms of needle placement and numbers of cores taken, leading in 2006 to the publication of national guidance in an effort to standardise practice, but this did not cover template biopsies.[6] Recent publications suggest only 24 cores are required for template biopsies,[7] whilst others suggest a larger number.[8]

The role of multiparametric MRI in the diagnosis of prostate cancer is becoming established in the UK.[9] In the update of the NICE guidance on diagnosis and treatment of prostate cancer,[3] there was a recommendation of its use following a set of negative core biopsies. If the MRI was negative and the man had no other risk factors such as abnormal DRE, previous high-grade prostatic intraepithelial neoplasia (PIN) or focus suspicious for malignancy, a repeat biopsy was not necessary. It is unclear whether this will be implemented, but the use of MRI will undoubtedly lead to an increase in template biopsies as anterior tumours are often missed with TRUS biopsies but may be detected on the MRI. There has already been a significant increase in the numbers of template biopsies in England and Wales over the last five years, with the numbers trebling (Figure 1). National guidance on the best technique and numbers of cores is not available, partly due to the upcoming results of various trials including the PROMIS study.[10]

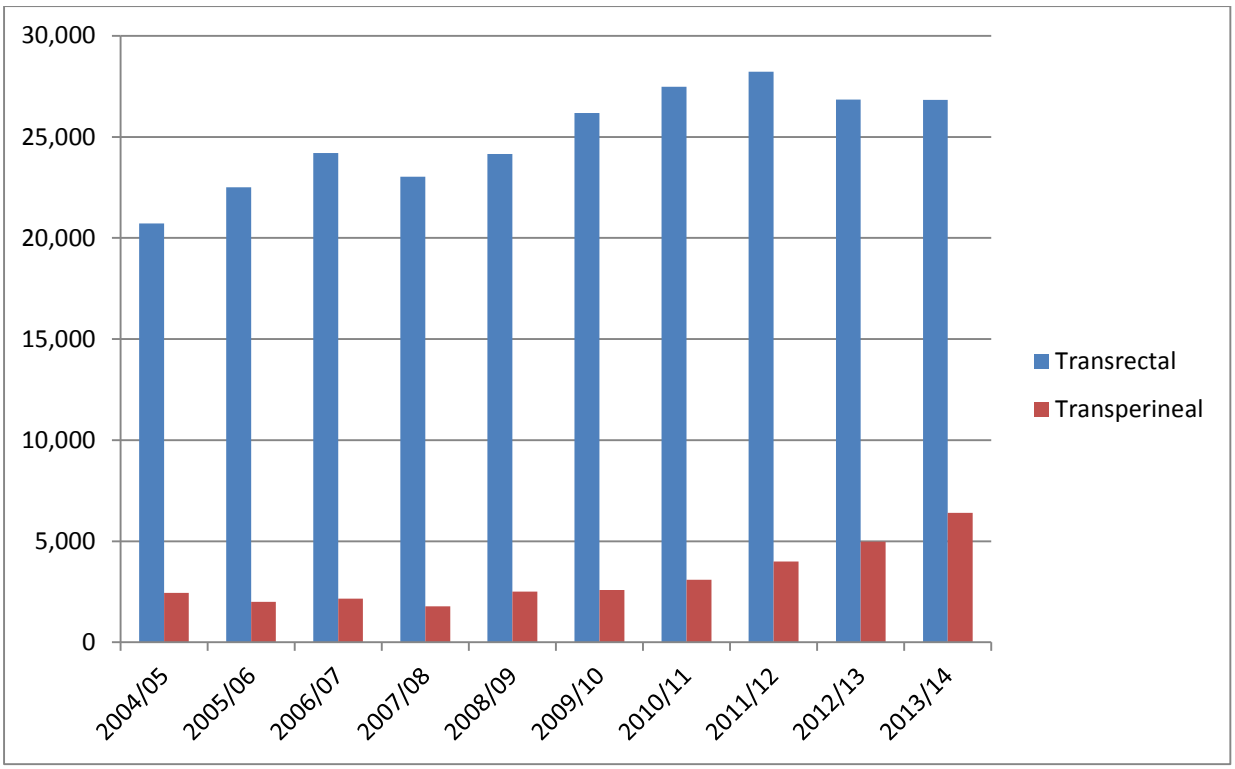

Figure 1: Number of inpatient and day-case SPELLs in England that mention either a transrectal prostate biopsy (M703) or a transperineal prostate biopsy (M702), by year of admission (1 April 2004 to 31 March 2014 (Source: *HSCIC Hospital Episode Statistics*, analysis performed by Public Health England (South West Knowledge and Intelligence Team)

The NICE guidance used D'Amico classification of risk in prostate cancer (Table 1).[11] Although this system has drawbacks – not least with the continued drift of Gleason score – it is regularly utilised by urologists.[12] Also it does not differentiate between Gleason 3+4=7 and 4+3=7. 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 in order to validate these for future datasets.

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

Level of risk	**PSA**		**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

2 Clinical information required on the specimen request form

This includes the presenting prostate specific antigen (PSA), the clinical context and the type of specimen, whether 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 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 two years after external beam radiation and for up to six years for brachytherapy.[17] It has been shown that two-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] Getting 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
- 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 Denonvillier’s 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 of 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 an adequate volume of formalin. 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 one 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 majority of biopsies are taken with the 18-gauge biopsy gun under transrectal ultrasound 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.[6] Optimising pre-embedding and embedding techniques can reduce the number of levels required and the rate of equivocal diagnoses.[24]

The cores are thinner than biopsies of breast, for instance, and have a tendency to curve and/or fragment. Care must be taken whilst straightening them for processing and embedding. Separation and flattening to subsequently optimise embedding of the cores is 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 two inserts, such as foam pads or nylon meshes,[24] 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, though some advocate multi-core embedding,[25] it is advised that embedding more than three cores in a single cassette can make assessment of numbers of cores involved by tumour very difficult and should be avoided.[26,27] If more than three cores are submitted per cassette, the quality of embedding and sectioning must be carefully monitored to avoid tissue loss.

Flat embedding is essential to optimise sectioning and representation of the full length of the core. At least three levels are taken: one from the top half, middle and lower portion of each core. Examining less than three levels may miss significant clinical findings, whether the diagnosis of cancer itself or prognostic features such as grade or perineural invasion.[28] In practice, the greatest problem is cutting too deep into the core for the first level and discarding

valuable tissue. Introducing a relatively superficial first section, with three subsequent levels, into the sectioning protocols can circumvent this problem.

Small foci suspicious for carcinoma may only be present at specific levels. Retaining spare sections from each level allows the use of immunocytochemistry 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.[29]

In addition to the costs of processing and sectioning additional blocks and workload implications, the value of retaining sections for immunocytochemistry makes embedding each core individually impractical in many laboratories. The disadvantages of combining multiple cores in one block are greatly 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.[26] 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.[26] 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.[28] There is no accepted definition for an adequate core length but this can be critical in measuring the amount of tumour in a core.[30] Poor quality cores (e.g. extraprostatic tissue only) should be recorded to allow audit of operator technique.

4.2 Transurethral resection of the prostate (TURP)

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, including the authors, assess the percentage 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.[31] '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 four years,[32] whereas disease progression is slower for patients with T1a disease, with up to 16% progressing at eight years.[32–34] More recent studies have shown that by giving the percentage of chips involved gives more information.[31] Ideally sampling protocols should identify all T1b patients and T1a patients with a life expectancy of eight years or more. A common protocol is to embed the entire specimen up to 12 g (six blocks) and a further 2 g (one 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 six blocks.[35] Examination of the entire specimen is justifiable for the small subset of patients who may benefit from radical treatment on the basis of 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.[36]

'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.

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 three dimensions. The International Society of Urological Pathologists (ISUP) consensus meeting recommended weighing the prostate after the seminal vesicles have been removed.[37]

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 has to 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 tumour is close to, but not necessarily at, the inked resection margin.[37]

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 guide 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. Also, 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.[38]

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.[37] 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.[39]

Protocols based on series of fewer than 100 patients have detailed sampling strategies to detect the majority of prostatic tumours[40] and identify adverse pathological factors.[41] 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[38]
- in a large study of 1383 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[42]
- 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,[37] whereas a European Network of Uropathology (ENUP) survey of uropathologists showed that 71% completely embedded these specimens.[43] 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.[37,43] 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 three 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 one 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.[44] 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.[45]

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 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.

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

5.3 Microscopic data items

5.3.1 Histological tumour type

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

5.3.2 Histological grading

Gleason grading of prostatic biopsies remains one of the most important factors in deciding further therapy. However, Gleason grading has undergone considerable revision since its initial conception. ISUP has produced two guidance documents.[46] The 2005 guidance on scoring is now utilised by nearly all pathologists in the UK.[47,48] The 2005 guidance changed two main areas: one 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 adenocarciomas and intraductal carcinoma, as well as advising the use of a new grading system.[49,50]

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 a number of independent papers suggesting that any form of cribriforming architecture confers a poor prognosis.[48,51–53] 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.[54]

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 (which is at odds with the radical prostatectomy specimens). 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.[12] 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.[46] 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 pattern 4.[50]

Intraductal carcinoma (IDC) of the prostate: The 2014 ISUP guidance recommends that intra-ductal carcinoma of the prostate without invasive carcinoma should not be assigned a Gleason grade,[50] but a comment as to its invariable association with aggressive prostate cancer should be made.

Percentage of pattern 4: The grouping of Gleason score 3+4 and 4+3 in many large cohort studies has meant that there is a need to separate this further, because at the lower end of the spectrum active monitoring could be offered but at the upper end this may not be appropriate. A cut off of 10% pattern 4 has been recommended by a recent Canadian guideline on active

surveillance.[55] The evidence of reproducibility of such a system is unclear and at this point in time this should be a non-core item.

New prostate cancer grading system: The 2014 ISUP guidance advised using a new grading system as previously published (Table 2).[49,50,56] 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 is a novel system, it is easy to use and an online guide is available at http://pathology.jhu.edu/ProstateCancer/NewGradingSystem.cfm.

Table 2: Grade Groups[49,50]

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 (RP), 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 intratumoral 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.[46] 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.[47]

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 recent survey of 114 urologists and oncologists in the UK conducted by the authors 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 (unpublished observations). 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 2, 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.[57]

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, then 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, then 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.

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 the radical prostatectomies there is a high proportion of multifocal prostatic adenocarcinomas and there are two methods of grading. One 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.[58] 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 International Collaboration on Cancer Reporting (ICCR) recommend giving the Gleason score of the dominant nodule.[46,59] We recommend giving the score of the dominant nodule.

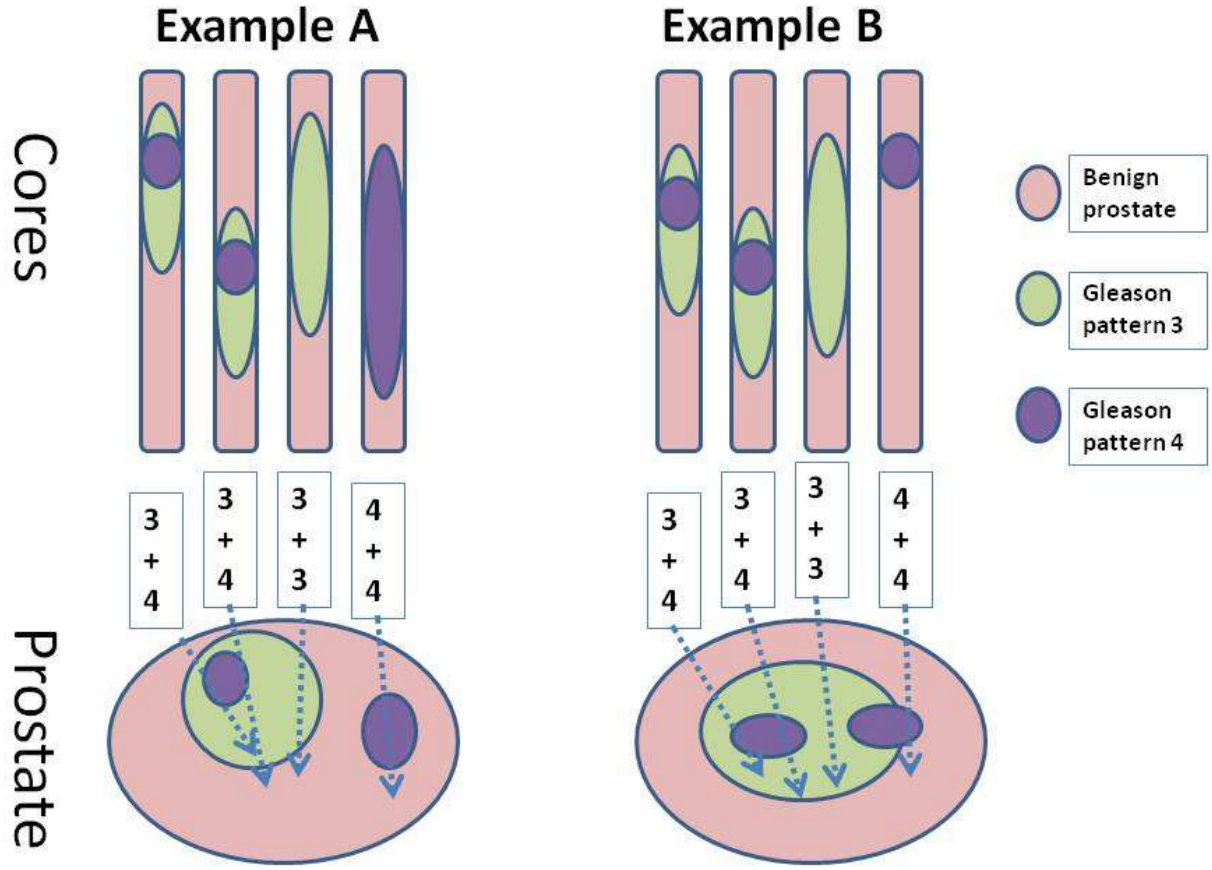

Figure 2: Grading in prostate biopsies. The Worst Gleason score is most likely to be appropriate in example A and the 'composite' score in example B

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 authors but we would advise this cut off as the largest series to date uses this method and is used in the WHO classification:[1,49]

- Example 1: 3+4=7 with <5% pattern 5 it 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).

[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 – Level of evidence C.]

5.3.3 Tumour extent in prostate core biopsies

Estimates of tumour extent are used in a number of predictive tools for outcomes (stage or recurrence) in prostate cancer.[60]

The number of positive cores appears to improve prediction of biochemical recurrence, whereas the number of positive cores expressed as a percentage of total cores is a better predictor of pathological stage.[61] There are also data to suggest that the percentage of positive cores on the dominant side has stronger independent predictive value than the total percentage.[62]

In terms of the significance of linear extent of cancer, two systematic reviews were conducted in preparation of the previous edition of this dataset. The first addressed the issue of 'microfocal' carcinoma.[63] The definition of small volume carcinoma varied widely, but even using the most stringent (only a few malignant glands in one core) or common (less than 3 mm of cancer in a single core, no Gleason grade 4 or 5), there was a significant risk of progressive disease even after radical surgery or radiotherapy.

The second addressed the prognostic value of linear measurements of tumour extent in general.[64] The amount of carcinoma as a percentage of overall prostatic tissue was established as an independent predictor of cancer-specific survival[65] in untreated or conservatively treated men, indicating that linear tumour measures are potential prognostic factors and not just predictive of response to one form of therapy. The weight of current evidence suggests that the percentage of cancer on biopsy may be more valuable in predicting PSA recurrence compared to the number of positive cores alone. The review found consistent data to support the use of either the total percentage of cancer (TPC) or the greatest percentage of cancer in any one core (GPC), both methods providing similar hazard ratios. Hazard ratios appeared to become more significant if intervening benign tissue was excluded for the GPC estimation. Results for absolute measurements (length in mm) were inconclusive. Calculating the percentage either by estimation or by measuring also varies. We would advise that estimating tumour length by comparing with field diameter (x400, x200, x100 field diameters are approximately 0.5 mm, 1 mm and 2 mm respectively) is a quicker, easier and sufficiently accurate alternate method. Giving exact measurements is unnecessary given the marked sampling error of the biopsy technique itself. Tumour extent in biopsy is also less important in targeted biopsies of MRI-detected lesions where the radiological size is likely to be more accurate.

There is also variation in how tumour length is calculated. If in a 12 mm core there is a 1mm focus of tumour at either end then some authors measure this as 12 mm length of tumour,[66] whilst others measure this as 2 mm if these foci are more than 5 mm apart.[67] Consensus on which method is better has not been reached and some suggest reporting the method used in the report stating there is a continuous/discontinuous focus of tumour measuring X.[30] This is inevitably going to cause difficulty when a dataset such as this one is being produced as there is no evidence to suggest which is better. The incidence of discontinuous foci is not common but if criteria for active surveillance are based on tumour length/percentage then this could be critical. Clearly this is an area requiring further research and in the meantime the method employed should be stated in those cases that this is an issue.

The TPC is the ratio between the total amount of cancer and the total amount of tissue sampled, so will therefore be strongly influenced by the latter. This may underestimate large tumours if they are unilateral or if additional centrally rather than peripherally directed biopsies are taken, as these do not generally increase cancer yield.[68] To estimate the GPC, first the core with the greatest amount of cancer is selected and the total length of cancer relative to the total length of the core is assessed. This may underestimate tumour burden if multiple cores are involved.

The recent NICE guidance[3] moved away from previous NICE guidance and removed any pathological measure of tumour volume from the classification of risk categories, instead

using the Gleason score, PSA level and clinical stage (Table 1). Pathologists need to be aware that this dataset is aimed at recording what is both practical and clinically relevant in all scenarios. The biopsy may be done as part of an active surveillance protocol and more information may be required than in a setting of clinically obvious prostate cancer.[13]

In the meantime, pathologists should report the number of cores involved and at least one of the methods of estimating tumour extent, gather data prospectively and audit outcomes.

[Tumour extent in cores is important for prognosis but there is no established best method to evaluate tumour extent – Level of evidence C.]

5.3.4 Perineural invasion in prostate core biopsies

A systematic review was undertaken to clarify the significance of perineural invasion in prostatic biopsies.[69] 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.[69]

Perineural invasion in radical prostatectomies is of less significance and is deemed a non-core item.

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

5.3.5 Invasion into periprostatic tissue in core biopsies

Small groups of adipose cells are very rarely seen within the prostate,[70] therefore the presence of tumour in fat is generally indicative of extraprostatic extension (EPE). Tumour within striated muscle is not deemed EPE as striated muscle merges with the prostatic stroma anteriorly and in the apex.[71] 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 – though there are no studies examining this.

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

5.3.6 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.[72] 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 5).

Staging using the TNM7 criteria[5] is mandatory, albeit with some provisos. In particular, as discussed in Section 6 regarding tumour volume measurements, subdividing the category of organ confined tumours (pT2) does not appear to provide useful independent prognostic information as it is very unlikely that a small midline tumour (pT2c) would behave more aggressively than a larger unilateral tumour.[73] pT2b tumours are also virtually an impossibility, as it is hard to conceive of a tumour that fills more than half of one prostate lobe without invading the contralateral lobe or showing extra-prostatic extension.

It should be noted that the T1 category is limited to biopsies and trans-urethral 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). Whilst invasion into seminal vesicles (pT3b) is generally easier to assess, identification of

extraprostatic extension (EPE, pT3a), defined as tumour extending beyond the normal confines of the prostate gland,[74,75] can be problematic.

The prostatic capsule is not a well-defined structure.[76] 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 that definitions of EPE have to be carefully defined. Although there are rare instances of fat within the prostate (usually only one or two adipose cells),[70] involvement of peri-prostatic fat by tumour indicates EPE and thus spread beyond the gland.[77] 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.[74] 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.[78]

The assessment of EPE at the apex is controversial, with no agreement at the ISUP consensus meeting on a reliable method for determining this.[78] 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[72] as indicative of EPE. However, EPE is most commonly seen in peripheral zone tumours posterolaterally.

[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 – Level of evidence C.]

5.3.7 Extent of EPE in radical prostatectomies

The degree of EPE can be subdivided into focal or established (non-focal or extensive).[79] In focal EPE, neoplastic glands occupy no more than one high-power field in no more than two sections, whereas established EPE represents more than this.[80] Other methods such as measuring the distance of extension from the capsule have been shown to have prognostic use,[81] 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.[79,82]

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

5.3.8 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[83–86] 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 3). 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.[87] 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.[88] Intraepithelial spread into the seminal vesicles has been described but this is extremely rare and it appears not to be a poor prognostic factor.[89] 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).[90]

[Seminal vesicle involvement in radical prostatectomies is of prognostic use – Level of evidence C.]

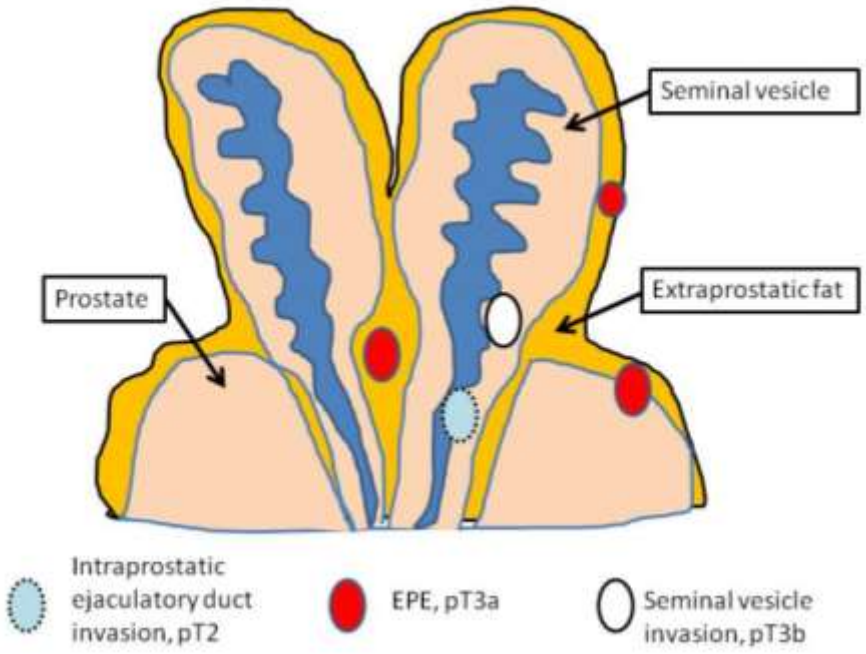

Figure 3: Definition of seminal vesicle invasion

5.3.9 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).[91] Although one 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,[92] larger, retrospective studies have not confirmed this.[93,94] Outcomes have been reported as better than those of patients with seminal vesicle invasion and similar to those of patients with EPE.[95,96] TNM 7 recognised this and this is now staged as pT3a.[5] 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 4). This can be identified in TURP specimens, though this can be extremely difficult. If 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.

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

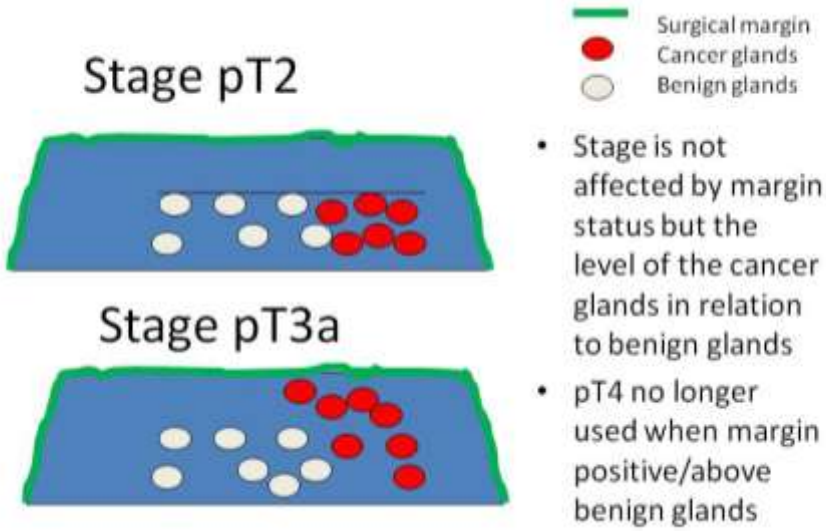

Figure 4: Definition of bladder neck invasion: the neoplastic glands have to be above the level of benign glands and in thick muscle bundles in the sections taken from the base of the radical prostatectomy to be staged as pT3a

5.3.10 Margin status in radical prostatectomies

Many studies have reported on the prognostic significance of involved margins.[97–105] A positive margin is identified when 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.[106]

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.[100,107] The location of positive margins is required for audit purposes, as a consistent pattern would indicate that changes to surgical technique are required (Figure 5).

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.[83,85,107] There is evidence that the five-year PSA recurrence risk appears to be significantly greater when the length of the involved margin is ≥3 mm (53% versus 14%).[108–110]

It has been suggested that extent of margin positivity is useful only in organ confined tumours.[111] The ISUP consensus recommended giving the location and the measurement in mm of the involved margin but the ICCR dataset required this as a non-core data element.[4,58] 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 was less predictive.[110] The updated ICCR dataset only recommends this, but as it is used in 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 where these are 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 next section then combine to give 2 mm rather than assuming block thickness being 3 mm and counting as 6 mm.

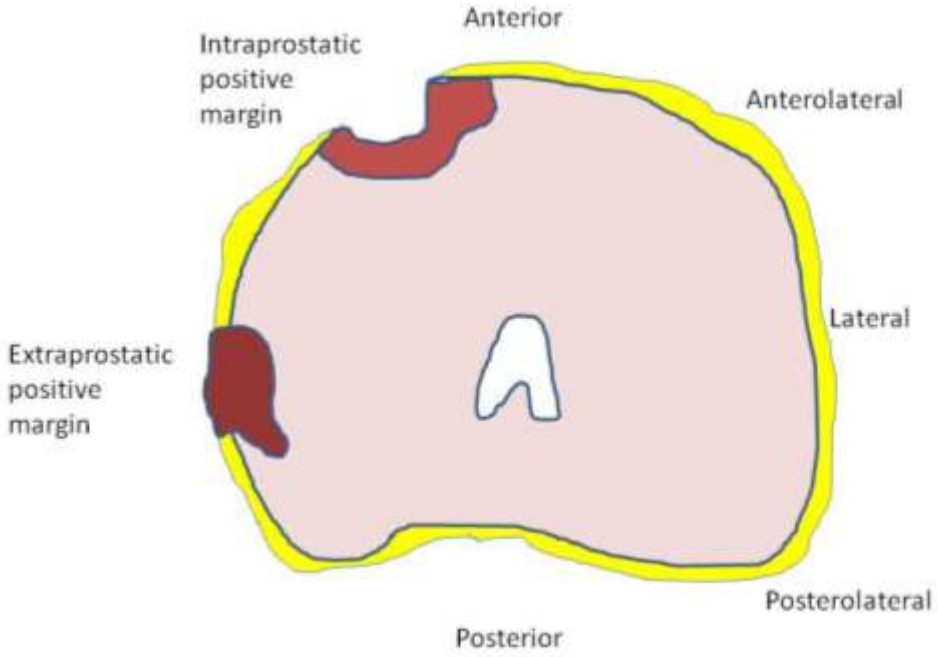

Figure 5 The location and whether intraprostatic or extraprostatic margin should be recorded

The Gleason grade at the surgical margin has been shown to predict recurrence,[112–114] 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.

[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 – Level of evidence C.]

5.3.11 Vascular invasion

This is extremely rare in core biopsies and though it has prognostic significance it is considered a non-core item.

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 hence should be reported.[108,115–122]

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

5.3.12 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. One 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.[45,123] Such high yields are not the norm in UK practice and the ISUP consensus conference found that <10% of respondents detected >10 lymph nodes.[90] The diameter of the largest metastasis appears to be more predictive of cancer-specific survival than the number of positive nodes

alone,[75,120] whereas the presence of extranodal extension was not predictive.[124]

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

6 Summary of core data items

6.1 Prostate biopsies

Clinical data:

- PSA
- 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 (eg midline, targeted) and total
- at least one of the following:
  - the total percentage of cancer in all cores
  - the greatest percentage of cancer in one core
  - longest length of tumour in one core
- perineural invasion, not identified/present
- involvement of adipose tissue by tumour, not identified/present.
- Gleason sum score
  - if only one grade is present, it is doubled (e.g. 3+3)
  - if two grades are present, both are included by order of prevalence
  - if more than two grades are present, the third is included in the sum score if it is of higher grade – no tertiary grade
- Grade Group

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
- 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 prevalence) 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.

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.

[Core length should only be recorded if a perceived difference in samples is noted.]

7.2 Intraductal carcinoma

The key features of intraductal prostatic carcinoma are based on morphology and are as follows:[1,125,126]

- malignant epithelial cells filling large acini and prostatic ducts with preservation of basal cells, and either:
- a solid or dense cribriform pattern, or:
- a loose cribriform or micropapillary pattern with
  - either: (a) marked nuclear atypia (i.e. nuclear size 6 x normal or larger)
  - or: (b) comedonecrosis.

It is extremely important to distinguish this from PIN. Although some of these features overlap with PIN, PIN has less architectural and cytological atypia. Intraductal carcinoma is strongly associated with high-volume, high-grade disease when present on a core biopsy, even when invasive disease is not present.[126] If no invasive tumour is identified this should not be Gleason graded and a repeat biopsy is normally indicated. Although there is increasing evidence of the significance of IDC, it has been considered as non-core for this dataset, but it is a diagnosis that pathologists should start to recognise.

7.3 Percentage of Gleason grade 4 in Gleason scores 3+4 or 4+3

Following the 2014 ISUP consensus meeting, it has been proposed that the percentage pattern 4 is recorded.[50] The evidence is insufficient for this to be a core data item at this point.

7.4 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,[26,47–54,108,115–122] it is likely to be of significance in biopsies, although specific data are scant. Due 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.

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

7.5 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.[127–129] 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.[130]

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.

7.6 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.

7.7 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 RP specimen involved by cancer has been reported to provide predictive information in a multivariate model by some authors,[131,132] this has been disputed by others,[133–135] including a study focusing on Gleason 6 score tumours.[136] Difficulties are compounded by the fact that some centres do not process the entire specimen[43] and, given the multifocal nature of the disease, there are questions about whether all tumours or merely the index tumour should be assessed.[138,139]

The assessment of studies of tumour volume is complicated by the numerous methodologies in use. These include visual extent of tumour,[139] the percentage of carcinoma relative to the overall prostatic volume,[132] more complex grid based estimates[140] and maximum tumour diameter.[141] The ISUP consensus meeting recommended that a volume of tumour was given, but there was no agreement on the methodology.[73] Maximum tumour diameter (in any of the three dimensions) is an easy measurement and has shown to be useful in a specific subset of cases.[142] This measurement has also been shown to be a surrogate of tumour volume.[138,143,144] If only a small, organ-confined tumour is present, the urologist may advise the patient that he is likely to be cured of his disease.

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

7.8 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.[145] 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.[145–148] 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.[149] 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.[145] 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.

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

7.9 Representative block

With the advent of personalised cancer therapy in other specialties, it is good practice 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.

8 Diagnostic coding

The 7th 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%.[150] 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.[151] As a result, frozen sections are rarely performed in routine practice.

Frozen sections can occasionally be requested to assess margin status at the bladder neck or the neurovascular bundles. The finding of carcinoma will then prompt a further excision at the bladder neck or complete excision of the affected neurovascular bundle. However, the yield of positive results is too low to justify frozen sections in routine practice,[152] although it can be helpful in high-risk cases.[153] Some surgeons are employing a Mohs-like technique to the neurovascular bundle, and though this has shown to improve margin rates, whether this correlates to long term recurrence rates is uncertain.[154]

[Frozen sections not routinely useful – Level of evidence C.]

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.[155]

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. Also, 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.

Immunohistochemistry for PSA and prostate specific acid phosphatase (PSAP) remains the definitive method for establishing the diagnosis in morphologically difficult cases. Several studies report the specific nature of both PSA and PSAP.[156,157] Both polyclonal and monoclonal anti-PSA antibodies are in use in the UK.[158] The monoclonal anti-PSA antibody is less sensitive in the identification of poorly differentiated prostate cancer.[159] No comparison of the sensitivity of monoclonal and polyclonal anti-PSAP antibodies in high- grade prostate cancer has been reported. However, two studies found PSAP to be more sensitive (though slightly less specific) than PSA in high-grade prostate cancer.[160,161] The distinction of prostate

cancer from other tumours, such as urothelial carcinoma, has important therapeutic implications, as a result an immunohistochemical panel including both markers is generally recommended. GATA3 is useful to distinguish urothelial carcinomas from prostatic adenocarcinoma.[155] NKX3.1 is another marker for prostatic glands and may also be useful in this setting.[155] The selection of tissue for use as a positive control is also important because the use of strongly positive tissue could mean that the lack of staining sensitivity is overlooked. It is known that PSA and PSAP expression is much higher in benign prostate glands and low-grade prostate cancer than in high-grade prostate cancer. In view of this variability, multiblocks containing benign prostate, well/moderately differentiated prostate cancer and poorly differentiated prostate cancer may provide the ideal positive control for PSA and PSAP immunohistochemistry.[158]

10.2 Differentiation patterns within prostatic cancer

The vast majority of prostatic malignancies are adenocarcinomas. Rarely sarcomas may arise requiring immunochemistry. The identification of neuroendocrine changes, especially if of small cell type, is important as these may be treated like small cell lung cancer.[162] These can be diagnosed on morphology alone but may be backed up with CD56, chromogranin, synaptophysin or other neuroendocrine markers, though PSA and PSAP may be negative.[163] CD56 is the most sensitive neuroendocrine marker but the least specific, whilst chromogranin A is the most specific but least sensitive. TTF-1 positivity does not indicate pulmonary origin as this marker is commonly positive in prostatic neuroendocrine carcinoma. Occasionally tumours will secrete endocrine factors such as adrenocorticotropic hormone (ACTH) and wider panels may be useful.[164]

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. In contrast, a ‘basal cell pattern’ of immunostaining is almost never seen in prostatic adenocarcinoma.[165] Aberrant expression of p63 has been shown in a subset of prostate carcinomas and this may cause confusion.[166] 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 should 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 as compared to benign prostate and widely used to help establish a diagnosis of prostate carcinoma in morphologically equivocal cases.[167,168] 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 that 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.[169] 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, whilst 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 two 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.[170] 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.

11 Criteria for audit of the dataset

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 are recommended by the RCPath as key performance indicators (see *Key Performance Indicators – Proposals for implementation*, July 2013, https://www.rcpath.org/profession/clinical-effectiveness/key-performance-indicators-kpi.html).

- cancer resections must 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 are required to implement the structured recording of core pathology data in the COSD by January 2016

  standard: 95% of reports must contain structured data
- histopathology cases that are reported, confirmed and authorised within 7–10 calendar days of the procedure

  standard: 80% of cases must be reported within seven calendar days and 90% within 10 calendar days.

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.

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Appendix A TNM (7th edition, UICC)[5]

The major change in the 7th edition compared to the 6th edition affects the staging of invasion into the bladder neck, which is now staged as pT3a.[5]

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
T2a	Tumour involves one half of one lobe or less
T2b	Tumour involves more than half of one lobe, but not both lobes
T2c	Tumour involves both lobes
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 one 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 Any T Any T	N0 N1 Any N	M0 M0 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 two left-hand columns of the table). SNOMED CT, also known as SNOMED International, is the newer SNOMED system, first introduced in 2002 with multiple updates (shown in the two 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

Morphological codes (cont'd)	SNOMED 2 or 3	SNOMED CT terminology	SNOMED CT code
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 Reporting proforma for prostatic biopsies

Surname…… Forenames…… Date of birth…… Sex…..

Hospital…… Hospital no…… NHS/CHI no…….....

Date of receipt…… Date of reporting……..... Report no…….....….

Pathologist…….…….... Surgeon…….…….

Clinical information

Pre biopsy PSA†: ……ng/ml Not available □

Type of specimen: TRUS biopsy □ Transperineal □ Targeted □ Other (specify) □ ……..

Nature of specimen(s) and core macroscopic items

Right side (specific locations below if applicable)	Number taken	Number received	Left side (specific locations below if applicable)	Number taken	Number received	Other (specific locations below if applicable)	Number taken	Number received

Core microscopic items

Histological tumour type†: Acinar adenocarcinoma □
Prostatic ductal adenocarcinoma □
Small cell neuroendocrine carcinoma □
Other (specify) ……

Number of cores involved.
Right …….. out of ……. Location(s): …….....
Left: ……... out of ……. Location(s): …….....
Other:…… out of ……. Location (s):……

Total number of cores involved: …... out of ……...

*Greatest **length** of cancer in one core: …….mm Location…… Not used* □
*Greatest **percentage** of cancer in one core: ……..% Location……. Not used* □
*Percentage of cancer in **all** cores: ……..% Not used* □
Perineural invasion†: Not identified □ Present □
Invasion into adipose tissue: Not identified □ Present □

Gleason score: Not applicable** □
Primary Gleason grade†: 3 □ 4 □ 5 □
Secondary Gleason grade†: 3 □ 4 □ 5 □
Gleason score: ……+……..=……
Grade Group: 1 □ 2 □ 3 □ 4 □ 5□ Not applicable □

SNOMED codes†: T…….M…….

Signature of pathologist…… Date……..

Notes

* At least one of these data items should be recorded.

** Post hormone or radiotherapy then Gleason score may not be reliable. Gleason score is not applicable to some morphological types (e.g. small cell neuroendocrine carcinoma).

† Data items that are currently part of the Cancer Outcomes and Services Dataset (COSD) version 6.

Appendix D Reporting proforma for transurethral resections or enucleations of the prostate

Surname……	Forenames……	Date of birth…… Sex…..
Hospital……	Hospital no……	NHS/CHI no…….....
Date of receipt……	Date of reporting…….....	Report no…….....
Pathologist……	Surgeon……	

Clinical information

Pre biopsy PSA†: ……ng/ml Not available □

Type of specimen

TURP □ Enucleation □

Microscopic items

Histological tumour type†:

- Acinar adenocarcinoma □
- Prostatic ductal adenocarcinoma □
- Small cell neuroendocrine carcinoma □
- Other (specify) ……

% of prostatic tissue involved by tumour based on area†: ……% Not used* □

% of prostatic tissue involved by tumour based on number of chips†: ……% Not used* □

Gleason score: Not applicable** □

Primary Gleason grade†:	2 □	3 □	4 □	5 □	
Secondary Gleason grade†:	2 □	3 □	4 □	5 □	
Gleason score: ……+……..=……					
Grade Group:	1 □	2 □	3 □	4 □	5 □ Not applicable** □

T category (TNM 2009): T1a □ (Incidental carcinoma in 5% or less of tissue resected)
T1b □ (Incidental carcinoma over 5% of tissue resected)
T3a □ (Bladder neck or EPE)

SNOMED codes†: T……M…….

Signature of pathologist…… Date……..

Notes

* At least one of these data items should be recorded. For enucleation specimens then area method should be used.

** Post hormone or radiotherapy then Gleason score may not be reliable. Gleason score is not applicable to some morphological types (e.g. small cell neuroendocrine carcinoma).

† Data items which are currently part of the Cancer Outcomes and Services Dataset (COSD) version 6.

Appendix E Reporting proforma for radical prostatectomies

Surname…… Forenames…… Date of birth…… Sex…..
Hospital…… Hospital no…….... NHS/CHI no…….....
Date of receipt…….…. Date of reporting……..... Report no…….....….
Pathologist……..... Surgeon…….…….

Clinical information

Pre biopsy serum PSA[† ‡],:……ng/ml Not available □

Nature of specimen(s) and macroscopic items

Specimen weight (i.e. prostate without seminal vesicles)[‡]: ……. g

Seminal vesicles[‡]: Present (partially or completely resected) □ Absent □
(If present, Laterality: Left □ Right □ Bilateral □)

Lymph nodes[‡]: Present □ Absent □
(If present, Laterality[‡]: Left □ Right □ Preprostatic □)

Core Microscopic items

Histological tumour type[†‡]:
- Acinar adenocarcinoma □
- Prostatic ductal adenocarcinoma □
- Small cell neuroendocrine carcinoma □
- Other (specify) ……
- No tumour □

Gleason score: Not applicable** □

Primary Gleason grade[†‡]:	2 □	3 □	4 □	5 □	
Secondary Gleason grade[†‡]:	2 □	3 □	4 □	5 □	
Tertiary Gleason grade (<5%)[†‡]:		3 □	4 □	5 □	Not applicable □
Gleason score:	……+……..=……				
Grade Group:	1 □	2 □	3 □	4 □	5 □ Not applicable** □

Location of dominant tumour: …….

Extraprostatic extension (EPE) pT3a[†‡]: Not identified □ Present □ Indeterminate □
If EPE: Location of EPE:……..
If EPE: Extent of EPE[‡]: Focal □ Established □
Bladder neck (pT3a): Involved □ Not involved □ Not applicable □

Seminal Vesicles (pT3b) [†‡]: Involved □ Not involved □ Not applicable □

Margin status[†‡]: Involved □ Not involved □ Indeterminate □
If involved: Extent (total): <3 mm □ > or = 3 mm □
If involved: Location: Apical □ Bladder neck □ Circumferential □
If circumferential margin involved[‡]: Intraprostatic □ Extraprostatic □
If circumferential margin involved: Location*(s)*……..

Lymphovascular invasion[‡]: Not identified □ Present □

Regional lymph node status

Number of lymph nodes examined[†‡]:……

Number of positive lymph nodes[†‡]: …….

Maximum dimension of largest deposit[‡]:……..mm

Primary tumour – T category (TNM 2009) [†‡]

pT0 □ (no tumour)
pT2 □ (organ confined)
pT3a □ (EPE, bladder neck)
pT3b □ (SV positive)
pT4 □ (involves other organs)

Regional lymph nodes – N category (TNM 2009) [†‡]

pNx □
pN0 □
pN1 □

Stage pT…….. pN……..

SNOMED codes[†]: T…….M…….

Signature of pathologist…… Date……..

Notes

** Post hormone or radiotherapy then Gleason score may not be reliable. Gleason score is not applicable to some morphological types (e.g. small cell neuroendocrine carcinoma).

† Data items which are currently part of the Cancer Outcomes and Services Dataset (COSD) version 6.

‡ Data items which are used in version 1.0 of the ICCR Prostate Cancer (Radical Prostatectomy) dataset.

Appendix F Reporting proforma for prostatic biopsies in list format

Element name	Values	Implementation comments
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	Multiple selection value list: • TRUS biopsy • Transperineal • Targeted • Other	
Type of specimen, other (specify)	Free text	Only applicable if 'Type of specimen – Other' selected.
Right side, location [n]	Free text	Repeating data item. n value increases as required.
Right side, number taken [n]	Integer	
Right side, number received [n]	Integer	
Left side, location [n]	Free text	Repeating data item. n value increases as required.
Left side, number taken [n]	Integer	
Left side, number received [n]	Integer	
Other, location [n]	Free text	Repeating data item. n value increases as required.
Other, number taken [n]	Integer	
Other, 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]
Number of right cores involved	Integer	Only applicable if total number of cores >0
Location of involved right cores	Free text	

Element name (cont'd)	Values	Implementation comments
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 cores	Integer	May be calculated from sum of 'Total number of left cores', 'Total number of right cores' and 'Total number of other cores'
Total number of cores involved	Integer	May be calculated from sum of 'Total number of left cores involved', 'Total number of right cores involved' and 'Total number of other cores involved'
Greatest length of cancer in one core	Distance in mm	
Location of greatest length of cancer in one core	Free text	
Greatest length of cancer in one core availability	Single selection value list: • Not used • Not applicable	Not applicable if 'Greatest length of cancer in one core' is completed.
Greatest percentage of cancer in one core	Numerical value (0–100)	
Location of greatest percentage of cancer in one core	Free text	
Greatest percentage of cancer in one core, availability	Single selection value list: • Not used • Not applicable	Not applicable if 'Greatest length of cancer in one core' is completed.
Percentage of cancer in all cores	Numerical value (0–100)	
Percentage of cancer in all cores, availability	Single selection value list: • Not used • Not applicable	Not applicable if 'Percentage of cancer in all cores' is completed.
Perineural invasion	Single selection value list: • Not identified • Present	

Element name (cont'd)	Values	Implementation comments
Invasion into adipose tissue	Single selection value list: • Not identified • Present	
Gleason score, applicable	Single selection value list: • Applicable • Not applicable	
Gleason score, primary Gleason grade	Single selection value list: • 3 • 4 • 5 • Not applicable	
Gleason score, secondary Gleason grade	Single selection value list: • 3 • 4 • 5 • Not applicable	
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	
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables.	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables.	

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

Element name	Values	Implementation comments
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)	
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	

Element name (cont'd)	Values	Implementation comments
Primary Gleason grade	Single selection value list: • 2 • 3 • 4 • 5 • Not applicable	
Secondary Gleason grade	Single selection value list: • 2 • 3 • 4 • 5 • Not applicable	
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	
T category	Single selection value list: • T1a • T1b • T3a	
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables.	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables.	

Appendix H Reporting proforma for radical prostatectomies in list format

Element name	Values	Implementation comments
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.
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	

Element name (cont'd)	Values	Implementation comments
Primary Gleason grade	Single selection value list: • 2 • 3 • 4 • 5 • Not applicable	
Secondary Gleason grade	Single selection value list: • 2 • 3 • 4 • 5 • Not applicable	
Tertiary Gleason grade	Single selection value list: • 3 • 4 • 5 • Not applicable	
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	
Location of extraprostatic extension	Free text	Not applicable if not identified

Element name (cont'd)	Values	Implementation comments
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	
Margin extent	Single selection value list: • <3mm • > or = 3mm • Not applicable	Not applicable if 'Margin status' is 'Not applicable'
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	
Number of lymph nodes examined	Integer	
Number of positive lymph nodes	Integer	
Maximum dimension of largest deposit	Size in mm	

Element name (cont'd)	Values	Implementation comments
T category	Single selection value list: • pT0 • pT2 • pT3a • pT3b • pT4	
N category	Single selection value list: • pNx • pN0 • pN1	
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables.	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables.	

Appendix I 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 one 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 J AGREE compliance monitoring sheet

The cancer datasets of The Royal College of Pathologists comply with the AGREE II standards for Good-quality clinical guidelines (www.agreetrust.org). The sections of this dataset that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE standard	Section of dataset
Scope and purpose	
1. The overall objective(s) of the guideline is (are) specifically described	Foreword, 1
2. The clinical question(s) covered by the guidelines is (are) specifically described	1
3. The patients to whom the guideline is meant to apply are specifically described	1
Stakeholder involvement	
4. The guideline development group includes individuals from all the relevant professional groups	Foreword
5. The patients' views and preferences have been sought	N/A
6. The target users of the guideline are clearly defined	1
7. The guideline has been piloted among target users	Foreword
Rigour of development	
8. Systematic methods were used to search for evidence	Foreword
9. The criteria for selecting the evidence are clearly described	Foreword
10. The methods used for formulating the recommendations are clearly described	Foreword
11. The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword
12. There is an explicit link between the recommendations and the supporting evidence	5
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	3–5,7–10
16. The different options for management of the condition are clearly presented	5,9,10
17. Key recommendations are easily identifiable	5,7–10
18. The guideline is supported with tools for application	Appendices A–H
Applicability	
19. The potential organisational barriers in applying the recommendations have been discussed	Foreword
20. The potential cost implications of applying the recommendations have been considered	Foreword
21. The guideline presents key review criteria for monitoring and/or audit purposes	11
Editorial independence	
22. The guideline is editorially independent from the funding body	Foreword
23. Conflicts of interest of guideline development members have been recorded	Foreword