



## Tissue pathways for urological pathology

July 2017

**Authors:** Dr Declan O'Rourke, Belfast City Hospital, Belfast Health and Social Care Trust  
Dr Derek Allen, Belfast City Hospital, Belfast Health and Social Care Trust

<b>Unique document number</b>	G099
<b>Document name</b>	Tissue pathways for urological pathology
<b>Version number</b>	2
<b>Produced by</b>	Dr Declan O'Rourke (lead author), Belfast City Hospital, Belfast Health and Social Care Trust and Honorary Clinical Lecturer, has written the urology chapters in a textbook on the handling and reporting of histopathology specimens; Dr Derek Allen, Belfast City Hospital, Belfast Health and Social Care Trust, has authored a textbook on the handling and reporting of histopathology specimens. Written on behalf of the College's Working Group on Cancer Services.
<b>Date active</b>	20 July 2017
<b>Date for review</b>	20 July 2022
<b>Comments</b>	<p>This document replaces the 1st edition of <i>Tissue Pathways for urological pathology</i> published in 2010.</p> <p>In accordance with the College's pre-publications policy, this document was on The Royal College of Pathologists' website for consultation from 27 March to 24 April 2017. Responses and authors' comments are available to view, following final publication of this dataset.</p> <p><b>Dr Lorna Williamson</b> <b>Director of Publishing and Engagement</b></p>

The Royal College of Pathologists  
4<sup>th</sup> Floor, 21 Prescot Street, London, E1 8BB  
Tel: 020 7451 6700, Web: [www.rcpath.org](http://www.rcpath.org)  
Registered charity in England and Wales, no. 261035

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NICE has accredited the process used by The Royal College of Pathologists to produce its Cancer Datasets and Tissue Pathways guidance. Accreditation is valid for 5 years from July 2012. More information on accreditation can be viewed at [www.nice.org.uk/accreditation](http://www.nice.org.uk/accreditation).

For full details on our accreditation visit: [www.nice.org.uk/accreditation](http://www.nice.org.uk/accreditation)

## Foreword

The tissue pathways published by The Royal College of Pathologists (RCPATH) are guidelines that enable pathologists to deal with routine surgical specimens in a consistent manner and to a high standard. This ensures that accurate diagnostic and prognostic information is available to clinicians for optimal patient care and ensures appropriate management for specific clinical circumstances. Rarely, it may 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 carefully considered by the reporting pathologist; just as adherence to the guidelines may not constitute defence against a claim of negligence, so a decision to deviate from them should not be deemed negligent or a failure of duty of care.

The guidelines themselves constitute the tools for implementation and dissemination of good practice. The information used to develop this tissue pathway was collected from electronic searches of the medical literature, previous recommendations of the RCPATH, and local guidelines in the United Kingdom. The level of evidence was either grade C or D, or met the GPP/good practice point criteria. Consensus of evidence in the tissue pathways was achieved by expert review. No major organisational changes or cost implications have been identified that would hinder the implementation of the tissue pathways. The document has been reviewed by some members of the International Collaboration on Cancer Reporting (ICCR), The National Institute for Health and Care Excellence (NICE) and the British Association of Urological Pathologists (BAUP).

The following is a list of supporting evidence and guidelines used in the tissue pathways:

- Pubmed searches on kidney, ureteric, bladder, urethral, prostate, penile, scrotal and testicular pathology (up to September 2016)
- *WHO Classification of Tumours of the Urinary System and Male Genital Organs (4<sup>th</sup> edition)*<sup>1,2</sup>
- NICE. *Improving Outcomes in Urological Cancers*. Accessed March 2017. [www.nice.org.uk/guidance/csg2](http://www.nice.org.uk/guidance/csg2).

A formal revision cycle for all tissue pathways takes place on a 5-yearly basis. However, each year, the College will ask the author/s, in conjunction with the relevant sub-specialty adviser to the College, to consider whether or not the document needs to be updated or revised. A full consultation process will be undertaken if major revisions are required. If minor revisions are required, an abridged consultation process will be undertaken whereby a short note of the proposed changes will be placed on the College website for 2 weeks for members' attention. If members do not object to the changes, the short notice of change will be incorporated into the pathways and the full revised version (incorporating the changes) will replace the existing version on the publications page of the College website.

The pathways document has been reviewed by the College's Clinical Effectiveness Department, Working Group on Cancer Services and Lay Governance Group. It was placed on the College website for consultation with the membership from 27 March to 24 April 2017. All comments received from the Working Group, College members and the Lay Governance Group were responded to by the authors to the satisfaction of the Chair and the Director of Publishing and Engagement.

This pathway was developed without external funding to the writing group. The College requires the authors of tissue pathways to provide a list of potential conflicts of interest; these are monitored by the Clinical Effectiveness Department and are available on request. The authors of this guideline have declared that there are no conflicts of interest.

## **1 General introduction**

### **1.1 Target users of this guideline**

The target primary users of the tissue pathway are trainee and consultant cellular pathologists. These recommendations will also be of value to trainee/qualified biomedical scientists involved in macroscopic description and dissection of all urological biopsies.

### **1.2 Staffing and workload**

Urological histopathology is a major element of most histopathology departments' workload. Pathologists reporting urological specimens will either be generalists with experience in uropathology or subspecialists in uropathology. In either circumstance, there must be enough pathologists to provide cover and to conform to The Royal College of Pathologists' guidance on staffing and workload levels.<sup>3</sup>

Pathologists reporting urological pathology should participate in an appropriate external quality assessment (EQA) scheme. Lead pathologists or those whose work consists predominantly of urological pathology should participate in the uropathology EQA scheme ([www.histopathologyeqa.org](http://www.histopathologyeqa.org)) which includes web-based prostate biopsy cases. Nominated pathways for referral of difficult cases for expert opinions should be in place. Histopathology laboratories should have a lead pathologist for each of the main cancers with responsibility for liaising with relevant local and clinical multidisciplinary teams (MDTs) and ensuring that the relevant specimens are examined, sampled and reported appropriately and in a consistent and timely fashion.

Pathologists should participate in audit and the College's Continuing Professional Development (CPD) scheme. Cancer centres and units should be supported by laboratories accredited by UK Accreditation Service (UKAS) or equivalent, and staffed in accordance with the recommendations of The Royal College of Pathologists and the Association of Clinical Pathologists.

The laboratory should be equipped to allow the recommended technical procedures to be performed safely, participate in the UK National EQA Scheme for Cellular Pathology Technique and participate in the UK National EQA Scheme for immunohistochemistry and in situ hybridisation (if these techniques are used in the diagnostic pathway).

Workload may vary considerably according to the nature of the specimens received. Pathologists undertaking a significant amount of oncology work will be able to report fewer requests per year than a pathologist dealing primarily with non-neoplastic specimens in accordance with the College workload guidelines.<sup>3</sup> The cancer datasets for reporting tumours are used in the system of standard setting, data collection, audit and feedback for those involved in caring for these patients.<sup>4,5</sup>

### **1.3 Laboratory facilities**

The full range of routine laboratory facilities is needed, including access to immunohistochemistry and electron microscopy (EM), which may be off site. The laboratory should be staffed to UKAS standards and the RCPATH staffing/workload document, and equipped and managed in a way that maintains safe and efficient throughput to a high standard.

Reports should be held on an electronic database that has facilities to search and retrieve specific data items and that is indexed according to Systematised Nomenclature of Medicine (SNOMED) T, M and P codes (or equivalent codes according to Systematised Nomenclature of Medicine Clinical Terms [SNOMED-CT]). It is acknowledged that existing laboratory

information systems may not meet this standard; nevertheless, the ability to store data in this way is recommended when laboratory systems are replaced or upgraded.

Workload data should be recorded in a format that facilitates the determination of the resources involved and which, if applicable, are suitable for mapping to Healthcare Resource Groups (HRGs).

#### **1.4 Specimen submission and dissection**

Most specimens are received in the laboratory in buffered formalin as routine diagnostic or therapeutic specimens according to standard procedures. Full patient details, clinical consultant, date of procedure and type of specimen must be provided. The indication for the biopsy should be stated. Relevant patient history and clinical findings must be described on the form accompanying the specimen. Details of previous histology should be mentioned, particularly if there is a history of dysplasia or carcinoma. The surgical indications for the procedure and its nature, i.e. biopsy or resection, are stated. Relevant patient historical clinical findings, e.g. appearances at cystoscopy, must be described.

Each specimen container should be labelled with the patient's details, the site of the biopsy and date of the procedure. Formalin should cover the specimen entirely to ensure proper fixation. No interference with the specimen should be allowed unless agreed, prior to receipt in the histopathology laboratory. The following guidelines should be observed in selecting and submitting tissue for microscopic study.

Small biopsies that will fit in one cassette are generally submitted in total. Diagnostic biopsies of larger size may need to be entirely submitted, but there are exceptions. See organ-specific instructions for sampling.

Excisional biopsies containing a tumour should be blocked to show margins. India ink (or equivalent) can be used to mark margins. Be careful to ensure that the ink does not spread elsewhere.

By convention, sections are cut from the *side facing down* in the cassette. If there is any reason to orientate the specimen another way, put instructions on the work sheet/form (e.g. 'on edge/end').

Tissues must be *thin* (2–3 mm or less than the thickness of the cassette) and must not be crowded into the cassette. Thick or crowded tissue cannot be processed properly and poor sections will result, especially if the tissue contains fat.

Ensure adequate fixation of large specimens (bladder resections, nephrectomies and prostatectomies) before cutting. Thinner, better anatomically orientated sections will result.

#### **1.5 Block selection and record**

Specimen dimensions are measured in mm. When sampling a specimen, document the site from which each block is taken. Each cassette must have a unique identifying number/letter preferably applied with a microwriter, and the number of pieces of tissue in each cassette recorded if <5. For most specimens, no special facilities are required for specimen dissection. Coloured inks for surgical resection margins should be available. Digital photography is now routine and it is good practice to photograph large specimens so that a permanent record of the macroscopic appearance and location of blocks can be recorded and filed in the patient records. Access to these images through a networked drive is preferable and time effective. Photography of all large specimens is an invaluable resource for MDT meetings, teaching and research. This may also be useful in medicolegal cases.

*[Level of evidence – GPP.]*

## 2 The kidney and renal pelvis

### 2.1 Nephrectomy non-malignant

#### 2.1.1 Indications for surgery

- removal of non-functioning kidney (simple nephrectomy) in patients with an irreversibly damaged kidney because of symptomatic chronic infection, obstruction, calculous disease, ischaemia (atheromatous/non-atheromatous) or severe traumatic injury
- to treat severe unilateral parenchymal damage from nephrosclerosis, pyelonephritis, reflux or congenital dysplasia of the kidney<sup>6</sup>
- failed renal transplant<sup>7-9</sup>
- assessment of primary disease, e.g. pelvi-ureteric junction obstruction, chronic obstructive or reflux uropathy, adult polycystic kidney disease (APCKD) or xanthogranulomatous pyelonephritis (XGP)<sup>6,10,11</sup>
- clinical presentation, radiological features and gross appearance of XGP may closely mimic a renal neoplasm making a correct pre-operative diagnosis difficult
- staghorn calculus
- radiation nephropathy, which may be either acute or chronic and related to dose
- to exclude malignancy (e.g. multilocular cystic lesions, incidental carcinoma in a polycystic kidney, long-term dialysis associated cystic lesions).<sup>11</sup>

*[Level of evidence – GPP.]*

#### 2.1.2 Staffing and workload (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology. Difficult cystic lesions may be referred for a second opinion.

Transplant nephrectomies should be reported by a specialist renal transplant pathologist who participates in the renal pathology EQA scheme. A renal transplant pathology educational slide scheme is available for those reporting renal transplant biopsies.<sup>12</sup>

#### 2.1.3 Laboratory facilities

- routine processing for light microscopy (LM)
- can require both histochemical and immunohistochemical (see below) analysis of background kidney to diagnose/categorise co-existing glomerulonephritis
- occasional use of immunohistochemistry (IHC) to categorise background renal neoplasia (see below).

There is very occasionally the need to extract formalin-fixed, paraffin-embedded material for subsequent electron microscopy (EM) examination.

Although glycogen and lipid are characteristic findings in clear cell renal cell carcinoma (CC-RCC), these histochemical stains offer little differential diagnostic power in RCC classification since tumours other than CC-RCC may also harbour lipid and/or glycogen.<sup>1</sup> The single differentiating histochemical stain useful in RCC classification is the Hale's colloidal iron for chromophobe carcinoma but is rarely used because of safety issues and supersedence by IHC.

*[Level of evidence – C.]*

#### 2.1.4 Specimen dissection

Treat the specimen as for a potential renal malignancy – weigh, measure (length, breadth and depth in mm) and orientate (ureter posterior to vessels, and the renal artery enters the hilum partially behind the renal vein but variations occur in 40%).

The presence or absence of the adrenal gland in the suprarenal fat should be noted and sampled. However, all clinicians should be encouraged to provide this information on the request form. The presence of lymph nodes near the hilum should also be noted and sampled.

Identify resection margins of the ureter, renal artery and vein. Submission for histology is unnecessary and not cost effective in non-neoplastic kidney diseases.

Check the renal artery for stenosis and take a block to confirm cause, if present (e.g. atheroma, arterial fibromuscular dysplasia).

The initial incision should pass through the midline of the kidney in the coronal plane. Photograph the bisected kidney.

Use the first cut surface to collect tumour (if present) and kidney tissue for special purposes (e.g. EM, imprints, flow cytometry, cytogenetics, tissue culture, snap freezing, tissue biobanking, etc.)

Take at least one block of normal residual kidney for future use if there is any suspicion of underlying glomerulonephritis.<sup>12</sup> If the patient subsequently develops renal impairment, a biopsy of the solitary remaining kidney may be contraindicated and archival tissue could be used to identify any aetiology.

In the absence of any tumour, embed blocks of pelvi-ureteric junction, pelvis and any focal lesions taken to include any abnormal area and one from otherwise normal parenchyma.

In XGP, numerous dilated calyces with yellow–brown calculi are seen. A staghorn calculus may be present. XGP may closely mimic a renal neoplasm.

For individual cystic lesions, take blocks of solid areas to exclude nests of clear cell carcinoma. For multicystic lesions, take at least one block/cm maximum kidney dimension for thorough sampling to exclude incidental background carcinoma, and for assessment of cysts in congenital disease. For paediatric multicystic conditions, whole mounts may be considered. For transplant nephrectomies – blocks should be taken serially (from without in) of the hilar vessels to examine the state of the renal vein and artery. Multiple blocks of cortex and medulla may be required for assessment of rejection. SV40 and C4d immunostaining (humoral rejection) are done as appropriate.

*[Level of evidence – GPP.]*

#### 2.1.5 Sectioning and staining

- routine processing for LM
- usually require only one haematoxylin and eosin (H&E) section per block
- may require both histochemical and immunohistochemical analysis of background kidney to diagnose/categorise co-existing glomerulonephritis (covered in the *Tissue pathway for medical renal biopsies*)<sup>12</sup>
- renal special set on kidney if indicated by H&E features – this includes basement membrane stain (PAS, Jones Silver), fibrous tissue stains (EVG, trichrome) and Congo red<sup>12,13</sup> (amyloid). The silver stain is also useful for assessing vascular abnormalities.

- access to immunoperoxidase for IgA, IgG, IgM, C3, C4, C1q, C4d, kappa/lambda light chains
- SV40 T Ag (polyoma virus infection) should be available if required
- very occasional need to extract formalin-fixed, paraffin-embedded material for subsequent EM examination
- occasional use of immunohistochemistry to categorise background renal neoplasia (e.g. clear cell lining of cystic lesions) and should include a panel of vimentin, cytokeratin, CK7, AMACR, CD10, EMA, CD117 (c-kit), RCC antibody, E-cadherin, ksp-cadherin, PAX2/PAX8 and TFE3/TFEB/melanocytic markers (if necessary – Xp11.2 translocation carcinomas). Please see appropriate cancer datasets for further detail.

[Level of evidence – C.]

### 2.1.6 Report content

Note the presence or absence of malignancy, background urothelial changes (dysplasia, carcinoma *in situ* [CIS]) and type and aetiology of chronic damage.

XGP is due to renal outflow obstruction (staghorn calculi) in the setting of infection.

Ensure pattern and size of cysts are described and features of renal dysplasia looked for (e.g. presence of cartilage). Solid areas and nephron-like elements are absent from cyst walls. In acquired cysts, the inner surface is smooth and there is no communication with the renal pelvis.

Cystic nephroma (classified now under mixed epithelial and stromal tumour, WHO 2016) should be excluded.<sup>1</sup> It is unilateral, solitary and multiloculated with non-communicating cysts sharply demarcated from adjacent kidney by a thick fibrous capsule with a nodular surface. Cysts have flat to hobnail epithelial lining and there is no renal parenchyma within the cysts (so not polycystic disease). The stroma may contain smooth muscle, skeletal muscle, cartilage or resemble ovarian stroma.

Examine cysts in APCKD for features of malignancy. Micropapillary adenomas are very common in the cyst lining.

Note the type and sites of rejection for transplant nephrectomy and any background pathology which might be relevant, e.g. CMV infection, post-transplant lymphoproliferative disorder (PTLD).

Description of transplant nephrectomies is not formally part of the Banff '97 classification and most have had their immunosuppression stopped and demonstrate mixed acute and chronic rejection.

Identify the cause of renal artery narrowing, if present, (e.g. atheromatous plaque, fibromuscular dysplasia, vasculitis) and the degree of ischaemic parenchymal renal damage.

Confirm radiation nephropathy if clinically indicated (e.g. glomerulosclerosis, fibrinoid necrosis, thickened glomerular capillary walls, fibrinoid necrosis of arterioles and small arteries with variable thrombosis).

If an incidental carcinoma is identified, it should be reported according to updated guidelines.<sup>1</sup>



## **2.2 Pelvi-ureteric junction (PUJ) specimen**

### **2.2.1 Indications for histology**

Primary causes of PUJ obstruction are usually congenital and may be the result of muscle bundle disarray or absence, increased collagen deposition, or abnormal anatomical location of the renal pelvis.<sup>14</sup>

Secondary causes are conditions such as crossing lower pole aberrant renal vessel (usually anterior), congenital abnormalities of the kidney (horseshoe kidneys or duplex anomalies), scarring secondary to surgery.<sup>14</sup> Urothelial carcinoma/transitional cell carcinoma (TCC) or external compression must be excluded.

Histological findings in this condition are not distinctive and usually have no bearing on the treatment or progress of the patient.

### **2.2.2 Staffing and workload** (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology. Refer problematic cases to the lead urological pathologist.

### **2.2.3 Laboratory facilities**

- routine processing for LM
- occasionally, use of immunohistochemistry to exclude or confirm urothelial dysplasia, CIS or malignancy.

### **2.2.4 Specimen dissection**

The specimen may be funnel shaped if unopened. The length, diameter at both ends and thickness of the wall are measured, and presence and size of any strictures described.

The specimen is opened along the long axis. If the specimen has been opened prior to receipt in the laboratory, it may look like a triangular fragment of mucosa.

Dimensions are measured in mm.

The mucosal surface is examined for lesions and irregularities in texture.

The outer surface is examined for mass lesions and fibrosis. Multiple sections taken along the long axis are submitted in one cassette. Submit the total number of sections if small sample.

### **2.2.5 Sectioning and staining**

- routine processing for LM
- usually require only one H&E section per block
- histochemical and immunohistochemical stains generally not required (exclude CIS with panel, CK20, p53, CD44s)
- rarely any requirement for EM or molecular investigations.

### **2.2.6 Report content**

- confirmation of pelvi-ureteric obstruction<sup>14,15</sup> or correlation with the clinical findings
- presence or absence of malignancy, background urothelial changes (dysplasia, CIS), type and aetiology of chronic damage.

*[Level of evidence – GPP.]*

### **3 The ureter**

#### **3.1 Ureteric biopsy**

Recent advances in the field of retrograde ureteroscopy include the development of small calibre fibre-optic endoscopes, improved optics and small calibre instruments enabling biopsy confirmation of previously inaccessible ureteric lesions. Miniaturisation of ureteroscopic instrumentation with smaller fibre-optics and enhanced digital imagers, improved biopsy accessories, and new energy sources will continue to improve and generate enhanced diagnostic material.

##### **3.1.1 Indications for histology**

- abnormal imaging findings – filling defect: a number of benign lesions can present with filling defects, including radiolucent stones, blood clots, sloughed renal papillae, hamartomatous lesions, ureteritis cystica, nephrogenic metaplasia, fibroepithelial polyps, florid von Brunn's nests, tuberculosis, schistosomiasis, amyloid and endometriosis
- evaluation of ureteric injury
- therapeutic indications include incision and biopsy of ureteric strictures
- to obtain an accurate diagnosis so that accurate treatment can be initiated
- to exclude dysplasia, CIS and malignancy
- to correlate with aspirated urine/fluid result if taken simultaneously.

##### **3.1.2 Staffing and workload** (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology.

##### **3.1.3 Laboratory facilities**

- routine processing for LM
- may require both histochemical and immunohistochemical (panel CK20, p53, CD44s) analysis.

##### **3.1.4 Specimen dissection**

Tiny pieces of tissue (several mm) retrieved using either 'cold' cup forceps or a small diathermy loop are counted, measured, processed intact and examined histologically through three levels.

Larger specimens (much less common) should be weighed collectively, the number of fragments counted and all tissue embedded.

Determine the number and size of biopsies (mm). The term 'multiple' should be restricted to cases where there are too many to count.

To avoid loss of smaller endoscopic biopsies during processing, ink with eosin and wrap in filter paper or similar commercial products.

Embed all fragments in their entirety. Embedding fragments in a line facilitates histological assessment.

##### **3.1.5 Sectioning and staining**

- one H&E section per cassette, at least three levels/serials
- may require unstained sections between levels, if suspicion of CIS – may be appropriate to cut additional sections at initial processing if there is a likelihood that these will be required

- routine processing for LM
- rarely need histochemical stains
- can occasionally require immunohistochemical analysis (panel CK20, p53, CD44s).<sup>16–18</sup>

### 3.1.6 Report content

Confirm benign changes if stricture is present.

Radiation injury subsequent to treatment for cervical or prostate cancer shows peri-ureteric and submucosal fibrosis with atypical fibroblasts.

Immunoglobulin G4-related disease (IgG4 RD) (sclerosing retroperitoneal fibrosis) is difficult to confirm and shows non-specific inflammatory changes and occasional granulomatous inflammation. Patterns include storiform type fibrosis, lymphoplasmacytoid inflammation and obliterative inflammatory changes in vessels (IgG4 antibody is occasionally useful if >50% ratio of IgG4-bearing plasma cells to IgG-bearing plasma cells).<sup>19</sup>

Exclude benign tumours, the commonest being exophytic and inverted urothelial papillomas, villous adenomas and leiomyomas.

Ureteritis cystica may be diffuse along the ureter. These lesions are typically incidentally discovered during evaluation of the urinary tract for other causes and appear as numerous small uniform filling defects.

Endometriosis results in either an intrinsic or extrinsic mass but is histologically similar to typical endometriosis elsewhere.

Exclude the presence or absence of malignancy, background urothelial changes (dysplasia, CIS).<sup>16–18</sup>

Uretero-ileal anastomotic sites for ileal conduits show various chronic microscopic changes e.g. cystically dilated intestinal glands, urothelial lined cysts, mucus pools and intestinal epithelial-lined cysts.

*[Level of evidence – C.]*

## 3.2 Ureteric resection

### 3.2.1 Indications for histology

- confirm nature of pathology (stricture)
- confirm other pathology: congenital anomalies (duplex ureter), ureteritis cystica, nephrogenic metaplasia, endometriosis, sclerosing retroperitoneal fibrosis (IgG4-RD)
- exclude dysplasia, CIS and malignancy.

### 3.2.2 Staffing and workload (see Introduction above)

### 3.2.3 Laboratory facilities

- routine processing for LM
- occasionally, use of immunohistochemistry (CK20, p53, CD44s)<sup>16</sup> to exclude or confirm urothelial dysplasia, CIS or malignancy
- immunohistochemistry for confirmation of lesions such as nephrogenic metaplasia occasionally required (CK7/20, AMACR, PAX2, PAX8).

### 3.2.4 Specimen dissection

- measure length – usually funnel shaped in PUJ specimens (see above)
- place probe to identify ureter
- photograph the ureter (particularly congenital anomalies)
- longitudinal sections from pelvic portion and transverse sections from ureter to include distal margin
- submit in total if small sample.

### 3.2.5 Sectioning and staining

- one H&E section per cassette, no need for routine unstained levels
- histochemical and immunohistochemical stains generally not required
- rarely any requirement for EM or molecular investigations.

### 3.2.6 Report content

- document presence of ureteric narrowing
- note presence of nephrogenic metaplasia, endometriosis, amyloid, ureteritis cystica, sclerosing retroperitoneal fibrosis
- comment on dysplasia or CIS particularly if at margins.

All carcinomas should be histologically typed, graded and staged according to the latest RCPATH cancer dataset *Dataset for tumours of the urinary collecting system (renal pelvis, ureter, urinary bladder and urethra)*.

[Level of evidence – B.]

## 4 The bladder

### 4.1 Bladder biopsies

#### 4.1.1 Indications for histology

- exclude primary urothelial dysplasia, CIS or malignancy
- follow up cystoscopy after previous urothelial carcinoma/TCC or intravesical treatment such as Bacillus Calmette-Guerin (BCG), mitomycin C therapy, thiotepa (triethylenethiophosphoramidate), valrubicin and cyclophosphamide<sup>18</sup> – confirm benign pathology such as infectious and non-infectious cystitis, nephrogenic metaplasia, trigonal squamous and keratinising squamous metaplasia, interstitial cystitis, ketamine cystitis, amyloid, malakoplakia or specific infections e.g. schistosomiasis
- radiation cystitis
- assessment of cystitis and aetiological factors
- abnormal urine cytology with normal cystoscopy (random bladder biopsies generally taken).

#### 4.1.2 Staffing and workload (see Introduction above)

#### 4.1.3 Laboratory facilities

- routine processing for LM

- availability of histochemical stains occasionally used including Congo Red +/- KMnO<sub>4</sub>, PAS ± diastase, von Kossa, Ziehl-Neelsen (ZN), Toluidine blue or other mast cell stain
- availability of immunohistochemistry for CK20 and/or other markers (including p53 or CD44s)<sup>16,18</sup> for diagnosis of CIS or incidental papillary lesions; also used for further typing of amyloid with AA protein, kappa/lambda light chains and transthyretin.

#### 4.1.4 Specimen dissection

Determine the number and size of biopsies (mm). The term 'multiple' should be restricted to cases where there are too many to count.

To avoid loss of smaller cystoscopic (and cold cup) biopsies during processing, ink (eosin/india) and wrap in filter paper or similar commercial products.

Larger specimens (much less common) should be weighed collectively, the number of fragments counted and all tissue embedded.

In the case of multiple biopsies, avoid embedding a large number of fragments in the same cassette, as it may be difficult to keep them properly orientated and at the same level if they are numerous. Embed no more than three in each cassette.

Embed all fragments in their entirety. Embedding fragments in a line facilitates histological assessment.

#### 4.1.5 Sectioning and staining

- one H&E section per cassette, at least three levels/serial sections
- may require unstained sections between levels, if suspicion of CIS
- may be appropriate to cut additional sections at initial processing if there is a likelihood that these will be required
- rarely any requirement for EM or molecular investigations.

#### 4.1.6 Report content

The adequacy of the biopsy should be noted, if relevant. A separate description for each separately submitted set of biopsies is required unless they all show the same or similar features.

If adequate details are not provided, this should be stated. Some features (i.e. interstitial cystitis/bladder pain syndrome) can only be interpreted with appropriate clinical and cystoscopic findings. Counting mast cells in bladder biopsies is of little pathological or clinical value, although higher numbers are found in interstitial cystitis relative to normal but not relative to other inflammatory conditions. MDT meetings may be helpful with regard to final interpretation.<sup>20</sup>

Detail presence or absence of urothelial dysplasia/CIS or malignancy.<sup>18</sup>

Ketamine cystitis can show urothelial ulceration and atypia that can mimic CIS. Microscopically, the urothelium is denuded and infiltrated by mast cells and eosinophils. The longer term risk cancer remains unknown.<sup>18</sup>

Detail surface urothelial changes or metaplasia (e.g. squamous, glandular, nephrogenic).

Squamous metaplasia can arise in the bladder secondary to chronic cystitis, schistosomiasis, diverticulum or non-functioning bladder. If keratinisation is present, this is a risk factor for subsequent development of carcinoma (mostly squamous cell carcinoma [SqCC]) and other complications such as bladder contracture and obstruction.<sup>21,22</sup>

Verrucous squamous hyperplasia (VSH) is a recently described entity that has been associated with the development of squamous cell carcinoma (SqCC) of the bladder.<sup>21</sup>

Glandular metaplasia of intestinal type is not associated with an increased risk for the development of adenocarcinoma but when associated with dysplasia there is an increased risk for subsequent adenocarcinoma. Therefore examine carefully for evidence of dysplasia.<sup>23</sup>

Comment on loss/ulceration or denudation of urothelium where this increases the chances of missing CIS.

Confirm benign conditions such as amyloid, malakoplakia, collagen polyp, endometriosis and related endocervicosis.

Note the presence or absence of inflammation – acute or chronic, follicular, eosinophilic, radiation cystitis or granulomatous post BCG treatment can produce urothelial changes that can mimic cancer histologically.<sup>24,25</sup>

Confirm features of radiation cystitis following treatment for prostate/cervical cancer in particular. Changes can be misinterpreted as neoplastic. Pseudoepitheliomatous (pseudocarcinomatous) hyperplasia can be found in association with radiation cystitis, as well as other forms of bladder injury and can mimic SqCC.<sup>25</sup>

There is a need for follow up in the case of specific infections such as viable schistosomal ova and to exclude infectious conditions such as TB.

*[Level of evidence – C.]*

## **4.2 Partial cystectomy**

### **4.2.1 Indications for histology**

- resection of bladder diverticula, cavernous haemangioma, paraganglioma, leiomyoma, refractory interstitial cystitis, colovesical fistula, vesicovaginal fistula and localised endometriosis of the bladder
- in the case of diverticulum, stagnation of urine, calculus formation and superimposed infection occur when they reach a large size and require surgery
- patient choice, palliation of severe local symptoms, preservation of native bladder function and continence
- suspected malignancy
- palliation for pain, bleeding or trauma.

### **4.2.2 Staffing and workload** (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology.

### **4.2.3 Laboratory facilities**

- routine processing for LM
- may need histochemical stains (ZN, PAS, Congo Red +/- KMnO<sub>4</sub>) and occasional use of immunohistochemistry to exclude or confirm background neoplasia.

### **4.2.4 Specimen dissection**

The specimen should be fixed in a volume of formalin that is at least sufficient to cover it. Time of fixation should usually be 48 hours after resection, but adequacy of fixation can be estimated fairly reliably by visual inspection. Photographs may be useful. They are required in cases of trauma.

Ink any relevant margins if there is a possibility of neoplasia.

Describe the external appearance. Perforations/defects in the wall: record number, site, size, and distance from nearest margin. Look for fistulas and apply probe to confirm. Consider the possibility that the defects are artefactual or iatrogenic.

Record measurements including dimensions of specimen (mm) and maximum dimension of attached fat.

Record appearance of the mucosa.

Take blocks to confirm gross findings.

The most common locations of diverticula are the lateral walls. Measure the size in mm and exclude tumours.

Record the presence of focal lesions, e.g. ulcer, abscess, stricture, polyp and tumour. Record the presence of any papillary tumour, any ulcerated or inflammatory areas.

Blocks should include the maximal depth of invasion of any tumour identified and any close surgical/serosal resection margin.

#### **4.2.5 Sectioning and staining**

- routine processing for LM
- usually require only one H&E section per block
- deeper levels may be useful if the slide does not show the full face of the block
- can require both histochemical and immunohistochemical analysis if neoplasia is detected or to confirm an inflammatory process.

#### **4.2.6 Report content**

Partial cystectomy, also known as segmental resection of the bladder, is a surgical method of removing a selected full-thickness portion of the bladder wall. It is being performed less frequently in benign conditions but is used in selected cancer cases (tumours in dome, preservation of bladder function and palliation).

Describe inflammatory changes and confirm benign pathological changes (fistula, haemangiomas and endometriosis).

The most common histological findings in a bladder diverticulum are inflammation, granulation tissue, erosion, florid cystitis cystica and glandularis and non-keratinising squamous metaplasia. The boundary between the lamina propria and the peri-vesical fat in most bladder diverticula is usually readily defined by a band of dense fibrous tissue of variable thickness.

Report the presence or absence of malignancy, background urothelial changes (dysplasia, CIS) and type and aetiology of chronic damage. Report, grade, stage and classify any tumour identified.<sup>5,26</sup>

*[Level of evidence – GPP.]*

### **4.3 Cystectomy**

#### **4.3.1 Indications for histology**

- intractable lower urinary tract symptoms – severe pain, frequency, urgency<sup>20</sup>

- rule out malignancy
- prophylactic cystectomy for management of keratinising metaplasia
- palliation for pain, bleeding or urinary frequency
- trauma.

#### 4.3.2 Staffing and workload (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology.

#### 4.3.3 Laboratory facilities

- routine processing for LM
- may need histochemical stains (ZN, PAS, Congo Red +/- KMnO<sub>4</sub>) and occasional use of immunohistochemistry to exclude or confirm neoplasia (see below).

#### 4.3.4 Specimen dissection

Specimen should be fixed in a volume of formalin that is at least sufficient to cover it. Some prefer to fix such specimens intact by overdistention with formalin whereas others open and pin the specimen and cover it with formalin.<sup>26</sup>

Time of fixation should usually be 48 hours after resection, but adequacy of fixation can be estimated fairly reliably by visual inspection. Photographs may be useful. They are required in cases of trauma.

Ink any relevant margins if there is a possibility of neoplasia.

Describe the external appearance. Perforations/defects in the wall: record number, site, size and distance from nearest margin. Consider the possibility that the defects are artefactual or iatrogenic.

Recorded measurements include dimensions of specimen (mm) and maximum dimension of attached fat.

Record appearance of the mucosa. Wash out bladder contents gently with tepid or cold water. Excess washing or hot water may damage the mucosa.

Take blocks to confirm gross findings and include ureteric and urethral resection margins.

Note any focal lesions e.g. ulcer, abscess, stricture, polyp and tumour. Record the presence of any papillary tumour, ulcerated or inflammatory areas.

Blocks should include the maximal depth of invasion of any tumour identified, and any close surgical resection margin and the serosa.

Cystectomies for bladder cancer should be handled and reported as per latest RCPATH cancer dataset (to include blocks of prostatic urethra, prostate [including minimum of three blocks from each lateral zone to identify synchronous prostatic adenocarcinoma], its margins and seminal vesicles).

If included or in perivesical fat, lymph nodes must be described and their site/s of origin specified.

#### 4.3.5 Sectioning and staining

- routine processing for LM
- usually require only one H&E section per block



- deeper levels may be useful if the slide does not show the full face of the block
- can require both histochemical and immunohistochemical analysis.

#### **4.3.6 Report content**

Describe inflammatory changes and confirm benign pathological changes.<sup>25</sup>

Report the presence or absence of malignancy, background urothelial changes (dysplasia, CIS), type and aetiology of chronic damage. Do IHC if required to confirm changes (CK5/6, CD44, p53, CK20). Classify, grade and stage any tumour identified.<sup>2,5</sup>

Note the presence of submucosal inflammation and oedema, denuded epithelium, ulceration, epithelial and basement membrane thickness, vascular ectasia, fibrosis, and detrusor muscle inflammation and fibrosis.

*[Level of evidence – GPP.]*

## **5 The urethra**

### **5.1 Urethral biopsy**

#### **5.1.1 Indications for histology**

- urethral caruncle, polypoid cystitis, benign stricture, nephrogenic adenoma, prostatic urethral polyp and malakoplakia<sup>27</sup>
- urethroscopy may be undertaken in isolation or, more commonly, in tandem with cystoscopy – small urethral lesions are snared using ‘cold’ cup forceps or resected with a small diathermy loop.

#### **5.1.2 Staffing and workload** (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology.

#### **5.1.3 Laboratory facilities**

- routine processing for LM
- may require both histochemical and immunohistochemical (CK5/6, CD44, CK7/20, p53) analysis.

#### **5.1.4 Specimen dissection**

- tiny pieces of tissue (several mm) retrieved using either ‘cold’ cup forceps or a small diathermy loop are counted, measured, processed intact and examined histologically through three levels.

#### **5.1.5 Sectioning and staining**

- usually require only one H&E section per block
- routine processing for LM
- rarely need histochemical stains
- can occasionally require immunohistochemical analysis (CK7/20, CD44s, p53).<sup>16</sup>

#### **5.1.6 Report content**

- confirmation of benign pathology, most commonly caruncle or polypoid urethritis both of which may be confused with a papillary neoplasm<sup>27</sup>

- be aware of minor changes in the male/female urethra in relation to subepithelial supporting structures
- if stricture, confirm benign changes
- exclude presence or absence of malignancy, background urothelial changes (dysplasia, CIS).<sup>17,18</sup>

## **5.2 Urethrectomy**

### **5.2.1 Indications for histology**

Most urethrectomy resection specimens are for neoplasia as part of a cystectomy/cystoprostatectomy in those deemed high risk for recurrence. Details of previous histology should be available, particularly if there is a history of dysplasia or carcinoma.

Occasionally isolated urethrectomy is performed. Urethrectomy is performed for a stricture, bladder cancer in continuity with cystoprostatectomy, recurrence of bladder cancer in the urethral stump (secondary urethrectomy) and for primary urethral carcinoma.

### **5.2.2 Staffing and workload** (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology.

### **5.2.3 Laboratory facilities**

- routine processing for LM
- may require both histochemical and immunohistochemical (CK20, CD44s, p53) analysis.

### **5.2.4 Specimen dissection**

The specimen may be in several tubular fragments labelled separately or with attached sutures to aid orientation. In the absence of such markers, definitive orientation may not be possible.

Measure (mm) each fragment. Record the number of fragments (weighing is optional).

Ink the external circumferential radial margin (CRM) comprising adventitial connective tissue.

Remove the proximal and distal surgical resection limits by taking circumferential transverse sections (rings) from the ends of the appropriate fragments.

The remaining urethra is serially sectioned transversely throughout its length at 3 mm intervals, and the sections laid out sequentially for examination and photography, if desired.

Sample any focal lesions e.g. ulcer (at least one block each). More blocks should be taken from any suspicious lesion e.g. stricture, warty growth.

### **5.2.5 Sectioning and staining**

- routine processing for LM
- usually require only one H&E section per block
- can require both histochemical and immunohistochemical analysis.

### **5.2.6 Report content**

- confirm benign changes such as caruncle, leiomyoma or viral papilloma
- record inflammatory changes present and correlate with history (e.g. stricture)

- record the presence or absence of malignancy,<sup>28</sup> background urothelial changes (dysplasia, CIS).

[Level of evidence – GPP.]

## 6 The prostate

Prostate needle core biopsy has been discussed thoroughly within the *Dataset for histopathology reports for prostatic carcinoma*<sup>5</sup> and does not require further discussion in this document.

### 6.1 Transurethral resection of prostatic chippings (TURP)

#### 6.1.1 Indications for histology

- exclude prostatic or other malignancy (remember TCC, stromal malignancies, phyllodes tumour)
- confirm nature of pathology – usually benign prostatic glandular or stromal hyperplasia (BPH).<sup>29,30</sup>

Transurethral resection is undertaken for obstructive or irritative lower urinary tract symptoms (LUTS), not as an alternative diagnostic investigation to detect prostate cancer. However, in patients with prior negative prostatic biopsies, there is a low but definite chance of detecting prostatic cancer on TURP,<sup>31</sup> which increases with abnormal clinical findings on rectal examination (digital rectal examination [DRE]) or raised prostatic specific antigen (PSA) level. This is due to a subset of cancers arising within the central or anterior (transition) zones, which are less likely to be detected with standard biopsy protocols not specifically targeting these areas. The clinical significance of some smaller volume cancers is not established.

The prevalence of prostate cancer in TURPs varies from 7% to 17% (newer versus older series respectively).<sup>31</sup> Clinically relevant cancer in procedures done for BPH (TURPs and enucleations respectively) is seen in approximately 1.5% of specimens.<sup>31</sup>

#### 6.1.2 Staffing and workload (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology. Occasional problematic cases may need intradepartmental opinion and clinicopathological correlation by discussion with the urologist in cases of suspicious foci; rarely referral of the case for a second specialist opinion.

#### 6.1.3 Laboratory facilities

- routine processing for LM
- availability of immunohistochemistry for suspicious foci (ideally including antibodies against basal cell markers: first-line high molecular weight cytokeratins – LP34, CK5/6 or 34βE12 (all react with CK5); p63 or cocktails of both ± positive marker for prostatic carcinoma racemase/P504S/AMACR)<sup>32–34</sup>
- the role of AMACR in routine practice is very useful though some use it in cocktails with basal cell markers. Prostatic intraepithelial neoplasia (PIN) usually expresses AMACR – note that similar expression may also be seen in benign mimics of cancer such as adenosis and nephrogenic metaplasia.<sup>32</sup>

#### 6.1.4 Specimen dissection

Weigh the chippings in grams. In general, gross examination of chippings does not provide distinctive evidence of tumour.

In cases where clinical history specifies a clinical suspicion of carcinoma, post treatment such as radiotherapy, cryotherapy or high-intensity frequency ultrasound (HIFU), embed whole specimen to detect residual carcinoma.

Prostatic chippings do not require sectioning prior to fixation.

Embed all of first 12 g in five to six cassettes.<sup>35</sup>

Sample further chippings – opinions vary as to the optimal amount. Recommend embedding the entire specimen up to 12 g (six blocks) and a further 2 g (one block) for every additional 5 g.<sup>35,36</sup> 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.<sup>35</sup>

Determining optimum sampling depends on a number of factors, as in any statistical sampling protocol. The site and extent of any tumour determines the percentage of chippings it will be seen in. Submission of all chippings in larger cases may not be cost- or time-effective.<sup>37</sup>

*[Level of evidence – C.]*

### **6.1.5 Sectioning and staining**

- one H&E section per cassette, no need for routine unstained levels as per prostate biopsies
- immunohistochemical staining of serial sections from blocks with PIN or atypical small acinar proliferation (ASAP) which are suspicious of carcinoma
- rarely any requirement for EM or molecular investigations.

### **6.1.6 Report content**

Detail the presence of stromal or glandular hyperplasia/hypertrophy, infarction, urothelial or squamous metaplasia.

Note the absence of invasive prostatic carcinoma, atypical foci suspicious of carcinoma or PIN. In cases where ASAP or PIN is seen, embed the rest of the specimen to exclude carcinoma. If PIN or ASAP is seen as an isolated finding, consider discussion with clinicians and/or recommend peripheral gland biopsies of residual prostate to exclude carcinoma.

If an 'incidental' carcinoma is found, calculate the number and percentage of chippings involved. A more extensive sampling technique should be considered dependent on the volume of tissue received.<sup>36-38</sup>

If this is less than 5% (stage T1a, WHO 2004 staging), submission of the remaining tissue may increase the percentage of chippings involved and thus the potential clinical significance of the tumour<sup>38</sup> and also allows more accurate determination of the Gleason grade.<sup>39,40</sup>

Where involvement in the initial slides is >5% (stage T1b, WHO 2004), embedding further sections may not increase the stage, but may influence accurate Gleason grading. However, T1 substaging is less important in contemporary practice (MRI and biopsies [TRUS/template] used to determine tumour extent).<sup>5,40</sup>

Incidental low volume stage T1a tumours can become clinically significant and therefore follow-up is advised, e.g. with PSA monitoring, active surveillance or residual gland (saturation) biopsies.<sup>38</sup>

Note the presence of the surrounding urothelium and comment on any urothelial abnormality present, looking for co-existing urothelial carcinoma or in situ change.

*[Level of evidence – C.]*

## **6.2 Retropubic prostatectomy (RP – enucleation)**

### **6.2.1 Indications for histology**

- as for TURP specimens
- exclude prostatic or other malignancy
- confirm nature of pathology (usually benign glandular or stromal hyperplasia).

As distinct from TURP, the RP procedure allows surgical exposure of the prostate with direct visualisation. There is also optimised preservation of urinary continence and better haemorrhage control with minimal bladder trauma.

Retropubic prostatectomy is still occasionally performed for obstructive lower urinary tract symptoms.

### **6.2.2 Staffing and workload**

This can be reported by a general pathologist with experience of urological pathology. Occasional problematic cases may need intradepartmental opinion and clinicopathological correlation by discussion with the urologist in cases of suspicious foci, rarely referral of the case for a second specialist opinion.

### **6.2.3 Laboratory facilities**

As above (6.1.3).

### **6.2.4 Specimen dissection**

There are few data on optimum block selection in enucleation specimens, and the best method is treating these similarly to TURP resections.

Enucleations or prostatectomies are generally restricted to large prostates in patients with lower urinary obstructive symptoms. Such specimens can benefit from incision to allow formalin penetration. Inking of margins is not necessarily 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.

Weigh gland in grams (often in several nodular pieces). Consider inking margins only where gross findings are suspicious.

Representative samples submitted by taking at least one block for each 5 g or three per lobe. It may be of value to select out chips that look different from the rest, yellow or white, when sampling these specimens.

### **6.2.5 Sectioning and staining**

- one H&E section per cassette, no need for routine unstained levels as per prostate biopsies
- immunohistochemical staining of serial sections from blocks with PIN or ASAP<sup>32-34</sup>
- rarely any requirement for EM or molecular investigations.

## 6.2.6 Report content

Include description of the histological changes (stromal or glandular hyperplasia/hypertrophy).

Note that some benign entities such as atrophy, adenosis, nephrogenic hyperplasia, basal cell hyperplasia and proliferations and mesonephric remnants/hyperplasia potentially mimic prostatic cancer and may be responsible for misdiagnosis in routine specimens.<sup>29</sup> Immunohistochemistry can be used for confirmation.<sup>32,33</sup>

Note the absence of invasive prostatic carcinoma, atypical foci suspicious of carcinoma or PIN.

If an 'incidental' carcinoma is found, a more extensive sampling technique should be considered dependent on the volume of tissue received.<sup>35,36</sup> If cancer is found then it should be reported as per the recommendations of the RCPATH *Dataset for histopathology reports for prostatic carcinoma*.<sup>5</sup>

[Level of evidence – C.]

## 7 The penis and scrotum

### 7.1 Penile biopsy

#### 7.1.1 Indications for histology

The clinical appearance of many benign conditions overlaps with neoplastic and pre-neoplastic lesions, particularly penile intraepithelial neoplasia (PeIN). Therefore biopsy is mandatory to exclude dysplasia and malignancy.

Confirm benign pathological conditions.

Occasionally Wegener's can present with penile ulceration and may mimic malignancy, requiring biopsy for confirmation.

#### 7.1.2 Staffing and workload (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology. There is an occasional need for a penile pathologist (supranetwork level) or specialist dermatopathology opinion.

#### 7.1.3 Laboratory facilities

- routine processing for LM.
- occasional need for histochemistry and immunohistochemistry to exclude or confirm neoplasia (see below).

#### 7.1.4 Specimen dissection

Fragments are counted and measured in aggregate. It is important to search the container and the under-surface of its lid to ensure that all fragments of tissue are recovered.

Larger pieces are measured individually. Embed as received, bisect or cut further.

For a punch, bisect if larger than 3 mm and epithelium is clearly visible for orientation.

For an ellipse, if narrower than 3 mm, embed as received. If an incisional biopsy, bisect in longitudinal section. Wider/larger excisional biopsies are cut in transverse section to include the nearest resection margins. Ink the margins as orientated by the marking sutures.

Identifiable surface lesions are described and measured, and the macroscopic distance from the closest margin noted.

### 7.1.5 Sectioning and staining

- usually require three H&E levels per block
- routine processing for LM
- may require both histochemical and immunohistochemical analysis.

### 7.1.6 Report content

Report median raphe cysts (midline in ventral shaft) and mucoid cysts.

Report benign lesions such as lentiginous melanosis (glans and foreskin), cutaneous verruciform xanthoma (rare – shaft of penis), epithelioid haemangioma, leiomyoma and myointimoma.

Inflammatory conditions include lichen sclerosus (LS) previously known as balanitis xerotica obliterans (BXO) (may occasionally be seen on the shaft), Zoon's balanoposthitis (balanitis circumscripta plasmacellularis) and Fournier's gangrene (necrotising fasciitis).

Zoon's balanitis is usually a disease of the glans but may extend onto the foreskin. Zoon's balanoposthitis should not be diagnosed unless the infiltrate is almost exclusively plasma cells and in the absence of necrosis and granulomas.

Condyloma acuminatum and large viral warty lesions can be difficult to distinguish from warty squamous carcinomas. Biopsy often only provides superficial fragments. Clinical terms, giant condyloma and Buschke-Lowenstein tumour are no longer recommended.

Wegener's can cause penile ulceration often with destructive urethritis (c-ANCA/PR3 positivity).

Exclude PeIN (differentiated and undifferentiated) and malignancy. There is no need to distinguish between Bowen's disease and Erythroplasia of Queyrat which are clinically rather than pathologically defined lesions. It is more appropriate to describe as PeIN with (undifferentiated) or without (differentiated) warty features. Bowenoid papulosis also shows PeIN (undifferentiated) but clinically has multiple warty lesions along the shaft. Squamous hyperplasia and pseudoepitheliomatous hyperplasia may be misinterpreted as low grade squamous cell carcinoma. Similarly verrucous carcinoma is frequently underdiagnosed.

Rarely the glans penis can show extramammary Paget's, usually in association with urothelial carcinomas of the urethra or bladder. Immunohistochemistry may be required for definitive diagnosis (see 7.3.5).

*[Level of evidence – GPP.]*

## 7.2 Prepuce specimens

### 7.2.1 Indications for histology

- most common indication is for elective circumcision
- the clinical appearance of many benign conditions overlaps with neoplastic and preneoplastic lesions particularly PeIN, therefore biopsy is mandatory to exclude dysplasia and malignancy
- confirm benign pathology<sup>41,42</sup> – condyloma, penile cysts and papules, LS/BXO, Zoon's balanitis and verruciform xanthoma

- exclude PeIN and malignancy.

### **7.2.2 Staffing and workload** (see Introduction above)

### **7.2.3 Laboratory facilities**

- routine processing for LM
- occasional need of histochemical stains and immunohistochemistry.

### **7.2.4 Specimen dissection**

- measure, inspect and orientate
- ideally pin the four corners of the specimen with the mucosa orientated on one side and the skin on the other
- if there is a history of dysplasia/PeIN, identify the coronal sulcus and ink the margins (the surgical cut area – coronal and penile shaft margins)
- fix the specimen overnight in formalin
- specimen photography may be necessary
- cut serial transverse sections clockwise
- include any obvious areas of surface scarring or raised lesions
- embed at least two thin sections per block (to aid orientation) in two blocks.

### **7.2.5 Sectioning and staining**

- usually require only one H&E section per block
- occasionally need histochemical stains like PAS for fungal infection, or amyloid
- although immunohistochemistry to exclude HPV in rare cases may be used, this has no diagnostic or prognostic role in routine practice.

### **7.2.6 Report content**

Comment on any evidence of LS/BXO, Zoon's balanitis (inner foreskin/glans). Histopathological findings of Zoon's include superficial erosions, haemosiderin deposition and basal vacuolar degeneration. Epidermal lozenge-shaped keratinocytes with dense dermal inflammatory infiltrate composed predominantly of dermal plasma cells, with scattered neutrophils and lymphocytes and upper dermal fibrosis, are often seen. Rarely dermatoses e.g. lichen planus can affect the prepuce or glans but these are usually associated with disease elsewhere.

Note recent case reports of granulomatous inflammation with vasculitis in association with the anti-anginal drug nicorandil.<sup>43</sup>

Report non-specific inflammatory changes in balanoposthitis.

Mucinous metaplasia is occasionally seen in older patients.

Exclude sexually-transmitted infections.

Exclude dysplasia or malignancy particularly with LS/BXO.<sup>44</sup>

*[Level of evidence – GPP.]*



### **7.3 Scrotal biopsy**

#### **7.3.1 Indications for histology**

- biopsy is necessary to confirm benign pathology
- removal of suspected cystic lesion or calcified nodule
- exclude dysplasia and malignancy.

#### **7.3.2 Staffing and workload** (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology.

#### **7.3.3 Laboratory facilities**

- routine processing for LM
- occasionally use of histochemistry and immunohistochemistry to exclude or confirm neoplasia (see below).

#### **7.3.4 Specimen dissection**

Fragments are counted and measured in aggregate. It is important to search the container and the under-surface of its lid to ensure that all fragments of tissue are recovered.

Larger pieces are measured individually. Embed these as received, bisect or cut further if necessary.

For a punch, bisect if larger than 3 mm and epithelium is clearly visible for orientation.

For an ellipse, if narrower than 3 mm, embed as received. If wider, bisect in longitudinal section. Wider/larger lesions are cut in transverse section to include the nearest resection margins. Ink the margins as orientated by the marking sutures.

Cystic lesions or nodules may require decalcification.

Identifiable surface lesions are described and measured, and the macroscopic distance from the closest margin noted.

#### **7.3.5 Sectioning and staining**

- usually require three H&E levels per block
- routine processing for LM
- can require both histochemical and immunohistochemical analysis e.g. extramammary Paget's disease of scrotal skin is positive with CK7, CAM 5.2, CEA, EMA, PAS, MUC1, MUC5AC and negative for 34βE12 (high molecular weight keratin), CK20 (to exclude pagetoid spread from urothelial tumours which are CK20, p63 and GATA3 positive), HMB45, Melan-A and S100.<sup>45</sup>

#### **7.3.6 Report content**

Non-neoplastic lesions of scrotum include fat necrosis, idiopathic calcinosis (multiple nodules in skin which may arise from keratinous cysts that have lost their lining), hidradenitis suppurativa, massive localised lymphoedema in morbidly obese patients, sclerosing lipogranuloma and post-traumatic spindle cell nodules.

Lymphoedema of the scrotum is most commonly idiopathic and may have genetic links to syndromes such as Milroy's disease. True lymphoedema following groin and perineal radiotherapy and in association with Crohn's disease is recognised. Chronic lymphoedema may produce verruciform squamous hyperplasia and there is a rare association with scrotal squamous cell carcinoma.

Note the presence or absence of dysplasia, CIS and malignancy. Exclude neoplastic lesions of scrotum such as aggressive angiomyxoma, angiomyofibroblastoma (similar to vulvovaginal angiomyofibroblastoma and spindle cell lipoma), desmoplastic round cell tumour and malignant mesothelioma involving scrotum from the tunica vaginalis/albuginea.

Extramammary Paget's disease – adenocarcinoma in situ of scrotal skin usually not associated with underlying malignancy and has characteristic immunoprofile<sup>45</sup> (see above) and squamous cell carcinoma (occupational exposure) in particular should be excluded. Extramammary Paget's disease when associated with malignancy is usually apocrine adenocarcinoma in type. Sarcomas although rare should be excluded with leiomyosarcoma and liposarcoma being the commoner types seen.

*[Level of evidence – GPP.]*

## **8 The testes**

### **8.1 Testicular biopsy**

#### **8.1.1 Indications for histology**

- assessment of male infertility – usually azoospermia
- testicular sperm extraction – multiple testicular biopsies are usually needed and part of the specimen should be histologically assessed to predict the chance for future successful sperm harvesting and to diagnose germ cell neoplasia in situ (GCNIS) of the testis<sup>46,47</sup>
- variable practice of biopsy at time of contralateral orchidectomy for malignancy,<sup>47</sup> to assess spermatogenesis and the presence of GCNIS. This is done particularly in small volume testes in younger males. Testicular biopsy during orchidopexy is occasionally recommended in adolescents with cryptorchidism for detection of GCNIS of the testis.<sup>48</sup>
- biopsy of undescended testis to exclude malignancy or GCNIS
- biopsy of vestigial remnants such as the appendix epididymis (remnant of mesonephric duct) and the appendix testis (hydatid of Morgagni) which have undergone torsion or infarction.

#### **8.1.2 Staffing and workload** (see Introduction above)

Specialised biopsies are often uncommon in routine clinical practice. This should be reported by a urological pathologist or someone with expertise in assessment of testicular biopsies for infertility, who is participating in specialist urological EQA. A close relationship required with urologists and/or fertility clinicians to ensure good clinicopathological correlation.

#### **8.1.3 Specimen submission**

- core lengths (mm) or tissue dimensions (mm)
- number of cores/pieces and orientation
- submit all tissue for microscopic evaluation
- may be fixed in Bouin's, Stieves's or Zenker's medium as opposed to formalin for better nuclear preservation and because there is less shrinkage artifact and luminal sloughing of cells, which can obscure cellular detail.<sup>46,47,49</sup>

#### **8.1.4 Specimen dissection**

- to prevent surface trauma and disruption, these specimens require careful handling
- recommend wrapping in tissue paper or similar commercial products to prevent loss during processing, as often small samples

- embed biopsies from separate testes in different cassettes.

### 8.1.5 Sectioning and staining

- routine processing for LM
- at least three H&E sections per biopsy with 4–5 mm sections
- may be appropriate to cut additional sections at initial processing or keep spares between the levels, if there is a likelihood that these will be required
- rarely need histochemical stains for fibrosis or amyloid
- occasional use of immunohistochemistry to assess tubular germ cell numbers (SALL4) and exclude or confirm background GCNIS, such as OCT3/4, PLAP, and podoplanin. OCT3/4 is now the gold standard marker for GCNIS. Immunohistochemistry with OCT 3/4 for the detection of GCNIS can be falsely negative if Stieve's or Bouin's solution is used.<sup>49</sup>

### 8.1.6 Report content

The adequacy of the sample should be noted and where artefact or loss impairs interpretation of the biopsy, this should be stated in the report.

If adequate clinical details are not provided, this should be stated. Clinicopathological meetings help refine interpretation.

Comment on background atrophy, fibrosis, tubular hyalinisation and dilation or changes to sex cord-stromal cells (Leydig cell hyperplasia) and microlithiasis.

Qualitatively describe spermatogenesis across the whole biopsy – it often varies between tubules. Recognise the individual germ cell types, which proceed through spermatogenesis.

Assess spermatogenesis with a quantitative scoring system (e.g. Johnsen score<sup>50</sup> and other modifications of the Johnsen score).<sup>49</sup> However, the need for Johnsen counts is now limited as even the slightest degree of spermatogenic activity allows modern fertilisation procedures.

Comment on the presence or absence of any GCNIS.

Confirm presence of the testicular appendix which is attached to tunica albuginea at the upper testicular pole and may undergo haemorrhagic infarction by twisting on its pedicle.

*[Level of evidence – D.]*

## 8.2 Orchidectomy non-malignant

### 8.2.1 Indications for histology

- incidental removal (non-descent, atrophy, hernia repairs)
- testicular regression syndrome (TRS) and previously termed vanishing testes syndrome<sup>51,52</sup>
- torsion
- infection, chronic pain and trauma
- granulomatous orchitis – some cases are associated with urinary tract infections, history of prostatectomy, inguinal hernia repair and trauma
- occasionally bilateral orchidectomy for hormonal control of prostate cancer
- treat all these specimens as potentially malignant and approach macroscopic cut-up in anticipation of finding an underlying tumour<sup>53</sup>

- any incidental tumour should be submitted for regional review to the local testicular germ cell tumour MDT.

### 8.2.2 Staffing and workload (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology. Torsion and cryptorchid testes cases are more often seen in the paediatric age group and reported by paediatric pathologists.

Cases with tumours should be reported to the local MDT.

### 8.2.3 Laboratory facilities

- routine processing for LM
- availability of histochemical stains
- occasional use of immunohistochemistry to exclude or confirm background GCNIS such as PLAP, podoplanin and nuclear marker OCT3/4
- wider immunohistochemical panel for any tumours, including cytokeratin, CD30, AFP, Glypican-3,  $\beta$ -hCG, HPL, PLAP, OCT 3/4, c-kit, SALL4, CK7, inhibin.<sup>53,54</sup>

### 8.2.4 Specimen dissection

- weigh, measure, orientate
- if any suspicion of a tumour, treat as a potentially malignant testis
- embed at least:
  - cord resection margin separately in case of incidental tumour
  - base of cord
  - hilum including rete and epididymis
  - any focal lesions
  - two to three random sections in one block of background testis.

### 8.2.5 Sectioning and staining

One H&E section per cassette, usually one level is sufficient.

Beware hyalinised or atrophic-looking areas with inflammation and coarse calcification within seminiferous tubules (possible 'burnt-out' germ cell tumour). Take levels and if necessary go back to the specimen and re-embed whole testis to look for residual viable tumour and do IHC for GCNIS. In paediatric testes, where the amount of tissue is small, embed all the tissue. This is particularly important in testicular regression syndrome where identification of the spermatic cord allows definitive diagnosis.

Granulomatous orchitis shows an irregular rim of lighter-coloured tissue around the periphery and the process seems to extend beyond the testis proper. The cut surface is vaguely nodular, yellowish and hard. It mimics tumour clinically and macroscopically.

Likewise, before making a diagnosis of epidermoid cyst, exclude mature teratoma by embedding the whole of the lesion and all of the testis (to look for immature teratoma and background GCNIS). When diagnosed, these should be referred to the testis MDT.

### 8.2.6 Report content

Comment on the degree of spermatogenesis, any GCNIS, fibrosis or any incidental changes to sex cord stromal cells (Leydig cell hyperplasia or nodules).

Confirm with clinicians if cryptorchid and intra-abdominal testes in particular, may be associated with intersex syndromes. Comment on degree of tubular atrophy, tubular basement membrane thickening, interstitial hyalinisation, Sertoli cell change and nodules.

In torsion, it is important to correlate histological changes with the clinical timeframe with respect to testis viability as this can have medicolegal significance (viable/nonviable). The Mikutz grade (1–3) can be applied.<sup>55,56</sup>

Granulomatous orchitis shows a granulomatous inflammatory process with lymphocytes, plasma cells, macrophages, fibroblasts and scattered multinucleated giant cells, but no demonstrable organisms. Marked inflammation can occasionally mask tumours.

TRS consists of a fibrovascular nodule with associated haemosiderin-laden macrophages and dystrophic calcification. Residual testicular tubules are found in less than 10% of cases.<sup>52,53</sup>

Splenogonadal fusion is a rare congenital malformation in which there is an abnormal connection between the spleen and testes, sometimes mimicking a testicular neoplasm.<sup>57,58</sup>

Histological examination confirms the diagnosis and excludes neoplasia. Exclude malignancy – if present, follow protocols for testicular tumours.

*[Level of evidence – D.]*

### **8.3 Hydrocele**

#### **8.3.1 Indications for histology**

- inability to distinguish from an inguinal hernia
- failure to resolve spontaneously after an appropriate interval of observation
- inability to examine testis properly
- association of hydrocele with other pathology (e.g. torsion, tumour)
- pain or discomfort
- male infertility.

#### **8.3.2 Staffing and workload** (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology.

#### **8.3.3 Laboratory facilities**

- routine processing for LM
- use of immunohistochemistry if required.

#### **8.3.4 Specimen dissection**

- weigh and measure strips of hydrocele (hydrocelectomy) – usually thickened tunica
- note irregular nodules or areas of firmness – submit these for histology
- two to three representative sections in one block if normal appearing.

#### **8.3.5 Sectioning and staining**

- usually require only one H&E section per block
- routine processing for LM
- can require both histochemical and immunohistochemical analysis. May need to exclude mesothelioma in cases with marked mesothelial proliferation. Immunohistochemical panel should include CAM5.2, calretinin, CK5/6, EMA, CK7, HBME1, D2-40 and BerEP4 (+/- GLUT-1, p53, WT1, Ki-67).<sup>59</sup> The EM findings help secure the diagnosis
- histochemistry with Gram, ZN or PAS required if suspicion of infection.

### 8.3.6 Report content

Confirm benign mesothelial lining and fibrous thickening. Mesothelial hyperplasia in the tunica represents the reactive sequelae to persistent or repetitive serosal injury, inflammation in hydroceles and inguinal hernia sacs. Florid mesothelial hyperplasia may give rise to surface papillae, tubules, solid nests, and cords which may be confused with malignant mesothelioma of the tunica vaginalis.<sup>60,61</sup>

Record the presence or absence of malignancy (mesothelial).<sup>6,61</sup> Hydroceles are sometimes seen in association with testicular tumours (10%). Tunica (vaginalis/albuginea) cysts can be multilocular and show positivity for mesothelial markers. Cysts of epididymal or intratesticular (benign cysts and mature teratomas) origin need to be excluded.

Most cases are idiopathic but may be associated with hernia, trauma, infections (mumps orchitis, filariasis, TB) or tumours.

*[Level of evidence – GPP.]*

## 9 The epididymis and spermatic cord

### 9.1 Epididymal biopsy/epididymectomy

#### 9.1.1 Indications for histology

- incidental findings on testicular self-examination or routine physical examination – failure to transilluminate suggests a solid lesion
- often detected incidentally on ultrasound
- lump may be painful and require removal
- removal due to chronic epididymal pain or postvasectomy pain syndrome.

#### 9.1.2 Staffing and workload (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology. Refer problematic cases to the lead urological pathologist.

#### 9.1.3 Laboratory facilities

- routine processing for LM
- occasionally use of immunohistochemistry to exclude or confirm benign tumours (adenomatoid) or malignancy.

#### 9.1.4 Specimen dissection

- specimen consists of a cystic structure which may be multiloculated if a spermatocele
- sometimes specimen also contains part of the adjacent normal epididymis (partial epididymectomy)
- dimensions are measured in mm
- fluid is clear in an epididymal cyst and opaque because of the presence of sperm in a spermatocele
- outer surface is examined for mass lesions
- cyst is bisected and two sections taken to include the epididymis if present
- if a nodule or mass is present take representative blocks (one per cm) – more often due to the small size of the specimen, all the tissue can be submitted.

### 9.1.5 Sectioning and staining

- routine processing for LM
- usually require only one H&E section per block
- histochemical and immunohistochemical stains generally not required
- rarely any requirement for EM or molecular investigations.

### 9.1.6 Report content

Microscopic examination reveals a cyst with a fibromuscular wall that is lined by bland cuboidal epithelium.

Spermatocele results from dilation of an efferent ductule and is lined by a single layer of flattened epithelial cells. The wall is composed of fibromuscular stroma. It may sometimes be difficult to see spermatozoa as they are 'washed' away during specimen processing.

Note any other lesions – adenomatoid tumour, epididymitis nodosa, hernia sac entrapped epididymis, granulomatous ischaemic lesion, vasculitis and cystadenoma of epididymis.

Report the presence or absence of malignancy.

*[Level of evidence – GPP.]*

## 9.2 Vasectomy

### 9.2.1 Indications for histology

- normally for sterilisation to confirm complete transaction<sup>62</sup>
- occasionally biopsies of lesions (vasiitis nodosum or benign adenomatoid tumour)
- rarely as part of fertility surgery such as epididymovasotomy
- note problems arising from a fairly minor specimen – medicolegal issues of failed vasectomy and subsequent pregnancy.

### 9.2.2 Staffing and workload (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology.

### 9.2.3 Laboratory facilities

- routine processing for LM.

### 9.2.4 Specimen dissection

Orientate and measure the length and diameter of the vas segment in mm and submit one block of each vas. It may be expedient to take two cross sections from each to obtain a full face section. Where possible, do not embed all of the specimen, to permit extra block if initial sections suboptimally embedded.

Note any splits or defects.

In cases of failed sterilisation, block the whole vas (levels may be necessary) to identify possible recanalization.

For any other indication (e.g. possible tumour), consider inking margins and embedding the whole lesion depending on size.

If markedly enlarged soft tissue mass, treat as potential sarcoma. Ink margins, sample at least one block/cm diameter and consider taking specimens for freezing or EM if it arrives

fresh. Nodular periorchitis involves the tunica, epididymis or spermatic cord and forms a mass lesion.

### 9.2.5 Sectioning and staining

- routine processing for LM
- usually require only one H&E section per block
- may require levels or re-embedding if the lumen is not clearly visualised
- availability of histochemical stains occasionally used including PAS ± diastase or ZN
- very occasionally use of immunohistochemistry for adenomatoid tumour (epithelial marker), where the histological features are suboptimal due to crush artifact (CD10 and pan cytokeratin are useful markers to highlight the vas deferens epithelium)<sup>63</sup> or incidental connective tissue lesions.

### 9.2.6 Report content

Confirm vas deferens and that the full cross section is seen.

In failed sterilisation, confirm that it is vas and a full cross section is seen.

Exclude other associated pathology e.g. sperm granuloma, vasitis nodosa, proliferative funiculitis and recanalisation.

Nodular periorchitis is a reactive myofibroblastic proliferation involving the tunica, epididymis or spermatic cord, usually in response to some form of injury or infection. It is known by a variety of names (inflammatory pseudotumour, chronic proliferative periorchitis, nodular and diffuse fibrous proliferation, paratesticular fibrous pseudotumour).

Exclude malignancy (paratesticular neoplasms). The proliferating ductules of vasitis nodosa may be mistaken for prostatic adenocarcinoma with vascular or perineural invasion of nerves of the spermatic cord.<sup>63</sup>

*[Level of evidence – GPP.]*

## 10 Criteria for audit of the tissue pathway

In keeping with the recommended key performance indicators published by The Royal College of Pathologists ([www.rcpath.org/profession/clinical-effectiveness/key-performance-indicators-kpi.html](http://www.rcpath.org/profession/clinical-effectiveness/key-performance-indicators-kpi.html)), reports on urological cancers should be audited for the following:

- the inclusion of SNOMED or SNOMED-CT codes
  - standard: 95% reports should have T, M and P codes.
- turnaround times for biopsies and resection specimens:
  - standard: 80% of diagnostic biopsies will be reported within 7 calendar days of the biopsy being taken
  - standard: 80% of all histopathology specimens (excluding those requiring decalcification) will be reported within 10 calendar days of the specimen being taken.



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## Appendix A 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	<p>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</p> <p>or</p> <p>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.</p>
Level B	<p>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</p> <p>or</p> <p>Extrapolation evidence from studies described in A.</p>
Level C	<p>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</p> <p>or</p> <p>Extrapolation evidence from studies described in B.</p>
Level D	<p>Non-analytic studies such as case reports, case series or expert opinion</p> <p>or</p> <p>Extrapolation evidence from studies described in C.</p>
Good practice point (GPP)	<p>Recommended best practice based on the clinical experience of the authors of the writing group.</p>

## Appendix B AGREE guideline monitoring sheet

The tissue pathways of the Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines ([www.agreetrust.org](http://www.agreetrust.org)). The sections of this tissue pathway that indicate compliance with each of the AGREE II standards are indicated below.

<b>AGREE standard</b>	<b>Section of guideline</b>
<b>SCOPE AND PURPOSE</b>	
1. The overall objective(s) of the guideline is (are) specifically described	1
2. The clinical question(s) covered by the guidelines is (are) specifically described	Foreword, 1
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword, 1
<b>STAKEHOLDER INVOLVEMENT</b>	
4. The guideline development group includes individuals from all the relevant professional groups	Foreword
5. The views and preferences of the target population (patients, public, etc.) have been sought	Foreword
6. The target users of the guideline are clearly defined	1
<b>RIGOUR OF DEVELOPMENT</b>	
7. Systematic methods were used to search for evidence	Foreword
8. The criteria for selecting the evidence are clearly described	Foreword
9. The strengths and limitations of the body of evidence are clearly described	Foreword
10. The methods 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, 1
12. There is an explicit link between the recommendations and the supporting evidence	2–9
13. The guideline has been externally reviewed by experts prior to its publication	Foreword
14. A procedure for updating the guideline is provided	Foreword
<b>CLARITY OF PRESENTATION</b>	
15. The recommendations are specific and unambiguous	2–9
16. The different options for management of the condition or health issue are clearly presented	2–9
17. Key recommendations are easily identifiable	2–9
<b>APPLICABILITY</b>	
18. The guideline describes facilitators and barriers to its application	Foreword
19. The guideline provides advice and/or tools on how the recommendations can be put into practice	1–9
20. The potential resource implications of applying the recommendations have been considered	Foreword
21. The guideline presents monitoring and/or auditing criteria	10
<b>EDITORIAL INDEPENDENCE</b>	
22. The views of the funding body have not influenced the content of the guideline	Foreword
23. Competing interest of guideline development group members have been recorded and addressed	Foreword