Recent Advances in the Treatment of Bladder Cancer

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Abstract:

Cystoscopy and urine cytology are the most important investigations in the diagnosis of bladder cancer. Various alternatives have been investigated, either to reduce the frequency of cystoscopy, or improve its sensitivity for detection of tumours. Novel techniques in diagnosis and surveillance include urine-based markers and point-of-care tests. However, for the time being they are to be used in conjunction with, and not in replacement of, current standard procedures. Narrow-band imaging and photodynamic diagnosis (PDD)/ blue-light cystoscopy (BLC) have shown promise in improving detection and trans-urethral resection of bladder tumours. The majority of patients with a new diagnosis of bladder cancer have non-muscle-invasive bladder cancer (NMIBC), which requires adjuvant intravesical chemotherapy and/ or immunotherapy. These patients undergo regular cystoscopic surveillance, which is often life-long. For patients with muscle-invasive bladder cancer (MIBC), laparoscopic radical cystectomy (LRC) and robot-assisted radical cystectomy (RARC) have been shown to reduce peri-operative morbidity, while oncologically equivalent to open radical cystectomy (ORC) in the medium-term. Bladder-preserving strategies entail chemo-radiation and in highly selected patients give equivalent results to surgery.

Keywords:

bladder cancer, narrow band imaging, photodynamic diagnosis cystoscopy, urinary markers, radical cystectomy

Review

Introduction

Bladder cancer is the commonest malignancy of the urinary tract. Although cystoscopy remains a fundamental investigation in the detection and surveillance of bladder cancer, small papillary tumours or carcinoma in situ (CIS) can be easily missed by standard white-light cystoscopy (WLC), which may account for early recurrences [1]. Approximately 75% of patients will have disease confined to the mucosa (Ta) or
submucosa (T1) i.e. non-muscle invasive bladder cancer (NMIBC), which has a high risk of recurrence. CIS is a high-risk disease for muscle-invasion. CIS that is refractory to bacillus Calmette-Guérin (BCG) immunotherapy, or muscle-invasive bladder cancer (MIBC) (>T2) should be managed with radical cystectomy. In this article, we summarise recent and evolving advances in the diagnosis and treatment of bladder cancer.

**Diagnosis**

**Cystoscopy**

Photodynamic Diagnosis (PDD)/ Blue light Cystoscopy (BLC)

Photodynamic diagnosis (PDD) improves the ability to detect inconspicuous bladder cancer. 5-aminolevulinic acid (5-ALA) dye, or its hexyl ester hexaminolevulate (Hexvix®) (HAL), is instilled into the bladder and absorbed by dysplastic tissue, enabling photosensitization. The abnormal tissue emits a red colour under blue reference light. Normal tissue appears blue (figure 1). PDD is recommended to aid diagnosis at initial TURBT, in patients with positive urine cytology but negative WLC for the assessment of tumour recurrences in patients not previously assessed with HAL, in the initial follow-up of patients with CIS or multifocal tumours [1]. A meta-analysis has shown that the sensitivity of BLC for detecting CIS using 5-ALA or HAL was 92.4%, while that of WLC was 60.5% [1].

One and 2 year recurrence rates are significantly decreased in patients undergoing BLC compared with WLC [1]. However, a multi-centre, randomised, double-blind, placebo-controlled trial [1] failed to show that BLC led to improved outcomes. Although more tumours per patient were detected in the BLC group, the higher detection rate did not translate into differences in long-term outcome.

Narrow-band imaging
Narrow-band imaging (NBI) cystoscopy enhances the fine structure of the bladder mucosal surface without the use of dyes. Longer wavelengths of light enable deeper penetration. NBI cystoscopy improves detection of recurrent NMIBC over standard WLC, with a comparative false-positive rate [6]. TURBT performed in the NBI modality reduces the recurrence risk of NMIBC by at least 10% at 1 yr [7].

**Urinary markers**

The most widely adopted non-invasive urine test is cytology, which has good specificity and sensitivity for the detection of high-grade tumours, but poor sensitivity for low-grade tumours [8], and has a delay in result availability. Numerous urinary markers have been investigated (Table 1) [9]. We discuss two of the most promising.

Fluorescence in situ hybridization (FISH) assay using UroVysion® detects aneuploidy in chromosomes 3, 7, and 17 as well as loss of the 9p21 locus of the P16 tumour suppressor gene [10]. In most comparative studies, FISH outperformed cytology across all stages and grades of bladder cancer [11, 12, 13]. FISH results can identify patients at risk for tumour recurrence and progression during BCG immunotherapy [14]. This information may be used to counsel patients about alternative treatment strategies.

Nuclear mitotic apparatus protein 22 (NMP22) is another marker that can be detected in voided urine. NMP22® Bladderchek® is a point-of-care test approved by the USA Food and Drug Administration for bladder cancer surveillance. In patients with both negative cystoscopy and NMP22® Bladderchek®, very few cancers are missed, and cytology is ineffective in detection [15]. However, for clinicians who have a low threshold for performing a cystoscopy to detect recurrence or progression in patients, NMP22 did not aid clinical decision-making [16].
Non-muscle invasive bladder cancer

Transurethral resection of bladder tumours (TURBT) is the first-line treatment in patients with NMIBC. Unfortunately, the high rate of recurrence and progression after TURBT necessitates the use of adjuvant treatments \([17, 18, 19]\). This entails instillation of chemotherapeutic, usually mitomycin-C (MMC), or immunotherapeutic agents such as BCG, either alone or in various combinations. A single dose of intravesical chemotherapy given the same day post-TURBT significantly reduces tumour recurrence \([20]\), although it is significantly underutilized \([21]\). Intravesical BCG is the standard treatment for high-grade NMIBC, particularly CIS, and should be given in a maintenance schedule \([22]\). Unfortunately, some patients are unable to tolerate the side-effects of urgency and frequency and/or are refractory to treatment.

BCG/ Electromotive drug administration (EMDA) Mitomycin C

To reduce BCG toxicity, some groups suggest reduced dose instillations of BCG. One-third dose has similar efficacy to full-dose BCG but with significantly less toxicity. However, full-dose BCG is more effective in multifocal tumours \([23, 24]\). Di Stasi et al have demonstrated that intravesical, sequential BCG and electromotive administration of mitomycin C – EMDA-MMC – for patients with high-risk superficial bladder leads to higher disease-free interval, lower recurrence and progression, and to improved overall survival and disease-specific survival compared with BCG alone \([25]\). More recently, the same group showed that intravesical EMDA-MMC before TURBT is feasible and safe. Importantly, it reduced recurrence rates and enhanced the disease-free interval compared with intravesical passive diffusion of MMC after TURBT, and TURBT alone \([26]\).

Hyperthermic MMC
A combined regimen of intravesical MMC and microwave-induced bladder wall hyperthermia (HT) for Ta/T1 bladder cancer was first introduced in 1995 [27]. A small randomised controlled trial (RCT) comparing MMC-HT vs. MMC alone has since shown a significantly improved disease-free survival rate at 10 years [28]. A systematic review suggests a 59% relative reduction in NMIBC recurrence when MMC-HT is administered, compared with MMC alone [29]. In the future, MMC-HT may become standard therapy for high-risk patients with recurrent tumours, for patients who are unsuitable for radical cystectomy, and in cases for which BCG treatment is contraindicated.

Intravesical gemcitabine

Administration of intravesical gemcitabine is being explored. A Cochrane review of the current evidence base of randomised trials is limited but promising, and it may be suitable for high-risk BCG-refractory patients. Multiple doses would be required, rather than a single shot after surgery [30].

**Muscle-invasive bladder cancer**

Minimally-invasive techniques in radical cystectomy

Open radical cystectomy (ORC) is the current gold-standard treatment for MIBC, or high-risk, recurrent NMIBC. Ideally, all patients with MIBC should receive platinum-based neo-adjuvant chemotherapy [31]. ORC has a perioperative complication rate of 25-62% [32].

Therefore, minimally invasive techniques in radical cystectomy have been explored. The majority of existing data comprises cohort studies. The advantages of laparoscopic radical cystectomy (LRC) include decreased blood loss, reduced postoperative pain, early return of bowel function and shorter hospital stay [33, 34]. However, the data should be interpreted with caution, given the problem of selection bias in most series.
Overall, current evidence suggests that LRC has good early oncologic outcomes with low morbidity in large cohorts with up to 5 years follow-up [35]. Nevertheless, LRC is considered an advanced laparoscopic procedure, because it has multiple difficult steps and fewer degrees of freedom.

In 2001 the da Vinci® robot (Intuitive Surgical Inc., CA, USA) was introduced as an innovative system for minimally invasive surgery. View of the operative field is improved by binocular 3-D high definition endoscopic vision. ‘Endowrists’ on the tip of each instrument can reproduce movements of the human hand. An RCT by Nix et al. has shown that robot-assisted radical cystectomy (RARC) allows for reduced operative blood loss, time for return of bowel function and analgesic requirements compared with ORC, with equivalent lymph node yields [36]. A group of motivated robotic surgeons have formed the International Robotic Radical Cystectomy Consortium (IRCC). Their collaborative datasets have also demonstrated comparable lymph node yields and positive surgical margin rates to ORC [37, 38]. Short-term outcomes of RARC are promising, with 70-90% overall survival (OS) rate in 2-3 years of follow-up [39, 40, 41]. Increasing experience has enabled intra-corporeal reconstruction of urinary diversion, whether this be ileal conduit or orthotopic neobladder formation. Clearly, the learning curve is steep. Operative times are longer, although patients have lower inpatient narcotic requirement and comparable short-term clinical outcomes to extra-corporeal diversion [42, 43, 44, 45].

Bladder preservation

Strategies for bladder preservation have been investigated in selected patients who decline surgery or are not fit for surgery. A Phase III trial of chemotherapy (fluorouracil + mitomycin) combined with radiotherapy was shown to improve 2-year disease-free survival, compared with radiotherapy alone; and also decreased salvage cystectomy rate, with good long-term bladder function [46]. Long-term data from Massachusetts General Hospital, USA has shown that combined multi-modal therapy in the form of concurrent cisplatin-based chemotherapy and radiotherapy after maximal TURBT achieves a complete response and preserves the native bladder in >70% of patients, while offering long-term survival rates comparable to contemporary
cystectomy series [47]. However, a number of different protocols were used in their centre, and so the optimal therapy regimen is still uncertain.

**Conclusions**

Although mortality from bladder cancer is improving, the challenge now is to reduce the morbidity associated with NMIBC and reduce recurrence rates. BLC enhances detection of bladder tumours and may prolong recurrence-free survival. As yet, no urinary markers exist that have substantial enough specificity or sensitivity to replace regular cystoscopic surveillance of NMIBC. The initial outcomes from RARC appear promising. However, there is a distinct lack of randomised-controlled trials to compare RARC with ORC. There are several that are currently underway, including the randomised CORAL radical cystectomy trial [48]; Open Vs Robotic-Assisted Radical Cystectomy: A Randomised Trial, University of Texas Health Science Centre, USA [49]; and BOLERO, Cardiff University, UK [50]. The long-term outcomes of the first cohort of patients who underwent RARC should be available in the next 1-2 years. Whilst the long-term benefits of RARC are awaited, ORC remains the gold-standard treatment for MIBC. Patients at high risk for complications from surgery may well benefit from bladder preservation with combined chemotherapy and radiotherapy regimens.

**List of abbreviations**

NBI – narrow band imaging

BCG – bacillus Calmette-Guérin

MMC – mitomycin C

MMC-HT – hyperthermic mitomycin C

NMIBC – non-muscle-invasive bladder cancer
MIBC – muscle-invasive bladder cancer

ORC – open radical cystectomy

LRC – laparoscopic radical cystectomy

RARC – robot-assisted radical cystectomy

**Competing interests**

*Financial competing interests*

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None

**Authors’ contributions**

GC and MB wrote the initial version of the manuscript. AS conceived the outline of the manuscript, reviewed the manuscript and made final changes. PD and MSK critically reviewed the manuscript. All authors read and approved the final manuscript.

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Ismail AF, Elhage O, Rimington P, Kelly JD, Dasgupta P, Khan MS. **Initial experience with a Randomised Controlled trial of Open, Robotic and Laparoscopic (CORAL) radical cystectomy.** *BJU Int.* 2010, **106**(Suppl 1), 7.

**Open Vs Robotic-Assisted Radical Cystectomy: A Randomized Trial** [http://clinicaltrials.gov](http://clinicaltrials.gov) NCT01157676

**Bladder cancer: Open versus Laparoscopic or Robotic cystectomy** [http://www.controlled-trials.com](http://www.controlled-trials.com) ISRCTN38528926
Figure 1 – white light (a) and blue light (b) endoscopic image of flat lesions adjacent to a small papillary tumour.

<table>
<thead>
<tr>
<th>Markers</th>
<th>Overall sensitivity (%)</th>
<th>Overall specificity (%)</th>
<th>Sensitivity for high-grade tumours (%)</th>
<th>Point-of-care test</th>
<th>Interference by BCG instillations and other bladder conditions</th>
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<td>30-72</td>
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BCG = Bacillus Calmette-Guérin; BTA = bladder tumour antigen.
Additional files provided with this submission:

Additional file 1: figure 1a.png, 553K
http://www.biomedcentral.com/imedia/1651582637323948/supp1.png
Additional file 2: figure 1b.png, 599K
http://www.biomedcentral.com/imedia/1308386732394898/supp2.png
Additional file 3: Khan 1116027539732394 BMC Edits.docx, 76K
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