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Management of transitional cell carcinoma of the bladder

A national clinical guideline

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December 2005

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

- 1⁺⁺ High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
- 1⁺ Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
- 1⁻ Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
- 2⁺⁺ High quality systematic reviews of case control or cohort studies
High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
- 2⁺ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
- 2⁻ Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
- 3 Non-analytic studies, eg case reports, case series
- 4 Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

- A** At least one meta-analysis, systematic review of RCTs, or RCT rated as 1⁺⁺ and directly applicable to the target population; *or*
A body of evidence consisting principally of studies rated as 1⁺, directly applicable to the target population, and demonstrating overall consistency of results
- B** A body of evidence including studies rated as 2⁺⁺, directly applicable to the target population, and demonstrating overall consistency of results; *or*
Extrapolated evidence from studies rated as 1⁺⁺ or 1⁺
- C** A body of evidence including studies rated as 2⁺, directly applicable to the target population and demonstrating overall consistency of results; *or*
Extrapolated evidence from studies rated as 2⁺⁺
- D** Evidence level 3 or 4; *or*
Extrapolated evidence from studies rated as 2⁺

GOOD PRACTICE POINTS

- Recommended best practice based on the clinical experience of the guideline development group

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1 Introduction

1.1 THE NEED FOR A GUIDELINE

In Scotland transitional cell carcinoma (TCC) of the bladder is the fifth most common cancer in men and the fifteenth in women.¹ Seventy five per cent of patients present with superficial tumours,² and in 10% this will progress to muscle invasive (pT2-4) cancer.^{3,4} Invasive cancer involving detrusor muscle, which is present at diagnosis in 25% of patients,² is an aggressive tumour with a poor prognosis. Superficial disease recurs in up to 80% of patients.^{5,6} This necessitates repeated and often prolonged cystoscopic follow up, which places a significant workload on urological departments.

There are considerable variations in surgical and non-surgical management of the disease.

1.1.1 SUPERFICIAL DISEASE

There is a need to review the body of evidence surrounding the management of superficial disease. Can its initial assessment and treatment be improved? Can the use of additional treatments, such as intravesical chemotherapy reduce recurrence and progression? What is the optimum follow-up regimen to balance the need for surveillance against over-frequent follow up, an imposition on the patient and costly to the health service? Is treatment of potentially progressive disease before progression occurs life saving? Should aggressive treatments such as cystectomy be confined to those at high risk?

1.1.2 INVASIVE DISEASE

There is no agreement as to whether muscle invasive disease is best managed by surgery or by radiotherapy. The role of lymph node dissection and orthotopic reconstruction in patients undergoing cystectomy needs to be defined, as does the optimum radiotherapy regimen. New data on the effectiveness of neoadjuvant chemotherapy may lead to a change in routine practice.

1.1.3 AETIOLOGY AND DISEASE PREVENTION

Specific aetiological factors related to lifestyle and occupation are recognised as risks for bladder cancer, and these are discussed, along with possibilities for prevention and modification of the course of the disease.

1.2 REMIT OF THE GUIDELINE

This guideline is primarily directed at management of TCC of the bladder once diagnosed. Less common tumours such as squamous cell carcinomas or adenocarcinomas and management of metastatic disease are not within the scope of this guideline. To address the main issues surrounding the management of bladder cancer, the guideline development group posed a series of key questions, which forms the basis of this guideline (see *Annex 1*).

The guideline has most relevance to those in secondary care. This does not undermine the importance of primary healthcare professionals in prompt referral of patients with haematuria and other symptoms suggestive of bladder cancer. Although the patient journey for those with bladder cancer will inevitably be largely within a hospital environment, the patient will frequently seek guidance and reassurance from the primary care team, who may find relevant information for discussion with the patient within this guideline.

Guidance on referral can be found in the “Scottish Referral Guidelines for Suspected Cancer” (see *Annex 2*).⁷

1.3 KEY CLINICAL RECOMMENDATIONS

The following key recommendations were highlighted by the guideline development group as being clinically very important. Although these recommendations may not all be supported by strong evidence, they should be prioritised for implementation.

1.3.1 LIFESTYLE ISSUES

- B** Smoking should be discouraged.
- B** Clinicians should be aware that previous treatments with radiotherapy and certain chemotherapy may predispose patients to transitional cell carcinoma of the bladder.
- Clinicians using radiotherapy and chemotherapy treatments should do so utilising best practice to minimise any unnecessary exposure of patients.

1.3.2 REFERRAL

- C** For optimum survival benefit, cystectomy for patients with muscle invasive bladder cancer should be performed within three months of diagnosis.
- Care of patients with bladder cancer should be managed within a cancer network.

1.3.3 MANAGEMENT OF SUPERFICIAL BLADDER CANCER

- B** Only patients with high grade tumours (*including CIS*) at time of diagnosis should have regular upper tract surveillance.
- C** Patients with a single pTa G1/G2 tumour at the time of diagnosis and who are recurrence free at three months after the original resection should have annual cystoscopy.
- A** A single instillation of intravesical chemotherapy should be used to reduce the risk of recurrent disease following resection in all patients considered to be at high risk of recurrence.
- C** Normal looking areas of the bladder need not be routinely biopsied at the time of diagnosis or follow up.
- C** Patients with CIS of the bladder should be treated with BCG.
- B** Maintenance therapy with BCG should be considered in patients with CIS to improve local control and reduce the incidence of progression.

1.3.4 SURGICAL TREATMENT

- C** Patients with muscle invasive bladder cancer should have cross-sectional imaging prior to treatment.
- Cross-sectional imaging should take place prior to tumour resection.
- C** Urethrectomy should be performed in high-risk patients having cystectomy and urinary diversion.
- C** All patients having curative radical cystectomy should have bilateral pelvic lymph node dissection.

1.3.5 NON-SURGICAL TREATMENT

B Radiotherapy using 21Gy in three fractions in one week should be considered for palliation of patients with bladder cancer.

- A**
- Neoadjuvant chemotherapy should be offered to suitable patients prior to definitive radical therapy for patients with T2-T4 transitional cell carcinoma of the bladder.
 - A combination chemotherapy regimen containing cisplatin should be used.

1.3.6 INFORMATION FOR DISCUSSION WITH PATIENTS AND CARERS

C Patients should be offered verbal and written information throughout their journey of care and should be made aware of the support mechanisms that are in place and how to access them.

1.4 DEFINITIONS USED IN THIS GUIDELINE

Frank haematuria

Frank (visible) haematuria (blood in the urine) is the most common presentation of bladder cancer.

Occult haematuria

Occult (microscopic) haematuria is usually identified microscopically, or chemically by dipstick testing.

Transitional cell carcinoma

The most common tumour arising from the urothelial lining of the bladder usually consisting of transitional epithelium.

1.4.1 TUMOUR GRADE

The grade of the tumour is defined by the degree of differentiation of the tumour cells (see *Annex 3*).

1.4.2 TUMOUR STAGE

The stage of the tumour is the extent of local spread into the wall of the bladder and is classified following the criteria of the TNM Classification of Malignant Tumours (see *Annex 4*).^{8,9} The following definitions are used in this guideline and are not mutually exclusive. For example, “superficial” includes pT1 tumours which for the purposes of this guideline are classified as “invasive” (see *Table 1*).

Carcinoma in situ (CIS)

This is full thickness, high grade dysplastic change in the urothelium. It is flat with no papillary formation and no invasion of the underlying tissue. It is non-invasive malignant change in the urothelium and has a high risk of progression to invasive disease.

Non-invasive tumour

There is no evidence of invasion beyond the basement membrane (pTa and pTis).

Superficial tumour

Conventionally tumours confined to the mucosa (non-invasive) or showing superficial invasion of the bladder wall (invasion of the lamina propria but not detrusor muscle) are said to be “superficial”, and include pTa, pTis and pT1 tumours. This convention disguises the fact that both pTis and pT1 have a poorer prognosis than pTa tumours.^{10,11}

Invasive tumours

These include all tumours invading beyond the basement membrane (pT1–pT4). Despite conventionally being classified as “superficial”, in this guideline superficial invasive tumours (pT1) are included in “invasive disease”. More deeply invasive tumours (pT2–4) are referred to as “muscle invasive tumours”.

Localised disease

Disease confined to the bladder with no evidence of distant spread. Such tumours are potentially curable, although with invasive tumours micrometastases undetected by current methods may already have occurred.

Advanced disease

Tumours with extravesical spread (T4), or metastases to lymph nodes (N1–3) or distant extranodal metastases (M1) are “advanced” and are likely to be incurable.

Table 1: Definition of invasive and non-invasive bladder cancer

Stage	Invasion		
CIS] superficial		
Ta			
T1] invasive		
T2			
T3			
T4			
]	non-invasive	
]	muscle invasive

1.4.3 RISK

Risk can be interpreted as risk either of recurrence, which includes tumours developing in the upper urinary tract, in the ureters or renal pelves, or of progression (see Annex 5).

1.5 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of medical care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the appropriate healthcare professional following discussion of the options with the patient, in light of the diagnostic and treatment choices available. It is advised however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient’s case notes at the time the relevant decision is taken.

2 Lifestyle issues

The Scottish population tends to have a less healthy lifestyle in relation to tobacco, alcohol, diet and exercise compared to other nationalities.¹²

2.1 SMOKING

Cigarette smoking is thought to be a significant risk factor for many cancers, including bladder cancer, and is likely to be detrimental to the general health of patients recovering from cancer.

Cigarette smoke metabolites secreted into smokers' urine have been estimated to cause more than 50% of bladder cancer cases in Europe and the United States.¹³ Smoking increases the risk of bladder cancer by two or three times,¹⁴⁻¹⁷ and stopping smoking leads to an immediate, although not statistically significant, reduction of bladder cancer risk (odds ratio, OR=0.68 95%, confidence interval, CI 0.38-1.2).¹⁵ 2+

While the direct relationship between continued smoking in patients with bladder cancer and a second new bladder cancer is inadequately studied, it is recognised that stopping smoking while recovering reduces the risk of complications after operations.^{18,19} 1+ 2+

B Smoking should be discouraged.

Healthcare professionals should refer smokers with bladder cancer to smoking cessation services.

2.2 DIET

The typical Scottish diet is poor, being high in fat, salt and refined carbohydrate and low in fruit and vegetables.¹²

Studies linking diet with outcomes such as the development of bladder cancer are difficult to undertake, due to the problem of collecting retrospective food diaries.

Evidence from one large meta-analysis and one systematic review showed that a balanced diet may reduce the incidence of bladder cancer. Increasing fruit and vegetable consumption while reducing animal fat in the diet is associated with a reduced incidence of bladder cancer.^{20,21} The studies gave no firm evidence about the specific effect of micronutrients in prevention of bladder cancer.^{20,21} 2++

B People should be encouraged to:

- eat more fruit and vegetables
- reduce the amount of animal fat in their diet.

People should be encouraged to follow healthy eating guidelines such as the NHS Health Scotland dietary recommendations "Eating for Health" and the WHO backed "5 a day" campaign.

The incidence of bladder cancer in coffee drinkers is slightly elevated but evidence from studies of different Western populations is not statistically significant at the 95% confidence interval nor strong enough to warrant advice about coffee consumption as a bladder cancer risk.^{17,22,23} No studies have looked at coffee consumption in patients who have bladder cancer. 2+

A large meta-analysis of case control and cohort studies showed that there is no evidence to link bladder cancer to drinking alcohol.²⁴ 2+

2.3 OCCUPATION

Occupational exposure to industrial chemicals has been estimated to account for up to 20% of bladder cancer cases in the United States, often with latency periods of more than 30 years.¹³

Historically, there have been many occupations in Scotland, such as those in the the rubber, dye and petrochemical industries, where workers were exposed to levels of aromatic amines that may have been linked to an elevated risk of bladder cancer. The Health and Safety Executive (HSE; www.hse.gov.uk) now enforces regulations through the Control of Substances Hazardous to Health Regulations 2002 (COSHH; www.hse.gov.uk/pubns/indg136.pdf) to ensure that workers are not exposed to dangerous chemicals. Similar regulations may not be enforced in other countries.

Studies linking occupational exposure to chemicals and rare outcomes such as bladder cancer rely on historical data about the length and nature of the exposure, making the risks difficult to quantify.

A meta-analysis of cohort studies describing mortality and cancer incidence among chemical workers in the United States and Western Europe has shown that occupational exposure to aromatic amines increases the risk of bladder cancer.²⁵ | 2⁺⁺

There is evidence from a systematic review of cancer risks among exposed workers that metal-working fluids increase the risk of bladder and other cancers.²⁶ | 2⁺⁺

There is a 30% increased risk of bladder cancer in painters, probably due to solvents used in the paints, although the definition of painter is not clear.²⁷ The confounding effects of smoking and other risk factors cannot be excluded from the studies included in this meta-analysis.²⁷ | 2⁺

There is evidence from a systematic review of cancer risks in the rubber industry that exposure to chemicals that have been used in this industry increased the risk of bladder cancer.²⁸ | 2⁺

A large meta-analysis of 69 cohort studies found no evidence of an association between asbestos exposure and bladder cancer.²⁹ | 2⁺

A careful occupational history should be taken from patients with bladder cancer.

Diseases currently reportable under Reporting of Injuries, Diseases and Dangerous Occurrences Regulations (RIDDOR), 1995 should be reported to the HSE Incident Contact Centre (www.riddor.gov.uk).

It is important that any reportable diseases are accurately identified. Guidance is available from the Health and Safety Executive (www.hse.gov.uk/pubns/hse31.pdf, www.hse.gov.uk/pubns/hse32.htm#6).

2.4 OTHER RISKS

2.4.1 RADIOTHERAPY AND CHEMOTHERAPY

Previous treatment with radiotherapy and chemotherapy may increase the lifetime risk of developing bladder cancer.¹³ For instance, pelvic radiotherapy and some cytotoxic agents, such as cyclophosphamide, to treat cancer and benign disease may lead to a small, unquantified, increase in risk. | 1⁺

B Clinicians should be aware that previous treatments with radiotherapy and certain chemotherapy may predispose patients to transitional cell carcinoma of the bladder.

Clinicians using radiotherapy and chemotherapy treatments should do so utilising best practice to minimise any unnecessary exposure of patients.

3 Referral

In the management of bladder cancer, healthcare professionals working in primary care have an important role in recognising people with suspicious symptoms and organising appropriate investigation and referral. Clinicians should follow the “Scottish Referral Guidelines for Suspected Cancer” (see Annex 2).⁷

- ☑ In any clinical network involving primary and secondary care, clinicians should develop a referral pathway. In Scotland this will involve the regional cancer networks and NHS Boards.

Teams setting up referral pathways may find the National Institute for Health and Clinical Excellence (NICE) guidance “Improving Outcomes in Urological Cancers” useful.³⁰

- ☑ An electronic referral facility from primary care, possibly linked to an intelligent system, for example, RefHelp (<http://www.refhelp.org.uk>) or reference to SIGN 31 “Report on a recommended referral document” may help to standardise referrals.³¹

Annex 6 gives an example of a referral proforma for people with frank haematuria (available from Lothian Referral Guidelines; <http://www.refhelp.org.uk>).

- ☑ There should be central collation of referrals, local or cancer network wide, to allow efficient triage and planning of investigation, clinic appointments and treatment.

The “Scottish Referral Guidelines for Suspected Cancer” state that patients with frank haematuria should be referred “urgently”, and an “early” referral made for those with occult (microscopic) haematuria.⁷

- ☑ Patients with frank haematuria should be referred and investigated so that primary treatment can be started within two months if bladder cancer is diagnosed.

3.1 TIMING OF TREATMENT

The Scottish Executive document “Cancer in Scotland: Action for Change” states that by 31st December 2005, the target for the wait from urgent referral to treatment for patients with any cancer will be two months.³² A similar “sixty two day” rule applies in England.³³ These decisions are based on expert opinion, as is the recommendation in the NICE guidance “Improving Outcomes in Urological Cancer” that patients with visible haematuria should be referred within two weeks to a dedicated haematuria clinic³⁰ and the “Scottish Referral Guidelines for Suspected Cancer”.⁷ Evidence in support of specific timescales for treatment is weak, as this is not a subject amenable to clinical trials.

3.1.1 TIME TO DIAGNOSIS

A study undertaken in 1965 demonstrated that delay in diagnosis was associated with a poorer outcome.³⁴ In a 2002 prospective study patients’ referral to hospital within 14 days of the onset of symptoms was associated with a significantly better survival.³⁵

3.1.3 TIME TO TREATMENT

Once the diagnosis is made, the effect of treatment delay is difficult to determine because treatment of patients with invasive disease with a poorer prognosis is usually given priority, distorting statistics on the impact of hospital delay on outcome.

Evidence for delay from diagnosis to treatment relates mainly to patients undergoing cystectomy for muscle invasive (pT2-4) bladder cancer. A delay of more than three months between diagnosis (by transurethral resection, TUR) and cystectomy has a detrimental effect on survival.³⁶ There is evidence that within that three month window, outcome is not affected by the timing of treatment.³⁷ These data may be less relevant if neoadjuvant chemotherapy prior to cystectomy is used (see section 6.3).

2+

C For optimum survival benefit, cystectomy for patients with muscle invasive bladder cancer should be performed within three months of diagnosis.

Although there is some evidence that delay affects the outcome of patients with T1 disease,³⁵ any effect of delay is less clear in patients with superficial disease and more complicated disease initially treated by intravesical chemotherapy or bacille Calmette-Guerin (BCG), or on the results of radiotherapy treatment.

3

The two month target times for treatment, which date from referral, not from diagnosis, are well within the limits suggested by the available evidence. These target times may be unnecessarily tight, bearing in mind the need for appropriate investigation prior to definitive treatment and the opportunity for patients to consider their treatment needs.

The need to treat the patient promptly should not prevent proper counselling and provision of information about treatment options.

3.2 CASE VOLUME AND MULTIDISCIPLINARY CLINICAL APPROACH

There is evidence that clinical outcome for some cancers is improved by having experienced clinicians working in major centres.³⁸ It is difficult to study the volume of procedures performed by a particular surgeon or hospital team using rare outcomes such as mortality as an end point. The NICE guidance “Improving Outcomes in Urological Cancer” states that surgeons and clinical teams should be experienced in performing complex procedures and work in a multidisciplinary manner.³⁰ In particular, it recommends that each team performing cystectomy should serve a population of at least one million, which equates to five teams in Scotland. The recommendation that patients should be offered the option of bladder reconstruction (see section 5.5) increases the need for cystectomy to be performed in centralised centres.

All new invasive and complicated bladder cancer cases must be discussed by a properly constituted multidisciplinary team.

Patients with cancer often have complex care needs that cannot be addressed by a single specialty or discipline. This has led to the development of multidisciplinary teams within Managed Clinical Networks (MCN) to ensure a consistent and equitable approach to planning and managing care.

It is recognised that the clinical nurse specialist (CNS) should be an integral part of this network. A key component of the CNS role is to coordinate care between settings, in addition to providing support, advice and information for patients and their carers throughout their illness.^{39,40}

The best clinical outcomes for patients with bladder cancer will be achieved where units treat a high volume of cases within a Managed Clinical Network thereby developing and maintaining expertise.³⁰ The three cancer networks in Scotland (South East Scotland Cancer Network, SCAN, North of Scotland Cancer Network, NoSCAN and West of Scotland Cancer Network, WoSCAN) have encouraged high volume services to develop.

4

A key criterion for Managed Clinical Network status is conducting rigorous clinical audit which is crucial to maintaining and improving quality of outcomes.³²

- ☑ Care of patients with bladder cancer should be managed within a cancer network.
- ☑ Within each network, bladder cancer should be managed by multidisciplinary teams, with surgical and other radical treatments administered by those with appropriate expertise and caseloads.
- ☑ All patients diagnosed with bladder cancer should have access to a clinical nurse specialist for support, advice and information.

3.3 INVOLVING THE PATIENT IN THE DECISION MAKING PROCESS

Patients and their families need information to help them understand and cope with the diagnosis of bladder cancer, the treatment options and possible outcomes.

There is increasing evidence that cancer patients wish to be more involved in making decisions regarding their own care than clinicians may think.⁴¹ One systematic review of a large number of controlled studies was only able to conclude that methods for achieving decision making are under-researched and that there was a need for more and better randomised trials.⁴² 2++
3

- D** Healthcare professionals should involve patients in making decisions about their treatment, if the patient expresses a wish to do so.

4 Management of superficial bladder cancer

4.1 IMAGING DURING FOLLOW UP

Imaging (intravenous urography, ultrasound and cross-sectional) for the investigation of patients with haematuria is principally used to detect tumours of the upper urinary tract. This is beyond the remit of a guideline on the management of bladder cancer. This section deals with follow up and treatment of patients already diagnosed with superficial bladder cancer.

Transitional cell carcinoma of the urinary bladder is a multifocal process with tumours occurring both synchronously and metachronously. Recurrence is common following appropriate treatment for the primary tumour and there is a need for cystoscopic monitoring. The malignant process can affect the urothelium of the renal calyces, pelvis and ureter, which may require monitoring of the upper urinary tract, traditionally by intravenous urography (IVU).

There is a subgroup of patients (9.8%) with high grade (G3) tumours, including CIS, at time of diagnosis that are at high risk of developing upper tract disease.⁴³ There is evidence that with regards to surveillance, high risk groups should have a regular IVU. There is no evidence that low or intermediate risk groups benefit from this treatment.⁴³

2⁺⁺

B Only patients with high grade tumours (including CIS) at time of diagnosis should have regular upper tract surveillance.

Annual intravenous urography is appropriate in patients at high risk of upper tract disease.

Upper tract imaging should be carried out for patients in all risk groups if haematuria occurs during follow up and the bladder is tumour free.

The incidence of upper tract TCC after cystectomy is low (2%). Most patients with upper tract TCC present with haematuria and usually have advanced disease.⁴⁴ There is little evidence to support regular upper tract surveillance in these patients. No evidence was identified for surveillance of patients following radiotherapy.

4.2 PHOTODYNAMIC AIDED RESECTION

Photodynamic (fluorescence) techniques using blue/violet light after instillation of a photosensitiser have been used to improve completeness of initial resection of bladder cancer.

Two observational studies demonstrate that tumour identification is improved by use of fluorescence.^{45,46} Randomised controlled trials (RCTs) show that the use of fluorescence reduces the incidence of residual tumour on repeat cystoscopy,^{47,48} and also, over an initial follow-up period, the number of recurrences.⁴⁹ The evidence suggests potential benefits from photodynamic techniques for patients with superficial bladder cancer undergoing initial resection of their tumour.⁴⁵⁻⁴⁹ Its role in patients developing recurrence during follow up is less clear.

1⁺2⁺

There is consistent evidence for improved tumour detection by use of fluorescence. Transurethral resection of bladder tumour (TURBT) done under fluorescence control achieves more complete clearance of the tumour. There is a high false positive fluorescence rate after intravesical chemotherapy and following TURBT and its value in these circumstances is not clear.^{50,51}

2⁺⁺

Some studies describe the use of fluorescence at the time of primary treatment.⁴⁶ Others describe its use to assess residual disease at follow up.⁵² There are currently no long term studies to demonstrate improved outcomes in terms of disease-free and overall survival, but the reduction in the number of patients with tumours found at first cystoscopy after resection is recognised as a favourable prognostic factor. A separate study demonstrating reduction in tumour recurrence rates suggests a beneficial long term effect.⁴⁹

1⁺2⁺2⁺⁺

The procedure appears most reliable if used at the stage of primary TUR.⁵¹

B Fluorescence cystoscopy under blue/violet light (wavelength 400 nm) which causes tumours to fluoresce red should be used to improve the completeness of resection of superficial bladder tumours.

- Fluorescence aided imaging should principally be used to monitor the initial TURBT.
- Histological confirmation of bladder cancer is essential where fluorescence aided imaging is used after TURBT or following intravesical chemotherapy.

4.3 FOLLOW UP

Although many different follow up regimens are used, there have been no randomised controlled trials to determine the most effective follow-up methods for patients with low-grade G1, G2 superficial bladder cancer.

Clinical guidance for follow up (mainly based on expert opinion) is given by NICE and the American Urological Association.^{13,30}

Patients with a single pTa G1 or G2 tumour at the time of diagnosis, whose bladder is clear at the first (three month) cystoscopy, are at low risk of recurrence, while patients with multiple tumours at first diagnosis and/or evidence of recurrent tumour at the first check cystoscopy are at greater risk of subsequent recurrences.⁶

1++

A cohort study of patients with transitional cell carcinoma following first resection confirmed that it is possible to distinguish tumours at low and high risk of recurrence.⁵³

2+

C Patients with a single pTa G1/G2 tumour at the time of diagnosis and who are recurrence free at three months after the original resection should have annual cystoscopy.

The optimal duration of follow up is not clear. There is no evidence to support routine cystoscopic follow up after a five year disease-free interval.

- Patients with a high risk of recurrence should be monitored closely and given an individualised cystoscopic follow up.
- When discharged, patients should be advised that they should seek urgent investigation should haematuria recur.

4.4 INTRAVESICAL THERAPY

An RCT demonstrated that intravesical mitomycin C decreases recurrence rates in patients with superficial bladder cancer after one year⁵⁴ and seven years of follow up.^{54,55}

1+

Prior to a 2002 meta-analysis there was little consensus that intravesical chemotherapy delays progression. The meta-analysis showed a delayed rate of progression only if following a maintenance regimen of BCG that is not common practice in the UK.⁵⁶ Confounding this analysis are the heterogeneous nature of the tumours studied and the small numbers of events of progression. No survival benefit was apparent.

1++

BCG instillations are as effective as mitomycin C, but have a greater potential toxicity.³⁰ There is evidence that superficial bladder cancer responds to other chemotherapeutic agents, such as epirubicin, which may be as effective as mitomycin C.³⁰

1++

A A single instillation of intravesical chemotherapy should be used to reduce the risk of recurrent disease following resection in all patients considered to be at high risk of recurrence.

Intravesical therapy for superficial bladder cancer may reduce risk of recurrence and therefore the frequency of cystoscopy. There is no evidence to suggest that intravesical therapy reduces disease progression to muscle invasion.

4.5 RANDOM BIOPSY OF NORMAL MUCOSA

Previous practice has been to take "random" biopsies, either at the time of diagnosis or at the time of follow-up cystoscopy. The rationale for this has been to diagnose CIS that might affect the patient's management. Random, near and far and quadrant biopsies have all been advocated. There is evidence demonstrating considerable interobserver variation by pathologists in interpreting such biopsies, particularly in the diagnosis of CIS.⁵⁷⁻⁵⁹

Observational studies have not demonstrated clinical benefit from taking random biopsies.^{60,61} | 2+

C Normal looking areas of the bladder need not be routinely biopsied at the time of diagnosis or follow up.

4.6 MANAGEMENT STRATEGIES

4.6.1 CARCINOMA IN SITU

CIS has a risk of progressing to invasive disease. There is no evidence from RCTs to define the best management strategy for CIS. Some practitioners recommend intravesical or other local treatments and others cystectomy.

There is a large body of evidence showing that CIS responds to intravesical BCG.⁶²⁻⁶⁴ Although response rates to BCG are high there is a risk of progression to muscle invasive (pT2-4) disease after intravesical therapy and patients may require further treatment including cystectomy.¹³ | 4
2+

C Patients with CIS of the bladder should be treated with BCG.

Persistence of CIS is an indication for cystectomy, although a second course of BCG may be considered.

There is a body of evidence showing that maintenance BCG is beneficial over induction therapy alone.⁶⁴⁻⁶⁶ | 1+
4

B Maintenance therapy with BCG should be considered in patients with CIS to improve local control and reduce the incidence of progression.

There is no evidence to define the best regimen for intravesical BCG. Current practice is:⁶⁴⁻⁶⁶

- induction: weekly for six weeks
- maintenance: weekly for three weeks at week 12
- further maintenance in complete responders: weekly for three weeks every six months.

There is some evidence to suggest that widespread CIS does not respond to radiotherapy.^{62,67}

4.6.2 G3pT1/G3pTa TUMOURS

The management of patients with G3pT1/G3pTa tumours is controversial, varying from repeated intravesical treatment to early cystectomy.

There is no evidence from RCTs to suggest an optimal management strategy for patients with G3pT1/G3pTa tumours, although a retrospective cohort study reports a 77% response rate to BCG, but with a recurrence rate of 28%, and progression to muscle invasive (pT2-4) disease in 10% of patients.⁶⁸

Some patients may be cured following complete TURBT but prognosis after recurrence is poor. Progression to muscle invasive disease (pT2-4) has been reported in 40% of patients.⁶⁹ Close follow up and early definitive treatment is common practice although some practitioners advocate immediate cystectomy.

Some authorities recommend re-resection of the base of the tumour 6-12 weeks after the initial resection.⁷⁰ This may reveal residual tumour and identify patients for whom more aggressive treatment is needed. Reports of this procedure are anecdotal and evidence that it will improve outcome is lacking. Re-resection may be indicated in cases where there has been insufficient material for the pathologist to stage the disease.

Initial results from the Medical Research Council (MRC) trial BS06,⁷¹ suggest that radiotherapy is not effective in reducing progression to muscle invasive cancer and cystectomy should be considered.⁷²

One study retrospectively compared patients treated with TURBT alone against those treated with TURBT and BCG.⁷³ There was a significant reduction in recurrence and increase in time to progression and survival in the group treated with BCG but the study was not randomised and the results may be biased.

2+

- If a G3pT1 tumour is diagnosed or suspected complete resection should be attempted
 - If pathological depth of invasion cannot be assessed in patients with G3pT1/G3pTa tumours re-resection should be attempted.
 - The role of BCG after complete resection is unclear but it does have a role to play in patients with multifocal and recurrent disease.
 - For patients with persistent or recurrent disease cystectomy should be offered.

4.7 PROGRESSION TO MUSCLE INVASIVE DISEASE (pT2-4)

Muscle invasion is associated with poorer prognosis, inevitable local progression and increased chance of developing metastases. Accurate prediction of progression to muscle invasion would facilitate curative treatment while the disease remains superficial.

4.7.1 PREDICTORS OF MUSCLE INVASION

The following biological markers have been assessed as predictors of progression to muscle invasion:

- deoxyribonucleic acid (DNA) index⁷⁴
- synthesis (S-) phase fraction⁷⁵
- p53 expression^{76,77}
- retinoblastoma (Rb) nuclear protein.⁷⁸

At present, none of these biological markers predict muscle invasion reliably enough to advocate their routine use.

4.7.2 PREDICTORS OF PROGRESSION

In a retrospective analysis of patients with pTa and pT1 disease the following were found to be statistically significant risk factors for progression to muscle invasion (pT2 or greater) on univariate analysis:⁷⁹

- presence of irritative symptoms
- positive urine cytology
- higher tumour stage (pT1)
- bladder neck involvement
- high tumour grade (G3).

On multivariate analysis independent risk factors were:⁷⁹

- bladder neck (presence versus absence)
- tumour stage (pT1 versus pTa)
- tumour grade (G3 versus G1-2).

No single variable was useful in predicting individual tumour progression. For people with a combination of two or three of these risk factors (high risk), the five and 15-year progression rates were 27.1% and 42.7% respectively compared to 4.6% and 20.1% for patients with one risk factor (intermediate risk) and 0.8% and 4% for patients with none of the risk factors (low risk).⁷⁹

2+

- Patients at high risk of recurrent disease should be monitored more frequently than those at low or intermediate risk.

Muscle invasive tumours (pT2-4) are at high risk of progression to more advanced disease. Superficially invasive (pT1) tumours have a lower risk, but the risk depends on the depth of invasion into the lamina propria. Although there is evidence that subclassification (microstaging) of superficially invasive (pT1) tumours has prognostic significance, the Union Internationale Contre le Cancer (UICC) does not subclassify pT1 and two systems of microstaging are currently in use (see Annex 4).

Patients with pT1a tumours have a better prognosis, as the characteristics of these tumours are often similar to pTa tumours. pT1c tumours are more aggressive and may lead to a prognosis similar to that of patients with pT2a tumours.

There is evidence from two cohort studies that an assessment of microinvasion is predictive of recurrence, with pT1b tumours having a significantly greater recurrence than pT1a.^{80,81}

2+

- C** **Routine pathological reporting should include microstaging of pT1 disease, where possible.**

- Training should be available for pathologists to become competent in microstaging.

5 Surgical treatment

5.1 IMAGING FOR STAGING OF INVASIVE DISEASE

Imaging plays a central role in the staging of bladder cancer and in the evaluation of response to treatment. Accurate appreciation of tumour stage is essential for prediction of prognosis and for planning appropriate treatment. Imaging improves accuracy, providing information about extension of tumour into perivesical fat, adjacent organs and local lymph nodes.⁸²

CT (computerised tomography) and MRI (magnetic resonance imaging) are the cross-sectional imaging techniques currently used to provide a radiological stage for bladder tumours. Both modalities are widely available in Scotland. CT scanning is better tolerated by patients because it requires shorter scanning times and is less likely to cause claustrophobia.⁸³ The development of multislice CT has dramatically improved the speed of scanning and allows multiplanar imaging. Older generation scanners allowed quality imaging in the axial plane only, which is a disadvantage compared to MRI. There has been no comparison of multislice CT scans with MRI.

MRI scanning is time consuming and requires a cooperative patient. The drawbacks of this are offset by improved spatial and contrast resolution. It may not be possible to image certain patients, such as those with claustrophobia and those with metallic implants/pacemakers, by this technique.

There is evidence that MRI is more accurate than older generation axial CT in terms of identifying extension of tumour through the bladder wall and involvement of adjacent organs.⁸⁴ Neither technique is able to identify tumours within normal sized lymph nodes. CT and MRI are comparable for the assessment of distant metastatic disease, although MRI will identify metastatic disease to bone with greater sensitivity than CT.⁸⁴

2+

Increasingly, the chest and whole abdomen are included in CT scans, but there is no evidence to support this practice.

C Patients with muscle invasive bladder cancer should have cross-sectional imaging prior to treatment.

C MRI is the best staging modality to assess invasion into or through bladder muscle.

Difficulty in distinguishing between tumour, oedema and fibrosis following biopsy can occur. For this reason, cross-sectional imaging should take place prior to tumour resection.⁸⁵

Cross-sectional imaging should take place prior to tumour resection.

5.2 RADIOTHERAPY AND CYSTECTOMY FOR PATIENTS WITH MUSCLE INVASIVE DISEASE

Radical cystectomy is the treatment of choice for muscle invasive bladder cancer in many countries, but many UK centres have favoured radiotherapy with salvage cystectomy for treatment failure.⁸⁶ There have been no randomised controlled trials comparing radical radiotherapy with radical cystectomy alone. There remains a lack of evidence for the overall superiority of surgery or radiotherapy. Performance status, comorbid factors, tumour grade and stage all influence the choice of treatment.

There has been much interest in organ sparing techniques using combinations of radiotherapy and chemotherapy along with planned salvage cystectomy. Comparison of different studies is difficult because many include one or more different surgical techniques, preradiotherapy, neoadjuvant, concomitant and adjuvant chemotherapy.

A meta-analysis of three RCTs comparing cystectomy following preoperative radiotherapy with radiotherapy alone suggested that cystectomy had a survival advantage over radical radiotherapy with salvage cystectomy (five year survival; 36% versus 20%).⁸⁷ The trials were small and took place before recent advances in radiotherapy and surgery. In addition, many patients did not receive the treatment to which they were randomised.

1+

Several large cohort studies had an overall five year survival rate of 60% after radical cystectomy.⁸⁸⁻⁹¹ There was some selection bias in these reports. Most include patients with high risk superficial TCC (pT1, G3 and Tis) who will have good prognosis and will bias comparisons with radiotherapy series that may not include such patients.

2+

In these series, there was often an attempt to completely resect the tumour prior to the cystectomy and a meticulous lymph node dissection was performed. These techniques may have contributed to the high disease-free survival rates.⁸⁸⁻⁹¹

There are relatively few contemporary radiotherapy studies. Observational studies indicate that five year survival of patients treated with radiotherapy is between 30% and 50%, with a salvage cystectomy rate of around 20%.^{86,92-95} Different selection criteria from surgical series, which may include more patients with favourable prognosis, invalidate direct comparison.

2+

5.2.1 RELATIVE INDICATIONS FOR RADICAL CYSTECTOMY

In the absence of high level evidence comparing the outcome of radiotherapy with surgery the most appropriate treatment has to be selected on an individual basis. Cystectomy is usually indicated in the following situations:

- high-risk superficial tumours (pT1, G3 and CIS)
- extensive papillary G1, G2 disease that cannot be controlled by conservative measures
- salvage cystectomy for post-radiotherapy/chemotherapy relapse
- patient preference
- severe bladder symptoms.

Contraindications for radical cystectomy are:

- advanced disease (T4b or distant metastases)
- patient unfit for major surgery
- patient preference.

5.2.2 RELATIVE INDICATIONS FOR RADICAL RADIOTHERAPY

Patients unfit for surgery may be considered suitable for radical radiotherapy. For patients who are treated with radical radiotherapy, the following are indicators of a good response to radiotherapy:⁹⁶

- younger patients
- low volume organ confined disease (T2/3)
- prior complete macroscopic resection of exophytic tumour
- high grade tumours.

Patients with large volume disease, symptomatic CIS or non-invasive disease may not respond well to radiotherapy.

Either radiotherapy or cystectomy is an option for:

- muscle invasive bladder cancer with no distant metastasis (T2-T4a, N0-N1, M0).

Salvage cystectomy can result in long term survival in some patients, but there is a lack of evidence on both ideal timing of cystoscopy post-radiotherapy and optimal timing of surgery.

- ☑ The choice of primary treatment for muscle invasive bladder cancer should be taken after the patient has been fully counselled on the short and long term risks and benefits of surgery and radiotherapy.
- ☑ Patients should be offered modern radiotherapeutic techniques, for example, conformal radiotherapy.
- ☑ Salvage cystectomy should be offered to those patients who have local recurrence after radiotherapy if they are fit for surgery.
- ☑ Meticulous surgical technique with complete lymph node dissection should be carried out at the time of radical cystectomy.
- ☑ Patients should have good postoperative care in a high dependency or intensive care unit.
- ☑ Preoperative radiotherapy for muscle invasive (pT2-4) bladder cancer is not recommended.
- ☑ Patients should have access to a stoma therapist for advice and counselling prior to cystectomy.

5.2.3 PATHOLOGICAL EXAMINATION OF CYSTECTOMY SPECIMENS

The resected bladder must undergo pathological assessment of the extent of disease. This is facilitated by inflating the specimen with formalin fixative when the specimen is fresh. If the bladder is allowed to fix in an uninflated state, the tumour is often difficult to locate, and autolytic changes may preclude histological interpretation.⁹⁷

- ☑ The bladder should be inflated with formalin as soon as it is removed from the patient.

5.3 INDICATIONS FOR REMOVAL OF THE URETHRA

The overall risk of recurrent transitional cell carcinoma in the anterior urethra following radical cystectomy is 10% after total cystectomy and external urinary division.⁹⁸ The risk is higher in patients with multifocal tumours.⁹⁸ 2+

The risk of anterior urethral recurrence in patients receiving radical radiotherapy for TCC of the bladder is much lower at 3.1%, (4.7% if the prostatic urethra is included)⁹⁹ which is comparable to that reported after orthotopic bladder reconstruction (2.9%).¹⁰⁰ 2+

- C Urethrectomy should be performed in high-risk patients having cystectomy and urinary diversion.**

Although a protective effect of the passage of urine has been postulated,¹⁰⁰ it remains unclear why urethral recurrence in patients may be reduced following orthotopic reconstruction or after radiotherapy.

There is evidence from one cohort study that a frozen section biopsy of the urethral margin during cystoprostatectomy and orthotopic reconstruction appears to accurately predict urethral recurrence.¹⁰¹ There is no evidence of recurrence after a 10 year minimum follow up in those patients with negative frozen section biopsies. Endoscopic biopsies from the prostatic urethra before cystectomy appeared to be less accurate at determining urethral recurrence.¹⁰¹ A retrospective series reported that the overall risk of urethral recurrence after orthotopic reconstruction was 4% at five years and 11% if the prostate was involved.¹⁰²

2+

C If frozen section biopsies of the urethral margin are negative the urethra can be preserved for orthotopic reconstruction.

Patients having orthotopic reconstruction should be made aware of the possible long term risks of urethral recurrence.

Due to the risk of recurrence, long term endoscopic follow up is advised for all patients where anterior urethrectomy has not been performed.

5.4 INDICATIONS FOR REMOVAL OF THE LYMPH NODES

There are no randomised controlled trials comparing radical cystectomy and pelvic lymph nodes dissection (PLND) with radical cystectomy alone. A number of cohort studies suggest that a more complete node dissection will improve survival and that some patients with positive nodes can be cured.¹⁰³⁻¹¹⁰

These studies emphasise the need for meticulous dissection of all pelvic lymph nodes to identify all positive nodes. As these patients are more accurately staged, comparison with other studies of incomplete PLND may be invalid.

The prognosis following PLND is indicated by the ratio of positive nodes to the total number of nodes removed. If the ratio is less than 20% there is a 60% five year survival. This compares to a 5% five year survival if the ratio is greater than 20%.¹⁰⁶ In a large retrospective study, the ten year survival was 43% compared to 17%.¹¹¹ The overall recurrence free survival at five years for lymph node positive disease was 35%, reflecting a potential survival advantage from attempting a complete PLND.¹¹¹

2+

There is no agreement on the ideal number of lymph nodes that should be retrieved. One study found that removing nine or more nodes from patients with positive nodes was associated with a significant survival difference (39% five year survival compared to 16% for removal of eight or fewer nodes).¹⁰⁵

2+

In a multicentre cohort study considering standardisation of surgical treatment it was recommended that a median of 10 to 14 nodes should be examined.¹¹²

2-

An extension of the normal limits of PLND up to the aortic bifurcation has been postulated to improve survival in patients with organ confined disease.¹⁰⁸ In a prospective multicentre study of extended PLND to above the aortic bifurcation the mean total number of nodes removed from patients with bladder cancer was 43.1 ± 16.1 and nodal metastases were present in 27.9% of patients.¹¹³ Of the patients who had pelvic nodal metastases 31% had positive nodes at the level of aortic bifurcation or above. Extended PLND takes longer to perform than PLND, but the subsequent cystectomy procedure may be more straightforward.^{105,106,108,113}

2+

Patients have also been shown to frequently develop nodal metastases on the side of the pelvis contralateral to the tumour and therefore all patients require bilateral dissection.^{107,113}

2+

There is no evidence that PLND or extended PLND leads to increased morbidity.^{105-111,113,114}

2+

C All patients having curative radical cystectomy should have bilateral pelvic lymph node dissection.

There is a body of evidence suggesting that to identify all positive nodes, lymph node dissection should be meticulous and thorough, and include all the external iliac, obturator and hypogastric nodes from both sides.^{105,106,108,113}

2+

C A meticulous lymph node dissection should be performed for retrieval of the maximum number of nodes.

- Lymph node dissection should include three main node groups from the external iliac, obturator and hypogastric nodes. Boundaries are:
 - the distal common iliac vessels superiorly
 - the genitofemoral nerve laterally
 - the inguinal ligament distally
 - the bladder wall medially.

Dissection in separate groups rather than an en-bloc resection (where en-bloc refers to lymph nodes and bladder or all of the nodes on one side of the pelvis taken together) appears to make pathological identification easier and increases the total number of lymph nodes retrieved for examination.¹¹⁵

2+

- The lymph node groups should be submitted separately for pathological examination.

5.5 BLADDER RECONSTRUCTION

Bladder reconstruction or orthotopic neobladder, as an alternative to ileal loop conduit or continent cutaneous diversion following radical cystectomy, has been adopted by large specialised cancer centres in the USA and Europe as the procedure of choice in selected patients.^{114,116-121}

As well as improving daily living and body image, the main advantage of bladder reconstruction is the absence of an ileal loop stoma and the associated frequent long term complications.¹²² The disadvantages include risk of nocturnal leakage and failure of voiding requiring catheterisation or intermittent self catheterisation.¹²³

There are no prospective randomised controlled trials comparing methods of diversion after radical cystectomy.

Quality of life studies show no major differences between ileal loop conduit and neobladder construction.^{124,125} The perceived advantages in daily living on the image and social function in patients receiving neobladder treatment have not been identified in these studies. There are specific problems arising from each type of diversion used, for instance, stoma care issues compared to nocturnal incontinence in patients with neobladder.

2+

Cohort studies considering morbidity and long term function report continence in 67% to 88% of patients during the day and 40% to 78% of patients at night. The early complication rate is between 20% and 30% of patients and late complications occur in 30% of patients, often caused by uretero-enteric and vesico-urethral strictures.^{114,116,117} Continuing technical modifications may lead to better continence rates.¹¹⁷

2+

Orthotopic diversion does not appear to compromise cancer control. There is no difference in cancer-specific survival¹²⁰ or pelvic tumour recurrence¹²⁶ in patients with orthotopic diversions.

2+

Reconstruction has been mainly performed in male patients. In female patients there is a risk of neobladder-vaginal fistula and of urethral recurrence. With careful selection, good functional results and negative surgical margins can be achieved, with vaginal and pelvic nerve sparing to maintain pelvic support.^{127, 128}

2+

Considerable experience in reconstruction in male patients is appropriate before embarking on the procedure in females.

C Where appropriate, patients should be given the option of bladder reconstruction after radical cystectomy.

Reconstruction is considered inadvisable for patients with:

- significant comorbidity^{116,129}
- metastatic disease^{116,120,129}
- positive urethral margin biopsies^{116,117,120,129}
- chronic bowel disease¹¹⁷
- voiding re-education concerns^{116,117,129}
- renal failure.¹¹⁷

6 Non-surgical treatment

6.1 PHOTODYNAMIC TREATMENT

Photodynamic treatment (as opposed to use of fluorescence as a diagnostic aid, (see section 4.2) with different photosensitisers and wavelengths of light has been used to treat otherwise uncontrollable superficial tumours, particularly CIS. Observational studies have shown eradication of CIS that are resistant to conventional treatment such as intravesical BCG. The studies involve small numbers of patients and different techniques regarding photosensitisers and type of light used.¹³⁰⁻¹³² There are no randomised studies and there is insufficient evidence to recommend routine use of photodynamic therapy.

6.2 RADIOTHERAPY

6.2.1 CONVENTIONAL RADIOTHERAPY

There are no RCTs investigating radical radiotherapy dose, fractionation and schedules. It is not possible to identify an optimal conventional radiation dose or fractionation scheme. Although CT based radiotherapy planning has improved target localisation, it is not possible to determine an optimal radiation technique.¹³³ It is unclear whether pelvis and bladder should be treated or bladder alone. Ongoing clinical trials may address the value of partial bladder versus whole bladder radiotherapy.¹³⁴

Individual case series from institutions reporting radical radiotherapy as monotherapy are available but must be interpreted with caution in view of potential case selection.⁹²

Commonly used radical radiotherapy schedules include:

- 50-55Gy in 20 fractions
- 64-66Gy in 32-33 fractions.

- A radical course of radiotherapy requires a minimum dose of 50Gy in 20 fractions over four weeks or 64Gy in 32 fractions if treating over 6.5 weeks.

6.2.2 ACCELERATED RADIOTHERAPY

There is evidence to suggest rapid repopulation of bladder cancer by surviving clonogens during radiotherapy.¹³⁵

An overview of two small RCTs including some bladder cancer patients treated with accelerated hyperfractionation suggested that accelerated shortened radiotherapy schedules may improve survival.¹³⁶

A recent UK run multicentre randomised phase III trial failed to demonstrate improved survival using 60.8Gy in 32 fractions over 26 days (two fractions per day) compared to 64Gy in 32 fractions in 45 days (one fraction per day).¹³⁷ Acute bowel toxicity was significantly increased with accelerated fractionation.

The value of accelerated radiotherapy in bladder cancer remains unclear and requires further evaluation.

6.2.3 CHEMO-IRRADIATION

A number of phase II studies have reported improved local control and survival using chemotherapy concurrently with radiation.^{86,138-141}

1+

6.2.4 PALLIATIVE RADIOTHERAPY

An RCT comparing 21Gy in three fractions over seven days with 35Gy in ten fractions over two weeks provided evidence to support the use of a shorter, potentially more convenient fractionation scheme without reducing efficacy.¹⁴²

1+

B Radiotherapy using 21Gy in three fractions in one week should be considered for palliation of patients with bladder cancer.

6.3 CHEMOTHERAPY

6.3.1 NEOADJUVANT CHEMOTHERAPY

A meta-analysis of neoadjuvant chemotherapy prior to radical therapy for patients with TCC of the bladder considered all the published RCTs on single agent and combination chemotherapy.¹⁴³

There is strong evidence to support the use of neoadjuvant chemotherapy before definitive radical therapy for patients with T2-T4 TCC of the bladder.¹⁴³ There was a 13% reduction in risk of death (hazard ratio 0.87; 0.78-0.97; $p=0.016$). This translates into a survival advantage of 5% at five years for patients with T2-T4 disease regardless of local therapy given.

1++

A Neoadjuvant chemotherapy should be offered to suitable patients prior to definitive radical therapy for patients with T2-T4 transitional cell carcinoma of the bladder.

The best regimen and precise number of cycles to use prior to definitive local therapy remains unclear but cisplatin-based combination chemotherapy is better than single agent cisplatin. Two to three cycles of cisplatin-based combination chemotherapy appears to be an acceptable minimum.¹⁴⁴

1++

A A combination chemotherapy regimen containing cisplatin should be used.

Common chemotherapy regimens include:

- gemcitabine + cisplatin (GC)
- cisplatin + methotrexate + vinblastine (CMV)
- methotrexate + vinblastine + doxorubicin + cisplatin (MVAC).

There is no evidence from RCTs to determine the best cisplatin combination to use in the neoadjuvant setting.

- Clinical judgement is required to assess the risks and benefits of prescribing chemotherapy
- The choice of chemotherapy should be based on local experience and expertise
- In elderly patients or in those with significant comorbid illness treatment related toxicity may outweigh any advantages to chemotherapy
- An informed discussion with patients of the aims, benefits and toxicity of treatment is required before therapy begins.

Various treatment strategies have been described where chemotherapy is used to select definitive treatment, for example, bladder preserving radiotherapy in complete responders and cystectomy in non-responders.¹⁴⁵ This is an area that requires further research.

6.3.2 ADJUVANT CHEMOTHERAPY

There is no evidence to support the use of adjuvant chemotherapy in patients with locally advanced disease. Ongoing clinical trials will help to address this.¹⁴⁶ A meta-analysis of the use of adjuvant chemotherapy is required to clarify survival advantage in view of the lack of power of the studies reported.

Patients given MVAC chemotherapy either neoadjuvantly or adjuvantly following cystectomy for high-risk disease demonstrated improved survival over historical controls. Toxicity was greater in those patients treated adjuvantly. A good response to neoadjuvant chemotherapy predicted improved survival. 2+

Patients at high risk of relapse following cystectomy are the group most likely to receive benefit from adjuvant chemotherapy and should be entered into appropriate clinical trials. Such patients may include those with:

- node positive disease¹⁴⁷
- T3/T4 disease,¹⁴⁷ especially if surgical margins are positive, and grade 3 disease
- lymphovascular invasion.¹⁴⁸

Adjuvant chemotherapy should be given within the context of a clinical trial.

Where entry into a clinical trial is not possible, some patients might wish to discuss the possibility of adjuvant treatment. Patients should be clearly informed of the lack of evidence to support its use.

The best chemotherapy regimen is not known.

There is no evidence to indicate a significant survival advantage of adjuvant chemotherapy over deferred palliative chemotherapy at relapse.

7 Information for discussion with patients and carers

7.1 KEY MESSAGES FROM PATIENTS

A literature review identified few papers on the experiences of patients with bladder cancer. Patient views were gathered in two ways:

- a focus group of ten patients from one multidisciplinary clinical team, held in Glasgow in November 2003, including patients with varying stage and grade of disease, and at least one man who had undergone cystectomy
- simple questionnaires and reply paid envelopes were distributed at a meeting of the only UK support group for bladder cancer patients and their families in Milton Keynes in December 2003. The support group is open to anyone who has had treatment for bladder cancer so the respondents may have or have had cancer at various stages. Six questionnaires were returned (12% response rate).

Referral

Most patients were reassured by a decisive and quick referral by their GP to a specialist unit and welcomed being told about the suspected problem and what the initial treatment could be. Anxiety was caused by symptoms such as cystitis, nasty smelling urine and blood in the urine without knowing the underlying cause.

Diagnosis

Patients wanted their diagnosis as soon as possible and also information about treatment at that time rather than waiting for a later appointment. Patients found administrative delays particularly frustrating. Specialist nurses were highly valued, particularly from the point of view of having time to discuss care plans, answer questions and “chat”. There were mixed views about the use of the word “cancer” during diagnosis. Some patients felt that they were not receiving useful literature because it described cancer and others just wanted to know whether they had cancer. For others a diagnosis of cancer was very shocking.

Treatment

Patients were keen to understand their treatment but still some felt unprepared for the discomfort of the treatment, for example, difficulties urinating, after endoscopy.

Follow up

Most patients welcomed follow-up appointments and cystoscopies with their consultant to be reassured that they are still “clear” and that recurrences would be picked up. One patient felt that being defined as a “bladder cancer patient” ensured that he was not lost in the system.

Support

The Milton Keynes support group was highly praised. Patients enjoyed being involved in a worthwhile organisation. In the Glasgow focus group, there was a much lower level of knowledge about support groups and a reluctance to participate in them.

7.2 INFORMATION REQUIREMENTS

Bladder cancer represents a spectrum of disease, ranging from relatively benign superficial tumours, some of which may never recur, to highly malignant life threatening carcinomas for which radical treatment is needed. Because of the risk of recurrence of superficial disease and the danger that some may progress, all these tumours are correctly classified as “carcinomas”. The use of terms like “warts”, which imply benign disease, in informing patients of their condition and prognosis, is no longer considered appropriate. The survival of patients with Ta G1/G2 is similar to that of an age and sex matched control population. The use of the word “cancer” in discussing the diagnosis with the patient must be carefully qualified, to avoid giving patients with superficial, well differentiated disease an over-pessimistic impression.

In most types of cancer, treatment demands early follow up, which provides an opportunity for patients to receive information about their condition. In superficial bladder cancer, after the presenting tumour has been treated, as far as disease management is concerned, no further action is needed until the first check cystoscopy, which is usually at three months. Full prognostic information depends on the pathology report following the resection, which may not be available while the patient is under treatment (usually during a short admission or as a day patient). There is a definite risk that patients with superficial bladder cancer will be left without adequate support and information unless specific provision is made.

- Information given to patients at time of diagnosis should be appropriate to the stage of disease.
- Units managing bladder cancer should ensure that patients are offered an early appointment with a uro-oncology clinical nurse specialist, to discuss the findings and receive prognostic information and appropriate counselling.
- Patients should be made aware of ongoing clinical trials with a view to participation.

7.3 SUPPORT NEEDS OF PATIENTS, FAMILIES AND CARERS

Patients diagnosed with cancer for the first time often want information addressing their immediate concerns regarding their disease, treatment options, what they might expect during return appointments and who to go to for information.

Four studies indicate that cancer patients want information on their treatment and prognosis.¹⁴⁹⁻¹⁵² Patients prefer to receive written information to assist in making an informed choice.¹⁵⁰ 2+

A cohort study carried out in the West of Scotland highlighted that cancer patients want to know the medical name of their illness, their treatment choices, how treatments work, the likely side effects and chances of cure.¹⁵² 2+

Evidence was identified in relation to the information and support needs of cancer patients.^{41,152-160} None of the studies was specific to patients with bladder cancer but were generalisable to the bladder cancer population. The number of participants in the trials varied from 36 to 525 and the groups were heterogeneous. The interventions studied included structured emotional support, relaxation techniques, the use of audiocassette recordings of consultations, orientation programmes and general psychological and emotional support. The interventions reduced anxiety levels and improved quality of life. 1+

- C** Patients should be offered verbal and written information throughout their journey of care and should be made aware of the support mechanisms that are in place and how to access them.
- C** Structured emotional support should be available to all patients and carers.
- Patients should get support from appropriate members of the multidisciplinary healthcare team.
- Voluntary sector agencies can be used to expand the levels of support available to patients and carers.

7.4 METHODS AND SOURCES OF COMMUNICATION

Complaints from cancer patients about poor communication with healthcare professionals and lack of continuity of care are common. There is evidence that training programmes for nurses can improve listening and communication skills.¹⁶¹ Although the included trials were small and heterogeneous, one systematic review has suggested that providing a record of the consultation with a specialist can increase both the amount of information recalled and satisfaction with the information given.¹⁵² One randomised trial showed that patients preferred information based on their own medical records rather than general information about their type of cancer.¹⁵⁶

1+

B Healthcare professionals in cancer care should be trained in listening and communication skills.

B Healthcare professionals in cancer care should consider giving either written summaries or audiotapes of consultations to people who have expressed a preference for them.

7.5 SOURCES OF FURTHER INFORMATION FOR PATIENTS AND CARERS

7.5.1 ORGANISATIONS SPECIFIC TO BLADDER CANCER

Milton Keynes Bladder Cancer Support Group

Milton Keynes General Hospital, Standing Way, Eaglestone
Milton Keynes MK6 5LD
Tel: 01908 243 131

Urology Nurse Practitioner-led support group for people with bladder cancer and their families. Provides patient information, telephone helpline, patient to patient contacts and a three monthly newsletter.

7.5.2 NATIONAL ORGANISATIONS RELATED TO CANCER

CancerBACUP Scotland

Suite 2, Third Floor, Cranston House, 104/114 Argyle Street
Glasgow G2 8BH
Tel: 0141 223 7676/0808 800 1234 • Fax: 0141 248 8422
www.cancerbacup.org.uk

A free one to one counselling service which provides counselling and emotional support for people with cancer and their families and friends. Produces BACUP NEWS three times a year and has over 50 published booklets.

Cancer Link Aberdeen and North (CLAN)

Cancer Support Centre, Clan House, Caroline Place
Aberdeen AB25 2TH
Tel: 01224 647 000 • Freephone: 0800 783 7922
www.clanhouse.org • Email: clan@btinternet.com

Provides emotional support and information through a team of volunteers trained in listening skills; CLAN counsellors, with their personal experience of cancer, provide the opportunity to talk with someone who cares and understands.

Cancer Research UK Scotland

Federation House, 222 Queensferry Road
Edinburgh EH4 2BN
Tel: 0131 343 1344
www.cancerresearchuk.org

Macmillan Cancer Relief (Scotland)

Osborne House, 1-5 Osborne Terrace
 Edinburgh EH1 2DP
 Tel: 0131 346 5346 • Fax: 0131 346 5347
 www.macmillan.org.uk • Email: agow@macmillan.org.uk

The Scottish office of the UK charity, which supports people with cancer and their families with specialist information, treatment and care.

Maggie's Centres Scotland

www.maggiescentres.org • Email: maggies.centre@ed.ac.uk

The aim of Maggie's Centres is to help people with cancer to be as healthy in mind and body as possible and enable them to make their own contribution to their medical treatment and recovery.

Maggie's Edinburgh

The Stables, Western General Hospital, Crewe Road South
 Edinburgh EH4 2XU
 Tel: 0131 537 3131 • Fax: 0131 537 3130

Maggie's Glasgow

The Gatehouse, Western Infirmary, 10 Dumbarton Road
 Glasgow G11 6PA
 Tel: 0141 330 3311 • Fax: 0141 330 3363

Maggie's Dundee

Tom McDonald Avenue, Ninewells Hospital
 Dundee DD2 1ZV
 Tel: 01382 632 999 • Fax: 01382 632 998

Marie Curie Cancer Care (Scotland)

29 Albany Street
 Edinburgh EH1 3QN
 Tel: 0131 456 3700 • Fax: 0131 456 3701
 www.mariecurie.org.uk

Marie Curie Cancer Care, a comprehensive cancer care charity, provides practical nursing care at home and specialist multidisciplinary care through its ten Marie Curie Centres.

Tak Tent Cancer Support Scotland

Flat 5, 30 Shelley Court, Gartnavel Complex
 Glasgow G12 0YN
 Tel: 0141 211 0122 • Fax: 0141 211 3988
 www.taktent.org.uk • Email: tak.tent@care4free.net

Promotes the care of cancer patients, their families, friends and the staff involved professionally in cancer care by providing practical and emotional support, information, counselling and therapies as required. Network of local support groups throughout Scotland. Youth Project started for 16-25 year olds to provide support.

7.5.3 NATIONAL ORGANISATIONS

ASH Scotland

8 Frederick Street
 Edinburgh EH2 2HB
 Tel. 0131 225 4725 • Fax. 0131 220 6604
 Email: ashscotland@ashscotland.org.uk

ASH Scotland is the leading voluntary organisation campaigning for effective tobacco control legislation and providing an expert information service.

Smokeline and Tobacco unwrapped

Tel: 0800 848484
www.hebs.org/topics/smoking/index.htm

Advice and support on giving up smoking.

NHS Health Scotland

Edinburgh Office
 Woodburn House, Canaan Lane
 Edinburgh EH10 4SG
 Tel: 0131 536 5500 • Textphone: 0131 536 5503 • Fax: 0131 536 5501

Glasgow Office
 Clifton House, Clifton Place
 Glasgow G3 7LS
 Tel: 0141 300 1010 • Fax: 0141 300 1020
www.healthscotland.com

Health Scotland provides a national focus for improving health, working with the Scottish Executive and other key partners to take action to improve health and reduce inequalities in Scotland.

Urostomy Association

Hazel Pixley, National Secretary, Central Office, 18 Foxglove Avenue
 Uttoxeter, Staffs. ST14 8UN
 Tel: 0870 770 7931 • Fax: 0870 770 7932
www.uagbi.org • Email: secretary.ua@classmail.co.uk

7.5.4 OTHER USEFUL RESOURCES

DIPex (Database of individual experiences)

www.dipex.org/main.asp

DIPex is a website that reports on a wide variety of personal experiences of health and illness. People can watch, listen to or read interviews, find reliable information on treatment choices and where to find support. The site covers heart disease, epilepsy, screening programmes and cancers.

8 Implementation and audit

8.1 LOCAL IMPLEMENTATION

Implementation of national clinical guidelines is the responsibility of local NHS organisations and is an essential part of clinical governance. It is acknowledged that not every guideline can be implemented immediately on publication, but mechanisms should be in place to ensure that the care provided is reviewed against the guideline recommendations and the reasons for any differences assessed and, where appropriate, addressed. These discussions should involve both clinical staff and management. Local arrangements may then be made to implement the national guideline in individual hospitals, units and practices, and to monitor compliance. This may be done by a variety of means including patient-specific reminders, continuing education and training, and clinical audit.

8.2 KEY POINTS FOR AUDIT

A Scottish National Core Data Set for urological cancers is available from Information Services, NHS National Services Scotland (www.isdscotland.org).

The aim of this dataset is to collect data for multiple purposes, such as audit of waiting times and implementation of SIGN recommendations.

Audit should be directed towards clinically important key recommendations regardless of their level of evidence (*see section 1.3*).

8.3 RESOURCE IMPLICATIONS

Group members identified three recommendations in the guideline which have resource implications for NHSScotland.

From section 4.2:

B Fluorescence cystoscopy under blue/violet light (wavelength 400 nm) which causes tumours to fluoresce red should be used to improve the completeness of resection of superficial bladder tumours.

All urology departments in NHSScotland currently treat bladder tumours, but fluorescence cystoscopy is only used in a small number of centres. Implementation of this recommendation would require capital investment in equipment, plus the continuing cost of fluorescent chemicals. There may also be costs associated with training staff in its use. It is unlikely that this recommendation could be implemented by service reorganisation alone.

From section 4.7.2:

C Routine pathological reporting should include microstaging of pT1 disease, where possible.

There is variation in the level of training and expertise in microstaging available within NHSScotland. Implementation of this recommendation would require some changes in training of junior pathologists and additional time for pathologists to undertake this work. This may have some implications for other pathology workload.

From section 6.3.1:

A Neoadjuvant chemotherapy should be offered to suitable patients prior to definitive radical therapy for patients with T2-T4 transitional cell carcinoma of the bladder.

Neoadjuvant chemotherapy prior to definitive radical treatment is not standard practice for patients with TCC within NHSScotland. Implementation of this recommendation would result in continuing revenue cost of chemotherapeutic agents and may have some implications for other oncology workload.

8.4 RECOMMENDATIONS FOR RESEARCH

- Predictive factors of tumour progression in superficial disease
- Optimal management of patients with pT1G3/pTaG3 and CIS
- RCTs of different radiotherapeutic techniques and regimens, volumes and doses
- Defining the optimal neoadjuvant chemotherapy
- The role of adjuvant chemotherapy and radiotherapy following surgery
- Selection of definitive treatment modality (if any) on the basis of response to neoadjuvant chemotherapy
- Comparison of the therapeutic effectiveness of radical cystectomy and radical radiotherapy
- The quality of life of people who have undergone radical cystectomy with bladder reconstruction compared to those having undergone radical radiotherapy
- Management of ureteric obstruction prior to definitive treatment
- Information and counselling for patients.

9 Development of the guideline

9.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations funded by NHS Quality Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in SIGN 50: A guideline developer's handbook, available at www.sign.ac.uk.

9.2 THE GUIDELINE DEVELOPMENT GROUP

Dr Grahame Howard (Co-chair)	<i>Consultant Radiation Oncologist, Western General Hospital, Edinburgh</i>
Professor David Kirk (Co-chair)	<i>Consultant Urologist, Gartnavel General Hospital, Glasgow</i>
Dr John Brush	<i>Consultant Radiologist, Western General Hospital, Edinburgh</i>
Ms Kirsty Carrie	<i>Oncology Dietitian, Beatson Oncology Centre, Glasgow</i>
Dr Dermot Gorman	<i>Consultant in Public Health, Edinburgh</i>
Dr Ken Grigor	<i>Consultant Pathologist, Western General Hospital, Edinburgh</i>
Dr Roberta James	<i>Programme Manager, SIGN</i>
Mr John MacFarlane	<i>Consultant Urologist, Queen Margaret Hospital, Dunfermline</i>
Mr Hamish Mackie	<i>Lay Representative, Edinburgh</i>
Dr Duncan McLaren	<i>Consultant Oncologist, Western General Hospital, Edinburgh</i>
Mr Stewart Orr	<i>Consultant Urologist, Monklands Hospital, Airdrie</i>
Dr Martin Russell	<i>Consultant Clinical Oncologist, Beatson Oncology Centre, Glasgow</i>
Mr Duncan Service	<i>Information Officer, SIGN</i>
Mrs Mary Squires	<i>Lay Representative, Raigmore Hospital Patients Council, Inverness</i>
Mr David Tulloch	<i>Consultant Urologist, Western General Hospital, Edinburgh</i>

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. Declarations of interests were made by all members of the guideline development group. Further details are available from the SIGN Executive.

9.3 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by the SIGN Information Officer in collaboration with members of the guideline development group.

Literature searches were initially conducted in Medline, Embase, Cinahl, and the Cochrane Library using the year range 1998-2003. The literature search was updated to cover the period up to October 2004. Key websites on the Internet were also used, such as the National Guidelines Clearinghouse. These searches were supplemented by the reference lists of relevant papers and group members' own files. The Medline version of the main search strategies can be found on the SIGN website.

9.4 ACKNOWLEDGEMENTS

SIGN is grateful to the following former members of the guideline development group and others who have contributed to the development of this guideline:

Mrs Lesley Cairns	<i>Deputy Superintendent, Beatson Oncology Centre, Glasgow</i>
Ms Eva Frigola Capell	<i>Clinical Psychologist, SIGN Visiting Fellow, Edinburgh</i>
Dr David Dodds	<i>Consultant Clinical Oncologist, Beatson Oncology Centre, Glasgow</i>
Ms Dawn Garner	<i>Cancer Manager, Lead Nurse, George Eliot NHS Trust, Nuneaton</i>
Ms Carolyn Hall	<i>Urology Nurse Specialist, Raigmore Hospital, Inverness</i>
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Ms Ailsa Stein	<i>Information Officer/Programme Manager, SIGN</i>
Ms Edi Stewart	<i>Urology-oncology Clinical Nurse Specialist, Beatson Oncology Centre, Glasgow</i>
Ms Joanne Topalian	<i>Programme Manager/Patient Involvement, SIGN</i>

9.5 CONSULTATION AND PEER REVIEW

9.5.1 NATIONAL OPEN MEETING

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for this guideline was held on 8th September 2004 and was attended by 77 representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

9.5.2 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. SIGN is very grateful to all of these experts for their contribution to the guideline.

Mr John Anderson	<i>Consultant Urological Surgeon, Royal Hallamshire Hospital, Sheffield</i>
Dr Alan Begg	<i>General Practitioner, Links Health Centre, Montrose</i>
Dr Graham Foster	<i>Consultant in Public Health Medicine, Forth Valley NHS Board, Stirling</i>
Ms Dawn Garner	<i>Cancer Manager, Lead Nurse, George Eliot NHS Trust, Nuneaton</i>
Dr Robert Huddart	<i>Senior Lecturer and Honorary Consultant in Radiotherapy and Oncology, The Royal Marsden NHS Foundation Trust, Sutton</i>
Dr Bill Mathewson	<i>Deputy Chief Director, Medical and Dental Defence Union of Scotland, Glasgow</i>
Mr Sam McClinton	<i>Chair of the Specialty Advisory Board in Urology, Royal College of Surgeons of Edinburgh</i>
Dr Ben Mead	<i>Consultant Medical Oncologist, Southampton General Hospital</i>
Dr Allan Merry	<i>General Practitioner, South Beach Surgery, Ardrossan</i>
Ms Melanie Mitchell	<i>Senior Dietitian, Aberdeen Royal Infirmary</i>
Dr Dorothy Moir	<i>Director of Public Health, Lanarkshire NHS Board, Hamilton</i>
Dr Sami Moussa	<i>Consultant Radiologist, Western General Hospital, Edinburgh</i>

Dr Morag Seywright	<i>Consultant Pathologist, Western Infirmary, Glasgow</i>
Mr Mike Wallace	<i>Consultant Urologist, Selly Oak Hospital, Birmingham</i>
Ms Susan Watt	<i>Education and Clinical Effectiveness Adviser, Royal College of Nursing, Edinburgh</i>

9.5.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline was reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows:

Professor Gordon Lowe	<i>Chair of SIGN; Co-Editor</i>
Dr Hugh Gilmour	<i>Senior Lecturer in Pathology, Royal Infirmary of Edinburgh</i>
Mr Douglas Harper	<i>Consultant Surgeon, Grampian NHS Board, Aberdeen</i>
Dr Allan Price	<i>Consultant Clinical Oncologist, Western General Hospital, Edinburgh</i>
Dr Safia Qureshi	<i>SIGN Programme Director; Co-Editor</i>
Dr Sara Twaddle	<i>Director of SIGN; Co-Editor</i>

Abbreviations

BCG	bacille Calmette-Guerin
CI	confidence interval
CIS	carcinoma in situ
CMV	cisplatin + methotrexate + vinblastine
CNS	clinical nurse specialist
COSHH	Control of Substances Hazardous to Health
CT	computerised tomography
DNA	deoxyribonucleic acid
EORTC	European Organisation for the Research and Treatment of Cancer
GC	gemcitabine + cisplatin
Gy	Gray
HSE	Health and Safety Executive
ICC	Incident Contact Centre
IVU	intravenous urography
MCN	Managed Clinical Network
MRC	Medical Research Council
MRI	magnetic resonance imaging
MVAC	methotrexate + vinblastine + doxorubicin + cisplatin
NHSQIS	NHS Quality Improvement Scotland
NICE	National Institute for Health and Clinical Excellence
NoSCAN	North of Scotland Cancer Network
OR	odds ratio
PLND	pelvic lymph nodes dissection
PSA	Prostate-Specific Antigen
Rb	retinoblastoma
RCT	randomised controlled trial
RIDDOR	Reporting of Injuries, Diseases and Dangerous Occurrences Regulations
SCAN	South East Scotland Cancer Network
SIGN	Scottish Intercollegiate Guidelines Network
TCC	transitional cell carcinoma
TUR	transurethral resection
TURBT	transurethral resection of bladder tumour
UICC	Union Internationale Contre le Cancer
WHO	World Health Organisation
WoSCAN	West of Scotland Cancer Network

Annex 1

Key Questions

Subgroup A: Superficial Cancer Management

1. What evidence is there for the most effective follow up methods for low-grade superficial bladder cancer? How often should patients be followed up and at what intervals?
2. What are the indications for intravesical therapy for superficial bladder cancer?
3. What is the evidence for the role of random biopsy in superficial disease?
4. What is the most effective management of carcinoma in situ/G3T1/G3Ta?
5. What factors predict progression to invasive disease?

Subgroup B: Patient and lifestyle issues

6. What evidence is there of patient information needs at time of haematuria and what communication methods are most effective?
7. What evidence is there that occupation, lifestyle changes (such as smoking cessation or drinking cranberry juice) affect the outcomes for bladder cancer?
8. What is the impact of case volume on patient outcomes for surgeons, pathologists, radiologists and oncologists?
9. What evidence is there for a specialist multidisciplinary approach affecting outcome (to include searches on specialist nurses, occupational therapists and physiotherapists)?

Subgroup C: Diagnosis and surgery

10. What evidence is there for the role of imaging of the upper urinary tract following diagnosis (ie not for diagnosis but for follow up)?
11. What evidence is there for the relative roles of radiotherapy and cystectomy for invasive transitional cell carcinoma?
12. What is the optimal imaging technique for staging bladder cancer (MRI/CT)?
13. What are the indications for the removal of the urethra?
14. What evidence is there for removal of the lymph nodes?
15. For which patients is bladder reconstruction appropriate?

Subgroup D: Non-surgical

16. What evidence is there for photodynamic techniques?
17. What is the most effective radiotherapy technique and regimen?
18. What is the role of adjuvant chemotherapy in locally advanced disease?
19. What are the indications for adjuvant chemotherapy or radiotherapy following cystectomy?
20. What evidence is there that waiting time affects outcome (waiting time from initial symptoms to initiating treatment)?

Annex 2

Referral of urological cancers

Section 6 (annotated) of the Scottish Referral Guidelines for Suspected Cancer,⁷ reproduced by kind permission of the Scottish Executive.

6 UROLOGICAL CANCERS

6.1 KEY POINTS

Incidence : Scotland

Prostate Approx	1,890 cases p.a	Testis Approx 200 cases p.a
Bladder Approx	950 cases p.a	Penis Approx 35 cases p.a
Kidney Approx	600 cases p.a	

Bladder/Urothelial Cancers

- 95% affect the bladder; 5% affect the upper tracts.
- 90% present with macroscopic haematuria.
- 5-10% present with microscopic haematuria.
- Both macroscopic and microscopic haematuria, when caused by a urothelial cancer, are intermittent. Repeat urine testing can be negative for haematuria in the presence of a tumour.
- Urothelial cancer is more likely in patients with microscopic haematuria if they are males, over 50 years and smokers.
- Microscopic haematuria in patients under 40 years should be considered for referral to a nephrologist, especially if there is proteinuria, hypertension or renal impairment.

6.2 UROLOGICAL CANCERS: GUIDELINES FOR URGENT REFERRAL

Urgent Referral

- Macroscopic haematuria in adults
- Swellings in the body of the testis
- Palpable renal masses.
- Solid renal masses found on imaging
- A high prostate-specific antigen (> 20ng/ml) in men with a clinically malignant prostate or bone pain
- Any suspected penile cancer.

Conditions requiring early referral

- Microscopic haematuria in adults over 40 years without obvious cause (eg urinary tract infection, menstruation, known renal or other urological disease such as calculi) on three separate occasions
- Elevated age-specific prostate-specific antigen in a man with a life expectancy greater than 10 years.

Annex 3

Grading of transitional cell carcinoma

Histopathological grading of transitional cell carcinoma following UICC/TNM classification.⁸

Grade	Definition
GX	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3-4	Poorly differentiated/undifferentiated

Annex 4

Staging of transitional cell carcinoma

Staging of transitional cell carcinoma following the criteria of the TNM.⁴

Stage	Primary tumour
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ: "flat tumour"
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades detrusor muscle:
T2a	Tumour invades superficial muscle (inner half; see <i>Figure 1</i>)
T2b	Tumour invades deep muscle (outer half; see <i>Figure 1</i>)
T3	Tumour invades perivesical tissue:
T3a	microscopically
T3b	macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate, uterus, or vagina
T4b	Tumour invades pelvic wall or abdominal wall
Stage	Regional lymph nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Single < 2 cm
N2	Single > 2-5 cm, multiple < 5 cm
N3	> 5 cm
Stage	Distant metastasis
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

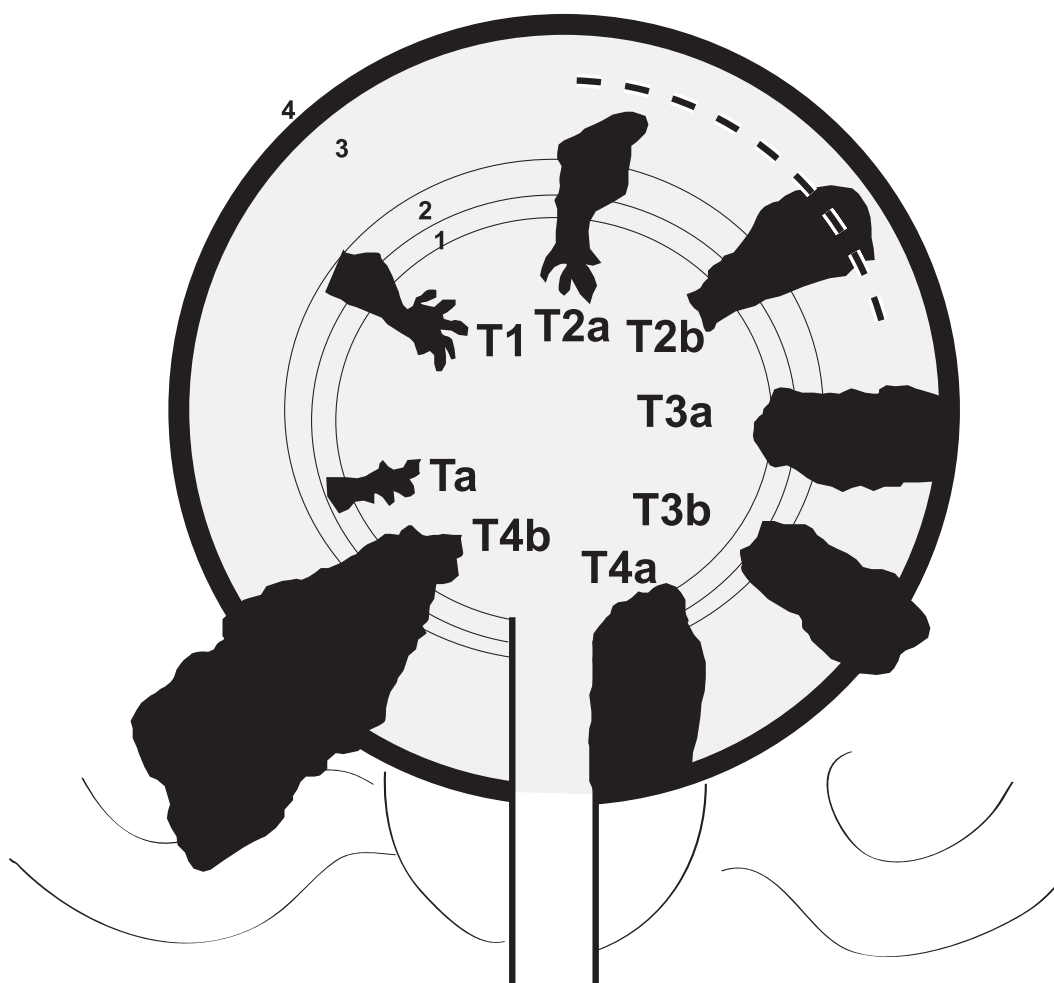
Two systems of subclassification (microstaging) of superficially invasive tumours (pT1).

Stage		Definition
System 1	System 2	
T1a	} T1a	invasion of papillary stalk but no invasion beyond the base of the tumour.
T1b		invasion into lamina propria at the base of the tumour but not into muscularis mucosae.
T1c	T1b	invasion into the muscularis mucosae, or around the thick-walled blood vessels deep in the lamina propria, but not into detrusor muscle (muscularis propria).

Figure 1

Pictorial depiction of transitional cell carcinoma staging after the TNM Atlas.⁹

1. epithelium
2. subepithelial connective tissue
3. muscle (inner and outer)
4. perivesical fat. T = pT



Annex 5

Risk factors

Risk factors for recurrence, progression and subsequent tumour development in TCCs.

Risk of recurrence

- High risk of recurrence
 - All high grade (G3) tumours and CIS
 - Large or multifocal tumours at first presentation
 - Tumours which recur at the first 3 month check cystoscopy
- Low/intermediate risk of recurrence
 - Other tumours

Risk of progression


- High risk of progression to higher stage
 - All high grade (G3) tumours and CIS
 - Muscle invasive tumours (T2-4)
- Low/intermediate risk of progression
 - Other tumours

Risk of subsequent upper tract TCC

- High risk
 - High grade (G3) tumours
 - Multifocal tumours
 - Frequently recurring tumours
- Low/intermediate risk
 - Other tumours.

Annex 6

Example of a proforma from RefHelp

Frank Haematuria Service - Referral Proforma			
DO NOT USE THIS FORM TO REFER MICROSCOPIC/DIPSTICK HAEMATURIA			
Patient Details:		Hospital Unit No:	
Date of Birth:	Age:	Address:	
CHI Number: Patient Tel No:		Postcode:	
Referring GP:		Tel:	
Practice Address (Stamp)		Fax:	
		E-mail:	
Examination			
1. Abdomen	Abdominal Mass	Yes/No	
	Other Notable Findings		
2. Investigations	MSSU	Yes/No	Result (if known)
	U&Es	Yes/No	Result (if known)
	FBC	Yes/No	Hb (if known)
	Has IVU Been Requested?	Yes/No	Date Dept Result (if known)
3. Additional Information			
Current Medication	Previous Medical History/ Allergies/Warnings		
Signature	Date: 09/12/2005		
(If sending by fax, keep signed copy of referral form in notes for medicolegal reasons)			

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LIFESTYLE ISSUES

B Smoking should be discouraged.

B People should be encouraged to:

- eat more fruit and vegetables
- reduce the amount of animal fat in their diet.

B Clinicians should be aware that previous treatments with radiotherapy and certain chemotherapy may predispose patients to transitional cell carcinoma of the bladder.

Clinicians using radiotherapy and chemotherapy treatments should do so utilising best practice to minimise any unnecessary exposure of patients.

REFERRAL

Patients with frank haematuria should be referred and investigated so that primary treatment can be started within two months if bladder cancer is diagnosed.

C For optimum survival benefit, cystectomy for muscle invasive bladder cancer should be performed within three months of diagnosis.

Care of patients with bladder cancer should be managed within a cancer network.

D Healthcare professionals should involve patients in making decisions about their treatment, if the patient expresses a wish to do so.

All patients diagnosed with bladder cancer should have access to a clinical nurse specialist for support, advice and information.

MANAGEMENT OF SUPERFICIAL BLADDER CANCER

FOLLOW UP

B Only patients with high grade tumours (including CIS) at time of diagnosis should have regular upper tract surveillance.

C Patients with a single pT_a G1/G2 tumour at the time of diagnosis and who are recurrence free at three months after the original resection should have annual cystoscopy.

INTRAVESICAL THERAPY

A A single instillation of intravesical chemotherapy should be used to reduce the risk of recurrent disease following resection in all patients considered to be at high risk of recurrence.

RANDOM BIOPSY OF NORMAL MUCCOSA

C Normal looking areas of the bladder need not be routinely biopsied at the time of diagnosis or follow up.

MANAGEMENT OF CARCINOMA IN SITU

C Patients with CIS of the bladder should be treated with BCG.

B Maintenance therapy with BCG should be considered in patients with CIS to improve local control and reduce the incidence of progression.

MANAGEMENT OF G3pT1/G3pTA TUMOURS

If a G3pT1 tumour is diagnosed or suspected complete resection should be attempted

- If pathological depth of invasion cannot be assessed in patients with G3pT1/G3pTA tumours re-resection should be attempted
- For patients with persistent or recurrent disease cystectomy should be offered.

SURGICAL TREATMENT

IMAGING FOR STAGING OF INVASIVE DISEASE

C Patients with invasive bladder cancer should have cross-sectional imaging prior to treatment.

Cross-sectional imaging should take place prior to tumour resection.

RADIO THERAPY AND CYSTECTOMY

The choice of primary treatment for muscle invasive bladder cancer should be taken after the patient has been fully counselled on the short and long term risks and benefits of surgery and radiotherapy

- Salvage cystectomy should be offered to those patients who have local recurrence after radiotherapy if they are fit for surgery
- Patients should have access to a stoma therapist for advice and counselling prior to cystectomy.

INDICATIONS FOR REMOVAL OF THE URETHRA

C Urethrectomy should be performed in high risk patients having cystectomy and urinary diversion.

INDICATIONS FOR REMOVAL OF THE LYMPH NODES

C All patients having curative radical cystectomy should have bilateral pelvic lymph node dissection.

C A meticulous node dissection should be performed for retrieval of the maximum number of nodes.

BLADDER RECONSTRUCTION

C Where appropriate, patients should be given the option of bladder reconstruction after radical cystectomy.

NON-SURGICAL TREATMENT

CONVENTIONAL RADIO THERAPY

A radical course of radiotherapy requires a minimum dose of 50Gy in 20 fractions over four weeks or 64Gy in 32 fractions if treating over 6.5 weeks.

PALLIATIVE RADIO THERAPY

B Radiotherapy using 21Gy in three fractions in one week should be considered for palliation of bladder cancer.

NEOADJUVANT CHEMOTHERAPY

A Neoadjuvant chemotherapy should be offered to suitable patients prior to definitive radical therapy for patients with T2-T4 transitional cell carcinoma of the bladder

- A combination chemotherapy regimen containing cisplatin should be used.

ADJUVANT CHEMOTHERAPY

Adjuvant chemotherapy should be given within the context of a clinical trial.

SUPPORT NEEDS

C Patients should be offered verbal and written information throughout their journey of care and should be made aware of the support mechanisms that are in place and how to access them.

SOURCES OF FURTHER INFORMATION

Milton Keynes Bladder Cancer Support Group
Milton Keynes General Hospital, Standing Way
Milton Keynes MK6 5LD • Tel: 01908 243 131

CancerBACUP Scotland
Suite 2, Third Floor, Cranston House
104/114 Argyll Street, Glasgow G2 8BH
Tel: 0141 223 7676/0808 800 1234 • Fax: 0141 248 8422
www.cancerbacup.org.uk

Macmillan Cancer Relief (Scotland)
Osborne House, 1-5 Osborne Terrace, Edinburgh EH1 2DP
Tel: 0131 346 5346 • Fax: 0131 346 5347
www.macmillan.org.uk • Email: agow@macmillan.org.uk

Maggie's Centres Scotland
www.maggiescentres.org • Email: maggies_centre@ed.ac.uk
Marie Curie Cancer Care (Scotland)
29 Albany Street, Edinburgh, EH1 3QN
Tel: 0131 456 3700 • Fax: 0131 456 3701
www.mariecurie.org.uk

Tak Tent Cancer Support Scotland
Flat 5, 30 Shelley Court, Gartnavel Complex, Glasgow G12 0YN
Tel: 0141 211 0122 • Fax: 0141 211 3988
www.taktent.org.uk • Email: tak.tent@care4free.net