1. Introduction

Bladder cancer is the fourth most common malignancy among men in the Western world (after prostate, lung, and colon cancers) [1] and accounts for approximately 5–10% of all cancers in Europe and the United States [2]. The incidence of bladder cancer increases with age [2] and is up to 3-fold more common in men than in women [3]. Although infection with schistosomiasis is linked to development of bladder cancer throughout Africa and parts of Asia [4], in Western countries cigarette smoking is the most closely linked risk factor, contributing to >50% of cases of bladder cancer [1]. Other risk
factors include a family history of bladder cancer, treatment with certain drugs (such as cyclophosphamide), and exposure to carcinogens in the workplace [1]. In general, bladder cancer is confined to one of two categories: noninvasive (Ta, TIS, T1) or invasive (T2–T4).

Using two clinical scenarios, this paper examines some recent advances in the management of both noninvasive and invasive bladder cancer. For non-invasive bladder cancer, these include the use of fluoroscopic and cystoscopic detection, intravesical therapy after transurethral resection (TUR), and restaging TUR in the management of disease progression. For muscle-invasive bladder cancer, new treatment options include neoadjuvant chemotherapy and bladder-sparing multimodal therapy. Finally, the use of markers for predictive purposes will be discussed.

2. Clinical scenario I: a patient with noninvasive bladder cancer

The initial presentation of the patient in our first clinical scenario (noninvasive bladder cancer, with a low initial risk of progression) is shown in Box 1.

2.1. Initial patient management

Fluorescence cystoscopy generally improves the detection of bladder tumours when compared with the standard white-light procedures by enhancing the visual contrast between benign and malignant cells [5], although the problem of false-positive results remains an issue [6]. Studies suggest that fluorescence cystoscopy is most beneficial to patients with positive urinary cytology or those with multiple tumours, because such patients are at high risk for recurrent bladder carcinoma [7]. Because the patient in this clinical scenario has negative urinary cytology and a single papillary lesion, fluorescence cystoscopy is probably not mandatory, although it remains potentially useful to ensure that other, smaller tumours are not overlooked.

The usual procedure for a patient with a single papillary lesion (low-grade tumour) is TUR (Fig. 1), although it is important that a high-quality procedure is carried out to minimise the risk of future recurrence [8]. After resection, a single instillation of intravesical chemotherapy should be considered to decrease tumour cell implantation in the bladder and further reduce the time to, and rate of, recurrence [9]. Although instillation within 6 h of TUR should not be given in cases of bladder perforation or significant bleeding due to toxicity effects, the data show that bladder treatment with 40 mg mitomycin C or 80 mg epirubicin for 1 hour, followed by complete irrigation, produces a 39% reduction in the risk of recurrence for a solitary lesion [9,10]. For patients with multiple lesions, alternative regimens may be advisable because the recurrence rate after a single treatment is 65% for multiple lesions, compared with 36% for a single lesion [10]. In addition, several new intravesical chemotherapeutic agents (including valrubicin, gemcitabine, and γ-linoleic acid) are currently in clinical development, although long-term data have yet to be obtained [11].

2.2. Patient follow-up after transurethral resection

Because the recurrence rate following TUR is approximately 60–70%, a continuing programme of cystoscopy is required. In those patients at high risk of high-grade tumours, it is advisable to perform cytology tests. Recurrences generally occur in the early stages of follow-up but late recurrences are possible [12] and, therefore, cystoscopy or cytology tests may need to be performed throughout the patient’s life [13]. A commonly used regimen involves cystoscopy every 3 mo for the first 2 yr, followed by every 6 mo for 2 yr, and yearly thereafter.

In higher-risk patients (such as those with high-grade T1 disease), a re-resection TUR should be routinely performed approximately 2–6 wk after the initial surgery to reduce the risk of residual tumour from 76% and prevent the disease upstaging to muscle-invasive bladder cancer in up to one third of patients [14].

2.3. Treatment following recurrence

The patient in this clinical scenario underwent TUR. A cystoscopy 6 mo later showed tumour recurrence and a repeat TUR demonstrated high-grade T1...
disease. In this scenario, the treating physician has several options from which to choose, as shown in Fig. 1 [15]. To provide the best treatment for patients, it is important to determine accurately the tumour stage. Microstaging is the pathologic evaluation of infiltration through the lamina propria. If there is an infiltration through the muscularis mucosae, the rate of progression increases; therefore, microstaging can be a good predictive tool to indicate the need for more aggressive therapy [16]. However, this technique is not currently in widespread use because it depends on reliable and consistent interpretation of uropathologic data, and dedicated urinary pathologists are not commonly available.

The most common treatment at this stage of disease progression is to repeat the TUR procedure; in a meeting of 746 specialists [17], audience polls revealed that 66% of respondent urologists would follow this approach. Following this, intravesical bacillus Calmette-Guérin (BCG) therapy, usually one dose per wk for 6 wk, is standard treatment for patients with high-grade tumours to reduce the rate of recurrence (Table 1) [18]. However, further BCG treatment may also prove beneficial for the
maintenance BCG is significantly superior to chemotherapy in reducing the rate of recurrence and progression, although the optimum schedule has yet to be determined [25,26]. The most popular maintenance schedule uses one dose per wk for 3 wk at 3 and 6 mo, and then at 6-mo intervals for 3 yr [27]. This regimen significantly improves disease-free survival, progression-free survival, and overall survival compared with no maintenance, but it has high rates of patient withdrawal due to toxicity. Recent studies have demonstrated that lower doses of BCG significantly reduced the toxicity without compromising efficacy [28–30] and clinical trials are ongoing to determine the best maintenance schedule with these lower doses; this may be beneficial for patients with multifocal or large-volume Ta carcinomas.

It is also possible to perform an early cystectomy following recurrence. Survival after cystectomy depends on the stage of the disease and patients with a T1 lesion have a greater chance of survival than those with a T2 lesion. Studies have shown that 40% of patients with a T1 lesion are upstaged at cystectomy; therefore, earlier procedures may be beneficial to halt disease progression and improve patient survival [31]. However, in a meeting of 746 specialists [17], audience polls revealed that <5% of respondent urologists and oncologists (clinical, medical, and radiation) would advocate a cystectomy at this early stage, preferring instead to continue with the bladder-sparing options of repeat TUR and BCG therapy.

### 2.4 Recurrence following intravesical BCG therapy

The patient in the clinical scenario presented here received a single 6-week cycle of BCG for high-grade T1 tumour recurrence. Cystoscopy performed 6 mo later showed tumour recurrence and the pathology results identified high-grade T1 disease. In general, the benefit of further intravesical therapy with BCG at this stage is questionable. Combination therapy with BCG plus interferon has the potential to produce a 45% recurrence-free follow-up rate [32] and this combination is currently under further clinical investigation. Most physicians would now opt for an immediate cystectomy before the disease progresses further to maximise patient survival [33].

### 3. Clinical scenario II: a patient with muscle-invasive bladder cancer

The initial presentation of the patient in our second clinical scenario (invasive bladder cancer, with a high risk of progression) is shown in Box 2.

#### 3.1 Initial patient management

Until recently, prostatic urethral biopsy would be performed as a standard procedure on the patient described in our second clinical scenario to define whether a urethrectomy was necessary [34]. However, this is no longer routine because it provides benefit to only a subset of patients in which the tumour is located in the trigone close to the urethra. Biopsy is recommended only if there is clinical cystoscopic evidence in these patients that there could be invasion of the prostatic ducts [35]. Instead,

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
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<th>TUR</th>
<th>TUR plus BCG</th>
<th>Difference</th>
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BCG = bacillus Calmette-Guérin; TUR = transurethral resection.


* Statistically significant difference.

© Review of 5 randomised trials.

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**Box 2. Presentation of patient in clinical scenario II**

- 73-yr-old man with one episode of painless gross haematuria.
- 22 pack-yr smoking history.
- Generally good health.
- Creatinine level 1.3 mg/dl and normal hepatic function.
- Cystoscopy showed a classic sessile lesion on the trigone of the bladder.
- Imaging of the chest, abdomen, and pelvis showed no adenopathy or metastatic disease.
most patients would be managed with TUR of the bladder lesion (Fig. 2).

### 3.2. Post-TUR therapy

The patient in the clinical scenario presented here elected for TUR of the bladder tumour (TURBT) and the pathology showed high-grade T2 cancer. The most commonly used procedure in this scenario is cystectomy. Studies have shown that cystectomy can be delayed by up to 12 wk after TUR without increasing the risk of death [36]. Partial cystectomy is usually a very limited option at this stage and is useful only for patients with adenocarcinoma. However, radical cystectomy, including lymphadenectomy, can produce significant improvements in patient survival. Prior to cystectomy, prostatic biopsy and bladder mapping may be useful to make decisions about the type of urinary diversion to be offered to the patient, and whether orthotopic neobladder construction would be a suitable option [37].

The use of multi-agent chemotherapy prior to local therapy (external-beam radiotherapy or cystectomy) can significantly improve the survival of patients with bladder cancer compared with local therapy alone [38]. In a recent meta-analysis, the use of neoadjuvant chemotherapy decreased the risk of death by 13% compared with local therapy alone, and the absolute survival benefit was between 5.5% and 6.5% (Fig. 3). However, benefits to survival must be weighed against the toxicity of the regimen (1% patient mortality and >30% grade 3/4 toxicity) [38].

More recently, clinical studies have indicated that the use of modern bladder-sparing treatments may be of significant benefit to the patient, without precluding cystectomy later on (Fig. 2). Traditionally, radiation has been in widespread use as a bladder-sparing therapy, although results have been variable [39]; in older studies, this may be due to the use of open-field treatment delivery rather than the newer, and more precise, three-dimensional conformational technology. Although radical radiotherapy is widely used in treatment centres as an alternative to cystectomy, dose-limiting toxicity has been a major impediment in many patients; doses of >64 Gy can cause long-term fibrosis and necessitate future cystectomy, thus negating the bladder-sparing aspect of the treatment. Studies are ongoing to examine smaller doses (up to 50 Gy) for microscopic disease with dose escalation at the tumour site [40]. Initial results suggest such regimes are well tolerated although long-term follow-up will be required before this approach can be routinely transferred to the clinical setting.

Chemoradiation has also been examined in patients with high-grade bladder carcinoma [41]. A clinical trial involving patients randomised to cisplatin plus radiotherapy versus radiotherapy alone demonstrated a significant improvement in pelvic recurrence-free survival with combined treatment, plus improved bladder preservation, although no overall survival difference was observed [42]. Further trials are, therefore, required to determine the overall benefit to the patient with these multimodal bladder-sparing treatments. Moreover, it may not be possible to administer trimodal therapy at all treatment centres due to the requirement for a collaborative group of diverse treatment specialists and the cost implications of this approach.

In a meeting of 746 specialists [17], audience polls revealed that although 89% of respondent urologists would opt for cystectomy, 74% of respondent radiation oncologists would proceed with bladder-sparing trimodal therapy. Less than 25% of the audience of urologists and oncologists (radiation,
medical, and clinical) who responded would use neoadjuvant chemotherapy, possibly due to toxicity concerns.

4. **Future directions: new markers for bladder tumours**

4.1. **Predicting recurrence and progression in noninvasive bladder cancer: the EORTC risk tables**

Determination of a patient’s risk of recurrence and progression is generally based on the stage and grade of tumour, as defined by the pathologist. Recently, the European Organisation for Research and Treatment of Cancer (EORTC) has attempted to predict recurrence and progression rates of non-invasive bladder cancer (Ta, T1) by identifying and defining prognostic risk factors [43]. For recurrence, the most important prognostic factors are the number of tumours, the incidence of previous recurrence, and tumour size. The risk factors for progression are the presence of carcinoma in situ and the tumour grade and stage (Fig. 4). The resulting predictions for short- and long-term risk of recurrence after TUR can be used to modify the subsequent treatment strategy, either by suggesting a more aggressive treatment regimen at an earlier stage or by increasing the follow-up of individual patients [43].

4.2. **Molecular prognostic factors**

The best-known prognostic factor for bladder carcinoma is p53, a tumour suppressor gene involved in cellular proliferation, apoptosis, and genetic stability. However, it is unrealistic to expect p53 to be the sole prognostic marker for bladder cancer because it has been implicated in many other
tumours and situations. Current research favours a combination of three markers: p53, pRb (retinoblastoma gene protein), and p21 (regulator of cell growth). In a retrospective study of patients who underwent cystectomy, levels and the mutational statuses of p53, pRb, and p21 were examined [44]. In patients with normal marker status, the rate of recurrence at 5 yr was 23%. The recurrence rate increased in patients who had alterations in one or more marker and peaked at 93% if all three markers were altered. Similar trends were seen in the 5-yr survival rates: 70% of patients with no marker alterations survived for at least 5 yr compared with 8% of patients with alterations in all three markers [44].

Current research is now beginning to elucidate the role of other molecular factors involved in the growth and spread of bladder tumours, and in the future it may be possible to use a battery of molecular markers to assess the phenotype of a tumour and how it will respond to therapy. Molecules that induce angiogenesis, such as epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) and their receptors (including human epidermal growth factor receptor 2 [HER2]), as well as cyclooxygenase-2 (COX-2) have all been shown to be overexpressed in urothelial tumours and may therefore provide prognostic information as well as therapeutic targets [45]. Another potentially useful molecular marker for bladder cancer is fibroblast growth factor receptor 3 (FGFR3), which is involved in the development and maintenance of bone and brain tissue. A mutation in FGFR3 has been found to correlate with a good prognosis in patients with bladder cancer [46]. Mutations are found significantly more frequently in Ta tumours (74%) than in T1 (21%) or T2-T4 tumours (16%). A similar trend was noted when the results were examined by cancer grade, with 84% of low-grade (grade 1) tumours having mutations in FGFR3 compared with just 7% of high-grade (grade 3/4) tumours [47]. Other studies have confirmed a link between the mutational status of FGFR3 and low recurrence rate [48,49] but have also implicated the combination of MIB-1 (a proliferation marker) and FGFR3 [50]. In addition, the combination of FGFR3 with p53 has been examined in patients with bladder cancer. Mutated FGFR3 plus wild-type p53 appears to correlate with a low risk (22%) of progression in patients with bladder cancer although a link with lower rates of recurrence was not seen [50].

### 4.3. Development of a biomarker

It is hoped that the prognostic information gained from biomarker status will be of use when determining the future treatment strategies for individual patients, particularly in terms of the aggressiveness of the therapy regimen recommended. However, although biomarker grading reproducibility is high (FGFR3, 100%; p53, 88%; MIB-1, 91%) compared with pathologic grading (47–61%), clinical trials using molecular markers are currently only in phases 2 and 3 [50]. It is hoped that within 10 yr, phase 4 trials will have been completed and physicians will be able to use such techniques as real markers in clinical practice.

### 5. Summary

Bladder cancer is a common urologic cancer among men in the United States and Europe. The management of noninvasive bladder cancer and muscle-invasive bladder cancer should be differentiated, although treatments within each category include both surgical and medical approaches. The high rate of disease recurrence and progression in bladder cancer underscores the need for careful follow-up studies, and optimal patient management requires an accurate knowledge of the stage and grade of the disease. New bladder-sparing multimodal therapy options may be used as curative treatments or to slow progression whilst preserving selected organs, and novel biomarker detection techniques are currently undergoing clinical evaluation. However,
for many patients, TUR and cystectomy will remain the mainstays of treatment for the foreseeable future, as reflected in the results of a poll of 746 specialists.

Conflicts of interest

Dr Christopher P. Evans, Dr Frans DeBruyne, and Dr Eduardo Solsona have no conflict of interest with respect to this article. Dr Heather Payne has attended advisory boards for AstraZeneca but does not have any commercial interests in the company. Professor Pierre Teillac has attended advisory boards for MSD, Negma Lerads, Pierre Fabre and Ipsen. Professor Andrea Tubaro is a consultant for Astellas. He has attended advisory boards for Novartis and Pfizer and has been a speaker for AstraZeneca.

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