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Current Perspectives in Bladder Cancer Management

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Int J Clin Pract. 2013;67(5):435-448.

Abstract

More than 350,000 new cases of bladder cancer are diagnosed worldwide each year; the vast majority (> 90%) of these are transitional cell carcinomas (TCC). The most important risk factors for the development of bladder cancer are smoking and occupational exposure to toxic chemicals. Painless visible haematuria is the most common presenting symptom of bladder cancer; significant haematuria requires referral to a specialist urology service. Cystoscopy and urine cytology are currently the recommended tools for diagnosis of bladder cancer. Excluding muscle invasion is an important diagnostic step, as outcomes for patients with muscle invasive TCC are less favourable. For non-muscle invasive bladder cancer, transurethral resection followed by intravesical chemotherapy (typically Mitomycin C or epirubicin) or immunotherapy [bacillus Calmette-Guérin (BCG)] is the current standard of care. For patients failing BCG therapy, cystectomy is recommended; for patients unsuitable for surgery, the choice of treatment options is currently limited. However, novel interventions, such as chemohyperthermia and electromotive drug administration, enhance the effects of conventional chemotherapeutic agents and are being evaluated in Phase III trials. Radical cystectomy (with pelvic lymphadenectomy and urinary diversion) or radical radiotherapy are the current established treatments for muscle invasive TCC. Neoadjuvant chemotherapy is recommended before definitive treatment of muscle invasive TCC; cisplatin-containing combination chemotherapy is the recommended regimen. Palliative chemotherapy is the first-choice treatment in metastatic TCC.

Methods

The rationale for this review of the literature was to discuss the latest evidence-base and to summarise key messages for the prevention, investigation, diagnosis and management of bladder cancer for non-specialists and specialists.

The literature searches were conducted using the timeframe of February 2012 to June 2012. The databases searched included PubMed and Trip, congress abstracts [European Association of Urology (EAU)] and current guidelines/consensus statements from within Europe [EAU; National Institute for Health and Clinical Excellence (NICE); The Renal Association; British Association of Urological Surgeons (BAUS)].

Introduction

summarises the key points concerning the diagnosis and management of bladder cancer for the non-specialist healthcare professional.

Table 1. Key points for the diagnosis and management of bladder cancer

Pathology	The vast majority of bladder cancers (> 90%) are TCC in origin
Risk factors	Smoking and occupational exposure to toxic chemicals are the key risk factors for bladder cancer
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	Clinically relevant haematuria: any episode of painless VH; any single episode of painful VH or s-NVH in the absence of UTI; recurrent or refractory UTI with VH, or persistent a-NVH (requires urgent investigation)
	Transient NVH or spurious causes of haematuria need to be excluded
Investigations within	All patients with s-NVH and persistent a-NVH should have their baseline blood pressure, eGFR

primary care	and ACR measured
	Further nephrological assessment should be considered in those aged < 40 years with persistent a-NVH if any one of the following are present: eGFR < 60 ml/min, ACR > 30 or blood pressure > 140/90 mmHg
Referral to specialist urology service	Routine referral: age 40–50 years with a-NVH or aged < 50 years with s-NVH
	Urgent referral: age > 50 years with a-NVH or s-NVH, or age > 40 years with recurrent or persistent UTI associated with haematuria
Tools to facilitate the diagnosis of bladder cancer	Cystoscopy and urine cytology are currently recommended tools
	Fluorescence cystoscopy (photodynamic diagnosis) is most useful for detection of CIS and guiding biopsies in patients with positive cytology or a history of high-grade NMIBC
	Narrow-band imaging cystoscopy has shown promise as an aid to facilitate detection without the need for an intravesical photosensitiser, but needs further evaluation in randomised trials
	Although currently available novel urinary biomarkers have higher sensitivity than cytology, they are not routinely recommended because of their higher false-positive rates
Non-muscle invasive TCC	Excluding muscle invasion is an important diagnostic step; one-half of patients with muscle invasive TCC will die of bladder cancer within 5 years
	EORTC risk group should be determined
	Most patients with NMIBC undergo surveillance cystoscopies and intravesical treatments
	Quality of first TUR can affect outcomes (tumour-free detrusor muscle/residual disease)
	A single postoperative intravesical instillation of chemotherapy within 24 h of TUR is recommended for all newly diagnosed bladder tumours
	The choice between further intravesical chemotherapy or immunotherapy is guided by the EORTC risk group
	Immediate radical cystectomy should be considered for patients whose risk of tumour progression is especially high, concomitant superficial urethral TCC is present, or where they request it in preference to intravesical BCG
	Treatment with intravesical BCG is considered to have failed if: T1 disease persists at the 3-month check cystoscopy following induction BCG; high-grade Ta disease/CIS is present at 6 months; or muscle invasive TCC is detected
	The incidence of concomitant UUT-TCC is low, but is increased in patients with trigonal tumours
Treatment after BCG failure	Radical cystectomy remains the mainstay of treatment for patients who have failed BCG treatment
	For patients who are unwilling or unfit to have a radical cystectomy after BCG failure, the treatment options are limited
	Currently available bladder-sparing treatments for those with BCG-refractory TCC are associated with 2-year disease-free survival of approximately 50%
	Treatments with the most promising clinical data, such as chemohyperthermia, are now being evaluated in Phase III trials
Muscle invasive TCC	Radical cystectomy (with pelvic lymphadenectomy and urinary diversion) or radical radiotherapy are the current established treatments for muscle invasive TCC
	Neoadjuvant chemotherapy is recommended before definitive treatment of muscle invasive TCC; cisplatin-containing combination chemotherapy is the recommended regimen
	Chemotherapy concurrent with radiotherapy improves loco-regional control compared with radiotherapy alone and confers separate benefits to neoadjuvant chemotherapy
Advanced/metastatic	

TCC	Palliative chemotherapy is the first-choice treatment in metastatic TCC

ACR, albumin/creatinine ratio; BCG, bacillus Calmette-Guérin; CIS, carcinoma *in situ*; eGFR, estimated glomerular filtration rate; EORTC, European Organization for Research and Treatment of Cancer; NMIBC, non-muscle invasive bladder cancer; NVH, non-visible haematuria; TCC, transitional cell carcinoma; TUR, transurethral resection; UTI, urinary tract infection; UUT, upper urinary tract; VH, visible haematuria.

Approximately 386,000 new bladder tumours were diagnosed worldwide in 2008, making bladder cancer the ninth most common cancer.[1] In the UK, bladder cancer is the fourth and twelfth most common cancer in men and women respectively;[2] it is up to three times more common in men than women, but women tend to present with more advanced disease and have worse outcomes.[3] Around eight in 10 cases are diagnosed in individuals over the age of 65,[2] and Caucasians generally have a higher risk of bladder cancer than people of other ethnicities.[4] In the USA, bladder cancer mortality in men decreased from the mid-1970s to the mid-1980s and was relatively stable to 2006; in women, there was a small, but steady decrease between 1975 and 2006.[4] Within Europe, bladder cancer mortality was stable in women between 1980 and 2006, but consistently decreased in men from around 1990 onwards.[5] The bladder cancer mortality rate in Japan has been stable for men since the early 1990s and has risen slightly during this period in women.[6] Putative reasons for reduced mortality include reduced exposure to tobacco and occupational carcinogens.

Transitional cell carcinoma (TCC; also known as urothelial cancer) represents over 90% of bladder cancers[7] and is consequently the focus of this review. Less common types include squamous cell carcinoma, adenocarcinoma and small cell carcinoma. Around 70–85% of TCCs are superficial [stages Ta, T1, carcinoma *in situ* (CIS)] at presentation and are now commonly termed non-muscle invasive bladder cancer (NMIBC).[7–10] Unlike in Europe or the USA, malignant non-muscle invasive tumours that also do not invade the lamina propria (Ta, CIS) are omitted from cancer registry statistics in England and Wales, therefore interpretation of epidemiological statistics varies across the world. However, in the management of bladder cancer, excluding muscle invasion is an important diagnostic step, as outcomes for patients with muscle invasive TCC (T2–T4) are less favourable; nearly one-half will die from bladder cancer within 5 years of diagnosis.[8,10] In the Middle East and Africa, squamous cell carcinoma was typically more common than in the developed world, largely caused by *Schistosoma haematobium* infection. However, improved knowledge of schistosomiasis over the last three decades has led to a reduction in squamous cell carcinoma such that TCC is now also the predominant type of bladder cancer in these countries.[11,12]

Risk Factors for Bladder Cancer

Numerous risk factors for TCC have been identified. Smoking is implicated in approximately two-thirds of bladder cancers in men and up to one-third in women.[13] There is a fourfold increased incidence in current smokers relative to never-smokers,[14] and bladder cancer risk is correlated with the number of cigarettes smoked, duration of smoking and age at smoking initiation.[14–16] Those who stop smoking reduce their bladder cancer risk by 10–40% within 4 years,[14,17] although former smokers retain a twofold higher incidence than never-smokers.[14,16]

Data from Western Europe suggest that around 4–7% of bladder cancers in men are attributable to a known occupational carcinogen; the latent period between exposure and the development of cancer is about 20 years.[18] Exposure to aniline dyes, aromatic amines (used in the manufacture of textiles, paints, plastics and rubber industries) and polycyclic aromatic amines are the primary toxins. Continuous arsenic exposure and ingestion has been reported to increase the risk of bladder cancer by as much as one thousand times.[19]

Carcinogen-metabolising enzymes are in part controlled by genetic polymorphism. Slow acetylation of *N*-acetyltransferase-2,[20,21] rapid cytochrome P1A2 activity[22] and glutathione *S*-transferase M1 null genotype[21] are associated with an increased risk of TCC. Approximately 20% of Europeans affected by bladder cancer are homozygous for a non-coding single nucleotide polymorphism (8q24.21) located close to the *c-Myc* oncogene.[23]

Older studies have shown that pelvic radiotherapy for cervical cancer was associated with a twofold to fourfold increased risk of secondary bladder cancer.[24,25] However, with contemporary radiotherapy, this risk has been reduced to a minimal level.[26] In men with prostate cancer who received external beam radiotherapy and/or brachytherapy between 1973 and 1999, at 5 years, after the initial diagnosis of the primary cancer, 1–1.5% had developed a secondary bladder malignancy.[27] However, it is estimated that with modern radiotherapy techniques, men with prostate cancer now have < 1% risk of a secondary malignancy.[26]

It has been reported that treatment with cyclophosphamide for primary malignancies and autoimmune disease increases the risk of bladder cancer by fourfold to ninefold, and is higher with greater cumulative doses and longer duration of exposure.[28–31] Mesna (2-mercaptoethanesulfonic acid) is commonly co-administered with cyclophosphamide to decrease the

development of cyclophosphamide-induced bladder cancer. It is speculated that Mesna, which is almost exclusively excreted by the kidneys counteracts the toxic effects of acrolein, an inactive metabolite of cyclophosphamide.[32] Historically, it has been reported that chronic abusers of the analgesic phenacetin had a four times higher risk of bladder malignancy relative to non-users.[33,34] The major metabolite of phenacetin is acetaminophen (paracetamol), which is often present in modern analgesics. However, heavy use of acetaminophen-containing analgesics did not increase bladder cancer risk in a number of studies.[34–36]

The oral antidiabetic drug pioglitazone is currently under post marketing pharmacovigilance, as a small excess of bladder cancer cases was shown in two studies evaluating its role in the management of diabetes. The risk was associated with drug exposure in excess of 2 years.[37,38] However, the benefits of pioglitazone are considered to outweigh this small risk for those who respond to treatment and in whom there is no history or other risk of bladder cancer. As a general principle, people with diabetes and non-visible haematuria (NVH) should be considered for further investigation in the same way as any other individuals with NVH.

There are also reported associations between increased risk of urothelial cancers and *Aristolochia fangchi* (a Chinese herb found in some over-the-counter diet pills).[39]

Presenting Symptoms

The majority of patients diagnosed with bladder cancer present with painless visible haematuria (VH).[13] Some patients, especially where CIS is present, may present with persistent irritative urinary symptoms that may be accompanied by haematuria present at dipstick testing [symptomatic NVH (s-NVH)]. Other tumours may be detected following investigation for asymptomatic NVH (a-NVH), or rarely with renal failure caused by bilateral ureteric obstruction or symptoms of metastatic disease.[13] Around 19% presenting with VH will have a urinary tract malignancy detected in a one-stop haematuria clinic setting, compared with around 5% presenting with NVH; this is more likely if they have symptoms.[40,41] However, there is currently no evidence-base to support population-based screening.[7]

What Is Significant Haematuria?

Recent publications from the UK have clarified what constitutes clinically relevant haematuria, which patients should be referred for clinical assessment, and whether they should be referred to a urologist, a nephrologist or both (summarised in).[42,43] Briefly, these are: NVH (≥ 1 + blood on dipstick); persistent a-NVH (2 of 3 ≥ 1 + blood on dipstick; clinically relevant haematuria [any episode of painless VH, painful VH or s-NVH in the absence of urinary tract infection (UTI), recurrent or refractory UTI with VH, or persistent a-NVH]. The latter requires urgent investigation.

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Investigations within primary care	All patients with s-NVH and persistent a-NVH should have their baseline blood pressure, eGFR and ACR measured
	Further nephrological assessment should be considered in those aged < 40 years with

	persistent a-NVH if any one of the following are present: eGFR < 60 ml/min, ACR > 30 or blood pressure > 140/90 mmHg
Referral to specialist urology service	Routine referral: age 40–50 years with a-NVH or aged < 50 years with s-NVH
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Tools to facilitate the diagnosis of bladder cancer	Cystoscopy and urine cytology are currently recommended tools
	Fluorescence cystoscopy (photodynamic diagnosis) is most useful for detection of CIS and guiding biopsies in patients with positive cytology or a history of high-grade NMIBC
	Narrow-band imaging cystoscopy has shown promise as an aid to facilitate detection without the need for an intravesical photosensitiser, but needs further evaluation in randomised trials
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Non-muscle invasive TCC	Excluding muscle invasion is an important diagnostic step; one-half of patients with muscle invasive TCC will die of bladder cancer within 5 years
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	Most patients with NMIBC undergo surveillance cystoscopies and intravesical treatments
	Quality of first TUR can affect outcomes (tumour-free detrusor muscle/residual disease)
	A single postoperative intravesical instillation of chemotherapy within 24 h of TUR is recommended for all newly diagnosed bladder tumours
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	Immediate radical cystectomy should be considered for patients whose risk of tumour progression is especially high, concomitant superficial urethral TCC is present, or where they request it in preference to intravesical BCG
	Treatment with intravesical BCG is considered to have failed if: T1 disease persists at the 3-month check cystoscopy following induction BCG; high-grade Ta disease/CIS is present at 6 months; or muscle invasive TCC is detected
	The incidence of concomitant UUT-TCC is low, but is increased in patients with trigonal tumours
Treatment after BCG failure	Radical cystectomy remains the mainstay of treatment for patients who have failed BCG treatment
	For patients who are unwilling or unfit to have a radical cystectomy after BCG failure, the treatment options are limited
	Currently available bladder-sparing treatments for those with BCG-refractory TCC are associated with 2-year disease-free survival of approximately 50%
	Treatments with the most promising clinical data, such as chemohyperthermia, are now being evaluated in Phase III trials
Muscle invasive TCC	Radical cystectomy (with pelvic lymphadenectomy and urinary diversion) or radical radiotherapy are the current established treatments for muscle invasive TCC
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	Chemotherapy concurrent with radiotherapy improves loco-regional control compared with radiotherapy alone and confers separate benefits to neoadjuvant chemotherapy
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rate; EORTC, European Organization for Research and Treatment of Cancer; NMIBC, non-muscle invasive bladder cancer; NVH, non-visible haematuria; TCC, transitional cell carcinoma; TUR, transurethral resection; UTI, urinary tract infection; UUT, upper urinary tract; VH, visible haematuria.

The American Urological Association (AUA) has also recently issued guidelines relating to the diagnosis and management of a-NVH.[44] A notable difference between these guidelines and the UK-based publications is that the AUA defines a-NVH as ≥ 3 red blood cells per high powered field on a properly collected urine specimen. The AUA Guidelines state that a positive dipstick does not define a-NVH. The strength of evidence for this AUA recommendation is based on expert opinion.

Causes of transient NVH include single episodes of UTI,[45] exercise[46] and benign prostatic hyperplasia.[44] Spurious causes of NVH include menstrual contamination, sexual intercourse, certain foods (beetroot, blackberries, rhubarb), rhabdomyolysis, drugs (doxorubicin, chloroquine, rifampicin) and chronic lead or mercury poisoning, and these should be excluded. However, haematuria in patients receiving anticoagulant therapy should not be attributed solely to these agents.[47,48] Recurrent or persistent UTI associated with haematuria is significant and merits urgent urological referral.

What Initial Investigations Should Be Performed in Primary Care?

A joint consensus statement published by the Renal Association and BAUS, followed by a review article, emphasised the importance of a basic nephrological screen in all patients with NVH.[42,43] Almost one-half of patients referred to urological haematuria clinics have NVH; however in this setting, patients with NVH are twice as likely to have nephrological disease (10%) than bladder cancer (5%).[49] The overall incidence of urological malignancy in screen-detected a-NVH is < 1%.[50]

All patients with s-NVH and persistent a-NVH should have their baseline blood pressure (BP), estimated glomerular filtration rate (eGFR), and albumin:creatinine ratio (ACR) measured (). Further nephrological assessment should be considered in those aged < 40 years with persistent a-NVH if any one of eGFR < 60 ml/min/1.73 m^2, ACR > 30 or BP > 140/90 mmHg are present.

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Tools to facilitate the diagnosis of bladder	Cystoscopy and urine cytology are currently recommended tools
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cancer	guiding biopsies in patients with positive cytology or a history of high-grade NMIBC
	Narrow-band imaging cystoscopy has shown promise as an aid to facilitate detection without the need for an intravesical photosensitiser, but needs further evaluation in randomised trials
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Treatment after BCG failure	Radical cystectomy remains the mainstay of treatment for patients who have failed BCG treatment
	For patients who are unwilling or unfit to have a radical cystectomy after BCG failure, the treatment options are limited
	Currently available bladder-sparing treatments for those with BCG-refractory TCC are associated with 2-year disease-free survival of approximately 50%
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Which Patients With Haematuria Require Urological Referral?

In the UK, referral guidelines for suspected cancer were published by NICE in 2005.[51] These included referral guidelines for haematuria (summarised in). If a patient is aged < 40 years and has persistent a-NVH, referral to a urology service is not considered necessary unless there are risk factors for bladder cancer. If aged 40–50 years with persistent a-NVH or aged <

50 years with s-NVH, routine referral to urology is recommended. If aged > 50 years with persistent a-NVH or s-NVH, urgent urological referral is recommended. If aged > 40 years with recurrent or persistent UTI associated with haematuria, an urgent urological referral should be made.

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What Tools Are Available to Facilitate Detection of Bladder Cancer?

Currently Recommended Tools

Cystoscopy remains the gold standard for the detection of both new and recurrent bladder cancer. Despite this, its sensitivity is limited to approximately 94% for the detection of tumours during follow-up,[52] and may be as low as 60% for the detection of CIS.[53]

First described in 1945, the specificity of urine cytology for underlying urothelial malignancy is > 95%. However, the overall sensitivity of voided urine cytology is only 30–50%, as low-grade tumours do not shed malignant cells. It is therefore most sensitive in patients with high-grade tumours and CIS.[54]

Photodynamic diagnosis (PDD) requires the intravesical instillation of a photosensitising agent, usually 5-aminolevulinic acid (5-ALA) or its hexyl ester [hexaminolevulinate (HAL)], at least 1 h prior to cystoscopy. The derivative is preferentially taken up by tumour cells and produces orange fluorescence when blue light of 400 nm wavelength is applied. Two meta-analyses, including data up to 2009, concluded that compared with white-light cystoscopy (WLC), PDD improved detection of bladder tumours (especially CIS), and PDD use was associated with a lower rate of tumour recurrence.[55,56] There was no evidence that PDD affected tumour progression or survival. However, the true added value of PDD in reducing tumour recurrence in routine practice is controversial because studies vary in the choice of photosensitiser (5-ALA or HAL) and use of immediate single-dose intravesical chemotherapy post transurethral resection (TUR). Four randomised controlled trials (RCTs) of PDD vs. WLC published since 2009 have shown conflicting data.[57–60]

Tools Undergoing Development

In general, novel urinary biomarkers possess greater sensitivity than cytology for the diagnosis of bladder cancer, at the expense of lower specificity, but none have sufficient sensitivity to obviate the need to perform cystoscopy.[54] Contemporary US Food and Drug Administration-approved and available tests are point-of-care (Nuclear Matrix Protein 22) and laboratory-based (ImmunoCyt™, Scimedx Corporation, Denville, NJ, USA and UroVysion™, Abbott Molecular Inc, Des Plaines, IL, USA). Their most promising application may be as part of surveillance protocols after treatment, but large prospective trials

validating such protocols are lacking. There is concern regarding their use as a diagnostic adjunct in patients presenting with haematuria, as the increased false-positive rate would lead to unnecessary invasive investigations in patients with otherwise normal cystoscopic appearances and imaging.

Narrow-band imaging (NBI) enhances the contrast between the bladder mucosa and vascular structures by filtering white light into two narrow bands (415 and 540 nm) without the need for a preoperative instillation of contrast agent. Improved detection of primary and recurrent tumours has been shown in small non-randomised studies,[61] and recurrence rates may be reduced when used as part of follow-up.[62] The role of NBI-cystoscopy as an aid to TUR and in surveillance needs further evaluation in RCTs.

Pivotal Considerations in the Management of NMIBC (TCC)

An algorithm outlining the primary management of NMIBC (TCC) is presented in Figure 1.

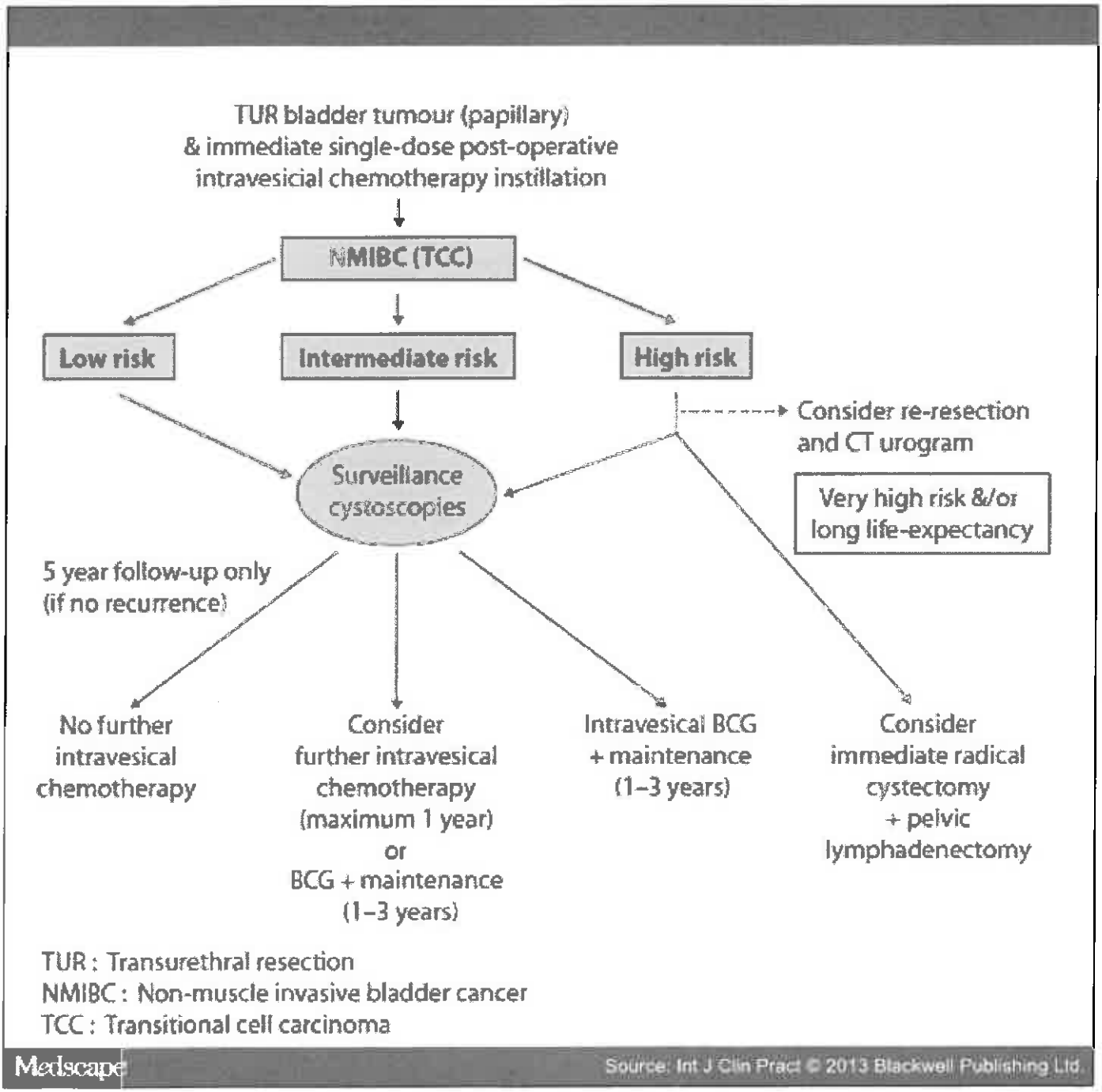

Figure 1.

Management of non-muscle invasive bladder cancer (TCC). BCG, bacillus Calmette-Guérin; CT, computed tomography; EORTC, European Organization for Research and Treatment of Cancer; NMIBC, non-muscle invasive bladder cancer; TCC,

transitional cell carcinoma; TUR, transurethral resection

Allocation to a Risk Group

Patients with NMIBC have a diverse prognosis. The European Organisation for Research and Treatment of Cancer (EORTC) has identified six key risk factors for the prediction of tumour recurrence and progression to muscle invasive disease.[63] These are: number of tumours; prior recurrence rate; tumour size; stage (T-category); histological grade (1973 World Health Organization grade); presence of concomitant CIS. From these, risk scores are developed to enable patients to be classified into low-, intermediate-and high-risk groups for recurrence and progression. Risks of recurrence and progression at 5 years following diagnosis vary from 31% to 78% and 0.8% to 45% respectively.[63]

Detrusor Muscle Status

The quality of the initial TUR has a substantial impact on outcomes – removal of adequate detrusor muscle is associated with reduced risk of recurrence.[64] Local recurrence rates for a single tumour at first-check cystoscopy can vary from 3.5% to 20.6% depending on the institution.[65]

To exclude muscle invasion at the primary TUR, larger tumours should be resected so that at least exophytic and deep biopsies are submitted in separate fractions.[66] Repeat TUR is recommended where the initial resection is judged to be incomplete, either because of the absence of detrusor muscle in a high-grade tumour or caused by macroscopic residual disease; this is also currently recommended in all high-grade T1 tumours even if detrusor muscle was present in the first TUR specimen.[66] Failure to adhere to these principles can adversely affect outcomes. Contemporary series have shown that in patients initially staged as T1, 20% were upstaged to muscle invasive disease after repeat TUR[67] and residual tumour rates were 25–33%.[68,69] Although EAU guidelines currently include high-grade Ta tumours in their recommendation for repeat resection,[66] the evidence for repeat resection of high-grade Ta tumours is less robust than for high-grade T1 tumours.

Requirement for Adjuvant Intravesical Treatment

The most commonly used intravesical chemotherapeutic agents are mitomycin C (MMC) and epirubicin. The intravesical immunotherapy of choice is bacillus Calmette-Guérin (BCG).

A single postoperative intravesical instillation of chemotherapy within 24 h of TUR (and ideally 6 h) is currently recommended for all newly diagnosed bladder tumours.[66] In clinical studies, this reduced tumour recurrence rates by 39%;[70] Another study involving patients with recurrent NMIBC showed that the recurrence rate was increased twofold if instillation was performed more than 24 h after TUR.[71]

Need for Further Instillations of Chemotherapy or BCG

The effect of a single instillation of intravesical chemotherapy lasts for approximately 500 days.[72] The choice between further intravesical chemotherapy or immunotherapy is guided by the patient's risk group. Further intravesical chemotherapy reduces the risk of recurrence, but has not been shown to reduce disease progression;[73] BCG is more effective than chemotherapy in reducing recurrence, provided maintenance treatment is administered,[74] but is associated with more side effects than chemotherapy. If maintenance therapy is given for at least 1 year, BCG is the only intravesical agent shown to reduce or at least delay the risk of disease progression, by around 37%.[75–78] Compared with epirubicin, maintenance BCG was superior in preventing progression and also improving overall survival (OS).[77] However, the relative benefit of maintenance BCG over MMC in terms of disease progression is more controversial.[74]

For patients at low risk of recurrence and progression (EORTC recurrence and progression scores = 0), no further treatment after TUR is recommended prior to a further recurrence. The probability of recurrence at 1 year is 15% and for progression is 0.2%.[63]

In intermediate-risk patients, the main priority is to reduce the risk of recurrence (46–62% at 5 years), although the risk of progression is not negligible (6–17% at 5 years).[63] A maximum of 1 year of intravesical chemotherapy or 1–3 years of intravesical BCG is currently recommended, although the superior efficacy of BCG needs to be balanced against its increased toxicity.[66] Three-year vs. one-year BCG maintenance at full-dose compared with one-third-dose BCG in patients with intermediate- and selected high-risk (solitary tumour without CIS) NMIBC has been tested in the EORTC 30962 RCT.[78] Superiority could not be formally concluded for either comparison, although patients receiving full-dose BCG for 3 years had the highest disease-free survival (DFS) at 5 years, whereas those receiving one-third-dose for 1 year had the lowest. Clearly, extending maintenance treatment for more than 1 year is a balance of efficacy, side effects and inconvenience and is worthy of discussion with the patient. In routine clinical practice, many urologists in the UK delay the decision until the patient develops a further recurrence. Some administer a further single-dose chemotherapy instillation after TUR for recurrent

disease, but this has not been validated for recurrent tumours. Others give six instillations (one instillation weekly for 6 weeks) of intravesical chemotherapy before the first-check cystoscopy at around 3 months after TUR.

In high-risk patients (EORTC progression score > 14), the 5-year probability of disease progression is 45%.[63] Here, the primary goal of intravesical treatment is not only to prevent recurrence, but also to prevent progression. Maintenance BCG has been established as the bladder-sparing treatment of choice in these patients. The optimal duration of treatment has not yet been established, but at least 1 year of maintenance is recommended.[66,78] The Southwest Oncology Group protocol is the most widely used and involves giving up to 27 instillations of BCG over a 3-year period.[79]

Considerations for Radical Cystectomy

There are no RCTs comparing BCG with immediate radical cystectomy. There is, however, consensus that immediate radical cystectomy should be considered for patients with high-risk NMIBC where the risk of tumour progression is especially high, or concomitant superficial urethral TCC is present, or where the patient requests it in preference to intravesical BCG. Added risk factors for progression in high-grade T1 disease include associated CIS,[80] multifocality, tumour size > 3 cm and persistent T1 disease at repeat resection.[81,82] If more than one of these risk factors is present, then radical cystectomy should be strongly considered. A growing body of urologists believe that radical cystectomy for high-grade T1 TCC is under-utilised at present. Their concerns are based on non-randomised evidence that suggests worse outcomes following cystectomy for failed intravesical treatment compared with immediate cystectomy, although such studies are likely to include selection bias.[83,84] Immediate radical cystectomy for NMIBC may also be indicated when aggressive variants of TCC are present, e.g. diffuse areas of micropapillary variant are detected[85,86] or in those where BCG is contraindicated, e.g. significant immunosuppression. Radical cystectomy is also indicated for squamous cell carcinoma and radical or partial cystectomy should be considered for adenocarcinoma.

Failure of BCG

The definition of BCG failure is controversial, but the persistence of T1 disease at the 3-month check cystoscopy after induction BCG (six instillations administered once-weekly for 6 weeks); high-grade Ta disease/CIS at 6 months; or detection of muscle invasive TCC should prompt consideration of radical cystectomy.

Increased Risk of Concomitant or Metachronous Upper Urinary Tract (UUT)-TCC

The incidence of concomitant UUT-TCC is low (1.8%), but in patients with trigonal tumours, the incidence is 7.5%.[87] During follow-up, patients with high-grade and multifocal NMIBC are more likely to develop UUT-TCC.[88] Ultrasound is routinely performed during diagnostic work-up of bladder cancer, but can miss small UUT-TCC. Computed tomography urography should therefore be considered where the bladder tumour is high-grade, multifocal or trigonal.[66]

Prevention of Bladder Tumours After Nephro-ureterectomy for Primary UUT-TCC

After a nephroureterectomy for UUT-TCC, up to 40% of patients will develop bladder cancer. In a phase III RCT (ODMIT-C), a single dose of postoperative intravesical MMC, administered at the time of urethral catheter removal, reduced the risk of a bladder tumour within the first year after nephroureterectomy; the absolute reduction in risk was 11%, the relative reduction was 40% and the number needed to treat to prevent one bladder tumour was 9.[89] The trial was the largest randomised study ever conducted in the management of patients with UUT-TCC. However, it was not designed to determine the most effective method of nephroureterectomy, and so a number of techniques were allowed for management of the distal ureter. Patients with a previous history of bladder cancer were excluded.

Bladder-Sparing Treatments After BCG Failure

Radical cystectomy remains the mainstay of treatment for patients who have failed BCG treatment. For patients who are unwilling or unfit to undergo this procedure, the treatment options are limited.

Intravesical chemotherapeutic agents, such as gemcitabine and docetaxel, novel immunotherapies, such as interferon-alpha, and device-assisted treatments have all shown promise. However, to date, much of the evidence to support their potential benefit is based on non-randomised or small Phase II studies. At best, currently available bladder-sparing treatments for those with BCG-refractory TCC are associated with 2-year DFS of approximately 50%.[90]

Chemohyperthermia (c-HT) describes the combination of intravesical chemotherapy and hyperthermia, where the chemotherapy and the bladder wall are heated to temperatures of between 44 and 45 °C. The most common form of c-HT uses the Synergo HT system in which local HT is administered via a 915 MHz intravesical microwave applicator. c-HT increases cell membrane permeability, enhances urothelial exposure and in particular lamina propria exposure, alters intracellular drug trafficking and enhances the effects of cytostatic chemotherapy.[91] Over the last 15 years, c-HT has been

tested in a variety of clinical settings, including small several Phase II RCTs, in the BCG-naïve setting.[92]

Data supporting the role of c-HT (using MMC) in BCG-refractory NMIBC has come from several proof-of-concept studies. In patients with BCG-refractory CIS, a complete response rate of 92% was shown, with 50% of patients remaining disease-free at 2-year follow-up.[93] In patients with BCG-refractory NMIBC (77% high-risk) treated with a maintenance c-HT schedule, the recurrence-free rate was 56% at 2 years; 3% progressed to muscle invasive disease and 5% withdrew from treatment because of adverse events.[94] The use of c-HT is being further evaluated in BCG-refractory patients with NMIBC who are unwilling or unfit for cystectomy in the UK-based HYMN Phase III trial (EUDRACT-2008-005428-99).

Electromotive drug administration (EMDA) is an alternative way of enhancing MMC absorption and urothelial exposure, by creating an electrical gradient across the bladder wall using electrodes placed within the catheter and on the lower abdominal wall. In patients with BCG-naïve high-risk NMIBC, EMDA-MMC has shown promise.[95,96] To date, no studies have specifically evaluated EMDA-MMC in the BCG-refractory setting, although one RCT allowed crossover of patients to EMDA-MMC alone if they did not respond to primary BCG treatment.[95]

Key Considerations When Treatment Intent for Muscle Invasive TCC Is Potentially Curative

An algorithm outlining the primary management of muscle invasive bladder cancer is presented in Figure 2.

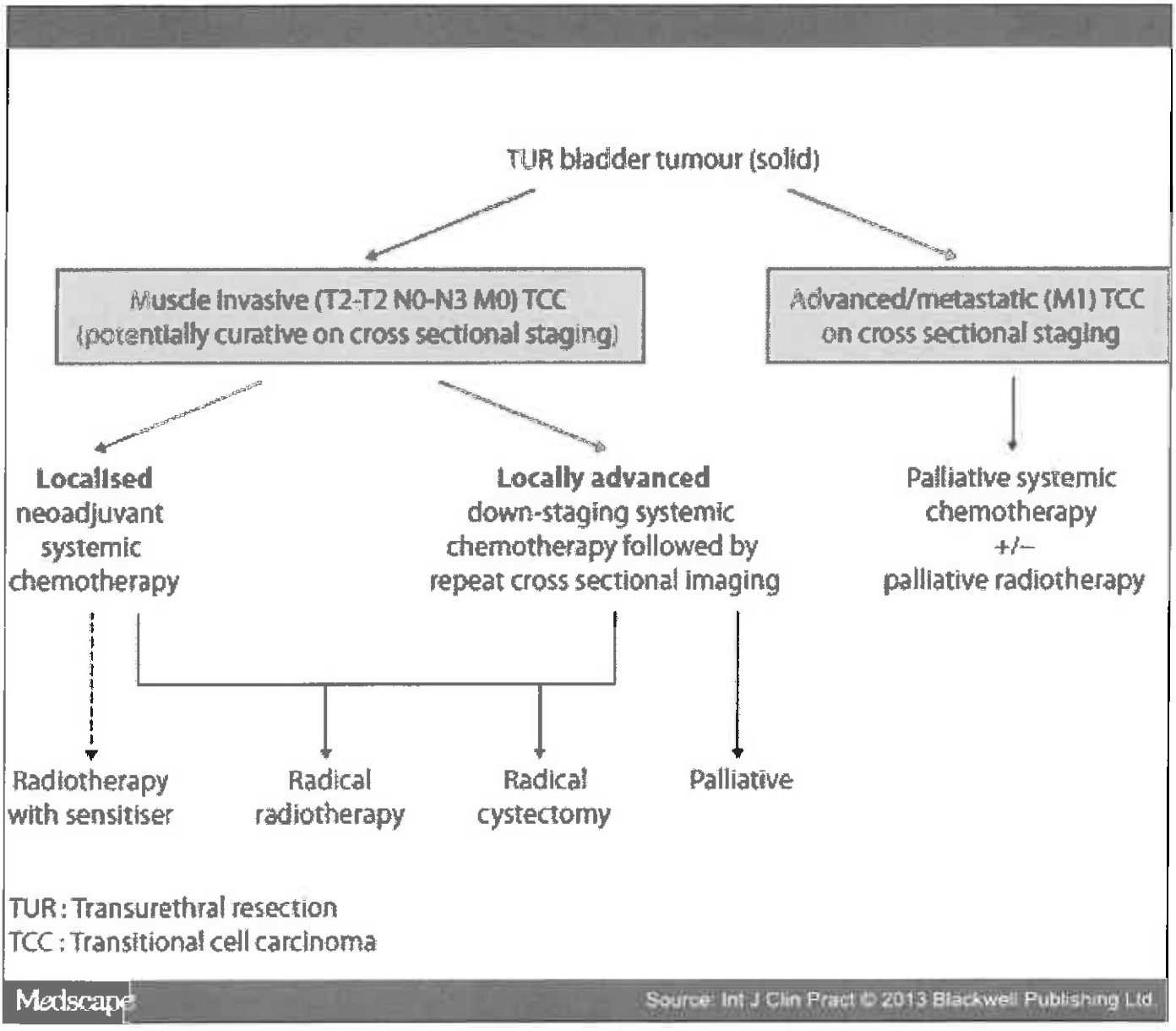

Figure 2.

Management of muscle invasive or advanced/metastatic bladder cancer (TCC). TCC, transitional cell carcinoma; TUR, transurethral resection

Radical Cystectomy or Radical Radiotherapy?

Worldwide, radical cystectomy and pelvic lymphadenectomy has been the cornerstone treatment for muscle invasive TCC, although no RCT data exist to support cystectomy over bladder preservation with radical radiotherapy. Non-randomised data from single gold-standard institutions show similar outcomes for DFS.[97,98] Typical radical radiotherapy schedules are 64 Gy in 32 fractions over 6.5 weeks or 55 Gy in 20 fractions over 4 weeks. An important confounding factor when comparing the results of radical cystectomy and radiotherapy is the discrepancy between pathological staging (cystectomy series) and clinical staging (radiotherapy series). Clinical staging is more likely to underestimate disease extent and so there is an outcome bias in favour of cystectomy series. For example, in one publication, only 23% of clinical stage T2 tumours (cT2) were confirmed to be pathological stage T2 (pT2) at cystectomy; 74% were pT3/pT4.[99] In a contemporary series assessing cystectomy and pelvic lymphadenectomy alone, the 5-year OS for the entire cohort was 59%.[100] In a separate study, following radical radiotherapy alone, 5-year OS was also approximately 60%.[101] When directly comparing radical cystectomy and radical radiotherapy, no significant difference between interventions in terms of 5-year OS was evident.[102]

Local disease control is a clinically relevant challenge in the management of muscle invasive TCC and is consistently better after cystectomy than radiotherapy alone, balanced against the benefits of retaining the native bladder; many urological surgeons do not offer reconstructive surgery in the salvage cystectomy setting. One concern is that salvage cystectomy for local disease recurrence after radiotherapy is technically more difficult than primary cystectomy, with a higher risk of complications. However, one large study demonstrated that OS after salvage cystectomy was identical to that of primary cystectomy, but dependent on the experience of the operator.[103] The local relapse rate following cystectomy is 10%,[104] but can be as low as 8% when a pelvic lymphadenectomy is performed.[100]

Factors that would favour cystectomy over radiotherapy include poor bladder function, widespread CIS, large volume tumours, preexisting hydronephrosis, previous pelvic radiotherapy and active inflammatory bowel disease. Where compliance with follow-up cystoscopic surveillance is likely to be difficult, cystectomy should be the preferred option. Overall, these factors must be weighed against morbidities associated with cystectomy, and patient preference.

Available Technologies Choices for Radical Cystectomy and Pelvic Lymphadenectomy

Radical cystectomy is a major operation; perioperative mortality is 3%, and 28% of patients develop a complication within 3 months of surgery.[105] Ninety-day mortality rates increase with patient age: < 70 years, 2%; 70–79 years, 5.4%; 80–89 years, 9.2%.[106] When strict reporting guidelines are implemented in high volume centres, surgical morbidity following radical cystectomy is reported to be even higher.[107,108] As well as removing the bladder and pelvic lymph nodes, the standard procedure is also to remove the prostate and seminal vesicles in men, and uterus and adnexa in women. The inclusion of the entire prostate in male patients and the extent of urethrectomy and vaginal resection in female patients have recently been questioned. There is a substantial amount of literature about the extent of lymphadenectomy, but consensus concerning the optimal extent remains elusive. Available data suggest that removal of least 11 lymph nodes may be associated with more favourable outcomes.[109] Most agree that the template for standard pelvic lymph node dissection should at least include pelvic lymph nodes and external iliac lymph nodes up to level of the common iliac bifurcation.[110] The extent of lymph node dissection and its impact on survival is currently the subject of RCTs, including the ongoing Southwest Oncology Group trial (SWOG-S1011; NCT01224665) in the United States and the AUO-multicentre RCT (AB 25/02; NCT01215071) in Germany, which is now closed to recruitment. Laparoscopic cystectomy and robotic-assisted cystectomy are feasible and also currently the subject of RCTs.

Following radical cystectomy, urinary diversion is necessary. The most established option is the ileal conduit. The second most common option is the construction of a detubularised ileal orthotopic neobladder that is anastomosed to the urethra. The third option is a continence pouch that can be self-catheterised via, e.g. an appendix stoma.

The presence of positive soft tissue surgical margins following radical cystoprostatectomy is a strong predictor of recurrence-free and disease-specific survival.[111] EAU guidelines recommend that urethrectomy should be performed if positive surgical margins are present at the level of the urethral dissection, if the tumour is located at the bladder neck or in the urethra (in women), or if the tumour extensively infiltrates the prostate.[13] Factors that may protect against urethral recurrence include orthotopic reconstruction and radical radiotherapy.

Evolving Radiotherapy Techniques

The volume treated by radiotherapy has historically been the whole bladder, but for unifocal disease, techniques have evolved using a lower total dose to the whole bladder with a boost to the tumour bed. The potential benefits of this approach are to reduce toxicity and allow dose-escalation to the primary disease. However, it is critical that organ motion and verification of the intended area of treatment is optimised.

Novel approaches to achieve this include image-guided radiotherapy, allowing pretreatment computed tomography verification to be performed on a daily basis prior to each fraction and real-time moves to be made. However, the cost of this technique is significant and not available throughout the UK, but represents a significant development in radiotherapy implementation.

Neoadjuvant, Down-staging or Adjuvant Chemotherapy

Up to 30% of patients relapse with distant metastases after radical cystectomy.[100] Use of neoadjuvant chemotherapy, prior to radical cystectomy or radiotherapy, is postulated to reduce the risk of micrometastatic disease and thereby confer a survival advantage. Cisplatin-containing combination chemotherapy is the recommended approach.[13] Typically, three cycles are given, and the most commonly used contemporary chemotherapy regimens are the gemcitabine-cisplatin (GC) and methotrexate-vinblastine-adriamycin-cisplatin (M-VAC) combinations. Neoadjuvant chemotherapy improves 5-year OS by 5–8%, irrespective of type of subsequent local treatment.[112–114] This translates into a 14–16% relative reduction in risk of death and a 22–26% relative improvement in DFS.[112,113] Adequate renal function and performance status (PS) is necessary for these treatments.

Down-staging chemotherapy should be considered for locally advanced bladder cancer (inoperable, but non-metastatic) where the aim is to increase the possibility of either successful cystectomy or radiotherapy. Three to six cycles are commonly given, with cross-sectional imaging performed after three cycles to assess response.

Currently, no RCT or meta-analysis has provided sufficient data to support the routine use of adjuvant chemotherapy because of underpowered studies and a difficulty in recruitment.[13] It remains unclear whether immediate adjuvant chemotherapy or chemotherapy at the time of relapse is superior or equivalent in terms of OS. However, adjuvant chemotherapy may be discussed on an individual basis particularly in patients with node-positive disease or locally advanced disease with high-grade pathology who have not already received neoadjuvant chemotherapy. Adequate renal function and PS is again mandated.

Selective Bladder Preservation Strategies

To optimise the success of selective bladder preservation, patients must be carefully selected to increase the likelihood of complete response, and meticulous cystoscopic follow-up must be performed to identify recurrent or persistent muscle invasive disease in candidates suitable for early salvage cystectomy. It is important to minimise the amount of normal tissue in the irradiated area, especially as the small bowel is used in an ileal conduit or in reconstruction in the event of salvage cystectomy.

Emerging data from RCTs suggests that the standard of care for bladder preservation is likely to become neoadjuvant chemotherapy followed by radiotherapy with a concurrent radiosensitiser.[115–117] The Phase III BC2001 trial of 360 patients that compared radiotherapy and concurrent 5-fluorouracil and MMC chemotherapy (a non-renal toxic regimen) with radiotherapy alone demonstrated a significant improvement in loco-regional recurrence-free survival (67% compared with 54%) at 2 years.[116] A similar degree of benefit was seen across all tumour stages (T2–T4) irrespective of age or whether the patient had received neoadjuvant chemotherapy. In a further Phase II study of patients receiving chemoradiation compared with historical radiotherapy controls, 89% of surviving patients at 3 years had an intact bladder following chemoradiotherapy with weekly gemcitabine.[117]

Tumour hypoxia has long been considered a cause of radiotherapy failure and one strategy to improve radiosensitivity is therefore to increase oxygenation of the tumour. In the BCON trial, radiotherapy administered with carbogen breathing apparatus and nicotinamide tablets improved OS by 13% compared with radiotherapy alone.[115] Of long-term survivors in the experimental arm, 83% retained intact bladders.

Quality of Life After Cystectomy and Selective Bladder Preservation

Radical cystectomy is associated with significant alteration in health-related quality of life (HRQoL), with most of the morbidity related to the use of intestinal segments for urinary diversion. A commonly held assumption is that patients who choose neobladders should have improved HRQoL compared with those who undergo ileal conduit formation. However, a systematic review has not determined a superior approach in terms of HRQoL.[118] As well as health and body image, patients identified non-health-related determinants, such as family, relationships, finances as important QoL factors.

A questionnaire-based study compared the HRQoL of 29 patients who received bladder preservation therapy (combination of chemoradiotherapy and TUR) and 30 patients who had undergone radical cystectomy.[119] Parameters associated with better HRQoL after bladder preservation than cystectomy included physical well-being (62% vs. 53%), anxiety (28% vs. 57%) and depression (24% vs. 47%). HRQoL after cystectomy was substantially impacted by stoma presence and a lack of sexual

activity, but social and recreational life was only minimally affected. Patients undergoing bladder preservation therapy reported dysuria (20%), frequency (44%), nocturia (42%) and difficulty controlling micturition (38%).[119]

A further study with long-term follow-up (median 6.3 years) evaluated HRQoL and bladder function assessed by urodynamics in patients treated with TUR, chemotherapy and radiotherapy.[120] Of 32 patients, most (75%) retained normal bladder function. Urinary flow problems were reported by 6% of patients, urgency by 15% and urinary leakage in 19%. Difficulty with bowel control occurred in seven men and three women. Of male patients, 59% reported they were satisfied with their sex life.

Palliative Care Approaches for Advanced (Metastatic) Bladder Cancer (TCC)

Palliative chemotherapy is the cornerstone treatment for patients with metastatic TCC (Figure 2). It is usually given to improve HRQoL, improve symptoms and also to improve prognosis, but is very unlikely to be a cure. Before the development of effective chemotherapy, patients with TCC and visceral metastases rarely exceeded the median survival of 3–6 months. In 'fit' patients with adequate renal function, cisplatin-containing combination chemotherapy with GC or M-VAC should be considered, which can achieve a median survival of up to 14–15 months;[121] GC may be associated with less toxicity than M-VAC. Carboplatin-based therapy is less effective than cisplatin-based therapy, but may be an option in patients 'unfit' for the former. Some patients who progress after first-line chemotherapy may benefit from agents, such as paclitaxel or vinflunine.

Palliative radiotherapy may also be administered to help control symptoms, such as haematuria and pain. Emerging data suggests that zoledronic acid, a bisphosphonate, may also be helpful in patients with bone metastases.[122]

Can Public and Professional Recognition of Bladder Cancer Be Improved?

A single episode of VH is a warning sign that needs prompt investigation and urological referral. This is a key message for both the public and doctors in Primary Care. Symptoms attributable to bladder cancer can mimic UTI. Failure to respond to antibiotics following a symptomatic UTI or an early recurrent UTI warrants flexible cystoscopic evaluation before considering repeat courses of antibiotics. Otherwise, diagnosis (particularly in postmenopausal women) is delayed and may be contributory to less favourable outcomes in women than men. It is important to get this message across to doctors in Primary Care and pharmacists.

Until recently, bladder cancer has been low on the public health agenda. However, the Department of Health has recognised the need for earlier diagnosis of bladder cancer, and has commenced a pilot study in three regions of the UK to determine the best way to promote these messages.

Action on Bladder Cancer (http://www.actiononbladdercancer.org) is the only UK national bladder cancer charity purely focussed on improving the lives of patients with bladder cancer. It has three primary aims, namely to: improve awareness; elevate the status of bladder cancer in the public health agenda; and improve medical knowledge. It is hoped that the website will provide a good resource for the general public, patients and healthcare professionals.

Sidebar

Review Criteria

To produce this non-systematic review, an extensive literature search was performed with the objective of identifying publications concerning the management of bladder cancer. Multiple sources were included, e.g. current European guidelines, National Institute for Health and Clinical Excellence guidelines, meta-analyses, randomised controlled trials (RCT), consensus statements by the Renal Association and British Association of Urological Surgeons and non-randomised study evidence where RCT evidence was not available.

Message for the Clinic

Patients with a single episode of visible haematuria (VH) and any patients with clinically relevant nonvisible haematuria (NVH) (defined in) need prompt investigation and urological referral. Symptoms attributable to bladder cancer can mimic urinary tract infection (UTI). Patients with a symptomatic UTI refractory to antibiotics or an early recurrent UTI warrant flexible cystoscopic evaluation before considering repeat courses of antibiotics.

Table 1. Key points for the diagnosis and management of bladder cancer

Pathology	The vast majority of bladder cancers (> 90%) are TCC in origin
Risk factors	Smoking and occupational exposure to toxic chemicals are the key risk factors for bladder

	cancer
	Smoking cessation is still worthwhile following diagnosis of bladder cancer
Definitions of significant haematuria	Painless VH is the most common presenting symptom of bladder cancer
	NVH: ≥ 1 + blood on dipstick testing; not necessary to confirm NVH using urine microscopy; a trace of blood only on dipstick is not regarded as significant.
	Persistent a-NVH: Defined in the UK as two out of three dipsticks ≥ 1 + blood. In contrast, the American Urological Association (AUA) defines a-NVH as ≥ 3 red blood cells per high powered field in a properly collected urine specimen.
	Clinically relevant haematuria: any episode of painless VH; any single episode of painful VH or s-NVH in the absence of UTI; recurrent or refractory UTI with VH, or persistent a-NVH (requires urgent investigation)
	Transient NVH or spurious causes of haematuria need to be excluded
Investigations within primary care	All patients with s-NVH and persistent a-NVH should have their baseline blood pressure, eGFR and ACR measured
	Further nephrological assessment should be considered in those aged < 40 years with persistent a-NVH if any one of the following are present: eGFR < 60 ml/min, ACR > 30 or blood pressure > 140/90 mmHg
Referral to specialist urology service	Routine referral: age 40–50 years with a-NVH or aged < 50 years with s-NVH
	Urgent referral: age > 50 years with a-NVH or s-NVH, or age > 40 years with recurrent or persistent UTI associated with haematuria
Tools to facilitate the diagnosis of bladder cancer	Cystoscopy and urine cytology are currently recommended tools
	Fluorescence cystoscopy (photodynamic diagnosis) is most useful for detection of CIS and guiding biopsies in patients with positive cytology or a history of high-grade NMIBC
	Narrow-band imaging cystoscopy has shown promise as an aid to facilitate detection without the need for an intravesical photosensitiser, but needs further evaluation in randomised trials
	Although currently available novel urinary biomarkers have higher sensitivity than cytology, they are not routinely recommended because of their higher false-positive rates
Non-muscle invasive TCC	Excluding muscle invasion is an important diagnostic step; one-half of patients with muscle invasive TCC will die of bladder cancer within 5 years
	EORTC risk group should be determined
	Most patients with NMIBC undergo surveillance cystoscopies and intravesical treatments
	Quality of first TUR can affect outcomes (tumour-free detrusor muscle/residual disease)
	A single postoperative intravesical instillation of chemotherapy within 24 h of TUR is recommended for all newly diagnosed bladder tumours
	The choice between further intravesical chemotherapy or immunotherapy is guided by the EORTC risk group
	Immediate radical cystectomy should be considered for patients whose risk of tumour progression is especially high, concomitant superficial urethral TCC is present, or where they request it in preference to intravesical BCG
	Treatment with intravesical BCG is considered to have failed if: T1 disease persists at the 3-month check cystoscopy following induction BCG; high-grade Ta disease/CIS is present at 6 months; or muscle invasive TCC is detected
	The incidence of concomitant UUT-TCC is low, but is increased in patients with trigonal tumours
Treatment after BCG failure	Radical cystectomy remains the mainstay of treatment for patients who have failed BCG treatment

	For patients who are unwilling or unfit to have a radical cystectomy after BCG failure, the treatment options are limited
	Currently available bladder-sparing treatments for those with BCG-refractory TCC are associated with 2-year disease-free survival of approximately 50%
	Treatments with the most promising clinical data, such as chemohyperthermia, are now being evaluated in Phase III trials
Muscle invasive TCC	Radical cystectomy (with pelvic lymphadenectomy and urinary diversion) or radical radiotherapy are the current established treatments for muscle invasive TCC
	Neoadjuvant chemotherapy is recommended before definitive treatment of muscle invasive TCC; cisplatin-containing combination chemotherapy is the recommended regimen
	Chemotherapy concurrent with radiotherapy improves loco-regional control compared with radiotherapy alone and confers separate benefits to neoadjuvant chemotherapy
Advanced/metastatic TCC	Palliative chemotherapy is the first-choice treatment in metastatic TCC

ACR, albumin/creatinine ratio; BCG, bacillus Calmette-Guérin; CIS, carcinoma *in situ*; eGFR, estimated glomerular filtration rate; EORTC, European Organization for Research and Treatment of Cancer; NMIBC, non-muscle invasive bladder cancer; NVH, non-visible haematuria; TCC, transitional cell carcinoma; TUR, transurethral resection; UTI, urinary tract infection; UUT, upper urinary tract; VH, visible haematuria.

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Acknowledgements

Sources of funding: None.

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This project was initiated by Mr Leyshon Griffiths (Consultant Urologist, Leicester, Secretary of Action on Bladder Cancer) and Mr Colin Bunce (Consultant Urologist, Middlesex, Chairman of Action on Bladder Cancer). Primary development of the manuscript and co-ordination was conducted by Mr Griffiths with support and advice from Right Angle Communications (Action on Bladder Cancer Secretariat).

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Int J Clin Pract. 2013;67(5):435-448.