



West Yorkshire & Harrogate Cancer Alliance

Guidelines for the Investigation and Treatment of Bladder, Renal and Prostate Cancers

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Version 3.0

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1 Introduction

1.1 National Guidance for Urological Cancer

The NICE 'Guidance on Cancer Services - Improving Outcomes in Urological Cancers - The Manual 2002', lists the following key recommendations:

- All patients with urological cancers should be managed by multidisciplinary urological cancer teams. These teams should function in the context of dedicated specialist services, with working arrangements and protocols agreed throughout each cancer network. Patients should be specifically assured of:
 - Streamlined services, designed to minimise delays;
 - Balanced information about management options for their condition;
 - Improved management for progressive and recurrent disease.
- Members of urological cancer teams should have specialised skills appropriate for their roles at each level of the service. Within each network, multidisciplinary teams should be formed in local hospitals (cancer units); at cancer centres, with the possibility in larger networks of additional specialist teams serving populations of at least one million; and at supra-network level to provide specialist management for some male genital cancers.
- Radical surgery for prostate and bladder cancer should be provided by teams typically serving populations of one million or more and carrying out a cumulative total of at least 50 such operations per annum. Whilst these teams are being established, surgeons carrying out small numbers (five or fewer per annum) of either operation should make arrangements within their network to pass this work on to more specialised colleagues.
- Major improvements are required in information and support services for patients and carers. Nurse specialist members of urological cancer teams will have key roles in these services.
- There are many areas of uncertainty about the optimum form of treatment for patients with urological cancers. High-quality research studies should be supported, with encouragement of greater rates of participation in clinical trials.

1.2 Purpose and Scope of these Guidelines

The purpose of this document is to set out agreed clinical guidelines for the investigation and management of Urological Cancer which are based on NICE Improving Outcome Guidance for Urological Cancers.

The document describes the investigation and management of prostate cancer, urothelial cancer and kidney cancer.

The document also describes the roles of the local care and specialist teams.

A separate Testicular Clinical Guideline has also been produced Plus a further guideline for penile and scrotal cancers. All three guidelines will be available electronically.

Urological Cancer Services in the West Yorkshire & Harrogate Cancer Alliance

The West Yorkshire & Harrogate Cancer Alliance (WY&H CA) has a resident population of approximately 2.6 million and there are 11 Clinical Commissioning Groups and 6 Acute Hospital Trusts within the Network. The Cancer Centre is based at Leeds Teaching Hospitals NHS Trust

Hospital Trust	Team
Airedale NHS Foundation Trust	Diagnostic/Local MDT
Bradford Teaching Hospitals NHS Foundation Trust	Diagnostic/Local /Specialist MDT
Calderdale & Huddersfield NHS Foundation Trust	Diagnostic/Local MDT
Harrogate and District NHS Foundation Trust	Diagnostic/Local MDT
Leeds Teaching Hospitals NHS Trust	Diagnostic/Local /Specialist MDT
Mid Yorkshire Hospitals NHS Trust	Diagnostic/Local /Specialist MDT
York Teaching Hospitals NHS Foundation Trust **	Diagnostic/Local MDT

** Please note - The York Hospitals NHS Foundation Trust is now part of the Humber Coast & Vale Cancer Alliance

Local MDT Teams

Hospital Trust	MDT Lead
Airedale NHS Foundation Trust	Mr P Koenig
Calderdale & Huddersfield NHS Foundation Trust	Mr N Bryan
Harrogate and District NHS Foundation Trust	Mrs Rachel Morrison
York Teaching Hospitals NHS Foundation Trust **	Mr R Wilson

Specialist Teams

Hospital Trust	MDT Lead
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Leeds Teaching Hospitals NHS Trust	Mr W Cross
Mid Yorkshire Hospitals NHS Trust	Mr M Dooldeniya

1.3 Network clinical pathways

The former YCN Urology Group developed Network clinical timed pathways for the following;

- Bladder Cancer Pathway
- Prostate Cancer Pathway
- Renal Cancer Pathway

Teenagers and Young Adults

The former YCN and HYCCN Teenage and Young Adult with Cancer Pathway (16-24 years) has been developed.

1.4 National Timed Prostate Cancer Diagnostic Pathway

NHS England have produced a National Prostate Cancer Timed Clinical Pathway (December 2017).

This can be accessed via the West Yorkshire & Harrogate Cancer Alliance Website

<https://www.england.nhs.uk/publication/rapid-cancer-diagnostic-and-assessment-pathways/>

1.5 Patient Information

Clinical teams offer all newly diagnosed cancer patients information specific to their site, treatment and relevant to their individual need. Patients can also access NHS choices for an information prescription and clinical teams will offer help to do this, if required.

2 Renal Cell Carcinoma

2.1 Introduction

This guidance is an update on the previous network guidance of 2005 instructed by current practice locally and the European Association of Urology Guidance under Management of Renal Cell Carcinoma.

2.2 Presentation of renal cell carcinoma

The classic triad of symptoms and signs in the presentation of renal cell carcinoma was always a rarity and with the ubiquity of ultrasound scanning it becomes rarer and rarer. The two week wait guidance for the management of cancer generally would stipulate that patients with a renal mass and patients with haematuria should be referred urgently to a urology service and a proportion of such cases of course will have renal cell carcinoma. All presentations with haematuria should be dealt with in a one-stop haematuria clinic and this is dealt with in the guidance for the management of bladder cancer in this document.

Widespread ultrasound scanning for gynaecological and general indications has massively increased the number of renal masses found incidentally. In most centres in the UK now more than half of renal cell cancers diagnosed are found in this asymptomatic state.

2.3 Diagnosis of RCC

Diagnostic radiology is central to the diagnosis of renal cell cancer. Biopsy before definitive therapy once rare is becoming more common with the increased offer of complex minimally invasive surgery. All patients with renal masses diagnosed on ultrasound, in whichever context described above, should have CT scan with contrast medium if renal function allows. The CT scan should be of the chest and abdomen. In the case of patients with creatinine over 300 μ M, MRI scanning is a suitable alternative. These diagnostic scans should be booked as urgent investigations and urgent discussion in the local multi-disciplinary team meeting should be arranged after those scans. Treatment plans can be made at the MDT meeting and any further investigations required identified.

2.4 Pre-operative investigations

Therapeutic choices may be instructed by poor renal function and especially lateralisation of renal function. The MRI scan and CT will often give a great deal of inferential information about the lateralisation and localisation of renal function but in the event of any doubt about the potential viability of renal tissue remaining after definitive treatment for renal cell cancer, radio isotope scans should be arranged. Most often, renal scanning will be sufficient, but occasionally dynamic renography would be more suitable. Patients should have general

investigation in the shape of blood biochemistry and haematological measures and MDT members should have an awareness of the paraneoplastic syndromes commonly associated with renal cell carcinoma and their potential effects on risk estimation for patients coming to major surgery.

In case of diagnostic doubt in terms of the radiological appearance of renal masses, percutaneous biopsy of tumours may occasionally be required. In the case of patients coming to surgery this should not form part of routine practice but again there should be a realisation that a small proportion of kidneys removed in the belief that they contain a renal cell carcinoma will prove to contain benign tumour or indeed non-tumourous conditions. This should be made clear to patients in the process of consent.

2.5 Multi-disciplinary discussion

In the initial MDT meeting after the radiological diagnosis and staging investigations, a decision as to suitable treatments for individual patients should be made. The MDT should assign a clinical stage to the disease and the TNM system of the UICC provides a suitable scheme.

Table updated 03.05.17

Primary tumors (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 7 cm in greatest dimension, limited to the kidney
T1a	Tumor ≤ 4 cm in greatest dimension, limited to the kidney
T1b	Tumor > 4 cm but ≤ 7 cm in greatest dimension, limited to the kidney
T2	Tumor > 7 cm in greatest dimension, limited to the kidney
T2a	Tumor > 7 cm but ≤ 10 cm in greatest dimension, limited to the kidney
T2b	Tumor > 10 cm, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond the Gerota fascia
T3a	Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond the Gerota fascia
T3b	Tumor grossly extends into the vena cava below the diaphragm
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond the Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)
Regional lymph node (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

All local stages of disease are potentially suitable to local radical treatment and if such treatment is considered feasible by the MDT, it should be offered. Disease in local lymph nodes may also be suitable for radical surgical excision and this too should be offered while more distant lymph node metastases, if multiple, are more suitably treated by systemic treatment as a primary treatment. Generally patients with distant metastases should be treated systemically in the first instance. The value of cytoreductive nephrectomy in the post-IFN era is unproven and such nephrectomy should be offered only on a case-by-case basis after multidisciplinary discussion. The exception is the case of the synchronous, solitary haematogenous metastases. For such patients excision of the primary tumour and the metastases would seem to offer the prospect of curing up to 35% of patients. The MDT is also a suitable venue to identify those patients who, on the basis of clinical findings, should be offered palliative or supportive care only.

2.6 Treatment of localised renal cell cancer

Radical nephrectomy has, at least until recently, been viewed as the gold standard treatment for localised kidney cancer. It is no longer thought that adrenalectomy is an essential component of every radical nephrectomy. It should be practiced for large upper pole tumours and for tumours of more than 7cm generally. Pre-operative embolization is rarely practiced now with the advent of safe laparoscopic surgery for larger renal tumours. It should be considered as an adjunct prior to surgery for complex open nephrectomy for large tumours.

In the case of small renal cancers (<4cm / T1a), nephron-sparing renal cancer surgery has oncological results equivalent to radical nephrectomy.

More recent data [summarised in Bensalah et al, 2007] would suggest that partial nephrectomy is also as efficacious as radical nephrectomy in the case of larger, organ confined renal tumours.

In a study of 9809 patients treated by radical nephrectomy or nephron sparing surgery, and with median follow-up of 46 and 36 months respectively, Zini et al found a relative risk of non-cancer mortality of 1.23 in the radical nephrectomy patients [2009]. Such data has not been replicated in all reports but has been taken to suggest that partial nephrectomy should be preferred to radical nephrectomy whenever it is technically feasible and the surgical skills required are available.

There are absolute indications to nephron sparing surgery in the case of the solitary kidney and in the case of patients in whom one can anticipate deterioration in renal function over time. Patients from lineages of Von Hippel-Lindau disease and hereditary papillary renal cell carcinoma would present such cases. In view of the fact that cancer outcomes seem to be the same with partial nephrectomy for the smaller renal tumours, such treatment should be offered to patients whenever available and with the end simply of preserving more renal function.

Both radical nephrectomy and partial nephrectomy should be performed with minimally invasive techniques. If these skills are not available locally patients should be referred to the central MDT for consideration of minimally invasive surgery. . Partial nephrectomy is a difficult laparoscopic procedure even in experienced hands. Laparoscopic nephron-sparing surgery will be provided alongside robot assisted surgery increasing the availability of minimally-invasive nephron-sparing surgery.

Nephron-sparing surgery must be considered to be a complex intervention and as such should be provided by Specialist MDTs only. As nephron-sparing surgery may be applicable to even large renal masses, all renal masses need to be discussed in the Specialist MDT to allow the providers of nephron sparing surgery properly to guide selection of suitable cases.

Radical

nephrectomy may continue to be performed in the local MDT following central discussion of cases that may have been considered for nephron-sparing surgery at the central MDT and considered inappropriate for that surgical technique.

Bensalah K, Cr epel M & Patard JJ. "Tumor size and nephron-sparing surgery: does it still matter?" *Eur.Urol.* (2007) **53**: 691-693

Zini L, Perrotte P, Capitanio U, Jeldres C, Shariat SF, Antebi E, Saad F, Patard J-J, Montorsi F & Karakiewicz. "Radical versus partial nephrectomy: effect on overall and noncancer mortality" *Cancer* (2009) **115**: 1465-1471

Sukumar S & Rogers CG, "Robot-assisted partial nephrectomy" *J.Endourol.* (2011) **25**: 151-157

2.7 Complex Radical Nephrectomy.

Renal cancers with local stage T3a and above should be operated in the cancer centre. Planned cavotomy, certainly for disease above the hepatic veins, should be exclusively provided in the cancer centre. The centralisation of these relatively rare cases allows the concentration of experience and the development of relationships with HPB and cardiothoracic surgeons whose help may be required for the excision of such tumours.

2.8 Image Guided Ablation

Image guided ablation using either radiofrequency, cryotherapy or Irreversible electroporation (IRE) are relatively new techniques for the destruction of renal tumours and tumours in other sites. They seem to offer similar cancer control to nephron-sparing renal surgery and as a minimally invasive technique can offer the less fit patient effective treatment for the small renal tumour. It is important to remember that these techniques are currently performed under a general anaesthetic, and like surgical excision, patients have to be medically fit for a safe anaesthetic to be offered these treatments. The longevity of RFA is such that long term results are only now becoming available but it does seem to provide a very viable alternative to surgery for small volume localised disease. It should be considered as a treatment option in discussion with the patient and in the first MDT discussion of available treatments.

2.9 Embolisation

Embolisation alone should be viewed only as a palliative treatment for renal cell carcinoma. It is effective in treating intractable and heavy haematuria as a consequence of such tumours. Its role in relieving pain from renal tumours is less well defined but it may sometimes be used as an analgesic technique. In recommending this treatment to patients it

should be realised that it is not without its own complications and there is a definite morbidity and indeed mortality associated with this technique as for all local treatments.

2.10 Nephrectomy as a debulking technique

Previously, debulking nephrectomy was practiced as routine for patients proceeding to biological therapies based on interferon alpha and there was useful evidence to suggest that such debulking increased the efficacy of those biological therapies. With the progress of systemic treatment to the angio-genesis inhibiting drugs such as sorafenib and sunitinib the case for debulking nephrectomy is less clear. This should be discussed on a case by case basis in the multi-disciplinary meeting in this setting.

2.11 Systemic therapies

Patients with a solitary metastasis from renal cell carcinoma should be offered surgery for both the renal primary and the metastasis. There is a long experience of such surgery reported in literature and long term survival is recorded in around a third of patients so treated. Synchronous primary and metastatic disease is a poor prognostic sign and the time elapsed between treatment of the primary cancer and the discovery of the metastases is positively correlated with survival. In the case of more than one site of metastatic disease, metastectomy is very much less likely to be effective and should be considered only after very full discussion in the MDT and with the patient.

2.12 Biological therapies

All patients with metastatic disease and many with extensive nodal metastatic disease should be referred to the centre for consideration of systemic treatment with palliative intent. Systemic treatment has until recently depended upon cytokines, especially interferon alpha. New angio-genesis inhibitors have been shown to be more effective, however, cytokines may still be appropriate in certain circumstances.

Patients with metastatic disease proceeding directly to systemic therapy should undergo a biopsy to confirm the diagnosis and histological cell type. The most accessible site is often the renal mass but this should be discussed in the MDT. With the availability of therapies targeted to non-clear cell and poor risk disease, histology can guide first line treatment. Biopsies should be performed in the patient's local hospital if at all possible.

Interferon- α alone is no longer routinely recommended as the first line treatment in metastatic RCC. Previous trials have shown a survival advantage for interferon- α . However, all recent data comparing interferon- α monotherapy to anigogenesis inhibitors in the first line setting have shown inferiority for interferon- α .

2.13 Angiogenesis inhibitors

These agents include sorafenib, sunitinib, bevacizumab and temsirolimus.

These agents include sunitinib, pazopanib, sorafenib, bevacizumab, temsirolimus and everolimus. In UK practice, sunitinib the most commonly used of these agents in the metastatic setting.

Response rates of 30-50% and improvements in survival compared with cytokines have been reported but long-term remissions are rare¹. Patients should be considered for treatments within a clinical trial setting. Renal cancer is generally considered radio-resistant, but local external beam radiotherapy to painful bony metastases may be useful in palliation.

First line biological treatments for metastatic RCC.

Sunitinib is an oral tyrosine kinase inhibitor and inhibits PDGFR, VEGFR, KIT and FLT-3. A pivotal study in the first line setting comparing sunitinib to interferon- α demonstrated a significantly longer median progression free survival in the sunitinib group (11 months vs 5 months) (Motzer et al, New Eng J Med, 2007). This is now standard of care for patients with good or intermediate prognosis disease. Patients with ECOG performance status of 0 or 1 will receive sunitinib 50mg po once daily.

Pazopanib is an oral tyrosine kinase inhibitor of VEGF and PDGF and also has NICE approval for use in the first line setting. A significant survival advantage has been demonstrated compared to placebo in treatment-naïve and cytokine treated patients (Sternberg et al, JCO, 2010). Pazopanib is given orally, 800mg daily.

Temsirolimus is an inhibitor of mTOR (mammalian target of rapamycin). This is currently funded via the Cancer Drugs Fund for first line use in patients with poor prognosis metastatic RCC. Patients must fulfil at least 3 of the following prognostic criteria to be eligible for funding:

1. Less than 1 year from time of initial diagnosis of RCC to initiation of treatment
2. Karnofsky performance status of 60-70
3. Haemoglobin less than the lower limit of normal
4. Corrected calcium greater than 10mg/100ml (or 2.5mmol/L)
5. Lactate dehydrogenase more than 1.5 times upper limit of normal
6. More than one metastatic organ site

The combination of bevacizumab and interferon has been shown to be effective in the first line setting but is not currently funded for routine use.

Second line treatments for metastatic RCC

Everolimus, an oral inhibitor of mTOR, is currently funded through the Cancer Drugs fund for the treatment of patients who have failed TKI therapy. It has been shown to improve progression free survival compared to placebo in patients that have failed prior VEGF targeted therapy. (Motzer et al, Lancet, 2008).

³ **Sternberg** CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, Barrios CH, Salman P, Gladkov OA, Kavina A, Zarba JJ, Chen M, McCann L, Pandite L, Roychowdhury DF, Hawkins RE. (2010)

¹ Motzer, R.J., Hutson, T.E., Tomczak, P., Michaelson, M.D., Bukowski, R.M., Rixe, O., Oudard, S., Negrier, S., Szczylik, C., Kim, S.T., Chen, I., Bycott, P.W., Baum, C.M., and Figlin, R.A. (2007) Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N. Engl. J. Med. 356, 115-24.

² Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grünwald V, Thompson JA, Figlin RA, Hollaender N, Urbanowitz G, Berg WJ, Kay A, Lebwohl D, Ravaud A; RECORD-1 Study Group (2008) Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomized, placebo-controlled phase III trial. Lancet. 372, 449-56

2.14 Follow up regimes after radical treatment

Suitable protocols for patients after surgery for renal cell cancer have been under much debate in the urological literature over several years. Suitable protocol is below.

Patients following radical nephrectomy can be classified as having low, intermediate and high risk disease with respect to the possibility of disease progression or recurrence. This will be determined at post operative pathological MDT review where guidance on future follow up intensity will be made. Network guidelines have been produced based on international follow up guidance published by the EAU and the AUA.

Table updated 03.05.17

	Months post-nephrectomy												
	1	3	6	12	18	24	30	36	42	48	54	60	Up to 10yrs
Low Risk	Partial Nephrectomy												
Clinical Examination	X		X	X		X		X		X		X	2 yearly
CT Thorax/Abdo				X		X		X		X		X	
Low Risk	Radical Nephrectomy												
Clinical Examination	X		X	X		X		X		X		X	Stop
CT Thorax/Abdo				X		X		X		X		X	
Intermediate Risk	Radical Nephrectomy, Partial Nephrectomy												
Clinical Examination	X		X	X	X	X		X		X		X	2 yearly
CT Thorax/Abdo			X	X	X	X		X		X		X	
High Risk	Radical Nephrectomy, Partial Nephrectomy												
Clinical Examination	X	X	X	X	X	X	X	X		X		X	2 yearly
CT Thorax/Abdo		X		X	X	X	X	X		X		X	

2.15 Management of recurrent disease

Any evidence of local or metastatic disease recurrence identified on follow up imaging should initially be discussed at the local MDT meeting. Single sites of recurrent disease may be suitable for treatment with surgical excision or radiotherapy and should be referred to the central MDT for consideration of treatment. All patients with recurrence or metastatic disease at multiple sites should be referred to the centre for consideration of systemic treatment. Blood biochemistry & haematology results should be included in the referral to allow risk stratification. Further follow up after treatment for recurrent or metastatic disease will be determined by the MDT.

3 Transitional Cell Carcinoma of Bladder (TCCB)

3.1 Diagnosis

Rapidity in diagnosis and treatment of bladder cancer remains an important goal¹. One-stop haematuria clinics with waiting times of less than two-weeks from the date of referral should be available to all patients referred on the suspected bladder cancer referral pathway. Two week wait suspected bladder cancer referral includes patients who are aged 45 and above with either unexplained visible haematuria without a UTI or visible haematuria that persists or recurs after successful treatment of UTI, and patients who are aged 60 and above and have unexplained non-visible haematuria and either dysuria or a raised white cell count on a blood test². Patients who are aged 60 and above with recurrent or persistent unexplained urinary tract infection and those with persistent storage type bladder symptoms are also appropriately investigated in this setting.

These patients should have upper tract imaging and cystoscopy. Upper tract imaging should include at least an USS of the KUB as this is preferred over intravenous urogram (IVU) for the investigation of the upper tracts because of its greater sensitivity in detection of renal parenchymal tumours and because of considerations of radiation exposure³. Whenever possible, CT urogram can be offered as the primary investigation because of its higher diagnostic accuracy and can potentially allow for 17% reduction in the number of flexible cystoscopies performed in haematuria patients⁴.

Urinary cytology is of little use in the diagnosis of lower and intermediate grade bladder cancer but is 95% sensitive in detection of poorly differentiated, high-risk disease⁵. In case of negative investigation of haematuria, urinary cytology provides additional reassurance that significant disease has not been overlooked.

The diagnostic role of commercial urinary molecular markers remains controversial. Many offer better sensitivity for detecting bladder cancer than urinary cytology, but specificity is lower. The tests also incur an additional cost.

Fluorescence-guided cystoscopy and biopsy are more sensitive than conventional white-light procedures in detecting bladder cancer, especially TIS. Application of this technology has been shown to improve recurrence-free survival and time to first recurrence, but at the price of increased false-positivity induced by inflammation, recent biopsies or intravesical chemotherapy/immunotherapy.

If invasive bladder cancer is suspected at the time of flexible cystoscopy, a staging computed tomography (CT) or magnetic resonance imaging (MRI) can be requested before TURBT. Such pre-emptive imaging expedites assessment and obviates the problem of distinguishing surgical artefact from extra-vesical disease when staging scans are performed after TURBT.

3.2 Histological Diagnosis and Staging

Transurethral resection of bladder tumour (TURBT)

TURBT is central to decisions in staging and management of bladder tumours. All visible tumours should be fully resected if this can be safely accomplished. Ideally, small tumours (<1cm) should be resected en bloc. The presence of underlying detrusor muscle in biopsies is essential in distinguishing non muscle invasive and muscle invasive disease and can be ensured by separate cold-cup biopsies after resection if the resectionist is in doubt. If the primary TURBT specimen does not include detrusor muscle, consider re-TURBT within 6 weeks to achieve accurate staging, especially for high risk bladder tumours.

The operating surgeon should record the number, size and location of the bladder tumours in the operation notes. Random, near-and-far biopsies of tissue which appears normal may carry risks of seeding of TCC to new sites⁶ and are not recommended. However any abnormal area in the bladder should be biopsied and sent in a separate container, as the presence of TIS should profoundly affect the management of the individual patient. TURBT should always be followed by examination under anaesthesia. If muscle invasive disease is suspected, prostatic biopsies may be taken at first resection. They are best taken by resection at 5 and 7 o'clock above the veru⁷. Prostatic urethral loop biopsies should also be considered in cases when the tumour is located on the trigone or bladder neck and when cytology is positive and there is no evidence of disease in the bladder or upper tracts.

Patients with suspected bladder cancer, especially those with low risk small tumours should be offered and whenever possible, receive a single dose of Intravesical Mitomycin C at the same time of the first TURBT^{8,9,10}.

Radiological Staging

Guidelines for imaging of bladder cancer had been developed by the former YCN Imaging Group and are described in detail in Chapter 8.

All patients with muscle-invasive disease and those with new or recurrent high risk non-muscle invasive disease should have cross-sectional imaging. CT urogram is the investigation of choice and patients with muscle invasive disease should also have a CT Thorax to exclude asymptomatic pulmonary metastases or lung malignancy which can co-exist in bladder cancer patients. It is variously reported to have 64-92% accuracy in local staging. In detection of lymph node metastases it is 70-96% accurate. MRI has similar published results to CT scanning but in individual studies, and anecdotally, it is more accurate than CT in terms of local staging¹¹.

Other radiological investigations (bone scintigraphy, CT/USS guided biopsy of liver and other organs) are not elements of routine staging investigation but may be indicated in individual cases where there is clinical suspicion of metastatic disease. In patients with muscle-invasive bladder cancer or high-risk non-muscle-invasive bladder cancer before radical treatment if there are indeterminate findings on CT or MRI, or a high risk of metastatic disease, central MDT should consider Fluorodeoxyglucose positron emission tomography (FDG PET-CT)¹².

3.3 Staging and Prognostic Categories/Groups

The TNM classification for staging of bladder cancer is provided below¹³

Primary tumour (T):

Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ: "flat tumour"
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscularis propria
T2a	Tumour invades superficial muscularis propria (inner half)
T2b	Tumour invades deep muscularis propria (outer half)
T3	Tumour invades perivesical tissue
T3a	Microscopic involvement
T3b	Macroscopic involvement (extravesical mass)
T4	Tumour invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostatic stroma, uterus, vagina
T4b	Tumour invades pelvic wall, abdominal wall

Regional lymph nodes (N): Regional lymph nodes include both primary and secondary drainage regions. All other nodes above the aortic bifurcation are considered distant lymph nodes.

Nx	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
N3	Lymph node metastasis to the common iliac lymph nodes

Distant metastasis (M)

Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Based on available prognostic factors and in particular data from the European Organisation for Research and Treatment of Cancer (EORTC) risk tables, the EAU guidelines panel recommended stratification of patients into three risk groups. Following table provides a definition of these risk groups, which takes into account the EORTC risk tables' probabilities of recurrence and especially progression¹⁴.

Risk classification in non-muscle-invasive bladder cancer:

Low risk	Urothelial cancer with any of: <ul style="list-style-type: none"> solitary pTaG1 with a diameter of less than 3 cm solitary pTaG2 (low grade) with a diameter of less than 3 cm any papillary urothelial neoplasm of low malignant potential
Intermediate risk	Urothelial cancer that is not low risk or high risk, including: <ul style="list-style-type: none"> solitary pTaG1 with a diameter of more than 3 cm multifocal pTaG1

	<ul style="list-style-type: none"> solitary pTaG2 (low grade) with a diameter of more than 3 cm multifocal pTaG2 (low grade) pTaG2 (high grade) any pTaG2 (grade not further specified) any low-risk non-muscle-invasive bladder cancer recurring within 12 months of last tumour occurrence
High risk	Urothelial cancer with any of: <ul style="list-style-type: none"> pTaG3 pT1G2 pT1G3 pTis (Cis) aggressive variants of urothelial carcinoma, for example micropapillary or nested variants

3.4 Management: Stage-by-Stage (NICE and EAU)

Low-risk non-muscle-invasive bladder cancer

These tumours are at low risk of recurrence and progression. Single-dose intravesical chemotherapy within 24 hours of TURBT for such disease has been shown to reduce recurrence by 29-35%^{9,10}. These studies had very low recurrence rates (16 and 10% in the control arms), however. All patients should enter a programme of surveillance by check cystoscopy at 3 and 12 months from the diagnosis. Those with no recurrence at 12 months can be discharged back to the primary care¹². Use of urinary biomarkers or urine cytology or prolonged cystoscopic follow up is not recommended in these patients.

3.4.2 Intermediate-risk non-muscle-invasive bladder cancer

These tumours are at high risk of recurrence but low risk of progression. These patients should be offered cystoscopic follow-up at 3, 9 and 18 months, and once a year thereafter. One should consider discharging these patients to primary care after 5 years of disease-free follow-up¹².

Full courses of intravesical chemotherapy agents are justified in multiply recurrent disease. In case of resistance to chemotherapy, BCG immunotherapy may be considered. Rarely cystectomy may be required. The uncommon well-differentiated Ta tumours require particularly careful surveillance.

3.4.3 High Risk non-muscle-invasive bladder cancer

Due to the implications of understaging a second TUR should be considered, especially when the initial resection was incomplete or when the initial specimen contained no muscle. The second resection should take place 2-6 weeks after the initial TUR and should include biopsies of the primary tumour site.

These tumours have around one chance in two of progression to muscle-invasive disease in five years. According to European Organisation for Research and Treatment of Cancer (EORTC) risk calculator, the risk of progression after five years is 45% for high-risk tumours. There is no evidence that intravesical chemotherapy can reduce this progression rate. Intravesical immunotherapy has been used in such high-risk disease for many years but remains controversial. Herr¹⁵ had reported a 10-year progression free rate of 62% in BCG-treated patients against 37% for control patients (TURBT only). In 2015, the EORTC group presented new nomograms based on two large phase III trials with a median follow up of 7.4 years. With 1 to 3 years of maintenance BCG, the risk for progression at five years was

much lower i.e. 19.3% for T1G3 tumours¹⁶. A meta-analysis of published trials suggested that the use of BCG with maintenance reduced the chance of progression of G3pT1 and CIS tumours by 27% ($p=0.001$)¹⁷. This benefit was not seen in trials which did not use maintenance regimes. It may be concluded that BCG-maintenance has benefits in the regime of 3, weekly instillations at 3 months, 6 months, 12 months and 6-monthly for one to three years. On this basis, it is recommended that high-risk superficial disease should be treated with a full (i.e. six, weekly doses) course of BCG instillations. Maintenance BCG should follow this induction with intensive cystoscopy surveillance.

BCG-refractory NMIBC tumours should be treated aggressively and these are defined as:

- whenever muscle-invasive tumour is detected during follow-up
- if high-grade, non-muscle-invasive papillary tumour is present at three months
- if CIS (without concomitant papillary tumour) is present at both three and six months
- if high-grade tumour appears during BCG therapy
- high-grade recurrence after BCG (grade 3/high-grade (HG) [WHO 1973/2004] tumour after completion of BCG maintenance, despite an initial response

Patients with BCG failure are unlikely to respond to further BCG therapy, therefore radical cystectomy is the preferred option. Some studies have suggested that repeat BCG therapy in combination with interferon is appropriate for non-high-grade and even for some high-grade recurrent tumours^{18,19}. The role of intravesical chemotherapy, device-assisted therapy (Hyperthermia and EMDA) can yield responses in selected cases with BCG treatment failure. However, treatments other than radical cystectomy must be considered oncologically inferior in patients with BCG failure, at the present time. There is no place for radiotherapy for management of persistent carcinoma in situ after BCG therapy. Radical cystectomy with urethrectomy is the treatment of choice, if the patient is fit.

Immediate radical cystectomy is an option for patients with high risk non-muscle invasive disease. There are several reasons to consider immediate RC for selected patients with NMIBC. The staging accuracy for T1 tumours by TURBT is low with 27-51% of patients being upstaged to muscle-invasive tumour at radical cystectomy and some patients with NMIBC will experience disease progression to muscle-invasive disease. Patients who experience disease progression to muscle-invasive stage, have a worse prognosis than those who present with 'primary' muscle-invasive disease^{20,21}. The potential benefit of RC must be weighed against its risks, morbidity, and impact on quality of life. The benefits and risks of immediate and delayed radical cystectomy should be discussed with patients in a shared decision-making process.

Recent EAU guidelines¹⁴ suggest discussing immediate radical cystectomy to the patients with non-muscle-invasive tumour, who are at highest risk of progression. Subgroup of highest-risk tumours includes:

- T1G3/HG associated with concurrent bladder CIS
- multiple and/or large T1G3/HG and/or recurrent T1G3/high-grade
- T1G3/HG with CIS in the prostatic urethra
- unusual histology of urothelial carcinoma
- lymphovascular invasion

Early radical cystectomy should be strongly recommended in patients with BCG-refractory tumours, as delay in radical cystectomy may lead to decreased disease-specific survival²². In patients in whom RC is performed before progression to muscle invasive disease, the 5-year disease-free survival rate exceeds 80%^{23,24}.

3.4.4 Muscle Invasive Bladder Cancer – Organ confined (Any grade, pT2 /pT3, N0, M0)

In the UK, the traditional treatment of muscle invasive bladder cancer (MIBC) has been with external beam radiotherapy (EBRT) followed by salvage cystectomy for patients with post-irradiation recurrence or persistence of invasive disease. In the USA, Europe and more recently in the UK, primary cystectomy has been more commonly practised, with EBRT reserved for patients unfit or unwilling to be subjected to cystectomy. These two approaches have not been subjected to randomised controlled trial on an intention-to-treat basis however, retrospective case series have shown radical radiotherapy to be a viable treatment option especially, for elderly patients²⁵.

The recommendation of this guideline is that patients should be able fully to discuss the likely outcomes of surgery (with or without reconstruction), as compared to radical pelvic radiotherapy and come to an informed decision on the treatment modality to be employed. A realistic assessment of local results and side effects of these modalities is critical²⁶.

3.4.4.1 Radical Radiotherapy

Pre-operative radiotherapy for operable muscle-invasive bladder cancer is not recommended as it has not been conclusively proven to improve survival. A recent randomised controlled trial of comparing pre-operative vs. post-operative radiotherapy in patients treated with radical cystectomy showed comparable overall and disease-free survival²⁷. Approximately half of these patients had urothelial cancer, while the other half had squamous cell cancer. In locally advanced bladder cancer (T3-T4, N0/N1, M0), the local recurrence rate seems to decrease with post-operative radiotherapy²⁸.

Concurrent chemoradiation offers a survival advantage over radiotherapy alone for suitable patients. A phase III RCT (BC2001) looked at whether synchronous chemotherapy and radiotherapy (CRT) improved loco-regional disease control when compared with radiotherapy alone in patients with muscle invasive bladder cancer. Chemotherapy was given as Mitomycin-C and continuous 5FU. At 5 years overall survival in the CRT group was 48% as compared to 35% in the radiotherapy alone group²⁹. Grade 3 and 4 adverse events were slightly more common in the CRT group.

Low dose gemcitabine as a radio-sensitiser has demonstrated high response rates and acceptable toxicity in a Phase 2 cohort study of CRT (52.5Gy in 20 fractions) in patients with T2-3 N0 M0 bladder TCC. 88% of patients achieved a complete endoscopic response at post-treatment cystoscopy. At a median follow up of 36 months 36 patients were alive and 32 of these had a functional and intact bladder. The three year cancer-specific survival was 82% with an overall survival of 75%³⁰. This regimen has been chosen as CRT of choice in Leeds Cancer Centre as it has advantages in terms of convenience and appears to be as effective as Mitomycin-C and continuous 5FU.

3.4.4.2 Neo-adjuvant and Adjuvant Chemotherapy

Cochrane metanalysis published in 2005, showed 5% absolute improvement in overall survival at five years with cisplatin-containing neoadjuvant combination chemotherapy. It should be considered and offered to patients with muscle-invasive bladder cancer, irrespective of definitive treatment³¹. Due to the lack of robust randomised trial evidence, adjuvant chemotherapy is not advised except in the context of a clinical trial.

3.4.4.3 Radical Cystectomy (RC)

Radical cystectomy is the standard treatment for organ-confined MIBC in most western countries. An interest in patient's quality of life (QoL) has promoted the trend toward bladder-

preserving treatment modalities. There is some evidence to suggest performance status (PS) and age influence the choice of primary therapy as well as the type of urinary diversion, with cystectomy being reserved for younger patients without concomitant disease and with a better PS²⁵. The value of assessing overall health before recommending and proceeding with surgery has been emphasised in a multivariate analysis³².

In men, standard RC includes removal of the bladder, prostate, seminal vesicles, distal ureters, and regional LNs. In women, standard RC includes removal of the bladder, entire urethra and adjacent vagina, uterus, distal ureters, and regional lymph nodes³³. A recent systematic review of nineteen eligible studies comparing lymphadenectomy vs no lymphadenectomy reported a better oncological outcome for the lymphadenectomy group³⁴. Surgery does have a survival advantage in patients with nodal disease. This probably only applies to N1 disease but, because of the uncertainties of pre-operative staging, all cystectomies for cancer should include extended lymph node dissection. Stein has reported 41% five-year survival among 161 patients with 1-4 positive lymph nodes treated with cystectomy and extended lymph node dissection, that is, from the aortic bifurcation to Cloquet's node bilaterally²³. This extended node dissection should be considered the norm in cystectomy for TCC. No difference in outcome was reported between extended and super-extended LND in a comparative study between two high volume centre studies³⁵. Further data from on-going randomised trials on the therapeutic impact of the extent of lymphadenectomy is awaited.

Different approaches have been described to improve voiding and sexual function in patients undergoing RC for bladder cancer. No consensus exists regarding which approach preserves function best and concern regarding the impact of "sparing-techniques" on oncological outcomes, still remain to be answered. Four main types of sexual-preserving techniques have been described:

Prostate sparing cystectomy: part or the whole prostate is preserved including seminal vesicles, vas deferens and neurovascular bundles.

Capsule sparing cystectomy: the capsule or peripheral part of the prostate is preserved with adenoma (including prostatic urethra) removed by TURP or en bloc with bladder. Seminal vesicles, vas deferens and neurovascular bundles are also preserved.

Seminal sparing cystectomy: seminal vesicles, vas deferens and neurovascular bundles are preserved.

Nerve sparing cystectomy: the neurovascular bundles are the only tissue left in place.

There is some evidence to suggest that these procedures may yield better sexual outcomes than standard cystectomy without compromising oncological outcomes³⁶. However, if a sexual-preserving technique is offered, patients must be carefully selected, counselled and closely monitored. Do not offer sexual-preserving cystectomy as standard therapy for muscle-invasive bladder cancer.

Robotic-assisted radical cystectomy – Open radical cystectomy is considered the gold standard surgical treatment invasive bladder cancer however, minimally invasive robotic approach is currently evolving at a fast pace and has become popular in recent years, owing to the proven advantage of decreased blood loss, blood transfusion rates, decreased length of stay and quicker recovery. A randomised trial from Memorial Sloan Kettering which included patients with extracorporeal urinary diversions showed similar 90-d complication rates, hospital stay, pathologic outcomes, and 3- and 6-mo QOL outcomes between open and robotic technique³⁷. Results from the most recent prospective, multicentre, randomized trial of open vs robotic radical cystectomy (RAZOR) were presented at the AUA 2017 meeting³⁸. The trial concluded that RARC was associated with a higher bladder soft tissue margin (10.6% vs 4.5%, $p=0.042$), longer operative time (425 vs 361 min, $p<0.001$), shorter median hospital stay (6.5 vs 7 days, $p=0.023$), associated with more patients staying ≤ 5 days (28.6% vs 18.7%), less estimated blood loss (mean 363 vs 829, $p<0.001$), less frequent

intraoperative transfusions (13.6% vs 33.6%, $p < 0.001$), and less post-operative transfusions (25.6% vs 41.0%) compared to ORC. There was no difference in extensiveness of lymph node dissection, complications or final pathology between the two arms. There was no difference in 2-year progression-free survival or overall survival (80.2% vs 79.1%, HR 0.80, $p = 0.31$). A randomised trial comparing open vs robotic cystectomy with intracorporeal urinary diversion is currently underway in the UK (iROC). Since there is a continuous flow of reports on RARC, this text section and the recommendations will be subject to significant updates in the coming years.

Clearly, patients need full information and time with a practitioner trained in counselling to come to a decision on the treatment they would wish to accept. Appointments with specifically trained clinical nurse specialist (CNS) staff should be available to all such patients. The CNS should be able to refer to other named specialists (surgical and clinical and medical oncological) as required by patients seeking more information and advice on treatment.

3.4.5 Locally Advanced (Any grade, T4)

Stein, in the work cited above, describes 43% five-year survival in these patients, the majority of whom had T4a disease (invasion of prostatic stroma)²³. In the case of T4b disease, and in many cases pre-operatively staged at T4a, resection is futile. Non-operated (for whatever reason) node positive patients should also be considered in this group. Where appropriate, these patients should be treated medically with combination cytotoxic chemotherapy, which will usually be administered in the Cancer Centre. Routine monitoring of response to chemotherapy includes CT scanning after every two or three cycles to a maximum of six cycles. Chemotherapy can, in some cases, be curative when combined with subsequent local treatment. Therapies for local control (radiotherapy or surgery) may therefore be indicated in patients with complete responses or near-complete responses. Where possible, such treatments should be delivered after full discussion in the Bladder MDT.

Locally advanced tumours (T4b, invading the pelvic or abdominal wall) may be accompanied by several debilitating symptoms, including bleeding, pain, dysuria and urinary obstruction. These patients are candidates for palliative treatments, such as palliative RT. Palliative cystectomy with urinary diversion carries the greatest morbidity and should be considered for symptom relief only if there are no other options.

Unilateral (best kidney) or bilateral nephrostomy tubes provide the easiest solution for upper urinary tract obstruction, but patients may find the tubes inconvenient and prefer ureteric stenting. However, stenting can be difficult to achieve, stents must be regularly replaced and there is risk of stent obstruction or displacement. Another possible solution is a urinary diversion with or without a palliative cystectomy.

In the case of bleeding, the patient must be assessed for coagulation disorders or the patient's use of anticoagulant drugs must be reviewed. Palliative TURBT and diathermy coagulation may be difficult in a bladder full of tumour or with a bleeding tumour. Intravesical rinsing of the bladder with 1% silver nitrate or 1-2% alum can be effective⁴⁰. It can usually be done without any anaesthesia. The instillation of formalin (2.5-4% for 30 minutes) is a more aggressive and painful procedure, requiring anaesthesia⁴⁰. Radiation therapy is another common strategy for control of bleeding, and is also used to control pain. An older study reported control of haematuria in 59% of patients and pain control in 73%⁴¹. Irritative bladder and bowel complaints due to irradiation are possible, but are usually mild. Non-conservative options are embolisation of specific arteries in the small pelvis, with success rates as high as 90%⁴⁰. Radical surgery is a last resort and includes cystectomy and diversion.

3.4.6 Distant Metastases (Any grade, any local stage, N2 or higher or M1.)

All patients with N2 disease or distant metastases should be referred to the centre for consideration of combination chemotherapy with palliative intent. Bladder cancer is relatively chemo-sensitive and although long-term remissions are rare in patients with visceral metastases, they are well-recognised in patients with lymph-node metastases³⁹. Referral to the centre also maximises the chance of such patients being treated in a clinical trial setting. Local external beam radiotherapy to painful metastases, and surgical toilet in the form of TURBT may be useful in palliation.

3.5 Orthotopic Bladder Reconstruction and Urethral Preservation

Previously, bladder CIS or multifocality of bladder tumours have been taken to be contraindications to urethral preservation (and hence to orthotopic reconstructions following cystectomy.) However, in a study of 34 urethral recurrences in 174 men with orthotopic reconstruction and 262 with cutaneous diversions, neither TIS nor multifocality were independent factors in significantly increasing risk of urethral recurrence⁴². In this study prostatic urethral disease and especially prostatic stromal disease did significantly increase risk. Interestingly this study suggested that orthotopic reconstructions protected the urethra from recurrence. This was the case even in the presence of prostatic stromal disease.

On the basis of these findings. it may be said that the only definite indications to urethrectomy with cystoprostatectomy are the presence of a positive margin, that is TCC on urethral frozen section at cystectomy and the presence of known urethral TCC. In the latter case urethrectomy enbloc should be performed. In the former, urethrectomy should be performed at cystectomy. Prostatic stromal TCC on final pathology is an indication for interval urethrectomy if cutaneous diversion has been made. If an orthotopic reconstruction has been performed careful and regular endoscopic surveillance of the urethra is required.

3.6 Surveillance Cystoscopy Regimes and Follow-up for NMIBC

Traditionally surveillance regimes in superficial bladder cancer have suggested 3-monthly cystoscopies for one year after diagnosis or recurrence, 6-monthly for a further year and annual cystoscopies thereafter. NICE guideline [NG2] published in Feb 2015, recommended the following surveillance strategies for NMIBC:

Low-risk non-muscle-invasive bladder cancer

- Offer people with low-risk non- muscle- invasive bladder cancer cystoscopic follow- up 3 months and 12 months after diagnosis.
- Do not use urinary biomarkers or cytology in addition to cystoscopy for follow- up after treatment for low- risk bladder cancer.
- Discharge to primary care people who have had low- risk non- muscle- invasive bladder cancer and who have no recurrence of the bladder cancer within 12 months.
- Do not offer routine urinary cytology or prolonged cystoscopic follow- up after 12 months for people with low- risk non- muscle- invasive bladder cancer.

Intermediate-risk non-muscle-invasive bladder cancer

- Offer people with intermediate-risk non- muscle- invasive bladder cancer cystoscopic follow- up at 3, 9 and 18 months, and once a year thereafter.

- Consider discharging people who have had intermediate- risk non- muscle- invasive bladder cancer to primary care after 5 years of disease- free follow- up.

High-risk non-muscle-invasive bladder cancer

- Offer people with high-risk non- muscle- invasive bladder cancer cystoscopic follow- up: every 3 months for the first 2 years then, every 6 months for the next 2 years then, once a year thereafter.

The European Organization for Research and Treatment of Cancer (EORTC) have developed a scoring system and risk tables to aide prediction of the short-term and long-term risks of both recurrence and progression in individual patients. The tables were developed from individual patient data from 2596 patients diagnosed with TaT1 tumours who were included in seven EORTC trials. Electronic calculators are available at <http://www.eortc.be/tools/bladdercalculator/>. It remains to be established whether this tool will be incorporated into routine clinical practice.

The current EAU guidelines recommends more aggressive follow up in comparison to the NICE guidance. It recommends 5-year follow-up for low risk tumours and life-long surveillance for intermediate or high risk NMIBC. However, it is anticipated that patients with low risk bladder cancer rarely develop high grade recurrences.

3.7 Follow up protocol after radical cystectomy for bladder cancer

There is no consensus on the appropriate surveillance strategy post radical cystectomy. This is in part due to the fact that radical cystectomy is performed for a variety of bladder cancer indications. It is felt that an appropriate follow up protocol should be able to address the natural timing, probability and site of local, distant or urothelial recurrences; functional monitoring after urinary diversion taking into account the potentially available management options.

Local pelvic recurrence involves soft tissues of the original surgical site or in lymph nodes. Majority of these recurrences occur during the first 24 months however, late recurrences can occur up to five years after radical cystectomy. Distant recurrence usually involve lung, liver, bones and can occurs in up to 50% of patients after radical cystectomy for muscle invasive bladder cancer. Both local and distant recurrences are more common in patients with locally advanced bladder cancer (pT3/pT4) and in patients with lymph node involvement (pN1/pN2).

The incidence of new urethral tumours after radical cystectomy is 1.5-6.0% in men, and these are likely to occur at one to three years after surgery. These recurrences are easily detectable by regular urethroscopy with a flexible cystoscope and/or cytology of urethral washings. Independent predictors for urethral recurrence are - cystectomy for NMIBC, prostatic urethral involvement and a history of recurrent NMIBC.

Upper urinary tract urothelial carcinomas occur in up to 6.0% of cases and represent the most common sites of late recurrence. A recent meta-analysis reported that 38% of upper tract recurrences were diagnosed by follow-up investigations and the rate of primary detection was better with upper tract imaging⁴⁷. This meta-analysis concluded that patients with non-invasive bladder cancer are twice as likely to have upper tract recurrences than patients with invasive disease. Multifocality increases the risk of recurrence by threefold, while positive ureteral margins increase the risk by sevenfold. Radical nephroureterectomy can prolong survival⁴⁸.

Early uretero-ileal anastomotic stricture although uncommon, can result in silent renal loss and compromise chances of adjuvant or palliative chemotherapy at a later date. These strictures can be easily detected by an early CT urogram at the time of initial 6 week post-op follow up. Renal function may deteriorate up to 15 to 20 years following cystectomy, therefore, it should be assessed by regular U/Es and eGFR measurements biennially for at least 15 years following radical cystectomy.

The approach of regular cystectomy follow up has been questioned by some studies and supported by others. A study of 1,270 radical cystectomies from Ulm in Germany, in which 444 developed recurrent disease, failed to demonstrate a survival benefit for detecting tumour recurrence early at an asymptomatic stage⁴⁴. However, there is growing evidence as alluded by large cystectomy series from Berne in Switzerland⁴⁵ and Mayo clinic in the USA⁴⁶ have suggested possible improvement in survival when asymptomatic recurrence are detected and treated. Boorjian et al⁴⁶ published results from their series of 1,599 radical cystectomy with a median follow up of 9.8 years. They found that 5- and 10-year overall survival in patients with symptomatic vs asymptomatic recurrence was 22% and 10% vs 46% and 26% respectively. On multivariate analysis, patients who were symptomatic at recurrence had a 60% increased risk of death as compared to asymptomatic patients. Currently, there is no available data from prospective trials demonstrating any potential benefit of early detection of recurrent disease, and its impact on overall survival. In the absence of any prospective data, it is difficult to recommend any robust follow-up protocols or guidelines. However, most units offer post cystectomy follow-up with regular clinical examinations, blood tests and some form of imaging but the practice differs in frequency and timings of these follow up visits. To address the nature of post cystectomy issues which have already been discussed in detail, the following pragmatic post cystectomy protocol is suggested.

Months after Radical Cystectomy									
	1.5	6	12	18	24	30	36	48	60
Clinical examination	X	X	X	X	X	X	X	X	X
Bloods: Hb / U&E's / eGFR / LFT's / Bicarbonate	X	X	X	X	X	X	X	X	X
Bone biochemistry	X		X		X		X	X	X
Vitamin B12			X		X		X	X	X
CT urogram + chest	X*		X		X		X		X
Renal US		X		X		X		X	
Urethroscopy		X	X	X	X		X		
Urine culture	X	X	X	X	X	X	X	X	X
US residual volume (neobladder only)		X	X	X	X				
3-day frequency volume chart (neobladder only)		X	X	X	X				

X* - Request 1st CT to be done at 3 month when patient attends for 6 week post-op appointment.

After initial 5 years of follow-up, cancer recurrence is uncommon, and the main driver for following the patient is functional monitoring which can be achieved by biennial renal function tests and annual renal USS scans.

After radiotherapy, traditional cystoscopic follow-up is appropriate. At least for early checks in this situation, the flexible instrument is not appropriate for such surveillance.

Similarly, early check cystoscopies after induction BCG treatment for high-risk, superficial disease should be performed with the rigid cystoscope.

Surveillance of orthotopic reconstructions for tumourigenesis in bowel mucosa and at urothelial-intestinal anastomoses should begin five years after reconstruction and continue annually. Cystoscopic surveillance in all these settings should be life-long.

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4 Upper Urinary Tract TCC

This section is still in the process of being updated by Mr S. Kotwal

Upper tract TCC's are very much less common than is TCCB. Around 5% of all TCC's arise in the renal pelvis and only 1% in the ureter. Their infrequency leads to a paucity of published evidence on which a guideline may be based.

4.1 Diagnosis and Staging

Diagnosis most commonly follows investigation of haematuria which should follow the course set out above. More commonly than is the case for lower tract disease, upper tract tumours are likely to present with manifestations of metastatic disease.

All patients should have cross-sectional imaging by MRI or CT before management decisions are made. In the past, many patients would be committed to nephroureterectomy on the basis of radiological findings alone. This is a dangerous practice both in terms of misdiagnosis and in terms of "over-treating" low stage upper-tract disease. Ureteroscopy (rigid or flexible) should allow visualisation and potentially biopsy of all upper-tract malignancies. At a bare minimum, lateralising cytology should be sought before committing the patient to loss of a renal unit.

4.2 Stage Groups for upper tract TCC tumours

Visualisation of the tumour, biopsy and cross-sectional images should allow stage grouping:

Classification	Grade	Stage
Low risk Superficial	G1-2	pTa or pT1
High Risk Superficial	G3	pTa or pT1, TIS
Invasive	Any grade	pT2 or T3 N0, MO
Advanced	Any grade	T4 N1 or higher or M1

4.3 Management – Stage-by-Stage

Low-risk and High-risk Superficial Tumours (G1-3, pTa or pT1).

The traditional treatment of these tumours has been by nephroureterectomy. This remains the “gold-standard” treatment but, with modern imaging and endourological techniques, many TCC-bearing renal units can be safely preserved.

In the largest available series (41 kidneys) of superficial upper tract TCC’s treated endoscopically, 86% were rendered tumour free after multiple treatments by fulguration. Regular endoscopic follow-up and the use of the Holmium-YAG laser for fulguration seemed to be critical to such success. Unsurprisingly, high-grade disease, large and multifocal tumours were most likely to recur¹. In this series no patient suffered tumour progression but there were only five patients with G3 disease. In skilled endourological hands, ureteric tumours are as well treated by these techniques, as are renal TCC’s.

There are numerous small reported series of upper-tract TCC’s successfully treated by instillations of MMC or BCG via nephrostomy tubes or retrograde catheters but no statistically significant case has been made for the use of such agents². In cases where preservation of the renal unit in question is critical, it is reasonable to use such treatments in an effort to reduce tumour recurrences.

Poorly differentiated superficial disease is still best treated by nephroureterectomy. Many well-differentiated tumours will still be treated in the same way given the necessary uncertainty in grading and staging of upper tract tumours in comparison to TCC’s of the bladder.

The main reason for nephroureterectomy is the high recurrence rate of tumour distal to the presenting lesion during follow up from nephrectomy alone. However recurrence more proximally is much less common and therefore for low risk tumours and the elderly or frail a distal ureterectomy alone may be appropriate for distal third uretic tumours. For those with only one functioning renal unit more proximally lesions may be treated by ureterectomy and ureteric replacement.

Muscle-Invasive Tumours (Any G, T2-3N0M0).

These tumours are best treated by nephroureterectomy. This may be accomplished as an open procedure, laparoscopically or by open surgery with laparoscopic assistance. The addition of lymphadenectomy is common in the United States but rare in the U.K. It provides additional prognostic information but probably little survival advantage.

Abercrombie’s modification of Semple’s “rip and pluck” is a safe approach for tumours confined to the renal pelvis³ but numerous isolated reports would suggest that it is not safe for ureteric tumours where there is an increased risk of the development of extra-vesical tumour recurrence. In the ureter, segmental ureterectomy is as safe as nephroureterectomy⁴.

Advanced Tumours (T4 or N1 or higher or M1).

These patients have a very poor prognosis. In common with such tumours arising in the bladder, combination chemotherapy should be the initial treatment and all such tumours should be referred to the cancer centre. Nephroureterectomy will very occasionally be indicated in motivated patients of good performance status after good responses to chemotherapy.

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5 Unusual Bladder Tumours

TCC's represent 95% of all bladder tumours or more. The rarity alone of other bladder tumours should lead to their management by the specialist MDT in the Cancer Centre.

5.1 Squamous Cell Tumours

These may represent 5% of bladder tumours and are aggressive. Distant metastases are less frequent in SCC (8-13% of cases) than TCC and failure to achieve locoregional control appears to be the main problem in managing these tumours. They have traditionally been managed by radical surgery with resulting poor survival figures, most patients dying 1 to 3 years post diagnosis. Squamous tumours are not generally multifocal and partial cystectomy was advocated in the past but this has largely been abandoned due to high local recurrence rates. Squamous tumours of other sites are generally radiosensitive. Local experience of DXT for squamous tumours is that at least some durable responses occur. Patients not fit for surgery for whatever reason should certainly be offered such treatment. The role of neoadjuvant or adjuvant chemotherapy in pure SCC of the bladder is uncertain.

5.2 Adenocarcinoma of Bladder

These yet rarer tumours are extremely aggressive and should be managed by radical surgery.

5.3 Urachal Adenocarcinomas

These represent around a third of bladder adenocarcinomas. They tend to be less aggressive and, if a surgical margin is available, partial cystectomy with bladder preservation is appropriate. Extra-vesical disease at diagnosis or later should be treated chemotherapeutically.

5.4 Small Cell and APUD Tumours

Chemotherapy in the cancer centre should be the first-line treatment for these tumours.

5.5 Adolescents

In adolescents, all bladder tumours are rare. All such patients should be referred to the adolescent unit of CRUK at St. James' in Leeds where appropriate specialist, and psychosocial, skills are available for these patients.

6 Prostate cancer

6.1 Introduction

The NICE guidance on the diagnosis and treatment of prostate cancer (February 2008) seeks to regulate and rationalise the management of prostate cancer in the UK. This guidance has been adopted by the former YCN Urology Group and this network guidance, therefore, is closely based on the NICE document. The NICE document led to widespread discussion in uro-oncological circles about some of its conclusions and, anecdotally at least, there is some change in the guidance as will be mentioned in this text. Additionally there are some new developments in the drug management especially of prostate cancer which have appeared even since the NICE guidance and these too are mentioned here.

The latest (2017) European Association of Urology (EUA) prostate cancer guidelines are available for download from the following website link:

<http://uroweb.org/guideline/prostate-cancer/>

6.2 Presentations of prostate cancer

Patients with prostate cancer will present to the urological services in a number of ways:

Two week wait referrals

Patients with raised PSA or an abnormal prostate examination maybe found by primary carers or other hospital practitioners having presented either with lower urinary tract symptoms or increasingly in the context of opportunistic screening by primary carers or requested screening by patients.

Incidental carcinoma

May be found at TURP or at cystoprostatectomy.

Patients may present with symptoms of advanced disease either locally or in the shape of bone pain and other manifestations of metastatic disease.

Indications to prostate biopsy.

Patients who already, incidentally, have a tissue diagnosis of prostate cancer clearly do not require prostate biopsy. Additionally, patients with advanced disease who may present with very high PSAs or with bone scan or radiological evidence of widespread prostatic carcinoma may safely be managed without a tissue diagnosis in certain cases. The need or benefit of prostate biopsy in these contexts has to be considered on a patient-by-patient basis by practitioners. A balance has to be struck between the usefulness of biopsy in prognosticating and its necessity in trial entry, against the significant morbidity and unpleasantness of prostate biopsy for patients.

6.3 Prostate biopsy

Transrectal prostate biopsy should always be supported by transrectal ultrasound and the quality of biopsies and the safety of biopsy is undoubtedly increased by transrectal ultrasound guidance.

A standard biopsy pattern of at least ten biopsy cores should be taken. Local anaesthetic should always be used and it is important that the procedure is covered with antibiotics. Hitherto, Ciprofloxacin has been the predominantly used antibiotic in this setting, but recent concerns about the role of Ciprofloxacin in HCAI and the risk of resistance to Ciprofloxacin would suggest that alternatives, especially Co-amoxiclav, should be considered. Healthcare providers should consider rectal swab screening for antibiotic resistance.

6.4 Stage groups and risk stratification.

The pathology report on the biopsied tissue should include information as to the number of biopsy cores involved and the percentage involvement of those cores. A Gleason score will be given and on the basis of this information and the PSA and clinical examination findings, and other clinical parameters the patient can be assigned to a stage group and, in the case of organ confined prostate cancer, to a high, medium or low risk category.

Negative biopsy and HG PIN. All negative biopsies should be discussed in the context of the MDTM. A decision should be made as to whether the patient should be rebiopsied, kept under further PSA surveillance or discharged back to primary care

In the case of a finding of high grade prostatic intratubular neoplasia on the biopsy, this too required MDT discussion and a decision made as to the relative indications to immediate or delayed rebiopsy or further PSA based surveillance.

Stage Groups and Stratification. Patients may be classified at this stage as having metastatic, locally advanced or organ confined prostate cancer. Organ confined prostate cancer should be stratified according to the NICE guidance into one of three risk groups:

- 1 Low risk disease encompasses those patients with PSA less than 10ng/ml, Gleason scores less than or equal to 6 and clinical stage T1 to T2a disease.
- 2 Intermediate risk patients have a PSA of 10 to 20ng/ml, Gleason scores of 7 or clinical stage T2b or c.
- 3 High risk patients would be considered to be those with PSAs of greater than 20ng/ml, Gleason scores of 8 or above or clinical stage T3 to 4.

Patients with suspected metastatic prostate cancer or locally advanced disease and those with organ confined prostate cancer but assigned to intermediate or high risk groups, should be further investigated with cross sectional staging usually by MRI scanning and with bone scintigraphy. Patients with PSA less than 10ng/ml should not be subject to bone scanning except in the presence of clinical suspicion and a judgement needs to be reached for each of these patients as to the need or otherwise of MRI scanning.

Further staging investigations then, in the form of cross sectional images or scintigraphy should be requested and when that information is available patients may more securely be assigned to the stage and risk groups described above.

Communication of diagnosis and staging information to the patient. Prostate cancer often presents particular problems of decision for patients. At all stages of disease a number of rational, reasonable and apparently successful treatment approaches may be adopted and choosing between these should always be a patient-centred decision. Information delivery at each stage within the diagnostic process, then, is crucial for successful management of prostate cancer. Such discussion with the patient and information delivery should always be supported by specially trained clinical nurse specialists therefore.

Clearly patients need full information and time with a practitioner trained in counselling to come to a decision on the treatment they would wish to accept. Appointments with specifically trained clinical nurse specialist (CNS) staff should be available to all such patients. The CNS should be able to refer to other named specialists (surgical and clinical and medical oncological) as required by patients seeking more information and advice on treatment.

6.5 Organ confined prostate cancer.

A number of primary treatments are available for patients with organ confined prostate cancer. NICE guidance has suggested preferred treatment options for low, intermediate and high risk disease as tabulated.

Risk Group	Active Surveillance	Brachytherapy	EBRT	Radical Surgery
Low	Y	O	O	O
Intermediate	O	O	Y	Y
High	N	N	Y	Y

Key: y =preferred, o = treatment option, n = not recommended

Please note that Brachytherapy refers to low dose rate brachytherapy and not high dose rate

Active surveillance

In active surveillance the object of treatment is to avoid over treatment of the indolent or very slowly growing prostate cancer. Patients accepting treatment by active surveillance are accepting a period of observation with fairly close monitoring to detect any evidence of progression of prostate cancer. Patients accepting such treatment should be followed up three monthly initially with PSA monitoring. Hitherto this was the mainstay of active surveillance protocols. An increase in PSA should trigger a clinical and potentially a radiological and histological re-evaluation for disease progression.

The NICE guidance has suggested too that such patients should, as a routine, have a rebiopsy around a year after the start of active surveillance. This may serve to demonstrate higher grade or higher volume disease than was on the first biopsy and may make patients

want to reconsider active surveillance as their primary treatment. This particular contention by the NICE guidance has been a cause of debate. Anecdotally it is understood that conversations between the British Association of Urological Surgeons and NICE have led to a dilution of this recommendation by NICE and it is probably safe for many patients to avoid rebiopsy and active surveillance protocols. Patients who have very well differentiated disease may represent a sub group in whom rebiopsy can be justified but at present this policy should be discussed with individual patients and often represents a patient choice issue. MDTs should decide on a protocol for routine imaging

Radical prostate surgery

Radical prostate surgery should be provided in specialist MDT-accredited cancer centres only. Such centres should perform at least fifty such procedures per annum and individual surgeons should perform ten such procedures per annum. The surgery is increasingly being delivered by minimally invasive techniques with or without the help of a surgical robot and, at least in experienced hands, such minimally invasive techniques would seem to provide as good a quality of cancer control as traditional open surgical techniques. There seems little advantage in minimally invasive surgery in terms of potency and continence outcomes. The advantages which are demonstrable relate to economic advantages both to the patient and the provider in terms of short hospital stay and early return to employment.

External beam radiotherapy.

Traditionally radiotherapy for prostate cancer has been provided as external beam radiotherapy (EBRT). This should be conformal EBRT or Intensity Modulated Radiotherapy (IMRT). NICE guidance (2008) recommends a minimum dose would be 74Gy, provided in fractions of no more than 2 Gy. The CHHiP trial has completed recruitment and recently reported 2 year toxicity results that are equivalent in the convention 2Gy per fraction and hypofractionated arms (Dearnaley D et al). It is likely that in the coming few years hypofractionated schedules will become routine.

Evidence is emerging that Image Guided Radiotherapy (IGRT) can reduce the risk of geographical miss and excess toxicity. (Gill S, Thomas J, Fox C et al). IGRT can be delivered using a number of techniques but prostate gold markers are most accurate and were the preferred IGRT technique in the CHHiP IGRT sub-study.

There is increasing interest in Stereotactic Ablative Radiotherapy (SABR) using a small number of high dose fractions and daily IGRT. SABR should be offered in the context of clinical trials.

Brachytherapy

Permanent I-125 interstitial radiation is a treatment option for low risk organ confined prostate cancer. Provided usually as an outpatient procedure at a single visit it may be said to cause the least upset to patient's lifestyle of the accepted treatments for organ confined prostate cancer. The results of brachytherapy for low risk disease would appear, on the basis of observational studies of patient cohorts, to have similar outcomes to external beam radiotherapy or radical surgery. The effects of brachytherapy in intermediate risk disease are more poorly understood.

I-125 brachytherapy treatment is only suitable for patients whose tumours are confined within the prostate capsule. For tumours of higher risk or those who have extended through the prostate capsule, radiation dose escalation can either be attempted with 3D conformal

radiation or IMRT or with a high dose rate brachytherapy (HDR) boost which is delivered with iridium-192. NICE approved HDR brachytherapy combined with external beam radiation in May 2006. A single dose boost schedule has been evaluated by the group in Toronto combining 37.5 Gy in 15 fractions with a single dose of 15Gy high dose rate brachytherapy and demonstrates good tolerance of this schedule and no untoward acute or medium term toxicities.

Leeds participates in a national UK protocol adopted by those centres offering high dose rate brachytherapy as a boost with external beam radiotherapy evaluating a single dose schedule with central data collection.

Suitable patients are as follows:

- A. Histologically confirmed locally confined adenocarcinoma of the prostate
- B. Clinical stage T1b-T3b, N0-1, M0 (For stage T3a macroscopic disease extension of \leq 3mm on MRI)
- C. Life expectancy in excess of 10 years
- D. No full anticoagulation with warfarin or heparin
- E. No recent (within 6 months) TURP
- F. IPSS \leq 15
- G. All patients should be staged with bone scan and MRI of pelvis

A single fraction of HDR brachytherapy giving 15Gy is delivered at St James's Institute of Oncology, Leeds, two weeks before external beam radiotherapy. External beam radiotherapy may be delivered at St James's or at the patients local cancer centre.

External beam radiotherapy is then delivered either to include the prostate capsule, seminal vesicles and margins to PTV giving 37.5Gy in 15 daily fractions over 3 weeks, or where there is concern regarding pelvic lymph node status, the internal/ external and common iliacs and prostate/seminal vesicles may be included in a CTV1. If there is gross lymph node enlargement then a CTV2 may be defined to cover these for an IMRT concomitant boost. Dose prescriptions for external beam are 46Gy in 23 daily fractions to CTV1 and/or 50.4Gy in 23 daily fractions to CTV2.

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Alternative energies

Treatment of localised prostate cancer by cryotherapy or high intensity focus ultrasound remains an experimental procedure. Such treatments should only be used in the context of a clinical trial and are currently not recommended by this guidance.

Follow up after interventions for organ confined prostate cancer

Oncological Follow-up.

Patients having early intervention for organ confined prostate cancer should be followed up with regular PSA assessment. If the PSA value increases to the Internationally accepted value for recurrence, for the radical treatment which had been delivered, the patient should be re-evaluation clinically and radiologically.

Patients treated in any of these modalities would normally be followed up three monthly in the first year of follow up followed by six monthly visits for two years and annual visits for two years thereafter. The PSA should be measured at each of these visits and change in the PSA should lead to discussion with the patient and indeed in the MDT.

Patients initially treated by surgery with should be considered for salvage external beam radiotherapy if their PSA increases to 0.2ng/ml or greater.

Patients with a high nadir PSA following surgery are more likely to suffer metastatic disease than local recurrence of disease after surgery and should be considered carefully before contemplating radiotherapeutic intervention. Very often these patients would be more appropriately treated with observation and, in the long term, hormonal manipulation of prostate cancer as deemed appropriate.

PSA defined relapse following primary radiation and treatment present too a dilemma. The majority are treated with hormone manipulation. Salvage treatments such as high intensity focus ultrasound, cryotherapy or HDR brachytherapy are recommended generally in the setting of a clinical trial. Patients with PSA defined relapse after radiotherapy should certainly be considered for salvage radical prostatectomy. Only a very select patient group would be suitable for such intervention.

Management of the adverse effects of intervention. Patients treated with radical surgery or radiotherapy or brachytherapy are commonly subject to change in their continence and potency. External beam radiotherapy also bears the possibility of bowel upset and brachytherapy more commonly would be associated with symptomatic bladder outflow obstruction and irritable bladder symptoms than are surgery or external beam radiotherapy.

All of these treatment side effects should be considered in routine follow-up along with oncological aspects of follow up as detailed above. Patients should have access to trained specialist nurse input as required to help them deal with these complications. Specialist andrology and continence services should also be available to all such patients.

6.6 Locally advanced prostate cancer

Locally advanced prostate cancer is the most difficult to define of these stage groups covering as it does disease ranging from that treated by early radical intervention which proves to in fact have been a T3a tumour, up to T4b prostate cancers which may be massive, deeply infiltrative and fixed.

Treatment of locally advanced prostate cancer

Men with locally advanced prostate cancers should be considered to have metastatic disease albeit that such metastasis may only be local. As such, central to the treatment is systemic treatment for prostate cancer in the first place usually by hormone manipulations. These are detailed more fully below with respect to metastatic disease.

Radical radiotherapy has now an established role in locally advanced prostate cancer. Two large randomised trials demonstrate a survival advantage of the order of 10% at 10 years in men treated with radiotherapy to the prostate +/- pelvis in addition to long term hormone manipulation (Widmark A et al) (3) Warde P et al (4) All men with a life expectancy from co-morbidity of > 5 years should be considered for radical radiotherapy in addition to long term hormone manipulation.

6.7 Metastatic prostate cancer

Patients with proven metastatic prostate cancer are beyond the control of local therapies whether radiotherapeutic or surgical and should be offered systemic treatment. Such systemic treatment has been based largely on hormonal manipulations for over sixty years and only recently have chemotherapeutic agents active in the prostate gland being described and become widely available. Hormonal manipulations however may be delivered in a number of ways.

In intermittent androgen depletion therapy anti-androgen treatments are stopped when prostate cancer is under good control and the patient is monitored clinically, and with PSA for relapse. Such treatment allows patients periods without the side-effects of treatment.

There is evidence of a small survival advantage for patients treated with therapies which induce low circulating androgen concentrations such as orchiectomy and LHRH-analogues, as opposed to those treated with orally active androgen receptor antagonists alone. Such oral anti-androgen monotherapy, however, has a better side-effect profile avoiding, as it does, climacteric symptoms. Patients may prefer oral antiandrogen monotherapy because of this but should be aware of this difference in efficacy.

Complete Androgen Blockade (CAB) is the simultaneous use of LH-RH analogue and oral anti-androgen. A small survival advantage for CAB over either of its components as a single agent has been demonstrated, but at significantly increased cost.

Patients commencing on hormonal manipulation are likely to undergo a number of changes in prescribing as their tumours demonstrate various degrees of progression as resistance to hormonal manipulation develops: thus patients commenced respectively on LH-RH analogue or oral monotherapy or LH-RH analogue in the event of progression; Patients on both may enjoy a falling PSA if oral anti-androgen is stopped ("Flutamide-withdrawal response");

oestrogen therapy may regain hormonal control of prostate cancer after LH-RH analogue and oral anti-androgens have failed.

Watchful waiting

Watchful waiting can be contrasted with active surveillance in organ confined disease. In watchful waiting patients are not suitable to radical early intervention. It is clear that deferring androgen depletion therapy until patients are symptomatic is mistaken. However, it is equally clear that immediate anti-androgens for all such patients is equally wrong: trials of such an approach were rapidly closed because of an excess cardiovascular mortality in the treatment group.

Patients are treated with watchful waiting until there is evidence of disease progression whether radiological, symptomatic or, most commonly, biochemical: a PSA of over 25ng/ml.

Bilateral subcapsular orchiectomy (BSO)

Bilateral subcapsular orchiectomy (BSO) is cheap and definitive. It is irreversible, unlike other forms of androgen depletion. For patients with acute complications of metastatic prostate cancer it offers the fastest method of inducing the castrate state. It should be offered to men who are embarking on "continuous" androgen depletion.

BSO is unpopular with patients, however, and is sometimes perceived to be mutilating. Its irreversibility renders intermittent androgen depletion impossible.

LH-RH Analogues

Goserelin ("Zoladex") and Leuprorelin ("Prostap") are available as one and three month preparations and suppress luteinizing hormone (LH) release from the hypophysis and hence testosterone release from the testis. Other agents (eg triptorelin) are available only in one-month preparations. Long acting (i.e. one-year) implants are now also becoming available.

All of these agents initially stimulate LH release which causes a rise in testosterone concentration at the start of treatment and the start of treatment with any of these agents has to be covered with an oral anti-androgen for a week before the first implant and for two to three weeks afterwards.

All of these agents cause climacteric side-effects.

The decision as to which LHRH-analogue to use should be cost-based.

LH-RH Antagonists

These agents (Abarelix and Degarelix) are available. They are formulated as one-month depot injections and avoid the initial testosterone concentration rise seen with LH-RH analogues. Their potential to replace the LH-RH analogues remains to be seen but, if they are competitive with LH-RH analogues for cost, they would seem a more logical treatment strategy. There are some claims that they may avoid transient small testosterone increases sometimes seen with LH-RH analogues ("micro-surges"), but whether this difference will translate into any clinical advantage remains to be seen. They can be useful in newly diagnosed prostate cancer patients presenting with obstructive uropathy or spinal cord

compression not fit for surgical castration, as castrate levels of testosterone can be achieved more rapidly.

Oral Anti-androgens

A number of such agents are available. All should avoid the climacteric side effects of the LH-RH analogues but all may cause LFT upset and dyspepsia. Rarely liver failure has been reported in the use of all of these agents. All patients starting on these agents require a pre-treatment LFT measurement.

Bicalutamide 150mg o.d. has the best side-effect profile of these agents and should be preferred. When used to cover initial LH-RH analogue injections 50mg bicalutamide is appropriate.

Oestrogens

As noted, after the failure of LH-RH analogue and oral anti-androgen, oral oestrogens may delay or reverse progression at least in the short to medium term (rarely responding for more than six months.). There is some rather weak evidence for a direct effect of oestrogens on the prostate cancer cell.

Stilboestrol 1mg o.d. is the standard dose. In the event of problems with stilboestrol supply, ethinyloestradiol is an alternative. The major side effect of the oestrogens is an excess of thrombo-embolic and cardiac events and also patients treated should also receive Aspirin 75mg o.d.

Taxane Chemotherapy

Following the results of the Stampede trial and the Chaarted study, Docetaxel chemotherapy is offered to (suitable) men who present with metastatic prostate cancer rather than wait until they develop CRPC.

Patients with hormone-refractory disease are no longer sensitive to any of these treatments and should be considered for treatment with Docetaxel ("Taxotere").

Docetaxel given in combination with prednisolone (5mg bd) has been associated with an improvement in symptoms (pain especially) and quality of life in 30% of patients and a modest (~3 months) improvement in overall survival^{1,2}. Long term remissions are rare.

¹ Tannock, I.F., de Wit, R., Berry, W.R., Horti, J., Pluzanska, A., Chi, K.N., Oudard, S., Théodore, C., James, N.D., Turesson, I., Rosenthal, M.A., Eisenberger, M.A.; TAX 327 Investigators. (2004) Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N. Engl. J. Med.* 351, 1502-12.

² Berthold, D.R., Pond, G.R., Soban, F., de Wit, R., Eisenberger, M., Tannock, I.F. (2008) Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. *J. Clin. Oncol.* 26, 242-5.

(3) Widmark A et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet* 2009;373:301-8.

(4) Warde P et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised phase III trial. *Lancet* 2011;378:2104-11

Patients should be considered for treatments within a clinical trial setting. Docetaxel should only be prescribed by accredited medical/clinical oncologists and its delivery should be monitored as for cytotoxic chemotherapies. The intention would be to deliver 6 – 10 cycles. More than 6 cycles are considered if patients specifically request ongoing therapy and demonstrate benefit in the absence of toxicity.

Palliative Treatment

Other agents and modalities may be useful in alleviating symptoms in advanced disease:

Zoledronic Acid may relieve bone pain and is indicated in its treatment. There is no evidence that its use prevents bone-related events such as cord-compression or fracture and it is not indicated in the prophylaxis of these events.

Corticosteroids (1-2mg dexamethasone o.d.) may contribute to hormonal treatment and certainly commonly increases well-being.

Radiotherapy is indicated in the treatment of specific sites of bone pain and in the treatment of acute cord compression.

Surgery: occasional patients will benefit from orthopaedic and neurosurgical intervention for pathological fracture and cord compression.

Ureteric bypass by percutaneous nephrostomy or internalised stent may be indicated in the case of acute renal failure because of malignant ureteric obstruction but such obstruction may often represent a terminal event and intervention has to be based on careful consideration with a fully informed patient.

7 Guidelines for the Examination and Reporting of Urological Specimens

Version 1.2 May 2011

7.1 Introduction

These guidelines for the examination and reporting of urological cancer specimens are supplementary to the following national guidance:

- Minimum dataset for urological cancer histopathology reports issued by the Royal College of Pathologists.

It is recommended in the Improving outcomes in urological cancers guidance published in 2002 that all new diagnoses of cancer are reviewed at a multidisciplinary team meeting where pathological features are taken into account in the formulation of the management plan. This will include consideration of the patient's eligibility for entry into trials.

Although pathologists are referred to the Minimum Datasets published by the Royal College of Pathologist, there are features which are not included in these Datasets but are relevant for inclusion into ongoing trials. These have been included in the following short guidelines.

All urological cancer cases should be reviewed by a Urological Cancer multidisciplinary team which has a histopathologist as a core member. There should be a nominated Lead urological pathologist for the service but all pathologists reporting urological cancer specimens should participate in urological MDT meetings, in an appropriate EQA scheme and in local audit (including an assessment of consistency of reporting, as appropriate to the site). If there is a significant discrepancy with the clinical/radiological findings the pathological material from diagnostic urological specimens should be reviewed, if possible by a second pathologist with an interest in urological cancer.

Specimens should be reported to an agreed timeframe so as to allow appropriate clinical decision making at a planned urological MDT meeting.

7.2 Specimen Types

Specimens relating to carcinomas of collecting system

Mucosal biopsies
Transurethral resections
Cystectomy and nephro-ureterectomy specimens
Urethrectomy specimens

Prostatic specimens

Prostatic biopsies
Transurethral resections
Radical prostatectomy specimens

Renal specimens for renal parenchymal tumours

Renal biopsies
Radical nephrectomy specimens
Partial nephrectomy specimens

Testicular specimens

Testicular biopsies
Orchidectomy
Retroperitoneal lymph node dissections

Penile specimens

Penile biopsies
Circumcision specimens
Penectomy specimens

7.3 Specimen Examination

Each pathology service should establish a defined protocol for each type of diagnostic and therapeutic urological specimen type received by the laboratory, taking into account the above guidance. The protocols should be regularly reviewed and updated by the Lead urological pathologist in consultation with other pathologists who participate in service delivery.

The protocols should include a code for specimen orientation as agreed with the local urological surgical team.

Access to specimen radiography or specialist radiological opinion should be available for relevant cases.

Urological tissue should only be removed and stored for the purposes of research if it is surplus to the requirements of the diagnostic process. Appropriate patient consent and ethical approval should be obtained.

Guidance about specific specimen types is given below.

Specimens relating to carcinomas of collecting system

Mucosal biopsies

These are measured, completely embedded and generally examined at 3 levels.

Transurethral resections

These are weighed or measured in aggregate, in small resections generally all embedded. But, in larger specimens if sampled, enough blocks (up to 3-4) should be taken to demonstrate whether detrusor muscle has been sampled for staging purposes. Occasionally, levels in selected blocks will clarify that.

A separate biopsy may be sent from the base of the lesion (including muscle) to assess invasion of deep tissues. Random biopsies from red areas or from cystoscopically normal urothelium may be sent to determine whether dysplasia or carcinoma in situ are present.

Cystectomy and nephro-ureterectomy specimens

Sampling should include the maximum depth of tumour invasion as well as all relevant margins.

Prostatic specimens

Prostatic biopsies

Cores may be sent to the laboratory as individual specimens or several cores may be placed in one pot. At the very minimum, cores should be separated into right and left sides as the surgical approach may vary depending on side-specific tumour burden.

Generally the cores received are counted and measured, all embedded, flat embedding is essential to optimise sectioning and representation of the full length of the core, at least 3 levels examined.

It can be useful to retain spare sections of the levels for immunocytochemistry (basal cell markers in particular) to better characterise atypical proliferations, which may only be present focally.

Transurethral resections

Recommendations for sampling strategies of transurethral resections performed for outflow obstruction in the absence of clinical suspicion of carcinoma are contained in the college Minimum Datasets. Consideration should be given to the biological age of the patient and intention to treat.

Radical prostatectomy specimens

Unless specimens are examined fresh when tumour can be identified by palpation, it is not possible to confidently identify areas of carcinoma and a strategy to circumvent this is to embed the whole specimen. If the specimen has not been prepared in theatre or received fresh, following removal of the clips and sutures, it should be examined and inked accordingly. The use of different colours to identify laterality is an advantage. These can usually be superimposed on India ink if required. The specimen is weighed and measured in three dimensions.

The vas resection margins are sampled and the seminal vesicles amputated close to the prostate base. The first section from the apex is perpendicular to the urethra. Precise depth will depend on the shape of the apex but is generally 6–7 mm thick and angled so that the prostate will be in the correct anatomical position when laid on the cutting board. The posterior aspect usually has to be thicker than the anterior to achieve this. This section is then coned to demonstrate the relationship between any potential tumour and the peripheral margins. Sections should be taken with the overall aim of demonstrating the margin as extensively as possible. So-called 'shave' resection margins are discouraged as the presence of tumour simply indicates that tumour is close to, but not necessarily at, the inked resection margin.

Holding the remaining specimen as close as possible to the correct anatomical position, the prostate is then sliced into 4 mm sections, perpendicular to the urethra, It is useful to section the last slice of the base perpendicular to the initial, horizontal plane of excision. This demonstrates the margins more effectively. Whole mount sections are easier to report and save on pathologist time but it is appreciated that this is not possible in all departments.

Nevertheless, all margins should be examined and the location of positive margins should be stated for prognosis and also surgical audit.

Nephrectomy specimens for renal parenchymal tumours

Renal biopsies: These are performed either for tissue diagnosis prior to trial entry in patients with inoperable or extensively metastatic tumours or when the radiological appearances are not characteristic of a renal parenchymal carcinoma. The biopsies are generally examined at 3 levels and it is useful to retain spares for immunocytochemistry as the diagnosis can be difficult on morphological grounds and the differential usually includes malignant lymphoma, collecting duct carcinoma and transitional cell carcinoma.

Radical nephrectomy specimens: These are still the most common specimen. Macroscopic close examination of the renal vein is essential for staging.

Partial nephrectomy specimens: These are becoming more frequent but are only possible in tumours of up to 40mm and peripherally located. It is useful to ink the resection margin prior to sectioning and to note the distance between the tumour and the resection margin.

Tumour size is recorded. It is important to examine for the possibility of perinephric fat invasion and to sample any suspicious areas. Sampling should include the junction between the tumour and adjacent kidney as well as the renal sinus for the identification of microvascular invasion,.

Testicular biopsies, orchidectomies and retroperitoneal lymph node dissections

Testicular biopsies: These are performed either in the context of investigations for infertility or in patients with contralateral testicular tumours, and in both cases, particularly if the testis is atrophic, there is a risk of intratubular germ cell neoplasia. Biopsies are generally examined at 3 levels and spares for immunocytochemistry (PLAP, c-kit) can be useful in the diagnosis of intratubular germ cell neoplasia.

Orchidectomies: The most important aspect of dealing with orchidectomies for tumours is to take sufficient numbers of blocks to ensure that all the different components of the tumours are represented and that the capsule and adjacent testicular parenchyma are sampled for the assessment of vascular invasion, a major determinant of treatment or entry into trials. The size of the primary tumour is essential in seminoma and the presence or absence of invasion of the rete testis is also useful in clinical decision-making in seminoma.

Retroperitoneal lymph node dissections: These are generally performed in patients with testicular germ cell tumours if a mass fails to resolve following chemotherapy. It is important to identify any potential residual tumour because of the implications for the subsequent management and prognosis. It is useful to ink the margins prior to sectioning as the completeness of excision influences outcome, to characterise two main clinical risks 1. continuing growth of unresected teratoma differentiated becoming inoperable, and 2. Malignant transformation of teratoma differentiated to another malignant germ cell tumour, sarcoma or carcinoma which may be chemoresistant in this group of patients.

Penile specimens

Penile biopsies - these are generally examined at 3 levels. Grading of the carcinoma can influence management as lymph node dissection are often only performed in patients with higher grade tumours.

Circumcision specimens - if carcinoma is expected, it can be useful to ink the margins prior to sectioning.

Penectomy specimens - the distance of the tumour to the resection margins (skin margins, urethral and corporal margins), which should be inked, should be noted as well as the pattern and location of the tumour. It is important to determine the relationship with the urethra for staging purposes.

7.4 Minimum Dataset for Reporting

Pathologists should refer to the minimum datasets published by the Royal College of Pathologists. Listed below are points of clarification and additional dataset items.

Reporting carcinomas of the collecting system

Characterisation of the tumour

- Histological type
- Degree of differentiation (1973 WHO grade) - it is particularly important to identify grade 3 tumours so that patients are offered additional therapy. The 1973 WHO classification probably remains the most widely used classification of tumours of the renal pelvis, ureter, urinary bladder and urethra. A large number of cohort studies performed since its publication have validated the grading system, and its prognostic value for non-invasive tumours, in particular, has been shown in the context of combined analyses of randomised clinical trials.
- The 1998 WHO/ISUP classification, subsequently published as the WHO 2004 classification, has not been universally endorsed by clinicians. The evidence available for its value is scanty and based only on retrospective data with some inconsistencies of results. These data do not provide the level of evidence that would justify unconsidered introduction of the 2004 classification. Although the 1973 WHO classification is not without its faults, it has been repeatedly validated and it is incorporated into clinical practice, and individual clinical teams may choose not to change their reporting practices.
- Otherwise, and in line with published international opinion it is recommended that both classifications are reported in parallel and results compared through prospective audit of patient outcomes.
- Stage – In biopsy or resection material, non-invasive tumours can be staged as pTa even in the absence of detrusor muscle if the lamina propria is well represented. Tumours invading the lamina propria can be coded as pT1 if deep lamina propria and detrusor muscle have been sampled in continuity with the tumour. If no deep tissues are present, this must be stated and the tumour coded as pTx.
- Presence of absence of vascular permeation.

Characterisation of flat mucosa.

Changes can range from low grade or mild dysplasia to severe dysplasia/carcinoma in situ. For therapeutic purposes, it is sufficient to distinguish between "dysplasia falling short of carcinoma insitu" and carcinoma in situ (which includes severe dysplasia). If carcinoma in

situ is present, it is useful to give some indication of its extent because this is one of the strongest predictors of progression.

Additional features in cystectomy or nephro-ureterectomy specimens

- State of the circumferential, urethral and ureteric resection margins
- Presence or absence of involvement of adjacent organs.
- Numbers of lymph nodes involved (usually sampled separately by the surgeon).

Reporting prostatic specimens

Characterisation of the tumour

Tumour grade

The Gleason system is the most commonly used and therefore allows comparisons of results between hospitals and centres. It should be appreciated that the Gleason system is based purely on architecture with no consideration given to the cytology of the tumour cells.

Modifications to the Gleason grading system have been proposed for biopsy specimens, the current proposal by the International Society of Urological Pathologists is to continue using the most prevalent and second most common grades to assign the Gleason sum score to radical prostatectomy specimens, and to mention the presence of a tertiary grade. A change to the grading of radical prostatectomy specimens has not been proposed

Site of the tumour (biopsy or radical prostatectomy specimen)

Tumour volume

On biopsy: Number of cores involved, length or proportion of the biopsy invaded by carcinoma.

Transurethral resections: If carcinoma is identified unexpectedly, the percentage of involved chips gives similar information to morphometric analysis of surface area.

Radical prostatectomy: The Royal College Data set for histology reports for prostate cancer October 2009, suggest that detailed tumour volume measurements in radical prostatectomy specimens is unnecessary. However, it is useful to give some indication of tumour extent using visual inspection of the percentage of tissue involved by cancer or other simple methods.

Tumour stage

Transurethral resections: The TNM system applies to carcinomas that are diagnosed unexpectedly. Patients with pT1a disease (involvement of 5% or less) have a slower progression rate than those with pT1b disease, a third of whom progress within 4 years.

Grade is not included in the TNM system although studies have shown that patients with small volume but high grade (Gleason 4 or 5 as either primary or secondary pattern) disease have similar progression rates to those with larger volume, low grade disease.

Radical prostatectomy specimens: The TNM Classification of Malignant Tumours. Seventh edition is applied and includes consideration of the margins, although focally positivity does not seem to increase the risk of biochemical recurrence. Sagittal sections of the first slice of the apex are useful to examine more thoroughly the apical margins (most common site of margin positivity). The TNM refers to the "capsule" of the prostate, a structure, which is at best incomplete and often difficult to identify. At low power, it is possible to determine the boundaries of the prostate and determine whether carcinoma is beyond the outline of the gland (pT3a) or present only within its confines (pT2). Striated muscle is intermingled with smooth muscle particularly at the apex, so that tumour within striated muscle does not equate with extraglandular spread. Microscopic bladder neck involvement is considered as Extra-prostatic Extension (EPE), pT3a. The degree of EPE can be subdivided into focal or

non-focal. In focal EPE, there are only a few neoplastic glands outside the prostate, whereas more substantial involvement of the periprostatic tissue is seen in non-focal EPE. Not uncommonly, a distinct tongue of tumour extending well into periprostatic connective tissue is seen. However, there is no standardised method of subdividing EPE into focal versus non-focal types, despite the fact that most studies, by their own local methodology, show it to be prognostically significant. T4 Tumour is fixed or invades adjacent structures other than seminal vesicles:external sphincter, rectum, levator muscles and/or pelvic wall.

Perineural invasion

The significance of this finding on biopsies is controversial but the balance of evidence suggests that it indicates a risk of extra glandular spread, particularly if multiple and/or large nerves are involved. At the very least, it may raise the question of whether to perform a nerve sparing operation on that side.

Vascular invasion is rarely observed and does not appear to be an independent prognostic factor.

Reporting nephrectomy specimens for renal parenchymal tumour

Characterisation of the tumour

The two main classification systems are the WHO and the consensus classifications. The consensus classification is recommended as it is based on cytogenetic differences, is simpler to apply and has become widely used in publications.

Stage (TNM classification system)

TNM 7 is recommended. Substaging of pT2 is useful, contiguous involvement of adrenal gland is staged as pT4 and renal vein invasion is recorded as pT3a. Record the data items and specify the version of TNM used.

Grade

There is no universally accepted and fully validated method but the Fuhrman system is reasonably easy to apply and is often quoted in publications. It should be noted that it has only really been investigated in conventional renal carcinomas and a small number of papillary carcinomas. There are various algorithms used in clinical management which are detailed In Appendix B of the RCPATH guidelines.

Presence or absence of microvascular invasion.

Presence or absence of necrosis.

Presence or absence of invasion into the collecting system.

Reporting orchidectomy specimens

Characterisation of the tumour

Tumour type - reference to the WHO classification allows the identification of different tumour components, which can then be grouped into general categories according to the British Classification.

Tumour stage

TNM 7 classification

The presence or absence of vascular invasion in teratomas is the sole of criterion for immediate chemotherapy rather than surveillance in clinically localised disease. In testicular seminoma, evaluation of tumour size is essential, and the reporting presence or absence of rete testis invasion is a useful parameter to inform post-surgical management.

Reporting retroperitoneal lymph node dissections

Characterisation of the specimen

Presence or absence of recognisable nodal tissue or any other retroperitoneal structures.
Presence or absence of residual tumour and its type.
Transformation of differentiated elements into somatic malignancies (carcinomas, sarcomas) should be noted as it is indicative of poor prognosis.
Completeness of excision - it is useful to ink these specimens prior to sectioning.

Reporting carcinomas of the penis

Characterisation of the tumour

Histological type
Generally squamous cell carcinomas.
Pattern of growth, whether multifocal or not.

Stage

Using the TNM 7 classification system, however the TNM includes a category for pTa, which it defines as “noninvasive verrucous carcinoma” (i/e not associated with destructive invasion) . This is a misnomer as by definition verrucous carcinomas are invasive although this can be difficult to ascertain because of the broad pushing margins of the invasive front. The RCPATH recommendation is that verrucous carcinoma should be recorded as pT1 or above.

The RCPATH recommend that the level of corpus involvement (cavernosum or spongiosum) should be specified for treatment planning.

Grade

Presence or absence of in situ carcinoma in the adjacent skin as it can be an indicator of risk of recurrence.

Completeness of resection

Patients with penile cancers diagnosed by local urological multidisciplinary cancer teams should be referred to the specialist supranetwork team and the diagnostic slides made available for review.

The dataset items should be reported in a proforma either within or instead of the free text part of the pathology report, or as a separate proforma. Departments and MDTs should work towards recording and storing the dataset items as individually categorised items in a relational database, so as to allow electronic retrieval and to facilitate the use of pathology data in clinical audit, service planning and monitoring, research and quality assurance.

Laboratories should use an agreed diagnostic coding system (e.g. SNOMED). All malignancies must be reported to the Northern and Yorkshire Cancer Registry, in accordance with the service level agreement with their host Trust.

7.5 Grading and Staging Conventions

Tumour grading

WHO Classification of Tumours, with the general acceptance that the highest grade is taken as the overall grade. Urothelial carcinoma in situ includes “severe dysplasia” and is distinguished from “dysplasia falling short of carcinoma in situ” but dysplasia is not further subdivided.

The exception is in prostatic carcinomas where Gleason grading classically uses the most common or primary grade and the second most common grade to obtain the Gleason sum score. If a tertiary grade is present, it should be noted, particularly if it is of higher grade.

Tumour staging

TNM classification of malignant tumours (7th edition, with caveats described above)

7.6 Use of Ancillary Laboratory Techniques

All laboratories providing a Pathology service in the network must have at least conditional laboratory (e.g. CPA) accreditation and ensure participation an appropriate external quality assurance programme, which demonstrates satisfactory laboratory performance.

Immunohistochemical procedures which may be of value include the following:

Diagnostic scenario	Immunohistochemical markers	Notes
Dysplasia /CIS v reactive states	CK20, CK14	Full thickness CK20 expression is common in urothelial dysplasia/CIS and does not distinguish between low and high grade. CK14 is positive in squamous CIS (CK20 negative).
Distinction between prostatic and urothelial carcinoma	CK5, CK7, PSA, PSAP	PSA and PSAP may be negative in high grade prostatic carcinoma and morphology is helpful (prominent nucleoli, relatively little pleomorphism in prostatic carcinoma compared with high grade urothelial carcinoma).
Oncocytoma v renal carcinoma v chromophobe carcinoma	CD10, vimentin, RCC	Beware as a proportion of renal carcinomas are negative. Electron microscopy is still the gold standard for the diagnosis of oncocytoma.
Renal cell carcinoma v other carcinomas	CD10, Vimentin, RCC,	Use with extreme caution as results can be variable
Chromophil v Eosinophilic chromophobe	Vimentin, CD10, CK7	Use with extreme caution as results can be variable. The gold standard for the identification of all chromophobe carcinomas is electron microscopy of unprocessed tumour.

Intratubular germ cell neoplasia v fixation artefact	PLAP, c-kit	c-kit generally more sensitive
Germ cell tumours	AFP, HCG, PLAP, CD30 OCT3/4	PLAP must show membrane staining otherwise it is non specific.
Embryonal carcinoma v Seminoma	Cytokeratin (CAM, CK8), CD30, c-kit, EMA	Cytokeratins can be variable. CD30 more commonly positive in teratoma, c-kit in seminoma, EMA in differentiated elements
Germ cell tumours v Sertoli or Leydig cell tumours.	PLAP, c-kit, inhibin R1, calretinin, vimentin	Inhibin positive in both Sertoli and Leydig cells, vimentin more common in Sertoli cells, calretinin in Leydig cells

7.7 Audit

All pathologists reporting urological cancer specimens should participate in a relevant EQA scheme and in local audit (including an assessment of consistency where more than one pathologist participates in service provision). Audit may take the form of

- review of compliance with procedures for specimen examination and reporting
- completeness of datasets
- systematic logging of diagnostic agreement/disagreement during review of cases for MDTMs
- review of diagnostic consistency between pathologists using data from cases in EQA circulations or blind circulations.

The results of the audit process should be discussed with all pathologists who participate in service delivery and used to inform the development of reporting protocols.

7.8 Referral for Review or Specialist Opinion

Referral for treatment

All patients referred for treatment at a hospital within the West Yorkshire & Harrogate Cancer Alliance following diagnosis elsewhere must be reviewed and discussed at the treating hospital's multidisciplinary team meeting (MDTM).

Testicular tumours and penile carcinomas must be referred to the Leeds Cancer Centre for management by the specialist urological cancer team. Review of the pathological material will occur routinely.

The complete diagnostic pathology report must be available at the MDTM, and wherever possible, the histological/cytological material should be reviewed prior to the meeting. This is particularly important if there is a significant discrepancy with the clinical/radiological findings. Pathological material should be requested at least 5 working days before and received at least 3 days before the relevant MDTM to allow sufficient time for review.

A formal report should be issued by the reviewing pathologist to the responsible clinician at the treating hospital. The results of the review should be sent to the original pathologist, either by copy of the review report or by letter.

Where patients have been referred for oncology treatment, requests for specialist biomarker studies will be co-ordinated between the treating oncology service, their local pathology service and the referring hospital's pathology service, as appropriate. The oncology service must agree a mechanism for requesting tests and the relevant pathological material with their

local pathology service. Requests for pathological material should be made in good time to ensure that results are available at the MDTM where the patient is to be discussed.

Referral for specialist opinion

All urological lymphomas should be referred to the Haematological Malignancy Diagnostic Service for phenotypic analysis and confirmation of diagnosis.

In cases of diagnostic difficulty, referral will usually be made to the lead pathologist of the relevant specialist MDT in the network, although referral to other specialists within or outwith the network may be appropriate in individual cases. Cases referred for individual specialist or second opinion will be dealt with by the individual pathologist and a report issued by them. Where relevant, tissue blocks should be made available to allow any further investigations that are deemed appropriate. The result of the review should be communicated to the referring pathologist by letter and also by fax/telephone as appropriate.

In instances when the patient is referred for an opinion by a specialist multidisciplinary team the case should be referred to the Lead Pathologist of the appropriate MDT and dealt with according to specialist team/Cancer Centre MDT guidelines.

7.9 References

1. Minimum dataset for tumours of the urinary collecting system (Renal pelvis, ureter, bladder and urethra)
The Royal College of Pathologists January 2007
2. Minimum dataset for testicular tumour and post chemotherapy residual masses histopathology reports. 2nd edition
The Royal College of Pathologists (2007)
3. The Royal College of Pathologists Dataset for histopathology reports for prostatic carcinoma. (2nd edition) October 2009
4. Minimum dataset for adult renal parenchymal cancer histopathology reports.
The Royal College of Pathologists (2006)
5. TNM Classification of Malignant Tumours (7th edition)
Sobin LH and Wittekind C (Eds) UICC (2009)
6. WHO Classification of Tumours. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs (2004)
7. Guidelines on inter-departmental dispatch of samples from patients sent to another hospital or centre for assessment and/or treatment.
The Royal College of Pathologists (2004)

8 Radiology

8.1 Imaging in Prostate Cancer

Diagnosis

Transrectal Ultrasound-guided biopsy is now the principal method of diagnosis. Biopsy practices vary. Healthcare professionals should carry out prostate biopsy generally following the procedure recommended in 'Undertaking a transrectal ultrasound guided biopsy of the prostate' PCRMP 2006 . (www.cancerscreening.nhs.uk/prostate/pcrmp01.pdf)

The results of all prostate biopsies should be reviewed by a urological cancer MDT.

Men should only be re-biopsied following a negative biopsy after an MDT review of the risk characteristics including life expectancy, PSA, DRE and prostate volume.

Local Guidelines should define:

1. Indications for imaging and biopsy based upon clinical findings and PSA data emphasising the difference between screening and symptomatic populations.
2. Antibiotic prophylaxis.
3. The use of local anaesthesia for biopsy.
4. Policies for rebiopsy with PIN and after negative biopsy but high suspicion of cancer.
5. Indications for inner gland biopsy.
6. Indications for seminal vesicle biopsy.
7. Audit procedure for assessing complications and positive biopsy rates .
8. Use of TRUS biopsy following radical treatment to assess local persistence in men with raised or rising PSA.

Staging of prostate cancer

The clinical presentation and the treatment intent influence the decision about when and how to image an individual. Men with localised prostate cancer are stratified into risk groups according to their risk of recurrence and this is the basis for decision-making on the need for imaging.

Risk stratification for men with localised prostate cancer.

	PSA		Gleason score		Clinical stage
Low risk	< 10 ng/ml	and	≤ 6	and	T1-T2a
Intermediate risk	10–20 ng/ml	or	7	or	T2b-T2c
High risk	> 20 ng/ml	or	8-10	or	T3-T4 ⁴

⁴ Clinical stage T3-T4 represents locally advanced disease.

Staging investigations must be tailored to the treatment planned. Healthcare professionals should determine the provisional treatment intent (radical or non-radical) before decisions on imaging are made. Imaging is not routinely recommended for men in whom no radical treatment is intended.

Men with high-risk localised and locally advanced prostate cancer who are being considered for radical treatment should have imaging with either magnetic resonance imaging (MRI), or CT if MRI is contraindicated. CT is not recommended for men with low- or intermediate-risk localised prostate cancer. Isotope bone scans are not routinely recommended for men with low-risk localised prostate cancer. Isotope bone scans should be performed when hormonal therapy is being deferred through watchful waiting in asymptomatic men who are at high risk of developing bone complications.

Positron emission tomography imaging for prostate cancer is not recommended in routine clinical practice.

Follow-up imaging in prostate cancer

PSA estimation is the mainstay of follow-up. There is no case for routine imaging follow-up in men without evidence of metastatic disease at diagnosis, except in the context of clinical trials.

For men with evidence of biochemical relapse following radical treatment and who are considering radical salvage therapy, routine MRI scanning should not be performed prior to salvage radiotherapy. An isotope bone scan should be performed if symptoms or PSA trends are suggestive of metastases.

Men with hormone-refractory prostate cancer shown to have extensive metastases in the spine (for example, on a bone scan), should have spinal MRI if they develop any spinal-related symptoms. The routine use of spinal MRI for all men with hormone-refractory prostate cancer and known bone metastases however is not recommended.

8.2 Imaging of Urothelial Cancers

Diagnosis

Most patients present with haematuria and require investigation initially with ultrasound +/- plain radiography and flexible cystoscopy. CT urography should be performed with continuing unexplained haematuria after negative initial investigation.

Bladder cancer is by far the most common malignant cause of haematuria. Upper tract tumours typically present de novo with non-functioning systems and as unexplained hydronephroses. Patients presenting with high risk superficial bladder cancer (G3 disease or carcinoma in situ) should have an initial CT urogram. There is a 12% chance of developing an Upper tract TCC .

Patients with known urothelial bladder tumours or who have haematuria and negative cystoscopic findings require contrast studies or endoscopy of their upper tracts, preferably at the time of cystoscopy, particularly focused on the side of bleeding when this is manifest.

Staging of urothelial tumours

Most cases of muscle-invasive bladder cancer require staging with contrast-enhanced CT of the abdomen and pelvis, prior to radical surgery or radical radiotherapy. Previously CT scan for staging muscle invasive disease was delayed for four to six weeks after TURBT. This delay aimed to reduce confusion in staging perivesical disease caused by perivesical changes following TURBT. Current targets do not allow such a delay. Meanwhile, from a clinical point of view, there has been a realisation that TURBT and EUA are sufficient for local staging while the purpose of the post-TURBT CT is nodal staging. Therefore CT scan should not be delayed after the finding of muscle -invasive disease on TURBT.

For radiotherapy planning, a further CT may be required as many Centres treat the bladder empty, whereas staging CT examinations require a distended bladder.

There is no case for routine skeletal scintigraphy of patients with newly-diagnosed bladder cancer unless there are symptoms or signs suggestive of bony metastases.

For local staging assessment prior to planned cystectomy for muscle-invasive disease (assessment of resectability), there is a case for examination with MRI. This should be performed in the hospital performing the surgery and after multidisciplinary discussion. The necessity of MRI for staging superficial urothelial tumours has not been demonstrated.

Upper abdominal CT should be used for staging of urothelial tumours of the renal collecting system. There is uncertainty about the need for chest and pelvic examination unless extensive metastasis is anticipated.

Follow-up imaging of urothelial tumours

Bladder cancer patients are at risk of development of TCCs at other sites in their urinary tract. The need for urographic surveillance of the upper urinary tract is contentious. There is some evidence that upper tract surveillance can be abandoned if the bladder remains clear for 2 years after initial diagnosis. However patients who have produced continued bladder tumour recurrences or have high risk disease should undergo upper urinary tract surveillance. This requires further careful audit.

Patients with an ileal conduit following cystectomy should be examined by loopogram and if reflux into the upper tracts provides satisfactory information this is all that is required. Otherwise CT urography may be required.

8.3 Imaging of renal cell cancer

Diagnosis

50% of renal masses are now incidentally identified with ultrasound and CT when investigating other conditions and there is some evidence that these carry a better prognosis. Haematuria is the most common symptom leading to a diagnosis of renal cell cancer. Investigation of haematuria remains controversial but evidence is accumulating that ultrasound +/- plain radiography and flexible cystoscopy should be the initial investigations.

Ultrasound is the key diagnostic study and establishes the diagnosis of renal cell cancer in most cases. Intravenous urography should not be used as in diagnosis and has no role in staging.

Indeterminate renal masses should be investigated with pre- and post-contrast CT using the Bosniak classification . In young patients, those with contraindication to intravenous contrast and in pregnancy, MRI offers an alternative. Some masses require biopsy after multidisciplinary discussion

Staging

Pre-operative CT of the chest and abdomen is the investigation of choice for staging renal tumours, employing contrast-enhanced examination using 5 to 10mm collimation. The pelvis does not require examination unless there are symptoms referable to it e.g. bone pain.

If there is any doubt about the extent of venous invasion after US and CT, MR should be considered. The multi-planar capacity of MR is of value if a partial nephrectomy is to be performed. 3D gadolinium-enhanced imaging should be used and referral to a Cancer Centre is appropriate for MR work-up.

When considering partial nephrectomy, 3D MR or volumetric CT with multiplanar imaging are alternatives.

The additional value of chest CT, with its higher sensitivity for pulmonary metastasis, is unclear. In patients with small confined tumours small CT nodules are likely to be false positive.

Bone scans are not routinely needed but should be performed in patients with bone pain, or other suggestion of bony metastases. Tumour embolisation by interventional radiologists is usually required with venous extension of renal tumour. By and large these tumours are going to be treated in Cancer Centres.

Facilities for interventional radiology may not be available in all Units and it may be necessary for patients requiring these to be referred to a Cancer Centre. If such facilities are available in Units it must demonstrate that they have adequate expertise and volume of work to do complex work to the same standard as that available in the Cancer Centre.

CT is the investigation of choice for the renal bed following nephrectomy and the retroperitoneum as these are difficult areas to examine using ultrasound.

It would seem reasonable to perform CT at six months post-nephrectomy and in patients considered to be at high risk for local recurrence, to obtain a new baseline and seek evidence of early recurrence, as suggested by the Working Party. This policy will require careful regional audit.

Abdominal CT is advised to assess clinically suspected local recurrences. Good oral contrast filling of bowel is essential as small and large bowel may become adherent within the surgical void and mimic recurrence. A chest X-ray or chest CT should also be performed at these times.

9 Palliative & End of Life Care

9.1 Definitions

This section has been updated in May 2017

Palliative care is part of supportive care. It embraces many elements of supportive care.

Palliative & End of life care is care that helps all those with advanced, progressive, incurable illness to live as well as possible until they die. It enables the supportive and palliative care needs of both patient and family to be identified and met throughout the last year(s) of life and into bereavement. It includes management of pain and other symptoms and provision of psychological, social, spiritual and practical support.

The Department of Health (2008) definition of end of life care states that it includes:

- Adults with advanced, progressive, incurable illness (e.g. advanced cancer, heart failure, COPD, stroke, chronic neurological conditions, dementia);
- Care given in all settings (e.g. home, acute hospital, ambulance, residential/nursing care home, hospice, community hospital, prison);
- Care given in the last year(s) of life
- Patients, carers and family members (including bereavement care).

End of Life Strategy, Department of Health 2008
National Council for Palliative Care Services 2006

9.2 Who Provides Palliative / End of Life Care?

Palliative / end of life care is provided by two distinct categories of health and social care professionals:

- All health care and social care professionals providing the day-to-day care to patients and carers in any care setting
- Those who specialize in palliative care (consultants in palliative medicine and clinical nurse specialists in palliative care, for example) who care for palliative care patients who have complex needs

Those providing day-to-day care should be able to:

- Assess the care needs of each patient and their families across the domains of physical, psychological, social spiritual and information needs
- Meet those needs within the limits of their knowledge, skills, competence in palliative care
- Know when to seek advice from or refer to specialist palliative care services

Training and education in the skills required for palliative / end of life care should be available to and undertaken by all health and social care professionals.

The national strategy *Ambitions for Palliative and End of Life Care 2015-2020* sets out the vision to improve end of life care through partnership and collaborative action between organisations at local level throughout England.

More information can be found at: <http://endoflifecareambitions.org.uk/>

For more information about local improvements, frameworks, tools to support best practice please contact your local End of Life Care Lead or Specialist Palliative Care Team. One aspect of care is to discuss with individuals, if they wish, their preferences regarding the type of care they would wish to receive and where they wish to be cared for in case they lose capacity or are unable to express a preference in the future. This is the process of Advance Care Planning (ACP).

An ACP discussion might include:

- the individual's concerns and wishes,
- their important values or personal goals for care,
- their understanding about their illness and prognosis,
- their preferences and wishes for types of care or treatment that may be beneficial in the future and the availability of these.

Such discussions can also inform shared decision-making regarding treatments with palliative intent. Local arrangements for recording this information for each individual patient will differ. Many services are developing/have developed Electronic Palliative Care Co-ordination Systems (EPaCCS) where by this information can be shared across professionals and settings (e.g on SystmOne). Contact your local specialist palliative care team for more information.

9.3 Specialist Palliative Care

Is provided by specialist multidisciplinary palliative care teams in services or units whose core specialty is palliative care (for example hospices, community or hospital palliative care teams). The specialist teams should include palliative medicine consultants and palliative care nurse specialists together with a range of expertise provided by physiotherapists, occupational therapists, dieticians, pharmacists, social workers and those able to give spiritual and psychological support.

Eligibility for referral to specialist palliative care services is based on patient need not diagnosis. The agreed criteria for referral are as follows:

1. The patient has active, progressive and usually advanced disease for which the prognosis is limited (although it may be several years) and the focus of care is quality of life.
2. The patient has unresolved complex needs that cannot be met by the caring team, for example:
 - Uncontrolled or complicated symptoms (e.g. symptoms not adequately controlled within 48 hours by the referring team, or sooner if causing overwhelming distress).
 - Complex psychological/emotional difficulties.
 - Complex social or family issues.
 - Difficult decision making about appropriate future care.

Patients fulfilling these criteria should be referred to and assessed by a member of the specialist palliative care team.

The subsequent care package will be dependent on this assessment and should be made in agreement with the patient, carer(s) and referring team. It is not appropriate for specialist palliative care services to be committed to patients by professionals outside these services. Equally, specialist services should ensure that the assessment process is accessible and responsive to patients in need.

The level of specialist palliative care support required may fluctuate. Shared care of patients between the specialist palliative care professionals and the referring team (for hospital patients) or the primary care team (for patients at home / care home) is usually appropriate. Timely and effective communication is essential in these situations. For these patients advice from specialist palliative care services on a 24 hour basis should be available in all care settings.

Sometimes the specialist palliative care consultant and team may take the lead role in patient care, usually in a specialist in-patient unit (hospice) or designated specialist palliative care beds.

Referral systems for specialist palliative care services vary in different areas. They should be clear to all local referring consultants and primary care teams.

9.4 Further Links and Information

Contact the local Specialist Palliative Care Team for further information

9.5 Directory of West Yorkshire & Harrogate Cancer Alliance Specialist Palliative Care Services

The Directory has been checked and updated in May 2017

Bradford, Airedale, Wharfedale and Craven
 Bradford Teaching Hospitals NHS Foundation Trust
 Airedale NHS Foundation Trust
 NHS Bradford, Airedale, Wharfedale and Craven
 Website: www.palliativecare.bradford.nhs.uk

Airedale General Hospital Palliative Care Team	Tel	01535 292184 01535 295016
	Fax	01535 295036
Sue Ryder Care – Manorlands Hospice (Oxenhope)	Tel	01535 642308
	Fax	01535 642902
Bradford Teaching Hospitals Palliative Care Team	Tel	01274 364035
	Fax	01274 366851
Bradford Community Palliative Care Team	Tel	01274 323511
	Fax	01274 215660
Marie Cure Hospice (Bradford)	Tel	01274 337000
	Fax	01274 337095
Out of Hours Advice via on-call Palliative Medicine Consultant via Marie Curie Hospice / Manorlands Hospice	Tel	01274 337000
	Tel	01535 642308

Calderdale and Huddersfield

Calderdale & Huddersfield NHS Foundation Trust

NHS Calderdale

NHS Kirklees

Web: <http://www.cht.nhs.uk/services/clinical-services/palliative-and-end-of-life-care/specialist-palliative-care/>

Calderdale Royal Hospital & Huddersfield Royal Infirmary Palliative Care Team	Tel	01484 342965
	Fax	none
Calderdale Community Palliative Care Team Left message to confirm fax	Tel	01422 310874
	Fax	01422 378425
Overgate Hospice	Tel	01422 379151
	Fax	01422 384210
Kirkwood Hospice and Community Palliative Care Team	Tel	01484 557906
	Fax	01484 557918
Out of Hours Advice via Hospices	Tel	01422 379151 01484 557900

Harrogate and District

Harrogate NHS Foundation Trust

NHS North Yorkshire and York

Website: <https://www.hdft.nhs.uk/services/palliative-care/>

Harrogate Hospital and Community Palliative Care Team	Tel	01423 553464
	Fax	01423 555763
St Michael's Hospice	Tel	01423 872658
	Fax	01423 815454
Out of Hours Advice via Hospice	Tel	01423 879687

Leeds

Leeds Palliative Care

Website: www.leedspalliativecare.co.uk

Leeds Teaching Hospitals NHS Trust Specialist Palliative Care Team	Tel	0113 2064563
	Fax	0113 2064863
Sue Ryder Care - Wheatfields Hospice and Community Palliative Care Team (West Leeds)	Tel	0113 2787249
	Fax	0113 2302778
St Gemma's Hospice and Community Palliative Care Team (East Leeds)	Tel	0113 2185500
	Fax	0113 2185524
Out of Hours Advice via SJUH Switchboard	Tel	0113 2433144

Mid Yorkshire

Mid Yorkshire Hospitals NHS Trust

NHS Wakefield District

Kirklees PCT

Website: <https://www.midyorks.nhs.uk/palliative-care1>

Dewsbury Hospital and Community Palliative Care Team	Tel	01924 816052
	Fax	01924 543883
Dewsbury Day Support and Drop-in (Rosewood Centre)	Tel	01924 512039
Mid Yorkshire Hospitals NHS Trust Palliative Care Team	Tel	01924 543801
	Fax	01924 543883
Pontefract Community Palliative Care Team (Prince of Wales Hospice)	Tel	01977 781456
	Fax	01977 796209
Prince of Wales Hospice (Pontefract)	Tel	01977 708 868
	Fax	01977 600097
Wakefield Hospice	Tel	01924 331400
	Fax	01924 362769
Out of Hours Advice via Pinderfields Hospital Switchboard	Tel	01924 541000

York

York Hospitals NHS Foundation Trust

NHS North Yorkshire and York

https://www.yorkhospitals.nhs.uk/our_services/az_of_services/palliative_care/

York Hospital Palliative Care Team both correct	Tel	01904 725835
	Fax	01904 726440
Community Palliative Care Team	Tel	01904 724476
	Fax	01904 777049
St Leonard's Hospice	Tel	01904 708553
	Fax	01904 704337
Out of Hours Advice via Hospice	Tel	01904 708553