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

Standards and datasets for reporting cancers

Dataset for tumours of the urinary collecting system (renal pelvis, ureter, urinary bladder and urethra) (2nd edition)

April 2013

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Unique document number	G044
Document name	Dataset for tumours of the urinary collecting system (renal pelvis, ureter, urinary bladder and urethra)
Version number	2
Produced by	Each of the authors is a consultant histopathologist with a special interest in urological pathology. JHS regularly speaks at national and international meetings and has co-authored over 80 publications, mostly in the field of urological pathology. AC is co-author of *ACP Best Practice: Cut up and reporting of bladder cancer specimens* and is on the NICE Clinical Guidelines Group for diagnosis and clinical management of bladder cancer. LMcW has been involved in national studies of Gleason grading, is a founder member of the British Association of Urological Pathologists and speaks on bladder and prostate pathology at their biannual courses. She helped to develop national and regional guidelines for best practice in urological pathology. MV is also founder member of BAUP, organises biannual uropathology courses on prostate and bladder pathology, and has published several original and review papers related to urological pathology.
Date active	April 2013
Date for review	April 2014
Comments	In accordance with the College's pre-publications policy, this document was put on The Royal College of Pathologists' website for consultation from 6 February to 6 March 2013. Thirty-eight items of feedback were received and the authors considered them and amended the document as appropriate. Please email publications@rcpath.org if you wish to see the responses and comments. This dataset will supersede the 2007 publication of the same name. **Dr Suzy Lishman** **Acting Director of Communications**

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Registered charity in England and Wales, no. 261035

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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 defense 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:

- BAUS/BAUS Section of Oncology
- British Uro-oncology Group
- NCRI Bladder Cancer Clinical Studies Group
- British Association of Urological Pathologists (BAUP)
- UK Association of Cancer Registries (UKACR)
- National Cancer Intelligence Network (NCIN) Urology Clinical Reference Group.

Supporting evidence and recommendations in this dataset are based on:

- PubMed literature searches (up to July 2012)
- WHO classifications, 1973[1] and 2004[2]
- NICE *Improving Outcomes Guidance*, 2002[3]
- TNM 7th edition staging classification, 2009[4]

Most of the supporting evidence is level C or D at least or meets the GPP (Good Practice Point) criteria. 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 2007 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.

The dataset has been reviewed by the WGCS and placed on the College website for consultation with the membership from 6 February to 6 March 2013. All comments received from the WGCS and membership have been addressed by the author to the satisfaction of the WGCS Chair and the Acting Director of Communications.

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

This document is the second edition of the dataset for tumours of the urinary collecting system, and follows publication of the first edition in January 2007.[5] Tumours of the urinary collecting system (renal pelvis, ureter, urinary bladder and urethra) are common. Most are reported by local teams that should include a uropathology lead who has a special interest in the field. Cystectomies are performed in larger centres where more than 50 radical procedures (to include cystectomies, cystoprostatectomies and radical prostatectomies) are performed per year according to recommendations in the NICE *Improving Outcomes Guidance* published a decade ago.[3] The recommended minimum is five cases per surgeon.

The most frequent tumour encountered is urothelial carcinoma (the term recommended by the WHO, although 'transitional cell carcinoma' is in common usage). A peculiar feature of the classification of this tumour type is that by longstanding convention the term 'carcinoma' has applied to most non-invasive papillary lesions as well as to invasive tumours. At least half of urothelial carcinomas are non-invasive at presentation.

This dataset applies only to malignant epithelial tumours (invasive or non-invasive) of the urinary collecting system. It is not intended to cover other tumour types, such as sarcoma. However, note that for sarcomatoid tumours of the lower urinary tract the possibility of a sarcomatoid carcinoma (which is covered by the dataset) should be considered.

In 1998, the International Society of Urological Pathology (ISUP) proposed a new classification, which was subsequently adopted in the 2004 WHO publication,[2] although it has been controversial (see section on core data items for further information). In the UK, the 1973 WHO classification[1] remains in more widespread use.

Urothelial carcinoma not infrequently displays divergent differentiation[6,7,8] and some relatively recently described subtypes such as the micropapillary variant are important to recognise because, when invasive, they are more aggressive than conventional invasive urothelial carcinoma. Pure squamous cell carcinoma, small cell carcinoma and primary adenocarcinoma also occur, but are uncommon.[6,7,8,9] Spread/metastasis from elsewhere should be considered and excluded, especially for pure adenocarcinoma.

Three years after the first edition of this dataset was published, the 7th edition of TNM appeared (in late 2009).[4] In its introduction, this TNM booklet states that substantial changes in the 2009 7th edition compared to the 2002 6th edition[10] are marked by a bar at the left-hand side of the page. However, at least one substantial amendment (to lymph node staging in bladder cancer) was not highlighted. For clarity, in the current dataset document, **all** changes from 6th edition to 7th edition TNM are highlighted by underlined text in Appendix A.

In addition to incorporation of TNM 7th edition criteria, the 2nd edition of this dataset has restructured the reporting proformas to produce separate forms for biopsy/TUR specimens and radical resections. This allows population of data fields appropriate for the specimen type as far as possible, rather than having multiple non-applicable data items. Occasional items have been added to the proforma, such as the micropapillary variant of urothelial carcinoma as an option in tumour subtyping and mention of the presence/absence of muscularis propria (detrusor muscle) in biopsy/TUR material. An occasional item has been removed, such as distance to resection margins, for which the authors are not aware of specific evidence, but resection margin status is retained.

Referral pathways should be established for difficult cases and, as a minimum, the uropathology lead at each site reporting tumours of the urinary collecting system should participate in the national urological EQA scheme. Discussion of cases will be at the local or specialist MDT meetings, according to the type of case. The uropathology lead should be a member of such a team.

Target users and health benefits of this guideline

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

2 Clinical information required on the specimen request form

In addition to demographic information about the patient and details of destination of the report, several items of clinical information can help the pathologist in the handling and reporting of specimens of the urinary collecting system. These should be available to the pathologist either on the specimen request form or by access to the electronic notes of the patient. It is good practice to include the clinical information obtained from these sources in the pathology report.

For bladder biopsy/TUR specimens, the anatomical location(s) within the bladder should be given to help in the distinction between the muscularis mucosae and muscularis propria (detrusor muscle), as there are regional variations in the morphology of the bladder wall.[11]

Cystoscopic appearances are critical in the assessment of biopsies and TURBT specimens. If the papillary lesion seen on cystoscopy is not identified in the initial levels of the biopsy/TURBT, examination of further levels is mandatory. In some borderline cases the morphology, while not diagnostic, would be consistent with origin from a small low-grade papillary urothelial neoplasm if the biopsy was from a papillary lesion. It is essential to know the clinical/radiological appearances in cases with small endoscopic biopsies of the ureter or renal pelvis, as there is particular potential for misinterpretation of tiny folded fragmented pieces of mucosa, polypoid ureteritis or pyelitis or other reactive changes, as tumour at these sites.[12]

Awareness of a urine cytology finding of high-grade urothelial neoplasia may indicate the need to examine further levels of a biopsy that shows only a low-grade urothelial neoplasm to exclude adjacent urothelial carcinoma *in situ*. Alternatively, this may prompt a search for high-grade tumour elsewhere in the bladder.

Results of staging investigations can be important as there is little point in exhaustive examination of a TURBT specimen if the patient has distant metastasis or unequivocal locally advanced bladder cancer on radiological investigation.

Details of current and previous therapy can aid morphological interpretation as well as inform the pathologist of the potential clinical implications of the report.[13] For example, recurrent carcinoma *in situ* following intravesical BCG therapy may be an indication for radical cystectomy. Various epithelial alterations have been described following intravesical chemotherapy[13] or occasionally as a result of non-therapeutic agents such as ketamine[14] that can mimic neoplastic changes. Pseudocarcinomatous epithelial proliferation can occur following treatments such as radiotherapy[15,16] or, occasionally, in the absence of therapy.[17] Any history of recent procedures, stones, infections or obstruction should be given.

In cystectomy specimens, it is useful for the pathologist to be aware of the rationale for the surgery in that patient. If cystectomy was performed to palliate pain, or for bleeding or urinary frequency, there is no need to exhaustively sample the specimen for residual cancer. On the other hand, if cystectomy was performed following a radiological impression of extravesical extension of the tumour, it is important to sample appropriate areas of the specimen to confirm or refute the radiological impression. It is important to be aware of the findings in a previous TURBT specimen when making an overall assessment of a cystectomy. This point is illustrated by cases where no invasive carcinoma is found at cystectomy, despite thorough sampling, even though muscularis propria (detrusor muscle) invasion was present in the prior TURBT specimen. Such a patient should be staged as pT2 following cystectomy. An appropriate comment can be made on the report, taking into account any neoadjuvant chemotherapy or radiotherapy that may have been administered, ideally accompanied by review of the previous pathology.

In cystoprostatectomy specimens, raised serum PSA or radiological evidence of prostate cancer may indicate the need to sample the prostate gland more extensively, although elevations of serum PSA levels may accompany transurethral resections and BCG therapy.

3 Preparation of specimens before dissection

Specimen types received from the urinary collecting system include the following.

3.1 Renal pelvis and ureter

- ureteroscopic biopsies
- transurethral resection (TUR)
- nephro-ureterectomy
- ureterectomy (including bladder cuff if distal ureterectomy)
- accompanying lymphadenectomy
- adherent adjacent organs in advanced cases
- cytological specimens – urine from renal pelvis or nephrostomy, brushings and washings.

3.2 Bladder and urethra

- cystoscopic biopsies
- transurethral resection (TUR)
- cystectomy (partial or radical)
- diverticulectomy
- urethrectomy
- anterior exenteration

- accompanying lymphadenectomy
- cytological specimens – brushings and washings from bladder, urethra or ileal conduit.

3.3 Request forms/tracking

Appropriate labelling of request form and containers must be observed by the requesting clinical team to avoid delays in the booking in of specimens.

If available, specimen tracking with bar coding should enable the progress of specimens to be followed during transport and processing in the laboratory, which would help auditing of turnaround times for reporting (see section 10).

3.4 Tissue banking/fixation

The majority of histological specimens are received in 10% buffered formalin. Adequate fixation requires 5–10 times the volume of formalin compared to the size of the specimen and a suitable size of container must be selected by the requestor. Adequate fixation is essential for good morphology which is required for grading of urothelial carcinoma and for the recognition of *in situ* neoplasia. However, if fresh tissue is required for research or bio-banking, this should be collected according to agreed protocols and under the guidance of the pathologist. Specimens may be transported on dry ice for collecting fresh tissue in the laboratory. Detailed protocols for tissue banking, including ethical and consent issues, are beyond the scope of this document but as a general principle fresh tissue banking protocols should be designed such that diagnosis, staging and resection margin assessment are not compromised. If this is likely in a given case, then tissue banking should not occur and the reasons should be recorded.

Endoscopic biopsies from the renal pelvis and ureter may be collected in Bouin's fluid, which provides good nuclear detail in these tiny specimens.[18]

Whether or not tissue banking is undertaken, once received in the laboratory, large specimens should be incised promptly for formalin penetration (if not already inflated with formalin), while small specimens that only require tissue transfer may be submitted by a biomedical scientist (BMS). With appropriate training and under the guidance of a histopathologist, advanced practitioners may prepare, as well as cut up, urological specimens.

3.5 Nephrectomy specimens for pelvic tumour

Nephrectomy specimens should be incised into anterior and posterior coronal halves for fixation, exposing the renal pelvic tumour but leaving the hilum intact. Further transverse slices are usually required if the tumour is large or to fix the kidney adequately. Vascular and ureteric margins at the hilum may be sampled at this time, placed in cassettes and returned to the container (within a small separate formalin-filled pot to avoid carry-over/contamination) until the remaining specimen is cut up. The perinephric fat and renal capsule should not be stripped for examination of the external surface.

3.6 Ureterectomy specimens

Ureterectomy specimens are generally received with one luminal end open and do not require incision prior to dissection.

3.7 Cystectomy/cystoprostatectomy+/– urethrectomy/anterior exenteration specimens

Partial cystectomy specimens are in the shape of a disc and do not need incision for fixation.

Diverticulectomy specimens are open at the site of communication with the bladder lumen and generally require no incision prior to dissection.

Radical cystectomy specimens may be received fresh or inflated with 150–250 ml buffered formalin for fixation of the mucosal surface, and the specimen immersed in a large pot of formalin.[19] After overnight fixation, the formalin within the bladder lumen is drained and the specimen incised in the following way. The specimen may be inked to indicate resection margins, anterior and posterior or left and right halves or simply to identify areas of interest to guide sampling. If the prostate is present, it may be severed below the level of the bladder neck. The bladder may then be bisected in the sagittal or coronal plane depending on the location of the tumour, and may be left attached at the fundus or bladder neck.

If the urethra is attached, it should be severed at the level of the prostatic apex. The proximal end is usually wider and more muscular than the distal end, but it is helpful to mark the specimen at this time to ensure reliable orientation later. Alternatively, the distal end may be sampled at this time in a cassette and returned to the container (within a small separate formalin-filled pot to avoid carry-over or contamination).

In anterior exenteration specimens from female patients, the urethral margin is usually small and irregular, and best sampled before bisecting the bladder. The urethral margin can be sampled as a shave placed face down. The bladder should be bisected in the coronal plane into anterior and posterior halves, and may be left attached at the fundus. The uterus and cervix should be opened.

3.8 Lymphadenectomy specimens

Lymphadenectomy specimens usually do not require incising, unless there is a large mass that requires slicing to facilitate fixation.

3.9 Cytology specimens

Cytological specimens are generally processed as cytospins and stained with the Papanicolaou (Pap) stain. Pap-stained liquid-based cytology (LBC) preparations may also be used, and unstained LBC slides can be used for FISH analysis, if required.

4 Specimen handling and block selection

4.1 Biopsies

The number of biopsies and the largest dimension of each piece should be recorded. These should be examined at three levels.

4.2 Bladder TUR specimens

The weight of the sample must be recorded and ideally all of the tissue should be submitted, particularly for re-resections following a previous diagnosis. If not all embedded, then as a minimum the first 20 g or 10 cassettes should be processed plus at least one cassette for every additional 5 g. Further tissue should always be submitted if no muscularis propria (detrusor muscle) is identified in the sections, until the entire specimen has been processed.

Transurethral *en bloc* resection of bladder tumours is not yet widespread, but the specimen can be orientated and the margins inked to assess completeness of excision.

4.3 Nephro-ureterectomy

The overall dimensions of the specimen, including the length of the ureter received, should be recorded. The location, size and number of the tumours (if multiple) should be recorded. The depth of invasion is easier to assess by transverse slicing through each half of the bisected kidney (performed when the specimen was received). Invasion of the pelvic and perinephric fat and renal parenchyma must be reported, as these determine the stage of renal pelvic tumours. Invasion of the perinephric fat by urothelial carcinoma of the renal pelvis is reported as pT4, in contrast to renal parenchymal tumours which would be staged as pT3. Areas of interest such as a close margin should be inked on the surface of the specimen.

In order to minimise the risk of carry over, blocks from the ureteric margin and vascular margins, the adrenal gland (if included) and normal renal parenchyma should be sampled before cutting into the friable, papillary tumour. The ureter should be sliced in cross-sections at regular (10 mm) intervals from the distal margin towards the renal pelvis. A few blocks should be selected from each third of the ureter in addition to sampling of any abnormal areas.

Blocks should include:

- ureteric margin
- vascular margins
- selected cross-sections of ureter at 10 mm intervals
- adrenal gland
- normal renal parenchyma
- normal renal pelvis
- tumour including the deepest point of invasion
- tumour invading fat or renal parenchyma
- ureteric tumour invading periureteric tissues
- hilar lymph nodes or tumour deposits in fat
- para-aortocaval lymph nodes (if included).

4.4 Partial cystectomy

Any margins or other areas indicated by orientating sutures should be inked and recorded in a schematic diagram. Generally, sampling of the specimen in serial slices perpendicular to the slit-like luminal cavity is adequate.

If partial cystectomy is performed for a urachal tumour at the fundus of the bladder, serial slices of the tumour bulging into the perivesical connective tissue and the remaining urachus should be examined. Slices of the urachus up to the umbilicus should be inspected and a few pieces selected for histological examination. The soft tissue margins of the urachal tract and the umbilical skin margins should be evaluated if tumour is present at these locations.

4.5 Diverticulectomy

These specimens should be sampled to include representative blocks of tumour with deepest point of invasion and the excision margins. Flat mucosa should also be sampled to look for carcinoma *in situ* (CIS). Muscularis propria (detrusor muscle) may be absent in the attenuated wall.

4.6 Radical cystectomy (with prostatectomy or anterior exenteration)

The included organs and their dimensions should be recorded. The prostate gland and seminal vesicles are inked and may be separated below the level of the bladder neck at the time of receipt (see above). The bisected bladder is inspected for tumour and other significant features in each half. A photograph of the specimen may be appropriate.

The ureteric margins are usually sent as separate specimens and each may bear orientating sutures to indicate the proximal and distal ends. There is no need to sample the ureteric margins of the bladder specimen in this instance. However, if a length of ureter is received attached to the bladder, this should be sampled to detect CIS. If no separate ureteric resection margins are received, a section from the ureteric margins of the cystectomy specimen should be examined histologically.

It is common to receive cystectomy specimens with little or no identifiable tumour following repeated resections, intravesical BCG therapy and neo-adjuvant chemotherapy and/or radiotherapy. As emphasised above, clinical data including sites of previous resected tumours in the bladder and any radiologically suspicious areas for extravesical spread must be known before the specimen is prepared for dissection. The mucosal surface of the bladder and urethra should be handled with care to avoid damage that may interfere with histological interpretation.

When no obvious tumour is evident, each half of the bladder should be sliced transversely at 5 mm intervals from the bladder neck towards the fundus. The slices are laid out on a board for selecting blocks for histological examination. The slices can be identified numerically, e.g. slice 3 posterior wall, for correlating with CT and MRI images. Regular cassettes and/or large blocks may be used according to requirements of individual cases.

If a polypoid or ulcerated tumour is identified, this should be described and sampled using large blocks, if appropriate. Additional blocks should be taken from flat mucosa to identify co-existing CIS. Careful gross examination of the specimen for extravesical extension and recording of its presence or absence is mandatory as any direct tumour spread into the perivesical fat that is found on macroscopic examination is regarded as pT3b in the TNM classification. According to TNM 7th edition, discrete tumour deposits (satellites) that are present separately from the main tumour mass in the perivesical fat, without histological evidence of residual lymph node in the nodule/deposit, may represent discontinuous spread, venous invasion or a completely replaced lymph node. The recommendation in TNM7 is that if the nodule (generally having a smooth contour) is considered by the pathologist to be a totally replaced lymph node, it should be recorded as a positive lymph node, and each such nodule should be counted separately as a lymph node in the final pN determination.

The prostate gland should be sampled with a view to identifying involvement by urothelial carcinoma. The most important block is the apical margin of the prostate gland as this represents the distal urethral margin and if CIS is present here, urethrectomy may be indicated. Unlike in a radical prostatectomy specimen for prostate cancer (in which the cone method is recommended for the apex), the prostate apex in a cystoprostatectomy for bladder cancer is best sampled as a transverse slice (shave), placed flat surface down in the cassette. At least the next transverse slice above this should also be submitted to ensure that the distal prostatic urethra (which tends to retract into the specimen) is sampled. Direct invasion of the upper prostate (base) by a bladder tumour may be best demonstrated by sections that include both the bladder and prostate base in continuity, taken as vertical slices. Bladder carcinoma infiltrating through the full thickness of the bladder wall to directly invade into the prostate gland (but not prostatic stromal invasion alone by a urothelial carcinoma arising in the urethra or prostatic ducts) is classified as pT4.

It may be convenient to submit the entire prostate gland in large blocks but if selective sampling is followed, the prostatic urethra and periurethral tissue should be sampled for CIS

and invasion into prostatic stroma. If carcinoma is confined to these blocks, this is regarded as either urethral or prostatic urothelial carcinoma, pT2 (assuming the bladder neck or specified adjacent organs are not invaded directly from a tumour extending through the prostate gland). Sampling may be performed by slicing the prostate perpendicular to the urethra as for a radical prostatectomy and then selecting the periurethral areas for histological examination. A few blocks from the peripheral zone of the prostate should also be included. The residual slices of the prostate may be submitted if prostatic adenocarcinoma is found. Blocks should be taken from the seminal vesicles to assess for tumour involvement.

Urethrectomy specimens[20] should be sampled in cross sections at 10 mm intervals and include sampling of the resection margins. Squamous carcinoma of the distal penile urethra is covered in the RCPath's *Dataset for Penile Cancer Histopathology Reports* (2nd edition in preparation).

For anterior exenteration specimens in females, if the bladder tumour is on the posterior wall and invasion into the uterus/cervix is suspected, transverse incisions should be made through the posterior wall of the bladder in continuity with the anterior half of the uterus and cervix to demonstrate the macroscopic extent of the tumour. Block selection of the uterus, cervix and vagina should include examination of these transverse slices. The vaginal resection margin should be sampled if the tumour appears in close proximity. This can either consist of a shave from the margin or longitudinal sections, depending on the individual circumstances of the case and location/distribution of the tumour.

Lymph nodes from the left and right iliacs and other node groups should be sent in different pots in accordance with the recommendations of TNM 7. If lymph nodes are received separately, these should be measured and described. They frequently consist of a rim of lymphoid tissue and abundant fat, making identification and dissection of individual nodes difficult. Lymph nodes should be identified by careful examination and palpation of the fat and all nodal tissue should be submitted. There should be a block key to enable the number of lymph nodes to be recorded, after correlation with the histological findings.

Blocks should include:

- ureteric and urethral margins
- tumour including the deepest point of invasion
- other mucosal abnormalities
- suspicious areas identified on imaging
- prostate and seminal vesicles to exclude involvement by urothelial carcinoma
- anterior wall of uterus, cervix and vagina to assess direct spread of tumour in continuity with the posterior bladder wall
- vaginal margin, if tumour appears in close proximity
- other representative blocks from included organs.
- all lymph nodes sent, including a block key to facilitate determination of the number of lymph nodes present

5 Core data items

Recommendations

5.1 Clinical information

It is good practice to include relevant clinical information in the report (see section 2).

5.2 Macroscopic data items

The type and site of specimen should be recorded. Tumour size is prognostically relevant to progression and outcome.[21–24] The presence or absence of perivesical fat invasion should specifically be recorded for cystectomy or diverticulectomy specimens. Multifocality of tumours is also a prognostic indicator in early stage bladder cancer and is predictive of recurrence.[25,26] In biopsies/TURs, it is not possible for pathologists to record this unless individual tumours are submitted separately. The presence or absence of resection margin involvement and site(s) of resection margin involvement should be noted for resection specimens. This needs to be correlated with the microscopic findings. If included, lymph nodes must be described and their site/s of origin must be specified.

5.3 Microscopic data items

5.3.1 Tumour types/variants

Tumours should be classified as urothelial, squamous or adenocarcinoma (the latter two must be pure to be so designated). Squamous or glandular differentiation within urothelial carcinoma is useful to mention and this may assist in interpretation of any subsequent biopsies of recurrences or metastases. Although cases with squamous or glandular differentiation are more likely to be seen in tumours of advanced grade and stage, there is no proven independent effect on survival after radical cystectomy compared with pure urothelial tumours.[27] Many other variants of urothelial carcinoma, including mixed forms, are recognised[6,7,8] and some behave more aggressively (for example small cell, micropapillary, nested and sarcomatoid variants). Mixed urothelial tumours are classified as urothelial carcinoma with divergent differentiation, specifying the variant element(s) present. In the proforma report for such tumours, more than one box should be ticked for each type of differentiation present, adding in the comments section any that do not appear on the proforma list. There is some evidence that the lymphoepithelioma-like variant, when pure or predominant, may respond better to chemotherapy rather than radical surgery or radiotherapy. Whether the lymphoepithelioma-like carcinoma element is pure or predominant should therefore be stated in the comments section for such tumours. Information on the relative percentages of urothelial carcinoma cases with other variant elements may optionally also be included as a comment, depending on local practice preferences. There is insufficient evidence to recommend recording the percentage of small cell carcinoma as a core data item and the presence of any component of small cell carcinoma or invasive micropapillary carcinoma, however limited, is considered to have adverse clinical significance.

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

5.3.2 Squamous tumours of the distal penile urethra

The majority of tumours of the distal penile urethra are squamous in type. These are dealt with in more detail in the RCPath penile tumours dataset and that document should be referred to when reporting such tumours (2nd edition in preparation).

5.3.3 Tumour classification and grade

Grading of urothelial tumours, particularly non-invasive neoplasms, is critical for prognostication and management. Revision of the well established 1973 WHO grading system[1] proposed by ISUP in 1998[28] led to the adoption of new classifications by the WHO in 1999 and 2004. The 1999 WHO classification incorporated papillary urothelial neoplasm of low malignant potential (PUNLMP) but retained a three-tier classification for carcinoma.[29] In contrast, the 2004 WHO that was identical to ISUP adopted a two-tier classification for carcinoma.[2]

These changes have been controversial and caused significant confusion among epidemiologists, pathologists and urologists. The systems cannot be easily mapped to each

other and this poses difficulties for cancer registration and comparison of results of recent studies with historic data.

The WHO 1973 system, which has been repeatedly validated,[26] remains the most widely used system in the UK. However, it has some significant drawbacks, particularly the vague definitions of the grades that led to a significant majority of non-invasive urothelial tumours being classed as grade 2. This formed a large heterogeneous group with tumours at the 'bad end' of the grade 2 spectrum having a significant risk of progression. On the other hand, even tumours showing very mild cytological atypia and associated with minimal risk of progression and normal life expectancy ('good grade 1 tumours') were classified as cancer (transitional cell carcinoma).

The ISUP/WHO 2004 system[2] provides detailed architectural and cytological criteria for the various grades of tumour. Adoption of a two-tier classification of carcinomas eliminated the issue of most tumours being categorised in the middle grade, while expansion of the high-grade category ensured that all patients likely to benefit would be offered more aggressive therapy. Moreover, the categorisation of tumours at the 'good end' of WHO 1973 grade 1 tumours as PUNLMP has avoided labelling these biologically indolent tumours as carcinomas. However, ISUP/WHO 2004 still classifies non-invasive tumours as cancers (in sharp contrast to tumour nomenclature in all other organs), with low-grade, non-invasive papillary tumours classed as carcinomas even though they have a much better prognosis than flat urothelial carcinoma *in situ*. This has led to calls for a more radical reclassification to be considered for non-invasive urothelial neoplasms.[30] The major problem with the 2004 WHO system remains its reproducibility, particularly in the distinction of PUNLMP from low-grade urothelial carcinoma. Since PUNLMP has been associated with a significant risk of recurrence/progression in some studies, treatment and follow-up regimes for PUNLMP are similar to low-grade urothelial carcinoma. Hence distinction between these two categories is not clinically critical and some experts have suggested abandoning PUNLMP.[31]

Some studies comparing WHO 1973 and 2004 grading systems have concluded that the latter is superior in predicting progression,[32,33] but the results of such studies would be largely dependent on the extremes of grade, as borderline cases in this morphological continuum would be equally distributed across the grade boundary. However, distinction between low-grade and high-grade would be clinically important for individual patients in the borderline grey zone as it could determine the need for immunotherapy, which is associated with significant morbidity. There is also evidence to suggest that high-grade (WHO 2004) tumours are heterogeneous and that prognostic information is lost if the two-tier ISUP/WHO 2004 system (based on ISUP 1998 grade) is used in isolation.[34,35]

The aim of any grading system should be to provide the clinician an accurate indication of where a particular tumour lies in the morphological and clinical continuum. In clinical practice, tumour grade is used in conjunction with clinical prognostic factors such as size and multiplicity of tumours, number of recurrences and interval to first recurrence. Comparison of a set of non-invasive papillary urothelial tumours using the criteria for both grading systems illustrates that the high-grade group contains a much broader spectrum of tumours than grade 3 in WHO 1973. Only 4.5% of cases were classified as grade 3, whereas 21.6% of the same cases were classified as high-grade carcinoma using WHO/ISUP criteria (on which WHO 2004 is based) by one expert group.[36] Thus, as shown in Table 1 these systems of classification do not directly align with each other. Use of both grading schemes in parallel would provide better stratification for non-invasive papillary urothelial tumours. This is especially so when grading is combined with the additional factors mentioned above and would minimise the clinical consequences of assigning the 'wrong' grade for cases that are borderline between grades in either scheme. In reality, tumour grade is a clinical and morphological continuum, which (other than for tumour at the extreme ends of the grading spectrum) is subject to problems of inter- and intra-observer reproducibility.

In view of the above considerations, we recommend the concurrent use of both grading systems (WHO 1973 and 2004) for urothelial neoplasms, as had been recommended in the previous edition of this dataset. Pathologists should focus in particular on the sub-categorisation of grade 2, non-invasive urothelial tumours into low grade and high grade.

Although subdivision of grade 1 into PUNLMP or low-grade is of limited clinical importance, the authors have adopted the pragmatic approach of using the entire WHO 2004 classification alongside WHO 1973, rather than a selected portion of it. All grade 3 tumours are high grade. Tumours not infrequently are of mixed grade and in this situation the highest grade should be used for the overall assessment, though the proportions of elements of differing grades may be mentioned in a descriptive comment.

Table 1: The 1973 and 2004 WHO grading systems for urothelial carcinoma

Squamous carcinoma or adenocarcinoma should be graded as well, moderately or poorly differentiated. Tumour variants such as small cell carcinoma, micropapillary carcinoma or sarcomatoid carcinoma often occur mixed with areas of urothelial carcinoma rather than in pure form. The presence of these variant features indicates a high-grade tumour by definition.[6,7,8] The grade of the conventional urothelial element present can be given (it will usually be high grade) with a comment regarding the prognostic significance of the variant component. WHO grading of the variant elements is not recommended and low-grade small cell carcinoma or sarcomatoid urothelial carcinoma do not exist. For nested variant urothelial carcinoma, a comment regarding potential for aggressive behaviour is applicable and conventional grading may be misleading in this subtype due to the relatively bland cytological features typically seen.

[Histological grade is important for prognostication – Level of evidence B.]

5.3.4 Associated carcinoma *in situ* (CIS)

The presence and extent of associated CIS is a criterion for selection for intravesical BCG therapy, and failure to respond to initial treatment is a risk factor for subsequent progression.[37] Carcinoma *in situ* may occur in the immediate vicinity of a tumour and/or further away from a tumour, for example in separate biopsies sent with a TUR specimen and the proformas allow for recording of this information in summarised form. The site(s) of separate positive biopsies should be specified in the 'Further comments' section if applicable, as this may have a bearing on subsequent management decisions.

[Level of evidence C.]

5.3.5 Lymphovascular invasion (LVI)

Despite previous legitimate criticism of the quality of some of the evidence,[38] the presence of LVI is generally considered to predict poor outcome.[39,40] The presence or absence of LVI must be noted in the microscopic report for invasive carcinoma, when assessable (this may not be possible for some very superficial biopsies). LVI should be reported as being present only when it is unequivocal. There is potential to mistake retraction artefact around tumour cells for LVI and immunohistochemistry for endothelial markers may be helpful in selected

cases. In radical cystectomy specimens with stratification for LVI, its presence was strongly and independently associated with recurrence and adverse outcome in lymph node negative patients.[41] LVI has been associated with increased risk of progression and adverse survival in stage T1 tumours diagnosed in TUR specimens.[42,43]

[Lymphovascular invasion predicts disease progression and adverse survival – Level of evidence B.]

5.3.6 Tumour stage, margin and nodal status

TNM 7th edition is recommended for tumour staging (Appendix A), bearing in mind the comments below about the TNM classification of small biopsy and TUR specimens. Stage is an important predictor of outcome. The TNM classification is produced by the International Union Against Cancer (UICC) in joint collaboration with the American Joint Committee on Cancer (AJCC). These organisations produce staging schema that are uniform between the two organisations for each update of the staging classification. Extent of tumour invasion and spread of tumour to nodal sites are powerful prognostic indicators.

One of the general rules of the TNM classification[4] is that "The pathological assessment of the primary tumour (pT) entails a resection of the primary tumour or a biopsy adequate to evaluate the highest pT category". The current AJCC staging manual,[44] which elaborates on the staging rules in some detail, states (regarding pathologic staging for bladder tumours): "Pathologic staging is based on the histologic review of the radical or partial cystectomy specimen. Microscopic examination and confirmation of extent are required. Total cystectomy and lymph node dissection are generally required for this staging; however, a pathologic staging classification should be given for partial cystectomy specimens". In the staging proformas throughout the AJCC manual, pathologic stage is prefaced by the qualifying remark: "Extent of disease through completion of definitive surgery".

This means that pathological (pT) classification requires not only (1) tissue enabling histological examination, *but also* (2) tissue that is adequate and sufficient for the pathologist to have reasonable confidence that it is representative of the whole tumour in terms of its extent, specifically that the deepest point of invasion of the whole tumour (not just of the submitted specimen in the case of a biopsy or TUR) is actually represented. TNM recognises that "There is a problem in the classification of bladder tumours after transurethral resection. The precondition for pT1 can only be met in cases of complete tumour resection, i.e. resection of all grossly visible tumour tissue from the remaining grossly tumour-free adjacent bladder wall (deep and laterally). If these additionally and separately submitted tissues are histologically negative, a complete resection can be assumed. Only in such patients can pT1 be considered".[45]

It is clear that unqualified use of pTa, pT1, pT2 (as is common practice) for small biopsies and many TUR specimens is therefore contrary to TNM/UICC staging definitions. The TNM editors (Wittekind C, personal communication, with responses copied to Sobin L and Gospodarowicz M) were consulted for specific guidance and recommend the following.

1. For small biopsies: use T rather than pT.

2. For TURs when no separately sent lateral and deep tissue received: use T rather than pT.

3. For TURBTs where adequate deep *and lateral tissue* received, not involved by tumour: use pT1 for tumours invading lamina propria but not invading muscularis propria (muscularis propria **must** be present in the sample to assess this).
   For tumours invading muscularis propria (detrusor muscle), use T2.

4. For single piece *en-bloc* transurethral resections (even though not commonly performed currently) that contain muscularis propria and have negative margins: pT1 is appropriate for tumours invading lamina propria but not invading muscularis

propria (detrusor muscle).
For tumours invading muscularis propria (detrusor muscle), use T2.

5. For biopsies/TURs with T1 invasive carcinoma where *either*:
   a. no muscularis propria present
   or
   b. smooth muscle present but of indeterminate type:

   use T1 but add comment "at least" to denote that there is a distinct possibility of higher T stage and early re-resection is required.

6. For definitive resection specimens, e.g. cystectomy: use pT.

During the consultation process for this dataset, the few respondents who commented on the issue had reservations about adopting the above TNM/AJCC recommendations for biopsy/TUR specimens. Use of pT rather than T classification (based on what is seen in biopsy material submitted, regardless of likelihood of representation of the true maximum extent of tumour) is deeply entrenched and comments received suggested that TNM/AJCC staging recommendations may not be followed. The draft sent for consultation has therefore been amended to adopt continuation of using pT rather than T classification, irrespective of specimen type (biopsy, TUR or definitive resection), even though this is contrary to TNM advice. In practice, there is unlikely to be any adverse consequence for patients because pathologists and urologists generally understand the staging limitations of small specimens. However, given the TNM/AJCC definition of pT rather than T tumour classification, it is crucial that epidemiologists and tumour registries fully comprehend that 'pT' category cancer data derived from a UK pathology report for either a bladder biopsy or TURBT may not necessarily correspond with the pT category of the same tumour by TNM/AJCC definitions. For the situations mentioned in 5a or 5b in the preceding paragraph, a comment to indicate that pT is "at least" should be added under 'Further comments' for the reason stated above.

pTX is reserved for cases of any specimen type containing tumour but with crush, diathermy artefact, etc. that precludes any attempt at TNM classification.

For tumours invading only the lamina propria, the depth and extent of invasion correlates with outcome, although there is no international agreement on which method should be used for this assessment (see section 6.2). For tumours invading muscularis propria (detrusor muscle), subdivision in cystectomy specimens into pT2a and pT2b according to inner and outer half of the muscularis propria (detrusor muscle)[46] or macroscopic (pT3b) *versus* microscopic (pT3a) extension into perivesical fat[47,48] had prognostic significance in several studies, although one group detected no difference in outcome between these stage categories.[49,50] Note that fat can be present normally in all layers of the bladder wall and tumour involvement of fat *per se* in biopsy/TUR material is not necessarily indicative of perivesical fat involvement.

[Tumour stage predicts outcome – Level of evidence A.]

In diverticulectomy specimens, staging may be difficult as the muscularis propria (detrusor muscle) may be absent in the attenuated wall and the muscularis mucosae may be hyperplastic. The pT2 category will not be applicable for tumour in a diverticulum lacking muscularis propria. pT1 should be used for invasive tumours involving up to and including the muscularis mucosae, but not beyond. pT3 will be applicable for invasion into perivesical tissue.

If the smooth muscle that is present in bladder biopsy/TURBT cases is indeterminate in type, this should be indicated – as alluded to above. It is important to state whether muscularis propria (detrusor muscle) is present or absent in bladder biopsies and TURBTs, especially in T1 tumours. Absence of muscularis propria (detrusor muscle) should prompt early re-

resection in most instances (following MDT discussion). Ideally, tumour base biopsies should be performed at initial resection to sample muscularis propria (detrusor muscle), and submitted in a separate container.

An alternative TUR method, the *en bloc* resection of bladder tumours, allows better specimen orientation for staging purposes[51,52] and completeness of excision can be more readily assessed, but this is not standard practice at present. Routine early re-resection following standard TUR is performed in some centres to ensure complete excision, as complete eradication of all visible tumours at first resection is not always achieved.[53]

Urothelial tumours involving/arising from the prostatic urethra and/or prostatic ducts with a concurrent bladder tumour are staged separately as though they were primary bladder and urethral tumours. Such tumours should not be classified as T4 bladder cancer unless they directly invade the prostatic stroma by invasion through the full thickness of the bladder wall. Subepithelial invasion of the prostatic urethra or stroma from the urethra does not constitute T4 bladder cancer.[44]

Positive margin status confers a worse outcome.[54] Five-year cancer-specific survival rates are much less for those with positive surgical margins.[54] Positive soft tissue margins are associated with an increased risk of local recurrence and cancer-specific mortality after cystectomy.[54,55] Distance of tumour to the nearest resection margin is not a core requirement (although it can be mentioned in a comment). Although it might be clinically important, it is not yet validated or in regular use for clinical management. This is in accordance with the most recent College of American Pathologists (CAP) guidelines.[56]

[Positive margins predict recurrence and cancer specific mortality – Level of evidence A.]

The number of positive lymph nodes and lymph node density, defined as the ratio of positive nodes to the total number of nodes sampled,[57] are predictors of cancer survival. The presence of nodal extracapsular spread confers a worse outcome and decreased recurrence free survival.[58,59,60] The size of metastatic nodal deposits needs to be taken into account for pN staging in nephroureterectomy and urethral tumours (see Appendix A).

[Nodal status predicts survival – Level of evidence B.]

Core data items: radical resections

Clinical

- Relevant clinical information, including previous histology or cytology.
- Nature of specimen/procedure.

Pathological

- **Macroscopic**
  - Tumour location
  - Number of tumours
  - Tumour size (largest) in millimetres
  - Extent of invasion (NB for bladder upstages to pT3b if seen macroscopically to extend into perivesical fat)
  - Positive margin(s) and sites
  - Lymph nodes present and their anatomical location(s)
  - Macroscopic size of largest metastasis, if grossly visible, in regional lymph nodes for tumours of renal pelvis, ureter or urethra (size of largest metastasis required for pN classification; may not be assessable by histology alone, if large).

- **Microscopic**
  - Tumour type (including variants of urothelial carcinoma and presence of divergent differentiation)
  - Tumour grade (both 1973 and 2004 WHO recommended)
  - Presence or absence of associated CIS; whether CIS adjacent to and/or away from tumour
  - Lymphovascular invasion
  - Tumour TNM classification (7th edition)
  - Margin status
  - Nodal status with sites and total number of nodes, number involved and presence or absence of extracapsular spread
  - Size of largest lymph node metastasis for tumour of the renal pelvis, ureter or urethra
  - Cystoprostatectomy: presence of prostatic adenocarcinoma with grade, stage and margin status.

Core data items: biopsies/TUR

Clinical

- Relevant clinical information including previous histology or cytology
- Nature of specimen/procedure

Pathological

- **Macroscopic**
  - Tissue size (for biopsies) or weight (for TUR)

- **Microscopic**
  - Tumour type (including variants of urothelial carcinoma and presence of divergent differentiation)
  - Tumour grade (both 1973 and 2004 WHO recommended)
  - Lymphovascular invasion
  - Presence or absence of associated CIS; whether CIS adjacent to or away from tumour (if assessable in separate biopsies)
  - Tumour TNM classification (7th edition). An additional comment “at least” should be appended for pT1 tumours in the specified circumstances stated in 5.3.6 (points 5a and 5b).
  - If TUR tissue includes prostate, whether there is prostatic involvement and extent of involvement (i.e. whether urothelial carcinoma *in situ* in prostatic ducts or prostatic stromal invasion).

6 Non-core data items

6.1 Urothelial dysplasia not amounting to carcinoma *in situ*

Since this does not influence patient treatment and is not recorded by UK cancer registries, it has been classified as a non-core data item. However, *de novo* dysplasia (which is described[61] but should be diagnosed with caution) would require follow-up[61] and dysplasia in background, flat urothelium adjacent to a papillary urothelial neoplasm suggests an unstable urothelium with a higher risk of recurrence.

6.2 Substaging of T1 urothelial carcinoma

Some studies suggest that substaging of pT1 urothelial carcinoma in TURBTs may be prognostically significant. However, there is currently no consensus on how these tumours should be substaged, with various studies suggesting criteria such as depth of invasion with respect to muscularis mucosae/vascular plexus[62,63] or else depth measured in millimetres.[64] A recent paper suggests categorising pT1 tumours as either microinvasive or extensively invasive based on the depth of invasion and the number of foci of microinvasion.[65] However, it is often difficult to substage tumours accurately in TURBTs due to issues related to tangential sectioning, inconsistency of the muscularis mucosae layer and variations in the lamina propria vascular plexus.[11] More studies are required to validate the prognostic significance of substaging systems based on ocular micrometer measurements. Hence this data item is classified as non-core.

6.3 Molecular markers

Recently, biomarkers (immunohistochemical and molecular) have been proposed to predict risk of recurrence and progression in patients with Ta/T1 bladder cancer and identify patients that would benefit from early aggressive management.[66] However, their clinical utility remains to be validated.

7 Diagnostic coding and staging

7.1 Staging

TNM classification

The 7th edition of TNM is recommended[4] (see Appendix A).

7.2 Diagnostic coding

Coding is recommended and is useful for data retrieval, workload measurement and audit. SNOMED coding should be applied (see Appendix B).

Morphologic coding of non-invasive urothelial neoplasia poses particular problems. Traditionally, non-invasive papillary urothelial carcinoma (Ta) has been coded as M81303, which is inappropriate as the behaviour code represented by the last digit (3) would indicate an invasive tumour.

Comments received during the drafting stages of the dataset indicate that UK Cancer Registries currently code grade 1 and grade 2 non-invasive tumours as M81301 and grade 3 tumours as M81302. However, when translated to the WHO 2004 classification, these codes apply to PUNLMP (M81301) and to low-grade and high-grade carcinoma (M81302) respectively. Going forward, in order to be comparable to international data we recommend that the UK Cancer Registries consider coding according to the WHO 2004 classification for non-invasive papillary urothelial tumours, whereby the majority of non-invasive papillary urothelial tumours (all those except for PUNLMP) would be coded as M81032. This would then map to international data. A possible solution for the Cancer Registries to differentiate between low- and high-grade carcinoma is using a sixth digit, such that low-grade carcinoma is M810321 and high-grade carcinoma is M810323, as recommended by the ICD-0 SNOMED codes specified in WHO 2004. The feasibility of this recommendation for the Cancer Registries would depend on pathologists across the UK using the WHO 2004 grading classification and using IT systems that can adapt to accommodate these codes. A comparison of SNOMED systems is given in Table 2 in Appendix B.

8 Reporting of small biopsy specimens

The presence or absence of papillary tumour and/or flat abnormalities (reactive atypia, dysplasia, CIS) should be stated. CIS has a number of morphological variants[67,68] and there are also various subtypes of bladder cancer that should be mentioned, if present.[6,7,8]

Neoplastic changes such as CIS often lead to loss of epithelial cell cohesion and the surface may be almost totally denuded, hence the need for levels. If surface epithelium is denuded, cytological follow-up would be advisable with clinical correlation. For TURBT specimens, ideally all of the tissue should be submitted, particularly for re-resections following a previous diagnosis. If not all embedded, then as a minimum the first 20 g or ten cassettes should be processed, plus at least one cassette for every additional 5 g. Further tissue should always be submitted if no muscularis propria (detrusor muscle) is identified in the sections, until the entire specimen has been processed. This is important to avoid staging error due to inadequate sampling of the specimen. For both small biopsies and TURBT specimens, the presence or absence of muscularis propria (detrusor muscle) should be stated. If the smooth muscle that is present is indeterminate in type, this should also be indicated.

Biopsies showing flat abnormalities should be assessed primarily by morphology, although immunohistochemistry may be of value in a proportion of cases. The markers most commonly used in conjunction with the morphology to assist in the separation of dysplasia/CIS from normal/reactive changes are CK20, CD44s and p53.[69,70] MIB-1 has also been used in this context and although increased staining can overlap in different disease states, a negative MIB-1 may be helpful since CIS is less likely. Immunohistochemistry does not help to distinguish urothelial dysplasia from CIS; a distinction that is based on morphology. These markers can be used individually, but are available commercially as a combined cocktail using different chromogens.

For tumours, the subtype, grade (both 1973 and 2004 WHO) and pT category should be reported; see section 5.3.6 regarding issues related to pT categorisation in bladder biopsies and TURBT specimens. Any abnormalities in flat urothelium elsewhere (e.g. CIS) should be reported, if assessable.

9 Reporting of frozen sections

Intraoperative frozen sections may be used to assess ureteric and urethral specimen margins at cystectomy and occasionally the ureteric margin at nephroureterectomy. Generally, only invasive carcinoma and CIS can be diagnosed on frozen sections as freezing artefact precludes reliable identification of urothelial dysplasia in these specimens.

The clinical utility of frozen section examination of these margins is controversial as skip lesions of multifocal CIS may result in false-negative frozen sections. Frozen sections of the urethral margin are usually performed only in cases of bladder reconstruction. In general, urethral frozen sections are more critical as a false-positive diagnosis would preclude bladder reconstruction. In contrast, a false-positive ureteric frozen section would only result in unnecessary excision of an additional segment of ureter.

Segments of ureter submitted for frozen section should be orientated preferably with a stitch at the end opposite the resection margin to avoid disrupting the margin from which the frozen section is taken. There should always be a clear understanding between the pathologist and surgeon as to the meaning of the terms ‘proximal’ and ‘distal’ (regarding excision margins, e.g. ureter with respect to kidney versus ureter with respect to bladder) to avoid any ambiguity of interpretation. Urethral frozen sections are difficult, especially in cystoprostatectomy specimens in which the urothelium at the specimen margin tends to retract into the specimen. In contrast to frozen sections from radical prostatectomy specimens for prostate cancer, the urethral margin section from cystoprostatectomy

specimens should therefore be taken a little deeper to include the urethral urothelium. In view of this technical difficulty in examining urethral margins as well as false negativity due to multifocality of CIS, urethral biopsies prior to radical surgery are preferred and routine intraoperative frozen sections of urethral margins are to be discouraged.

Routine frozen section examination of pelvic lymph nodes at cystectomy is not recommended due to problems with histological sampling. Frozen sections should be limited to lymph nodes that appear to be grossly involved by tumour.

10 Criteria for audit of the dataset

The availability of pathology reports and data at MDT meetings:

- 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.

Recommended by the RCPath as key performance indicators (www.rcpath.org):

- SNOMED T, M and P coding: standard 95% by April 2012 and 100% by April 2014
- core data items in report: standard 90% present
- excisions using template or proforma and including dataset information: standard 80% by April 2012 and 90% by April 2014
- diagnostic biopsies reported within 7 days: standard 80% by April 2012 and 90% by April 2014
- all histopathology specimens reported within 10 calendar days: standard 80% by April 2012 and 90% by April 2014.

11 Acknowledgements

The authors are indebted to Dr Patricia Harnden, consultant histopathologist at St James's University Hospital, Leeds, and her team of coordinators for the solid foundation laid by the first edition of this dataset, upon which this second edition has been built. We are also most grateful to Dr Harnden for her comments on the first draft manuscript.

We also thank Professor Noel Clarke, consultant urologist at The Christie and Salford Royal NHS Foundation Trusts, for his comments on the first draft manuscript.

We are grateful to Dr Jon Oxley, consultant histopathologist at Southmead Hospital, Bristol, for invaluable assistance regarding SNOMED and for the information in Appendix B that allows comparison of codes across the different SNOMED systems.

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Appendix A TNM classification of malignant tumours (7th edition 2009)[4]

For the purposes of clarity, <u>all</u> changes from 6th edition to 7th edition TNM are highlighted by underlined text in this Appendix. Italicised text in square brackets denotes an explanatory note added by the authors of this dataset.

RENAL PELVIS AND URETER

pT	**Primary tumour**
pTX	Primary tumour cannot be assessed
pT0	No evidence of primary tumour
pTa	Non-invasive papillary carcinoma
pTis	Carcinoma *in situ*
pT1	Tumour invades subepithelial connective tissue
pT2	Tumour invades muscularis
pT3	(Renal pelvis): Tumour invades beyond muscularis into peripelvic fat or renal parenchyma (Ureter): Tumour invades beyond muscularis into periureteric fat
pT4	Tumour invades adjacent organs or through the kidney into perinephric fat

pN	Regional lymph nodes *[defined in 7th edition TNM as "hilar, abdominal para-aortic and paracaval nodes and, for the ureter, intrapelvic nodes"]*
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis*
pN1	Metastasis to a single lymph node 2 cm or less in greatest dimension *[refers to the size of the largest metastasis, not the size of the largest lymph node]***
pN2	Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension *[refers to the size of the largest metastasis]*
pN3	Metastasis in a lymph node more than 5 cm in greatest dimension *[refers to the size of the largest metastasis]*

*pN0 (i+)	Isolated tumour cells [defined as "single tumour cells or small clusters of tumour cells (in a regional lymph node) not more than 0.2 mm in greatest extent that can be detected by routine H&E stains or immunohistochemistry"]
**pN1(mi)	Micrometastasis (defined as a metastasis in a regional lymph node >0.2 mm but ≤2.0 mm)

pM	**Distant metastasis**
pM1	Distant metastasis

[Categories pMX and pM0 have been removed in 7th edition TNM.
M0 can only be assigned as a clinical stage, not as a pathological stage]

Stage grouping

Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IV	T4	N0	M0
	Any T	N1, N2, N3	M0
	Any T	Any N	M1

URINARY BLADDER

pT **Primary tumour**

pTX Primary tumour cannot be assessed

pT0 No evidence of primary tumour

pTa Non-invasive papillary carcinoma

pTis Carcinoma *in situ*

pT1 Tumour invades subepithelial connective tissue

pT2 Tumour invades muscle *[the term 'muscle' here means 'muscularis propria (detrusor muscle) not muscularis mucosae']*

- pT2a Tumour invades superficial muscle (inner half)
- pT2b Tumour invades deep muscle (outer half)

pT3 Tumour invades perivesical tissue

- pT3a microscopically
- pT3b macroscopically

pT4 Tumour invades any of the following: prostate <u>stroma, seminal vesicles,</u> uterus, vagina, pelvic wall, abdominal wall

- pT4a Tumour invades prostate <u>stroma, seminal vesicles,</u> uterus or vagina
- pT4b Tumour invades pelvic wall or abdominal wall

pN **Regional lymph nodes** *[defined in 7th edition TNM as "the nodes of the true pelvis which essentially are the pelvic nodes below the bifurcation of the common iliac arteries but include the lymph nodes along the common iliac artery too" – see also node groups specified below]*

pNX Regional lymph nodes cannot be assessed

pN0 No regional lymph node metastasis*

pN1 <u>Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac or presacral)</u>**

pN2 Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac or presacral)

pN3 <u>Metastasis in a common iliac lymph node(s)</u>

*pN0 (i+) Isolated tumour cells [defined as “single tumour cells or small clusters of tumour cells (in a regional lymph node) not more than 0.2 mm in greatest extent that can be detected by routine H&E stains or immunohistochemistry”]

**pN1(mi) Micrometastasis (defined as a metastasis in a regional lymph node >0.2 mm but ≤2.0 mm)

pM Distant metastasis

pM1 Distant metastasis

[Categories pMX and pM0 have been removed in 7th edition TNM. M0 can only be assigned as a clinical stage, not as a pathological stage]

Stage grouping

Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a,b	N0	M0
Stage III	T3a,b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1, N2, N3	M0
	Any T	Any N	M1

URETHRA

pT Primary tumour

pTX Primary tumour cannot be assessed

pT0 No evidence of primary tumour

Urethra (male and female)

pTa Non-invasive papillary, polypoid or verrucous carcinoma*

*[*Most verrucous carcinomas arise from the penile skin rather than urethra; readers are referred to the penile dataset for clarification]*

pTis Carcinoma *in situ*

pT1 Tumour invades subepithelial connective tissue

pT2 Tumour invades any of the following: corpus spongiosum, prostate, periurethral muscle

pT3 Tumour invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension) *[text “anterior vagina” omitted from TNM 7]*

pT4 Tumour invades other adjacent organs (invasion of the bladder)

Urothelial (transitional cell) carcinoma of the prostate

pTis pu	Carcinoma *in situ*, involvement of prostatic urethra
pTis pd	Carcinoma *in situ*, involvement of prostatic ducts
pT1	Tumour invades subepithelial connective tissue (for tumours involving prostatic urethra only)
pT2	Tumour invades any of the following: corpus spongiosum, prostate, periurethral muscle
pT3	Tumour invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
pT4	Tumour invades other adjacent organs (invasion of bladder).

pN **Regional lymph nodes** *[defined in 7th edition TNM as the inguinal and the pelvic nodes]*

pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis*
pN1	Metastasis in a single lymph node 2 cm or less in greatest dimension *[refers to the size of the largest metastasis, not the size of the largest lymph node]***
pN2	Metastasis in a single lymph node more than 2 cm in greatest dimension, or in multiple lymph nodes *[refers to the size of the largest metastasis]*

*pN0 (i+) Isolated tumour cells [defined as "single tumour cells or small clusters of tumour cells (in a regional lymph node) not more than 0.2 mm in greatest extent that can be detected by routine H&E stains or immunohistochemistry"]

**pN1(mi) Micrometastasis (defined as a metastasis in a regional lymph node >0.2 mm but ≤2.0 mm)

pM **Distant metastasis**

pM1 Distant metastasis

[Categories pMX and pM0 have been removed in 7th edition TNM.
M0 can only be assigned as a clinical stage, not as a pathological stage]

Stage grouping

Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
	Tis pu	N0	M0
	Tis pd	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T3	N0, N1	M0
Stage IV	T4	N0, N1	M0
	Any T	N2	M0
	Any T	Any N	M1

Appendix B SNOMED codes

Topographical codes (T) and morphological codes (M)

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

SNOMED versions

Different versions of SNOMED are in use and are compared in Table 2 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 the same 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 (it is 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 2: A comparison of SNOMED 2 or 3 with SNOMED CT codes

Topographical codes	SNOMED 2 or 3	SNOMED CT terminology	SNOMED CT code
Kidney	T-71000	Kidney structure (body structure)	64033007
Kidney, right	T-71010	Right kidney structure (body structure)	9846003
Kidney, left	T-71020	Left kidney structure (body structure)	18639004
Renal pelvis	T-72000	Renal pelvis structure (body structure)	25990002
Renal pelvis, right	T-72010	Structure of right renal pelvis (body structure)	54444007
Renal pelvis, left	T-72020	Structure of left renal pelvis (body structure)	38594006
Ureter	T-73000	Ureteric structure (body structure)	87953007
Ureter, right	T-73010	Structure of right ureter (body structure)	25308007
Ureter, left	T-73020	Structure of left ureter (body structure)	26559004
Urinary bladder	T-74000	Urinary bladder structure (body structure)	89837001
Urethra	T-75000	Urethral structure (body structure)	13648007

Morphological codes	SNOMED 2 or 3	SNOMED CT terminology	SNOMED CT code
Papillary urothelial neoplasm of low malignant potential	M81301	Papillary transitional cell neoplasm of low malignant potential (morphologic abnormality)	128625004
Papillary urothelial neoplasm, non-invasive, low grade or high grade	M81302	Papillary transitional cell carcinoma, non-invasive (morphologic abnormality)	128877008
Urothelial carcinoma *in situ*	M-81202	Transitional cell carcinoma *in situ* (morphologic abnormality)	53530009
Invasive urothelial carcinoma	M-81203	Transitional cell carcinoma (morphologic abnormality)	27090000
Squamous carcinoma *in situ*	M-80702	Squamous cell carcinoma *in situ*, no ICD-O subtype (morphologic abnormality)	59529006
Squamous carcinoma	M-80703	Squamous cell carcinoma, no ICD-O subtype (morphologic abnormality)	28899001
Adenocarcinoma	M-81403	Adenocarcinoma, no subtype (morphologic abnormality)	35917007
Small cell carcinoma	M-80413	Small cell carcinoma (morphologic abnormality)	74364000
Sarcomatoid carcinoma	M-81223	Transitional cell carcinoma, spindle cell (morphologic abnormality)	112676006

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 Histopathology reporting proforma: radical resections of renal pelvis and/or ureter

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

Relevant clinical information/associated or previous specimens (histology and/or cytology)

Macroscopy

Nature of specimen/procedure

Ureter: left □ Nephroureterectomy: left □
right □ right □

Tumour location……
Number of tumours…….
Maximum tumour size (mm)…… *or* No obvious tumour visible macroscopically □

Resection margins: Not assessable □
(Macroscopically visible lesions) Not involved □ Involved □
Site(s)……

Lymph nodes: Present □ Absent □
Site of lymph nodes……..

Size of largest visible regional lymph node metastasis……. *or* Not applicable □

Microscopy

Tumour subtypes (1 or more)
- Urothelial carcinoma □
- Squamous carcinoma □
- Adenocarcinoma □
- Micropapillary carcinoma □
- Small cell carcinoma □
- Sarcomatoid carcinoma □
- Other (specify) □ ……..

Comment: ……..

Associated CIS: Yes □ No □
Not assessable □

For CIS:
- Adjacent to tumour □
- Elsewhere □
- Not applicable □

WHO 1973 **WHO 2004**
PUNLMP □

For urothelial carcinoma:

Grade 1 □ Low grade □
Grade 2 □
Grade 3 □ High grade □

For squamous or adenocarcinoma:
- Well differentiated □
- Moderately differentiated □
- Poorly differentiated □

Lymphovascular invasion:
Yes □ No □ Not assessable □

Resection margins: Not assessable □
Not involved □
Involved □ Site(s)……

Regional lymph nodes:
Not applicable □
Total number …….
Number +ve …….
Size of largest regional nodal metastasis……. *or* Not applicable □
Extracapsular spread: Yes □ No □ Not applicable □

Other disease process(es) present/comments …….....

.....

---

pTNM classification: pT…… pN…….. pM*……

*pM should either be pM1 or entered as not applicable (N/A)

TNM edition number used……..

SNOMED codes T……

M……..

Further comments:

Pathologist……..... **Date……..**

Appendix D Histopathology reporting proforma: transurethral specimens (biopsy or TUR)

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

Relevant clinical information/associated or previous specimens (histology and/or cytology)

Site of the specimen

Renal pelvis □
Ureter □
Bladder □ Site(s) in bladder (if known)…….
Prostate/prostatic urethra □
Urethra (other) □

Macroscopy

Nature of specimen/procedure
Biopsy □
TUR □ Weight of TUR…….(g)

Microscopy

Tumour subtypes (one or more):
- Urothelial carcinoma □
- Squamous carcinoma □
- Adenocarcinoma □
- Micropapillary carcinoma □
- Small cell carcinoma □
- Sarcomatoid carcinoma □
- Other □
  Please specify…….

Comment:……..

Associated CIS:
Yes □ No □ Not assessable □

CIS:
Adjacent to tumour □
Elsewhere (in ≥1 separate biopsy) □
Not applicable □

Lymphovascular invasion
Yes □ No □ Not assessable □

WHO 1973 **WHO 2004**
PUNLMP □

For urothelial carcinoma:

Grade 1 □ Low grade □
Grade 2 □
Grade 3 □ High grade □

For squamous or adenocarcinoma:
Well differentiated □
Moderately differentiated □
Poorly differentiated □

Muscularis propria present in the biopsy/TUR:
Yes □
No □
Indeterminate □ (smooth muscle present but impossible to be certain whether muscularis mucosae or muscularis propria)
Not applicable (e.g. for prostatic urethra biopsy) □

TNM classification

Refer to Appendix A for TNM classification criteria according to site of biopsy/TUR.

pT……..

In a biopsy or TUR of prostate/prostatic urethra involved by invasive urothelial carcinoma, it may not be possible to determine from the specimen whether prostatic stromal invasion represents invasion of bladder cancer into the prostate (T4 bladder cancer) or prostatic stromal invasion from a carcinoma of the urethra (which could be a stage T2 urethral tumour depending on its overall extent). Tick here if this applies □

TNM edition number used……..

Other disease process(es) present/comments (if applicable) ..…….....

SNOMED codes

T……

M……..

Further comments:

Pathologist……..... **Date……..**

Appendix E Histopathology reporting proforma: urinary bladder (cystectomy or diverticulectomy)

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

Relevant clinical information/associated or previous specimens (histology and/or cytology)

Macroscopy

Nature of specimen/procedure

Radical cystectomy □ Tumour location……..
Partial cystectomy □ Maximum tumour size..... (mm)
Diverticulectomy □ Number of tumours…….
Or no obvious tumour visible macroscopically □

Other tissues/organs included…….....

Abnormalities in other tissues/organs included…….

Invasion into perivesical tissue (as assessed macroscopically) i.e. pT3b:

Yes □ No □ Not assessable □

Resection margins: Not assessable □ Not involved □ Involved □
Site(s)…….

Comments…….

Regional lymph nodes present:

Right Yes □ No □
Left Yes □ No □

Other lymph nodes

Yes □ Specify site (if applicable)…….. No □

Microscopy

Tumour subtypes (one or more):
- Urothelial carcinoma □
- Squamous carcinoma □
- Adenocarcinoma □
- Micropapillary carcinoma □
- Small cell carcinoma □
- Sarcomatoid carcinoma □
- Other □
  Please specify……

Comment……..

Associated CIS:
Yes □ No □

CIS:
- Adjacent to tumour □
- Elsewhere □
- Not applicable □

WHO 1973 **WHO 2004**
PUNLMP □

For urothelial carcinoma:

Grade 1 □ Low grade □
Grade 2 □
Grade 3 □ High grade □

For squamous or adenocarcinoma:
Well differentiated □
Moderately differentiated □
Poorly differentiated □

Lymphovascular invasion: Yes □ No □ Not assessable □

Other disease process(es) (if present)/comments (if applicable)……

Resection margins: Not assessable □ Not involved □
Involved □ Site(s)…….

Regional lymph nodes:
Not sent □

Right Total ….
Number positive….
Extracapsular spread:
Yes □ No □ Not applicable □

Left Total ….
Number positive ….
Extracapsular spread:
Yes □ No □ Not applicable □

Is a common iliac lymph node involved within regional lymph nodes (pN3)?
Yes □ No □ Not assessable □

Other lymph nodes involved? (pM1 if involved)
Not applicable □
Involved □ Total number present…… Number involved……
Extracapsular spread: Yes □ No □ Not applicable □
Not involved □

---

pTNM classification: pT…… pN…….. pM*……

*pM should either be pM1 or entered as not applicable (N/A)

TNM edition number used……..

SNOMED codes T……

M……..

Further comments:

Pathologist……..... **Date……..**

Appendix F Histopathology reporting proforma: urethrectomy or urethral diverticulectomy

(For squamous tumours of distal penile urethra refer to RCPath penile dataset, 2nd edition)

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

Relevant clinical information/associated or previous specimens (histology and/or cytology)

Macroscopy

Nature of specimen/procedure

Urethrectomy □ Tumour location……..
Urethral diverticulectomy □ Maximum tumour size..... (mm)
Number of tumours…….
Or no obvious tumour visible macroscopically □
Other tissues/organs included…….....
Abnormalities in other tissues/organs included…….

Resection margins:
Not assessable □
Not involved □
Involved □ Site(s)…….
Comments…….

Regional lymph nodes present (see Appendix A for definition):
Yes □ Specify site(s) if applicable…….
No □

Other lymph nodes
Yes □ Specify site(s) if applicable…….
No □

Microscopy

Tumour subtypes (1 or more)
- Urothelial carcinoma □
- Squamous carcinoma □
- Adenocarcinoma □
- Micropapillary carcinoma □
- Small cell carcinoma □
- Sarcomatoid carcinoma □
- Other □
  Please specify……

Comment…….

WHO 1973	**WHO 2004**
	PUNLMP □

For urothelial carcinoma:

Grade 1 □	Low grade □
Grade 2 □	
Grade 3 □	High grade □

Associated CIS: Yes □ No □

CIS:

Adjacent to tumour □

Elsewhere □ Not applicable □

Lymphovascular invasion:

Yes □ No □

For squamous or adenocarcinoma:

Well differentiated □

Moderately differentiated □

Poorly differentiated □

Not assessable □

Other disease process(es) (if present)……

Resection margins:

Not assessable □

Not involved □

Involved □ Site(s)…….

Regional lymph nodes:

Not applicable □

Right Total ….

Number pos ….

Extracapsular spread:

Yes □

No □

Not applicable □

Left Total ….

Number pos ….

Extracapsular spread:

Yes □

No □

Not applicable □

Size of largest metastasis…… *or* Not applicable □

Other lymph nodes involved? (pM1, if involved):

Not applicable □

Involved □ Total number present…… Number involved…

Extracapsular spread: Yes □ No □ Not applicable □

Not involved □

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pTNM classification: pT…… pN…….. pM*……

*pM should either be 1 or entered as not applicable (N/A)

SNOMED codes

TNM edition number used……..

T……

M……..

Further comments:

Pathologist……..... **Date……..**

Appendix G Summary table – Explanation of levels of evidence

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

Level of evidence	Nature of evidence
Level A	At least 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 H AGREE compliance monitoring sheet

The cancer datasets of The Royal College of Pathologists comply with the AGREE standards for good quality clinical guidelines (www.agreecollaboration.org). The sections of this dataset that indicate compliance with each of the AGREE 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	Foreword
7. The guideline has been piloted among target users	1st edition
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	3,4,5,7,8,9
16. The different options for management of the condition are clearly presented	5,9
17. Key recommendations are easily identifiable	5,7,8,9
18. The guideline is supported with tools for application	Appendices A to E
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/audit purposes	10
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

* The Lay Advisory Committee (LAC) of The Royal College of Pathologists has advised the Director of Communications that there is no reason to consult directly with patients or the public regarding this dataset because it is technical in nature and intended to guide pathologists in their practice. The authors will refer to the LAC for further advice if necessary.