MDT (Multi-disciplinary Team) Guidance for Managing Bladder Cancer

Produced by:

- British Association of Urological Surgeons (BAUS) Section of Oncology
- British Uro-oncology Group (BUG)

This guidance has been developed for healthcare professionals and multi-disciplinary teams with the following aims:

- To provide evidence-based guidance on the management options for superficial, muscle-invasive and advanced bladder cancer
- To ensure clarity on the role of the MDT on the management of superficial, muscle-invasive and advanced bladder cancer

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Integrated care and the multi-disciplinary team (MDT)

The provision of a consistent treatment strategy across a multi-disciplinary team (MDT), as well as the model of integrated care is increasingly being adapted as a valuable approach to overcome the fragmentation of patient management. In addition, a MDT provides an ideal framework to conduct audits and facilitate peer review.

The management strategies proposed for patients with superficial, muscle-invasive and advanced bladder cancer within the MDT can be successfully driven when the members of the MDT work together with ongoing support provided by the wider team (Table 1). The MDT can provide patients with treatment options that are specifically tailored to address their individual needs, such as disease state, co-morbid conditions and lifestyle. To ensure the success of the MDT approach, familiarity with the entire spectrum of management strategies is recommended.

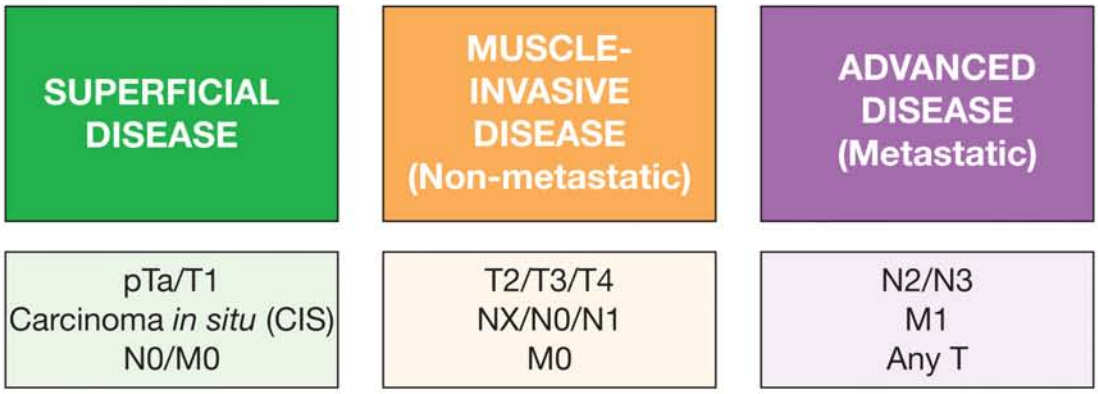
Table 1: Proposed composition of the MDT in the superficial, muscle-invasive and advanced bladder cancer setting

Urological surgeons	Urology and oncology nurse specialists
Clinical and medical oncologists*	Palliative care specialists
MDT co-ordinator and secretarial support	
Radiologists	
Pathologists	

*Medical oncologist attendance is not necessary for low risk superficial disease

The purpose of the treatment algorithms presented in this document is to provide a unique framework that can be adapted for the management of the three main types of bladder cancer: superficial, muscle-invasive and advanced disease (Figure 1). Management of the less common tumours such as squamous cell carcinomas or adenocarcinomas are not addressed within this document. The treatment algorithms illustrated in Figures 2 to 7 depict a management structure where the MDT functions as an efficient single integrated unit.

Figure 1: Summary of the definition of bladder cancer stages



2002 Tumour Node Metastases classification of urinary bladder cancer (2002)

T – 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 muscle
  - T2a Tumour invades superficial muscle (inner half)
  - T2b Tumour invades deep muscle (outer half)
- 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

N – Lymph nodes

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in a single lymph node 2 cm or less in greatest dimension
- N2 Metastasis in a single nymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension
- N3 Metastasis in a lymph node more than 5 cm in greatest dimension

M – Distant metastasis

- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis

Figure 2: Treatment algorithm for superficial disease

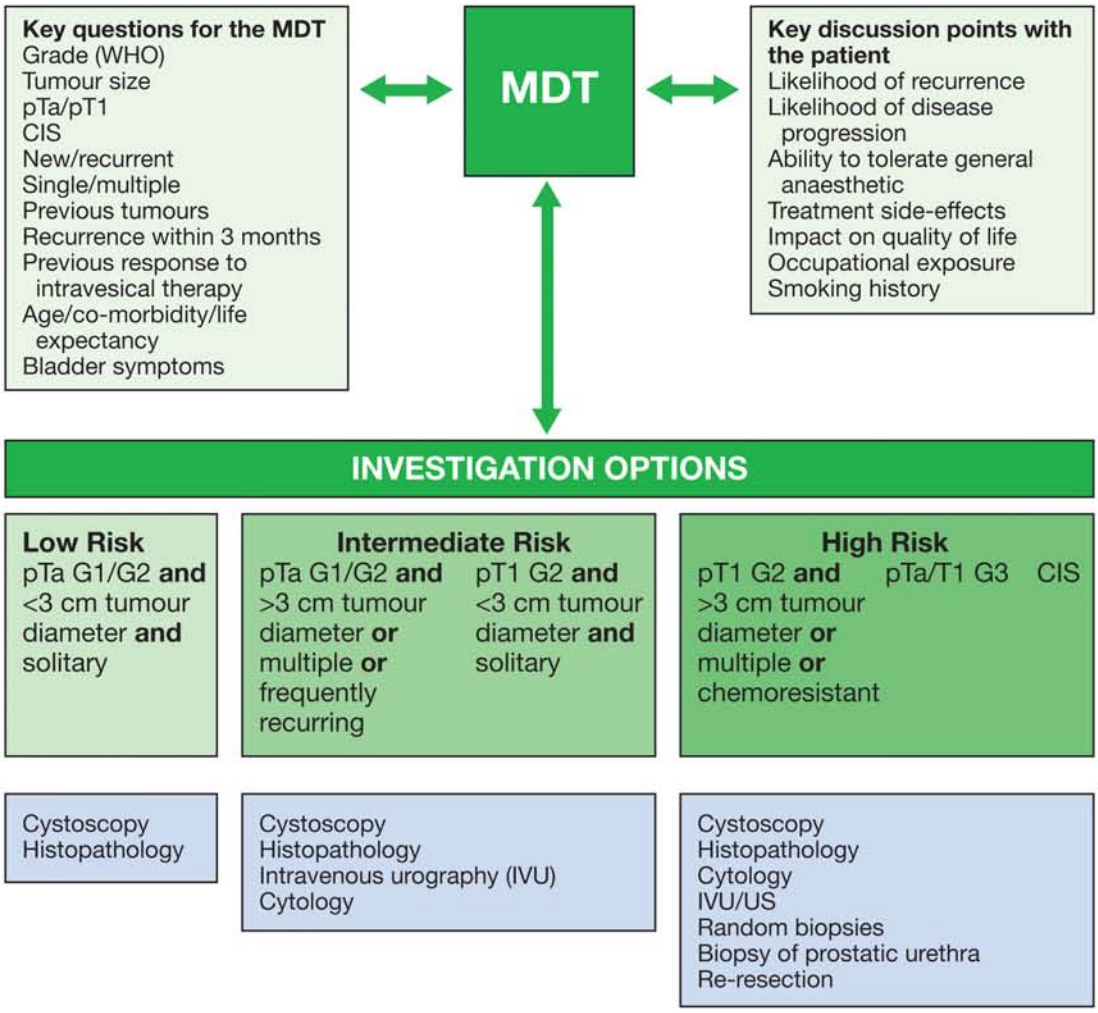


Figure 3: Treatment algorithm for low risk superficial disease

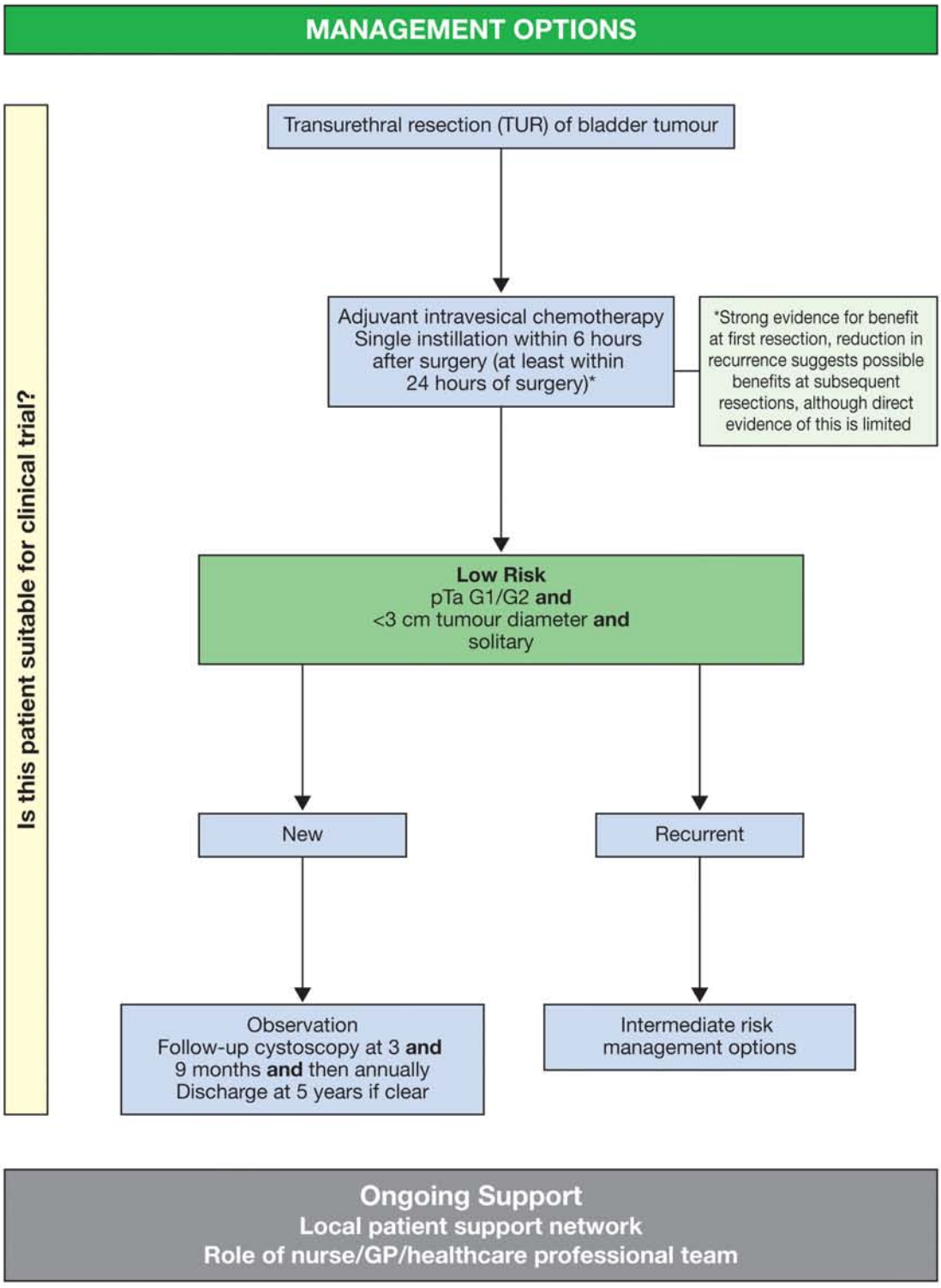


Figure 4: Treatment algorithm for intermediate risk superficial disease

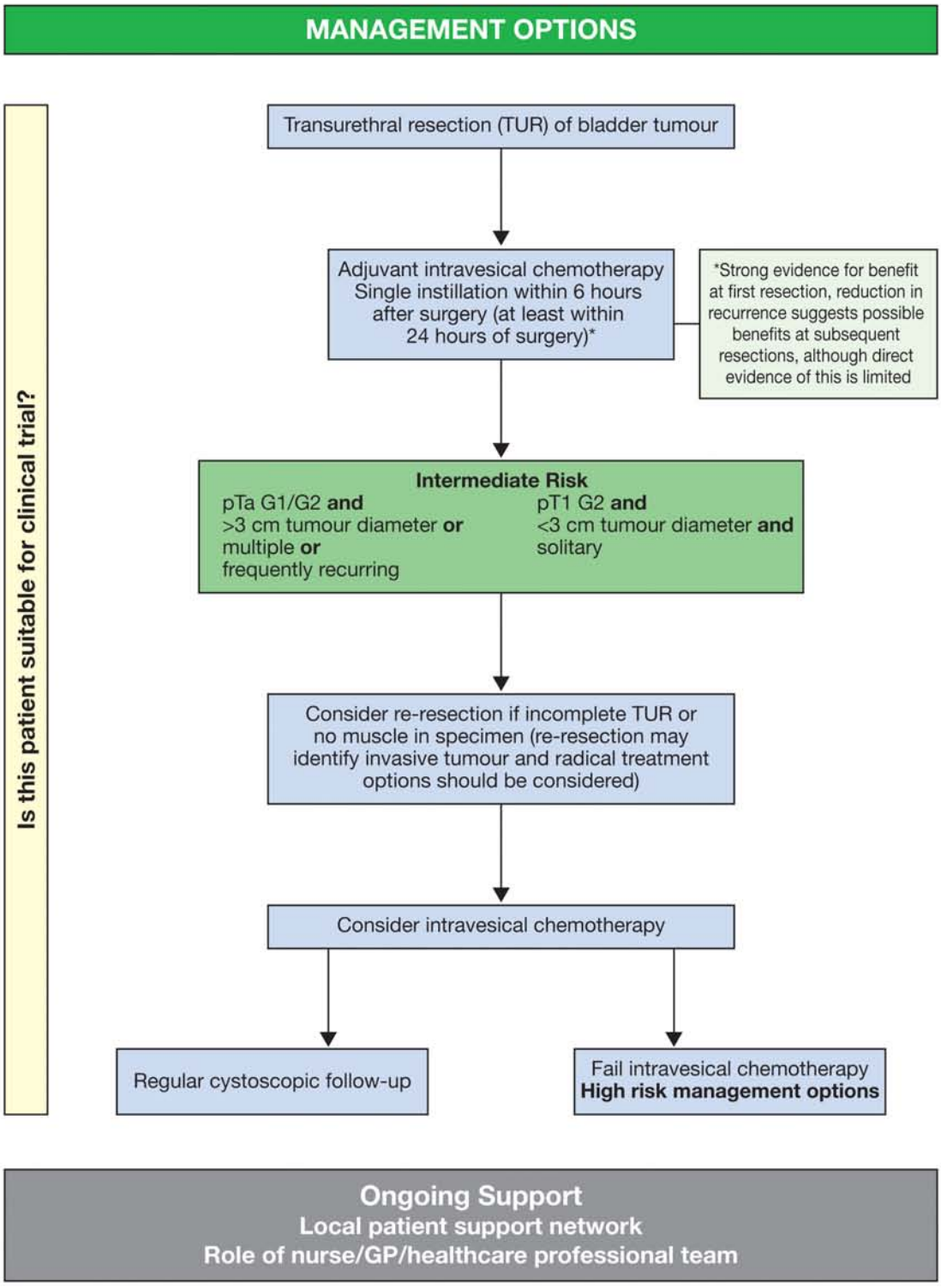


Figure 5: Treatment algorithm for high risk superficial disease

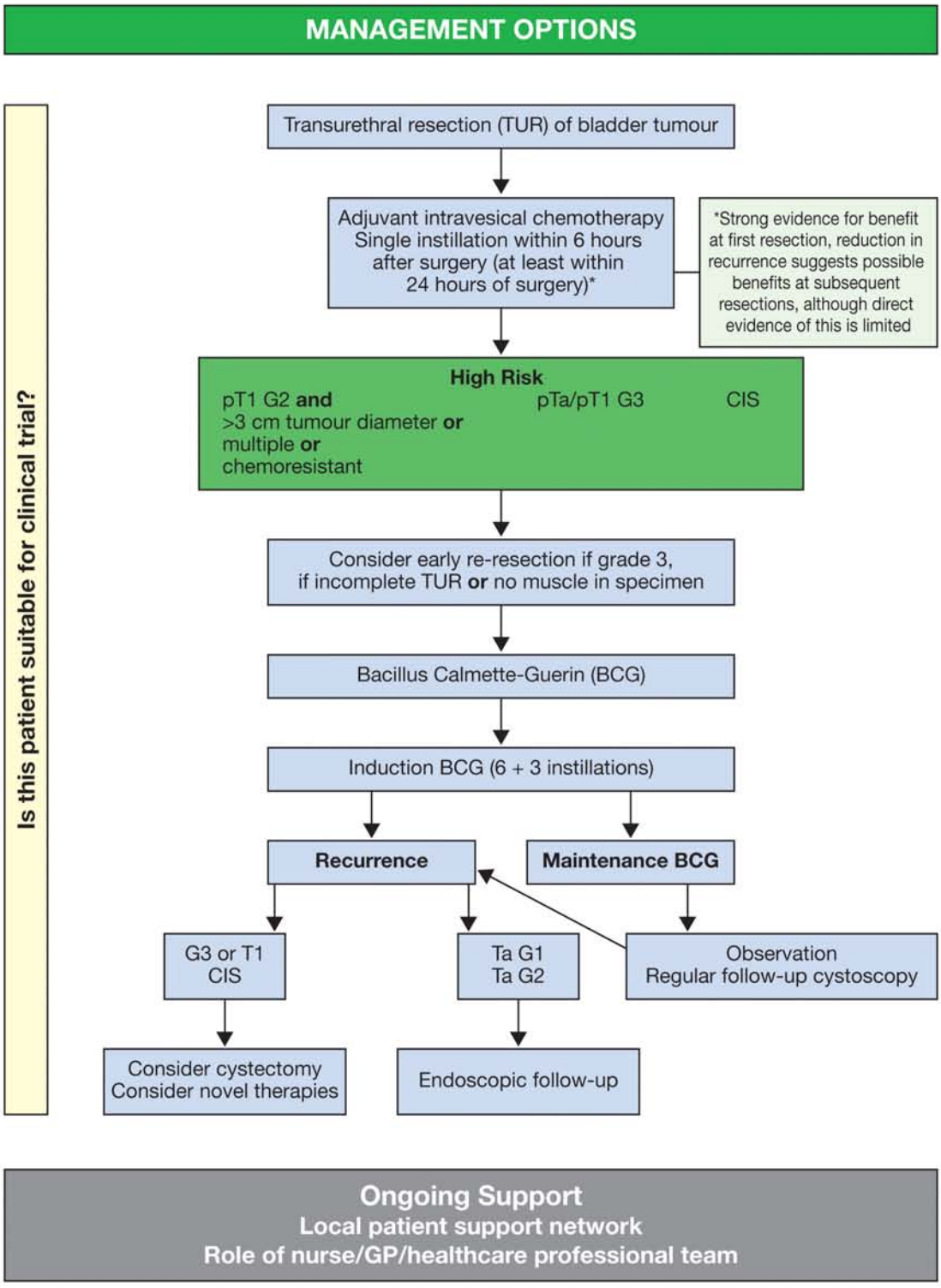


Figure 6: Treatment algorithm for muscle-invasive disease (non-metastatic)

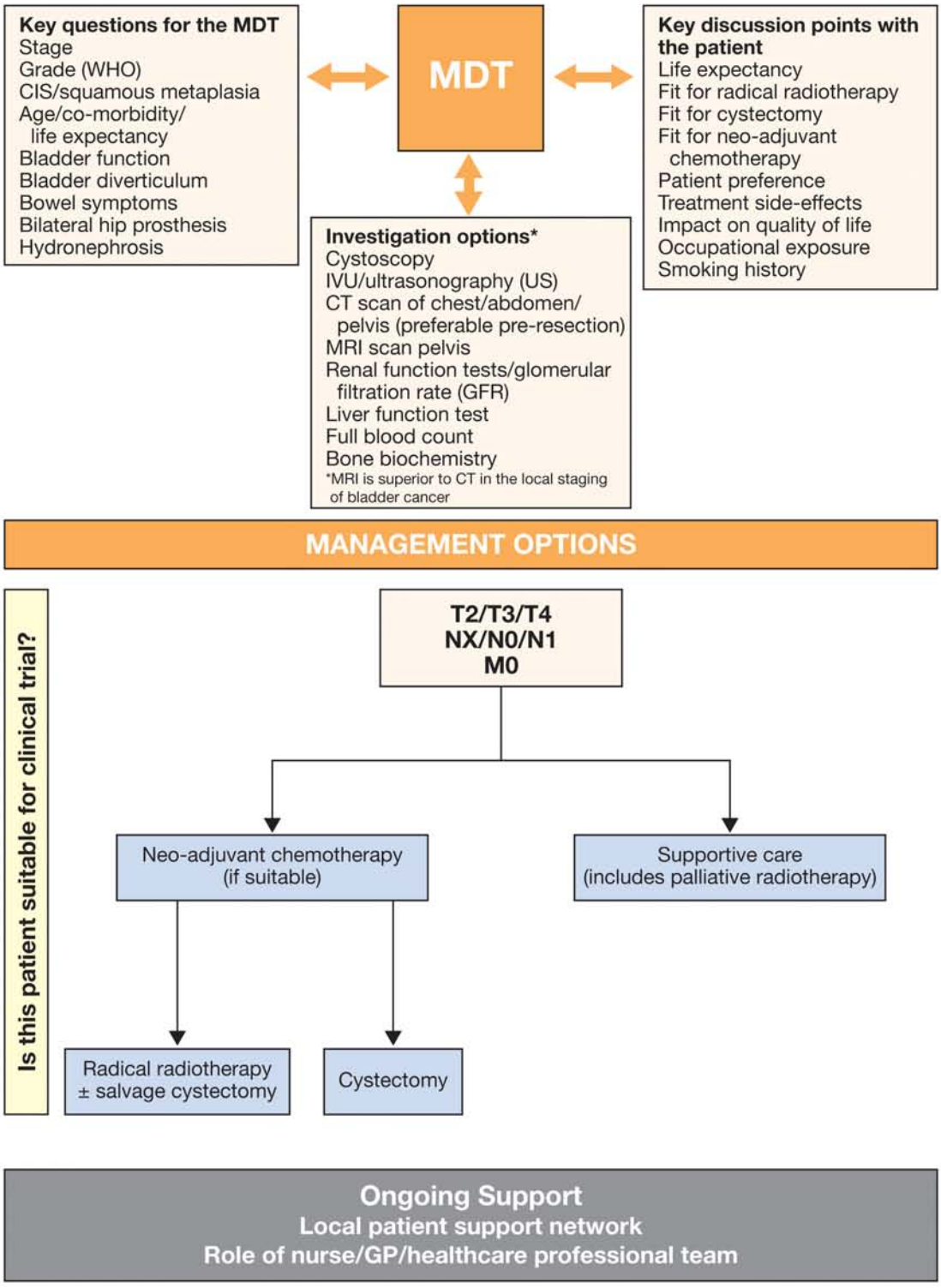
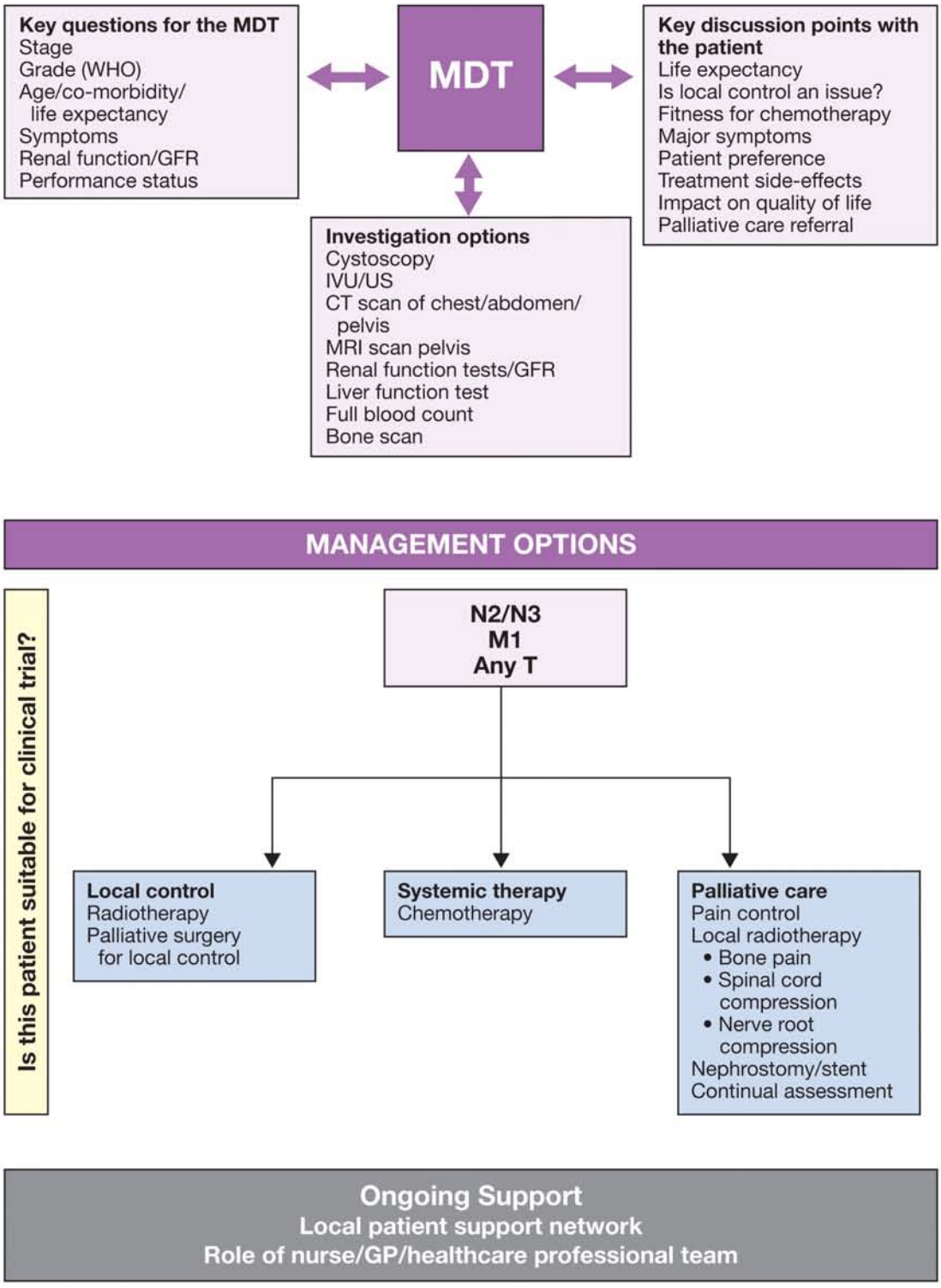


Figure 7: Treatment algorithm for advanced disease (metastatic)



Approach within the MDT

Key questions for the MDT

- Grade (WHO)
- Tumour size
- Stage
- New/recurrent
- Single/multiple
- Previous tumours
- Previous response to intravesical therapy
- Bladder symptoms/function
- Bladder diverticula diagnosis
- Bowel symptoms
- Bilateral hip prosthesis
- Hydronephrosis
- Renal function/GFR
- Age/co-morbidity/life expectancy
- Clinical trials

The MDT plays an essential role in superficial, muscle-invasive and advanced bladder cancer management. However, it is often difficult to know which patients warrant discussion; thus it is essential to ensure that individual patients' details together with their diagnosis are available, as well as a record of any decisions that may have resulted from meetings. It is crucial that in order to fully discuss a particular patients' treatment plan, a member of the MDT team should have already seen the patient. As the majority of patients are sourced through pathology, relapses are more difficult to identify and as such patient identification continues to be a problem.

To ensure that all professional groups and appropriate disciplines contribute to, and participate in, decisions on the clinical management of patients, MDTs have repeatedly been endorsed as the principal way to do this.

One of the key concepts of integrated care is to support the role of the MDT (working as a single unit) but it should not be forgotten that the MDT has the freedom to clinically tailor management strategies for the specific needs of an individual patient.

Treatment strategies are influenced by the following:

- The stage of the bladder cancer, as well as the risk of disease progression, survival and patient characteristics, such as age and general fitness, influence the treatment strategy employed by the MDT. All these factors should be discussed to determine the most appropriate treatment modality for an individual patient. For example, age may be a restrictive factor in opting for surgery for some patients with bladder cancer.

- Patient preference should be discussed within the MDT and the MDT should ensure the involvement of the patient in determining the most appropriate treatment strategy.

- Patient case notes, pathology reports, laboratory test results and radiology data should be made available for discussion at the meeting.

- The inclusion of a patient in an appropriate clinical trial should also be considered.

Approach to the patient

Key discussion points with the patient

- Likelihood of recurrence
- Likelihood of disease progression
- Ability to tolerate general anaesthetic
- Treatment side-effects
- Impact on quality of life
- Occupational exposure and advice
- Smoking history and cessation advice
- Life expectancy
- Fit for radical radiotherapy
- Fit for cystectomy
- Fit for neo-adjuvant chemotherapy/chemotherapy
- Patient preference
- Is local control an issue?
- Major symptoms
- Palliative care referral
- Clinical trials

Patient's expectations

The patient should have the right to discuss their treatment strategy with appropriately trained members of the MDT

The occurrence of any potential adverse-effects associated with each treatment modality and the implications for future lifestyle changes should be discussed with the patient by the healthcare professional when determining an appropriate management option.

To ensure the patient and his/her partner, family and/or carers can make an informed decision, based upon the treatment options that are offered, all the points detailed above should be addressed. For example, the choice between radical radiotherapy and radical cystectomy may be influenced by a patient's anticipated effect of treatment on quality of life.

The available treatment modalities and the potential adverse effects they may have on lifestyle and quality of life should be discussed with all patients.

The lack of guidance for how healthcare professionals should effectively exchange clinical evidence supporting various treatment options to patients facing decisions is acknowledged. However, if recommendations are largely based on appropriate clinical studies and expert opinion, it is possible to achieve the five communication tasks when framing and communicating clinical evidence (Figure 8).

Figure 8: Exchange of clinical evidence with patients

1. Understand the patient's experience, expectations and preferences
2. Build partnerships between the patient and carer
3. Provide evidence, including uncertainties, and discuss adverse events
4. Provide and present recommendations
5. Check for understanding and agreement

Superficial bladder cancer: management options

Transurethral resection of a bladder tumour – first resection

Overview

- Transurethral resection (TUR) is the gold standard for the initial diagnosis and treatment of newly diagnosed, apparently superficial bladder cancer
- The adequacy of the initial TUR and the skills and experience of the surgeon may have a substantial impact on the recurrence rate at the first follow-up cystoscopy

Patient selection

- Newly diagnosed, superficial bladder cancer

Side-effects

- Bleeding
- Infection
- Perforation of the bladder wall
- Clot retention

Clinical evidence

- TUR is used to remove the tumour and to obtain a biopsy specimen, which is subject to pathological analysis to determine the tumour type stage and grade. The pathological report should contain information on the type of specimen, tumour histology, growth pattern, grade and depth of invasion and the involvement of adjacent urothelium. Further details can be obtained in the standards and databases for reporting cancers prepared by the Royal College of Pathologists (Harnden, Ball et al. 2006)
- Brausi et al highlighted that the quality of the initial TUR performed by the individual surgeon may have a substantial impact on the local recurrence rate at the first follow-up cystoscopy (Brausi, Collette et al. 2002). An overall evaluation of 2,410 patients who participated in 7 studies revealed that 316 (13.1%) patients had a recurrence at the first follow-up cystoscopy. When the data were analysed by the number of institutions who enrolled a median of 30 patients with a single tumour, local recurrence rates at the first cystoscopy check-up ranged from 3.5% to 20.6%, which suggested that the quality of the initial TUR was highly variable (Brausi, Collette et al. 2002)

Immediate, single instillation of adjuvant intravesical chemotherapy

Overview

- Based on clinical evidence, a single instillation of adjuvant intravesical chemotherapy after the first resection should be considered the standard of care for all superficial bladder cancer patients
- There is strong evidence for the use of single dose intravesical chemotherapy at first resection. As this reduces recurrence, there is a pragmatic view that it should also be used at each episode of recurrence, but the direct evidence for this is limited
- A meta-analysis conducted by the European Organization for the Research and Treatment of Cancer (EORTC) demonstrated that a single instillation of adjuvant intravesical chemotherapy immediately after TUR reduces the relative risk of local recurrence by 39% in all risk groups (Sylvester, Oosterlinck et al. 2004)
- The single instillation of chemotherapy after TUR is thought to eradicate any tumour left behind after an incomplete TUR and to destroy any circulating tumour cells that could implant at the resection site to prevent recurrence
- Evidence suggests that the first instillation of adjuvant intravesical chemotherapy should be administered on the same day as TUR (Sylvester, Oosterlinck et al. 2004)
- The chemotherapeutic agents mitomycin C, epirubicin, and doxorubicin are all considered to have similar efficacy (Sylvester, Oosterlinck et al. 2004)
- A single instillation of adjuvant intravesical chemotherapy after TUR is cost-effective
- An immediate single instillation of adjuvant intravesical chemotherapy should be avoided when it is obvious or even suspected that the bladder wall is perforated (Oddens, van der Meijden et al. 2004)

Patient selection

- First resection or re-resection after diagnosis of any superficial bladder cancer

Side-effects

- Irritative bladder symptoms including dysuria and frequency, and haematuria
- Allergic skin reactions with mitomycin (Solsona, Iborra et al. 1999)
- Irritative bladder symptoms with epirubicin

Clinical evidence

- A meta-analysis of 7 randomized clinical trials compared one immediate post-operative instillation of adjuvant chemotherapy using mitomycin C, epirubicin, doxorubicin and thiotepa, with TUR alone to determine whether adjuvant chemotherapy decreased the risk of recurrence in patients with single and multiple Ta T1 tumours (Sylvester, Oosterlinck et al. 2004). Recurrence data were available for 1,476 patients at a median follow-up of 3.4 years. One immediate post-operative instillation of adjuvant chemotherapy was associated with a decreased risk of recurrence by 39% (OR 0.61; 95% CI: 0.49 to 0.75; p<0.0001) in patients with Ta T1 cancer. Recurrence occurred in 48.4% (362/748) of patients who had TUR and in 36.7% (267/728) of patients receiving one post-operative instillation of chemotherapy
- Patients with a single tumour (OR 0.61; 95% CI: 0.46 to 0.80; p=0.0005) or multiple tumours (OR 0.44; 95% CI: 0.18 to 1.02; p=0.06) benefited from one immediate instillation of adjuvant chemotherapy; 65.2% of patients with multiple tumours had recurrence compared with 35.8% of patients with single tumours (Sylvester, Oosterlinck et al. 2004). However, in patients with multiple tumours, one instillation may be suboptimal and additional adjuvant treatment is necessary (discussed in more detail below)
- The meta-analysis conducted by the EORTC highlighted that adjuvant chemotherapy is cost-effective. For every 100 patients treated with a single instillation of adjuvant chemotherapy 12 TURs were avoided. Thus, 9 patients must be treated with a single instillation of adjuvant chemotherapy to prevent a recurrence. The cost of a TUR, anaesthesia and hospitalisation is probably more than 9 times that of one instillation of adjuvant chemotherapy (Sylvester, Oosterlinck et al. 2004)
- Kaasinen et al found that the risk of recurrence doubled if the first instillation of mitomycin C was not administered within 24 hours of TUR (Kaasinen, Rintala et al. 2002)
- Bouffioux et al demonstrated that when the first instillation of adjuvant chemotherapy was given within 24 hours after TUR with long-term maintenance chemotherapy patients tended to have less recurrences than those who received treatment later than 24 hours (Bouffioux, Kurth et al. 1995)

Follow-up of patients with low-risk superficial bladder cancer

Overview

- Data on the optimal follow-up regimen for patients with low-risk superficial bladder cancer is limited
- The EAU guidelines recommend that patients with low-risk tumour should have a follow-up cystoscopy at 3 months after the first resection. If recurrence free at 3 months the next cystoscopy is advised at 9 months, and afterwards yearly for 5 years

Clinical evidence

- Oge et al retrospectively evaluated the recurrence and progression rates of 120 patients with pTa G1 or G2 and small (<4 cm) transitional cell carcinoma. The recurrence rate was 6.5% (8/120) at 3 months, and 6.7% (8/119) and 3.6% (4/112) at 6 and 9 months, respectively. When the first 3-month follow-up cystoscopy was clear, the 6-, 9- and 12-month cystoscopy recurrence rates were 4.3% (5/116), 2.7% (3/111) and 8% (8/99) respectively. The progression rate was <1% for the first year (Oge, Erdem et al. 2000)

Additional intravesical chemotherapy for intermediate-risk superficial bladder cancer

Overview

- Tumour recurrence is the main concern with intermediate-risk superficial bladder cancer patients. Tumour recurrence occurs in 45% of patients while progression to muscle-invasive disease is 1.8% (Millan-Rodriguez, Chechile-Toniolo et al. 2000)
- The results of an EORTC and Medical Research Council (MRC) meta-analysis showed that adjuvant chemotherapy after TUR prevents disease recurrence; however, it has no apparent effect on disease progression (Pawinski, Sylvester et al. 1996)
- The prophylactic effect of a single instillation of chemotherapy after TUR lasts for one to two years (Hinotsu, Akaza et al. 1999; Solsona, Iborra et al. 1999)
- However, the optimal schedule and ideal additional adjuvant chemotherapy regimen needs to be determined for this patient population

Patient selection

- Recurrent pTa G1/G2
- pTa GI/G2 and either >3 cm tumour diameter or multiple tumours
- pT1 G2 and <3 cm tumour diameter and single

Side-effects

- Irritative bladder symptoms and haematuria
- Infection

Clinical evidence

- A meta-analysis of 5 studies of the Japanese Urological Cancer Research Group (JUCRGA) which included 1,732 patients with superficial bladder cancer revealed that the prophylactic effect of intravesical chemotherapy after TUR continues for a period of 500 days (Hinotsu, Akaza et al. 1999)
- Two parallel randomized studies conducted by the EORTC highlighted that 1-year of monthly (15 instillations) maintenance chemotherapy was no more effective than 6 months (9 instillations) of treatment in reducing the recurrence rate when the first instillation was given immediately after TUR (Bouffioux, Kurth et al. 1995)
- Similar findings were reported by Nomata and colleagues who showed that the 3 year recurrence-free survival rates were comparable between short-term and long-term epirubicin treatment (55.1% versus 48.5% respectively) (Nomata, Noguchi et al. 2002)
- More recently, a Japanese randomized trial of 150 patients with Ta T1 bladder cancer demonstrated that long-term epirubicin therapy was more effective than short-term treatment after TUR in preventing recurrence (Koga, Kuroiwa et al. 2004). At 3 years, the recurrence rate was 14.8% in the group who received 1-year of epirubicin (19 instillations) compared with 36.1% in those who received 3 months of epirubicin (9 instillations) after TUR (Koga, Kuroiwa et al. 2004)
- The MRC have shown that five doses of adjuvant chemotherapy is not superior to a single dose and that the treatment effect of a single dose lasts for at least 7 years (Tolley, Parmar et al. 1996)

Adjuvant BCG for high-risk superficial bladder cancer

Overview

- The risk for tumour recurrence and progression to muscle-invasive disease is high within this group of patients with superficial bladder cancer (Heney, Ahmed et al. 1983; Torti, Lum et al. 1987; Parmar, Freedman et al. 1989). Patients who have multiple tumours at presentation and recurrence at 3 months have a 1-year risk of recurrence of 90% (Parmar, Freedman et al. 1989)
- Clinical evidence from meta-analyses of randomized clinical trials has demonstrated that maintenance BCG reduces recurrence and prevents or delays muscle-invasive disease progression (Sylvester, van der Meijden et al. 2002; Bohle and Bock 2004; Shelley, Wilt et al. 2004)
- The evidence is that BCG without maintenance is not better than TUR alone. BCG with maintenance is superior to no maintenance, but the optimum maintenance schedule is not yet known. A commonly used schedule is that described by Lamm et al, who recommends 27 doses over 3 years (Lamm, Blumenstein et al. 2000)

Patient selection

- pT1 G2 and either >3 cm tumour diameter or multiple tumours
- pTa/T1 G3
- Carcinoma in situ (CIS)
- Immunocompetent (avoid patients with leukaemia/lymphoma, HIV infection, organ transplant, steroid and active and previous GU TB infection)
- Caution if previous pelvic radiotherapy > 40Gy

Side-effects

- Local side effects such as bacterial cystitis, BCG induced cystitis, and macroscopic haematuria occur in 75% of patients (van der Meijden, Sylvester et al. 2003)
- Systemic side effects such as fever, general malaise and skin rash were reported in 39% of patients (van der Meijden, Sylvester et al. 2003)

Clinical evidence

- Intravesical maintenance BCG is statistically superior to mitomycin C in reducing recurrence in high-risk patients. A sub-analysis of a meta-analysis which included data from high-risk patients demonstrated that the log hazard ratio for tumour recurrence was –0.37 (variance 0.01) which translated into a 31% reduction in the hazard of recurrence with BCG ($p<0.001$) (Shelley, Wilt et al. 2004)
- A meta-analysis of 11 clinical trials performed by Bohle and colleagues demonstrated that adjuvant intravesical BCG therapy was statistically superior to mitomycin C in reducing tumour recurrence (OR 0.56; 95% CI: 0.38 to 0.84; $p=0.005$) (Bohle, Jocham et al. 2003; Bohle and Bock 2004)
- A meta-analysis of 24 clinical trials with data relating to progression on 4,863 patients was conducted by the EORTC (Sylvester, van der Meijden et al. 2002). Of the 24 trials, BCG maintenance therapy was not given in 4 studies, and 5 different strains of BCG were used. Overall, 81.6% (n = 3,967) of patients had papillary tumours and 18.4% (n = 896) had primary or concomitant CIS. At a median follow-up of 2.5 years with a maximum of 15 years, 9.8% (260/2,658) of patients on TUR plus BCG progressed compared with 13.8% (304/2,205) of patients who received TUR alone, TUR plus intravesical chemotherapy or TUR plus another immunotherapy. Overall, treatment with maintenance BCG was associated with a 27% reduction in tumour progression (OR 0.73; 95% CI: 0.60 to 0.89; $p=0.001$) (Sylvester, van der Meijden et al. 2002)
- Similar treatment effects were reported in the 2,880 patients with only papillary tumours (OR 0.68; 95% CI: 0.50 to 0.93; $p=0.001$) and in the 403 patients with CIS (OR 0.65; 95% CI: 0.36 to 1.16; $p=0.001$) (Sylvester, van der Meijden et al. 2002)
- Patients receiving maintenance BCG benefited and a 37% reduction in progression was observed (OR 0.63; 95% CI 0.51 to 0.78; $p =0.00004$). No reduction in progression was reported in the 4 trials where maintenance BCG was not administered (Sylvester, van der Meijden et al. 2002)
- A second meta-analysis of 9 clinical trials performed by Bohle and colleagues demonstrated that maintenance BCG therapy was statistically superior to mitomycin C in preventing disease progression (OR 0.66; 95% CI: 0.47 to 0.94; $p=0.02$) (Bohle and Bock 2004). The authors concluded that maintenance BCG should be provided for at least 1 year to demonstrate superiority to mitomycin C (Bohle and Bock 2004)

- The results of the SWOG 8507 study authored by Lamm and colleagues reported that maintenance BCG therapy for 3 years was associated with a disease free survival period of nearly twice as long compared with no maintenance BCG therapy (76.8 months; 95% CI: 64.3 to 93.2 versus 35.7 months; 95% CI: 25.1 to 56.8; p<0.0001). The schedule reported in this paper (27 doses over 3 years) has become commonplace in the high-risk bladder cancer setting (Lamm, Blumenstein et al. 2000)
- The EORTC GU Group carried out a large number of randomised trials in superficial bladder cancer patients which has allowed the development of a risk assessment for recurrence and progression (Sylvester, van der Meijden et al. 2006). The annual risk of and cumulative risk of tumour recurrence and progression can be made using the EORTC scoring system which combines data on previous tumour recurrence rate, number of tumours, tumour diameter, T category and WHO grade and presence or absence of concomitant CIS. The web based EORTC risk calculator can be downloaded from http://www.eortc.be/tools/bladdercalculator/default.htm

Complications of BCG therapy

- BCG therapy may provoke both local and systemic side effects and these can be serious in approximately 5% of treated patients. Only the systemic side effects can be serious and life threatening and require early systemic therapy
- Therefore, it is important to prevent complications and BCG instillation should be avoided after traumatic catheterisation, when frank haematuria persists after bladder biopsy, during the first 14 days after TUR and when irritative voiding symptoms or systemic upset persist after previous instillations of BCG
- It is expected that with repeated instillation, patients will develop short lived bladder irritative symptoms lasting perhaps 48-72 hours associated with mild fever and arthralgia and even frank haematuria. Persistence of these symptoms is a warning to defer the next instillation until they have settled and to consider dose reduction to 1/3 to 1/10
- Granulomatous prostatitis occurs in the majority of treated men, it is usually asymptomatic and requires no treatment
- Epididymitis can be due to either BCG infection or more usual uropathogens. Appropriate initial treatment is with a quinolone antibiotic which covers both these possibilities with the addition of isoniazid 300mg daily for 6 weeks

- Generalised polyarthritis, often associated with conjunctivitis, does occur and there is an association with the HLA-B27 genotype. Treatment with systemic steroids and isoniazid is required and no further BCG therapy should be given
- Miliary BCG infection affecting lungs, liver, kidneys and brain may rarely occur as may BCG septicaemia. If clinically suspected then there should not be a delay before the administration of triple anti-tuberculosis chemotherapy and high dose systemic steroids. Blood PCR testing for TB can help with more rapid diagnosis. The recommended regime is isoniazid 300 mg daily for 3 months, rifampicin 600 mg daily and ethambutol 1,200 mg daily for 6 weeks and prednisolone 40 mg daily or greater iv during the acute stages (Bohle and Jocham 2000)

Therapies for patients who fail to respond to BCG therapy

Overview

- A change in approach should be undertaken for high-risk superficial disease patients who fail to respond to BCG within 6 months of initiating therapy
- Standard treatment should be radical cystectomy and delaying beyond this may lead to progression and advanced disease (discussed in more detail in the management options for muscle-invasive bladder cancer). Radiotherapy has no place in the management of superficial bladder cancer which has failed to respond to BCG therapy
- Some patients will be either unfit or unwilling to undergo cystectomy and could be offered other therapies. The use of these is not well established and therefore the risks need to be conveyed to the patient
    - Small studies have shown that 1/3 dose of BCG combined with 50 mega units of interferon alpha given intravesically will produce a complete tumour response in 50% patients who have failed on BCG alone (O'Donnell, Krohn et al. 2001)
    - More recently, it has been shown that the combination of sequential BCG and electromotive mitomycin is associated with higher disease free survival intervals compared with BCG alone. The authors proposed that the BCG-induced inflammation may have increased the bladder uptake of mitomycin (Di Stasi, Giannantoni et al. 2006)
    - Carcinoma *in situ* is an ideal tumour type that can be treated with photodynamic therapy but there are few centres with suitable equipment

Muscle-invasive bladder cancer: management options

Radical treatments

- There is no consistent evidence for superiority of the two main radical treatments: radical radiotherapy or radical cystectomy
- Patient preference and the presence or absence of co-morbidities should be considered when determining the appropriate treatment

Patient selection

- A number of factors result in the selection of either cystectomy or radical radiotherapy as the preferred treatment modality. Where there are no clear medical indications for either treatment then patient choice becomes the dominant selection criteria

The following factors favour surgical treatment

1. Poor bladder function, especially small capacity
2. Widespread CIS or CIS remote from muscle invasive tumour
3. Large volume tumours
4. Multifocal disease
5. Pre-existing hydronephrosis
6. Previous pelvic radiotherapy
7. Active inflammatory bowel disease
8. Bilateral total hip replacements
9. Pregnancy

The following factors favour radiotherapy

1. Extreme old age
2. Unfit for surgery

Radical radiotherapy

Overview

- Overall survival rates of 40–50% for T2 tumours, 20–30% for T3 tumours and 5–10% for T4 tumours have been reported with radical radiotherapy
- More recently, clinical studies of chemo-radiotherapy have demonstrated improvements in survival rates and bladder preservation rates
- The results of the UK BC 2001 study should help to clarify whether non platinum-containing chemo-radiotherapy is a valuable option in the conservative management of invasive bladder cancer

Patient selection

- T2/T3/T4
- NX/N0/N1
- M0

Side-effects

- Acute side effects include diarrhoea, tenesmus, proctitis, cystitis and lethargy
- Late side effects such as bladder fibrosis, second malignancies, haematuria and impotence

Clinical evidence

- Bell et al evaluated the efficacy and morbidity of definitive external beam radiotherapy (40–65 Gy, median fractions = 20) in 120 patients with muscle–invasive bladder cancer over an 8-year period in the UK (Bell, Lydon et al. 1999). Overall morbidity at 12 months was 12% (proctitis 8% and cystitis 4%). Local recurrence developed in 77 (59%) patients, which was invasive in 36 (30%) patients. The overall median survival rate at 5 years was 50% and 33 (27%) patients underwent a salvage cystectomy (Bell, Lydon et al. 1999)
- Clinical studies of chemo-radiotherapy have been associated with 5-year survival rates of 50–60%, with bladder preservation (Housset, Maulard et al. 1993; Kachnic, Kaufman et al. 1997; Sauer, Birkenhake et al. 1998)

- Coppin et al (NCI of Canada) demonstrated that concurrent cisplatin (3 cycles of 100 mg/m2 at 2 weekly intervals) with radiotherapy improved pelvic control of locally advanced bladder cancer (Coppin, Gospodarowicz et al. 1996). The risk of pelvic failure was significantly reduced with chemo-radiotherapy compared with radiotherapy (15/51 versus 36/48, p=0.026) with a corresponding improvement in pelvic-progression free survival (67% versus 47% at 2 years, p=0.038) and bladder preservation (70% versus 36%, p=0.16). The chemo-radiotherapy was not associated with any significant improvements in overall survival compared with radiotherapy alone (47% versus 33% at 3 years) (Coppin, Gospodarowicz et al. 1996)

Radical cystectomy

Overview

- Radical cystectomy is used for muscle-invasive bladder cancer
- Patients should be informed of the urinary diversion techniques performed after radical cystectomy which include an ileal conduit; a bladder reconstruction or a continent diversion

Lymph node dissection

- Long term survival has been reported in patients with positive lymph nodes who have undergone lymphadenectomy. Hence, lymphadenectomy appears to be curative in some patients. There is disagreement regarding the extent of lymphadenectomy required and it has been reported in the literature that if 9–16 nodes are removed prognosis is improved. However, this is most marked in patients who are node negative. Currently, it is believed that the removal of 10 or more nodes is a marker of high quality surgery (Ghoneim and Abol-Enein 2004; Simms, Mann et al. 2005; Honma, Masumori et al. 2006; Stein, Quek et al. 2006; Stein, Quek et al. 2006)

Urethrectomy

- There is no clear consensus on the role of urethrectomy. Those who favour a non selective approach claim that risk factors cannot predict all patients who will develop a urethral recurrence, while those who offer a selective approach point to the decreased morbidity of this strategy (Carrion and Seigne 2002; Van Poppel and Sorgeloose 2003; Clark and Hall 2005)

Factors which predict urethral recurrence

- Distant CIS
- Prostatic urethral involvement
- Positive urethral resection margin

Factors which may protect against urethral recurrence

- Orthotopic bladder reconstruction
- Radical radiotherapy

Patient selection

- T2 T3 T4
- NX/N0/N1
- M0
- Anaesthetic fitness
- Performance status
- Age

Side-effects

- High risk of infection and bleeding associated with the surgical procedure. Morbidity in around 30% of patients, operative morbidity in 1–6% in contemporary literature

Clinical evidence

- Stein et al reported the long-term effects of radical cystectomy with pelvic lymph node dissection in 1,054 patients with invasive bladder cancer (Stein, Lieskovsky et al. 2001). Overall, there were 27 (2.5%) perioperative deaths and 292 (28%) early complications. Recurrence-free and overall survival at 5 years was 68% and 60%, respectively, and 66% and 43%, respectively, at 10 years. Furthermore, in patients with muscle invasive (P2 and P3a), lymph node–negative tumours, 89% and 87%, and 78% and 76% had 5- and 10-year recurrence-free survival, respectively (Stein, Lieskovsky et al. 2001)
- The role of pre-operative radiotherapy prior to cystectomy was compared with cystectomy alone in a meta-analysis of 5 randomized controlled trials (Huncharek, Muscat et al. 1998). The data did not support the routine use of pre-operative radiotherapy prior to cystectomy

- A meta-analysis of 3 randomized trials compared pre-operative radiotherapy (40 Gy to 50 Gy in 4 to 5 weeks) followed by radical cystectomy with radical radiotherapy and salvage cystectomy in 439 patients with T2 to T4a bladder cancer (Shelley, Barber et al. 2002). The intention to treat analysis revealed that there was an overall survival benefit with pre-operative radiotherapy followed by radical cystectomy at 3 years (OR 1.91; 95% CI: 1.30 to –2.82) and 5 years (OR 1.85; 95% CI:1.22 to –2.82). Mean overall survival at 3 and 5 years was higher with pre-operative radiotherapy followed by radical cystectomy than radical radiotherapy (45% and 36% for cystectomy and 28% and 20% for radical radiotherapy) (Shelley, Barber et al. 2002). In light of the advances in both radiotherapy and cystectomy, the significance of these findings are uncertain

Neo-adjuvant chemotherapy

Overview

- The use of neo-adjuvant chemotherapy prior to radical radiotherapy or radical cystectomy in muscle invasive bladder cancer is associated with improvements in survival rates (Advanced Bladder Cancer (ABC) Meta-analysis Collaboration 2003)

Patient selection

- T2 T3 T4
- NX/N0/N1
- M0

Clinical evidence

- A neo-adjuvant chemotherapy trial randomized 976 patients with T2–T4a bladder cancer to curative cystectomy or external beam radiotherapy alone or 3 cycles of neo-adjuvant cisplatin, methotrexate and vinblastine (CMV) chemotherapy prior to cystectomy or radiotherapy (International collaboration of trialists 1999). The survival rate was consistently higher among patients who received neo-adjuvant CMV chemotherapy compared with those who did not receive chemotherapy (5-year survival rate of 50% versus 44% and an 8-year survival rate of 43% versus 37%, respectively) (Hall 2002)

- A meta-analysis of 10 neo-adjuvant chemotherapy clinical trials with data on 2,688 patients revealed that neo-adjuvant chemotherapy had a beneficial effect on overall survival with an improvement of 3% at 5 years (Advanced Bladder Cancer (ABC) Meta-analysis Collaboration 2003). However, combination platinum-based neo-adjuvant chemotherapy was better with a 5% improvement in survival at 5 years, improving overall survival from 45% to 50% (HR 0.87; 95% CI: 0.78 to 0.97; p=0.016) (Advanced Bladder Cancer (ABC) Meta-analysis Collaboration 2003)
- A further study by Grossman et al (SWOG 8710) randomized 307 patients with T2–T4a muscle invasive bladder cancer to radical cystectomy alone or 3 cycles of neo-adjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) chemotherapy before radical cystectomy (Grossman, Natale et al. 2003). The median survival was clinically and significantly higher among patients who received neo-adjuvant chemotherapy compared with patients in the cystectomy group (77 months versus 46 months; p=0.06). The estimated risk of death was reduced by 25% (HR 1.33; 95% CI: 1 to 1.760) in the neo-adjuvant chemotherapy plus cystectomy group (Grossman, Natale et al. 2003)

Advanced (metastatic) disease: management options

Local control

- The MRC trial BA09, compared the efficacy of 35 Gy in 10 fractions over 2 weeks with 21 Gy in 3 fractions over 10 days in 272 patients considered to be unsuitable for curative treatment through disease stage or co-morbidity (Duchesne, Bolger et al. 2000). The shorter, fractioned schedule of palliative radiotherapy (21 Gy in 3 fractions) was as effective as the 35 Gy in 10 fractions in providing overall symptomatic improvement (64% versus 71% respectively) (Duchesne, Bolger et al. 2000)

Systemic chemotherapy

Overview

- The M-VAC regimen and gemcitabine/cisplatin (GC) combination schedule can be used for the management of advanced bladder cancer
- Median survival rates of 12-14 months have been reported with these regimens

Side-effects

- M-VAC treatment is associated with substantial toxicity, including neutropenia, mucositis and toxic deaths. Side effects may be problematic for older patients, who may also present with co-morbidities
- GC has a better safety and tolerability profile then M-VAC, with a reduced frequency of grade 3/4 neutropenia, neutropenic fever, mucositis and alopecia occurring in GC treated patients

Clinical evidence

- The superiority of M-VAC compared with single agent cisplatin has been demonstrated in a randomized trial of 269 patients with advanced bladder cancer (Loehrer, Einhorn et al. 1992). The median overall survival was 12.5 months for M-VAC versus 8.2 months for cisplatin (p=0.04). M-VAC was associated with a greater toxicity, in particular leukopenia, mucositis and granulocytopenic fever (Loehrer, Einhorn et al. 1992). Long-term follow-up confirmed that M-VAC was superior to single-agent cisplatin; however, at 6 years, only 3.7% of the patients randomized to M-VAC were alive and continuously disease-free (Saxman, Propert et al. 1997)

- M-VAC was also compared with cisplatin, cyclophosphamide, and doxorubicin (CISCA) in a randomized trial of 110 patients (Logothetis, Dexeus et al. 1990). M-VAC had a higher response rate and longer median survival compared with CISCA (65% versus 46%, $p<0.05$; 48 weeks versus 36 weeks, respectively) (Logothetis, Dexeus et al. 1990)
- Furthermore, M-VAC given as a 2 weekly schedule with granulocyte colony stimulating factor (GCSF) (known as accelerated M-VAC) was associated with improved outcomes and lower toxicity than standard M-VAC. In a randomised trial of 263 patients with advanced bladder cancer, accelerated M-VAC achieved higher response rates than standard M-VAC (62% versus 50%, respectively; $p=0.06$) (Sternberg, de Mulder et al. 2001). Progression free survival was also significantly better with accelerated M-VAC compared with standard M-VAC (9.1 months versus 8.2 months, respectively; HR 0.75; 95% CI: 0.58 to 0.98; $p=0.037$) (Sternberg, de Mulder et al. 2001). The 2- and 5- year survival rates were 36.7% and 21.8% for accelerated MVAC compared with 26.2% and 13.5% for standard MVAC (Sternberg, de Mulder et al. 2006). The mortality HR was 0.76 (Sternberg, de Mulder et al. 2006)
- GC has shown similar survival rates to M-VAC but appears to be better tolerated (von der Maase, Hansen et al. 2000). In a randomized trial of 405 patients with advanced bladder cancer, median overall survival was comparable in both groups (HR 1.04; 95% CI: 0.82 to 1.32; $p=0.75$). Median survival was 13.8 months with GC compared with 14.8 months with M-VAC (von der Maase, Hansen et al. 2000). Time to progressive disease, time to treatment failure and response rate were comparable in both groups. Toxicity with GC was substantially lower than with M-VAC. Grade 3/4 neutropenia, neutropenic fever, mucositis and alopecia occurred more frequently in patients who received M-VAC. The toxic death rate was lower among patients who received GC compared with M-VAC (1% versus 3%, respectively) (von der Maase, Hansen et al. 2000)
- The combination of cisplatin, gemcitabine and taxol in a phase I/II study in 60 previously untreated advanced disease patients demonstrated an overall response rate of 77.6% (95% CI: 60 to 98) and a complete response rate of 27.6% (Bellmunt, Guillem et al. 2000)
- Sternberg et al demonstrated that a gemcitabine and taxol regimen in patients who had previously failed M-VAC was associated with a median survival of 14.4 months (Sternberg, Calabro et al. 2001)

Palliative care

- Short courses of radiotherapy can provide effective palliation of the symptoms of locally advanced disease in the pelvis or painful metastatic bone lesions

Investigation options

- Intravenous urography (IVU)
- Urinary cytology
- Cystoscopy
- Histopathology
- Computed tomography (CT) scan chest/abdomen/pelvic region
- Magnetic resonance imaging (MRI) scan of pelvis
- Renal function test/glomerular filtration rate (GFR)
- Liver function test
- Full blood count
- Bone scan
- Bone biochemistry

Symptoms

- Haematuria is usually the first sign of bladder cancer, it is microscopically present in almost all patients with cystoscopically detectable tumours (Messing and Vaillancourt 1990)
- Lynch et al reported that only 50% of patients with a tumour have micro haematuria on repeat testing (Lynch, Waymont et al. 1994)
- Voiding difficulties such as urgency, increased frequency and dysuria are associated with more advanced bladder cancer

Urinary cytology

- The diagnosis of a high-grade tumour or CIS can be made from a cytological examination of voided urine. Urinary cytology is very useful for the detection and monitoring of bladder cancer, based on its proven high specificity and because it is non-invasive and widely available (Badalament, Fair et al. 1988)

Cystoscopy

- Cystoscopy guided by white light is the gold standard for the detection and follow-up of bladder cancer
- Fluorescence cystoscopy is a new investigational diagnostic procedure which has been shown to improve the detection of bladder tumours, especially CIS (Jichlinski, Guillou et al. 2003; Schmidbauer, Witjes et al. 2004)
- Filbeck et al reported that a single blue light cystoscopy reduces recurrence by 24% (Filbeck, Pichlmeier et al. 2002)

Histopathology

- To limit the variability in classifying and grading Ta and T1 tumours, it is recommended that the urologist review the histological findings with the pathologist (Murphy, Takezawa et al. 2002; Bol, Baak et al. 2003)

Intravenous urography (IVU)

- The incidence of upper urinary tract tumours increases in high grade bladder cancer. Performing a routine IVU procedure for patients with primary bladder cancer may not be necessary (Hastie, Hamdy et al. 1991; Holmang, Hedelin et al. 1995; Goessl, Knispel et al. 1997; Herranz-Amo, Diez-Cordero et al. 1999; Hession, Flynn et al. 1999)
- High risk superficial disease (CIS, multifocal tumours, tumours in the trigone, patients receiving intravesical chemotherapy)
    - The risk of synchronous and metachronous upper tract tumours in this group of patients is higher and IVU at diagnosis and yearly surveillance is recommended (Miller, Eure et al. 1993; Holmang, Hedelin et al. 1995; Solsona, Iborra et al. 1997; Hession, Flynn et al. 1999)
    - CT urography can be used in patients having equivocal IVU

Ultrasonography (US)

- There is no role for US in the investigation of established bladder cancer. It should be restricted for the evaluation of metastases in patients who have contraindications to CT or MRI. The sensitivity of US for the evaluation of metastatic disease is low compared to CT or MRI (Kinkel, Lu et al. 2002)

Computed tomography (CT) scan chest/abdomen/pelvic region

- CT scanning is useful for assessing the extent of an invasive tumour and for monitoring patients undergoing adjuvant chemotherapy or bladder sparing treatment options
- There is no published evidence supporting the role of whole body CT evaluation of metastatic disease in patients with bladder cancer. However, some centres use CT scanning for patients with muscle invasive disease

Magnetic resonance imaging (MRI) scan of pelvic region

- MRI scanning of the bladder should be used for the staging of suspected muscle invasive disease. MRI scanning is superior to CT scanning in evaluating the T staging of bladder cancer (Barentsz and Witjes 1998; Tekes, Kamel et al. 2005; Zhang, Gerst et al. 2007)

Renal function test/GFR/liver function test/full blood count/bone biochemistry

- These tests are useful in the detection of advanced disease

Bone scans

- Evidence suggests that there is no useful correlation between the findings of a pre-cystectomy bone scan and the clinical course of the disease in patients with ≥T2 stage bladder cancer and no clinical suspicion of bone metastases (Braendengen, Winderen et al. 1996). Therefore, routine bone scans for all patients with bladder cancer are not recommended

Ongoing support
Local patient support network
Role of nurse/GP/healthcare professional team

- Regular communication between the MDT and the primary care team are key to providing ongoing support, and may include the following:
    - Provision of detailed discharge or out-patient summaries in a timely manner
    - Rationale why a particular treatment option has been chosen
    - Details of the patient's response to the chosen treatment
    - Exchange of protocols
    - Electronic educational resources
    - Agreement on prescribing policies
    - Provision of contact details for information exchange

- In addition to the MDT and primary care team, the local patient support network, such as a partner or family member, should be included in the exchange of information and/or education process which may include patient information material

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