Review Article

# Selection of patients and benefit of immediate radical cystectomy for non-muscle invasive bladder cancer

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**Abstract:** Bladder cancer (BC) is a common disease in both sexes and majority of cases present as non-muscle invasive BC (NMIBC). The percentage of NMIBC progressing to muscle invasive BC (MIBC) varies between 25% and 75% and currently there are no reliable molecular markers that may predict the outcome of high-risk (HR) NMIBC. Transurethral resection of the bladder tumour (TURBT) with intravesical bacillus Calmette-Guérin (BCG) or immediate radical cystectomy (RC) are the current gold standard treatment options. The European Association of Urology (EAU) guidelines recommend immediate or delayed RC for HR- and a subgroup of "highest-risk" NMIBC. These cases include pT1, carcinoma in-situ (CIS), multifocal disease, histological variants such as micropapillary and sarcomatoid, and patients who have contraindications to, or have failed with BCG. The comparative risks between maintenance BCG (mBCG) and immediate RC are unclear. However, RC may give patients the best oncological outcome.

**Keywords:** Immediate radical cystectomy; primary cystectomy; bladder cancer; non-muscle invasive bladder cancer (NMIBC)

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## Introduction

Bladder cancer (BC) is the seventh most common malignancy in men and the eleventh most common in both sexes (1). BC is one of the most expensive malignancy to manage as patient's with non-muscle invasive bladder cancer (NMIBC) managed with bladder-sparing approaches require long-term follow-up with flexible cystoscopy, and often require repeated treatment for recurrences (2). Approximately 75% of cases present as NMIBC, which include mucosal lesions (pTa), lamina propria invasion (pT1) or CIS (3). Tobacco smoking and occupational exposure to polycyclic aromatic hydrocarbons and aromatic amines are the most important risk factors for BC (4,5).

Management of low-risk disease (G1, pTa) focuses on preventing recurrence or progression to high-risk NMIBC (HR-NMIBC) (G3, pT1, CIS) or MIBC (pT2+). The management of HR-NMIBC is aimed at preventing both recurrence and progression to muscle invasive (pT2+) BC (MIBC). Recurrence is a common event in HR-NMIBC and results in significant morbidity and costs. Patients with HR-NMIBC may reduce their risk of disease progression by undergoing immediate RC or bladder-sparing approaches using intravesical immunotherapy such as mBCG (6,7). Although the European Organisation for the

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**Table 1** EAU recommendations for immediate/delated RC in HR-NMIBC

| Risk category | Definition | Alternative |
|---|---|---|
| HR-NMIBC | pT1 | Intravesical BCG |
| | Grade 3 (G3) | |
| | CIS | |
| | Multiple, recurrent and large (>3 cm) G1-2pTa | |
| Subgroup of highest-risk NMIBC | G3pT1 + bladder CIS | Intravesical BCG |
| | Multiple and/or large G3pT1 and/or recurrent G3pT1 | |
| | G3pT1 with prostatic urethra CIS | |
| | Lymphovascular invasion | |
| | Variant histology (micropapillary, plasmacytoid, sarcomatoid) | |
| Other | BCG-refractory tumours | |
| | Progression to MIBC | |

RC, radical cystectomy; NMIBC, non-muscle invasive bladder cancer; CIS, carcinoma in-situ; BCG, bacillus Calmette-Guérin.

Research and Treatment of Cancer-Genito-Urinary Cancer Group (EORTC-GUCG) developed scoring system/risk tables to predict risks of disease recurrence and progression in individual patients, the incidence of HR-NMIBC progressing to MIBC varies significantly (25–75%). It is known that progression increases the risk of metastasis and disease-specific mortality (DSM), therefore the care of patients with HR disease is aimed at preventing, or the early detection of MIBC (8). However, the poor precision in identifying which patients with HR-NMIBC should be offered mBCG or immediate RC produces a major challenge. In addition, the comparative risks between the two curative treatment options are unclear. Here, we discuss the role of immediate RC in HR-NMIBC.

## EAU recommendation on primary RC

The current EAU guidelines recommend immediate RC for HR tumours including CIS alone, multiple, recurrent and large (>3 cm) G1-2pTa, G3pT1 associated with concurrent bladder and or prostatic urethra CIS, and multiple and/or large G3pT1 (6) (*Table 1*). Lymphovascular invasion (LVI) in transurethral resection of the bladder tumour (TURBT) specimens is associated with an increased risk of pathological upstaging and a poor prognostic factor in pT1 tumours. A meta-analysis studied 3,905 patients, 18% with LVI and showed significant associations with upstaging [odds ratio (OR): 2.21, 95% CI: 1.44–3.39] and progression-free survival (hazard ratio: 2.28, 95% CI: 1.45–3.58) and disease-specific survival (hazard ratio: 1.35, 95% CI: 1.01–1.81). Hence, immediate RC is recommended in tumours with LVI (9,10).

Immediate RC is also recommended for variants of urothelial cell carcinoma (UCC) that have been reported to have a worse prognosis than classical UCC, such as micropapillary, small cell, squamous, glandular, plasmacytoid and sarcomatoid. Variants of UCC represent approximately 25% of RC histologies and are associated with advanced tumour stage, LVI and lymph node metastasis (11,12).

The UK National Institute for Health and Care Excellence (NICE) guidelines also recommend immediate RC as an alternative treatment option to BCG in managing HR-NMIBC (13). The UK national RC (bladder removal) against intravesical BCG immunotherapy for HR-NMIBC (BRAVO) randomised controlled feasibility study initially aimed to compare RC with BCG, however, it failed to recruit target numbers, therefore level 1 evidence is still unavailable (14).

## Bladder-sparing treatment for HR-NMIBC

It has been estimated that the DSM of patients with HR-NMIBC is approximately 20–25% (8). The use of post TURBT intravesical immunotherapy such as BCG, mitomycin C (MMC) or epirubicin may reduce both recurrence and progression. Intravesical immunotherapy aims to induce an immune response against the tumour to reduce recurrence or progression. BCG treatment requires

 

an induction phase followed by a maintenance phase of 3 years. Studies have confirmed the superiority of BCG in preventing tumour recurrence over MMC alone, epirubicin alone or a combination of epirubicin and interferon (15-17). A meta-analysis analysed 4,767 patients and showed that the addition of BCG reduced the risk of recurrence compared to TURBT alone (OR: 0.5, 95% CI: 0.33–0.75, P=0.0008) (18). Progression rate was also reduced in BCG therapy compared to TURBT alone when 4863 patients were analysed in another meta-analysis (OR: 0.73, P=0.001) (17). Although mBCG is a bladder-sparing treatment option, it subjects patients to risk of disease recurrence and progression and may impact quality of life (QoL) through local symptoms and potential severe BCG-toxicity, such as BCG sepsis with tuberculosis infection (19). In addition, there is the risk of BCG intolerability and failure. BCG-failure can be a result of MIBC detected during follow-up [progression rate of ~9.8% (17)] or BCG-refractory defined as high-grade NMIBC detected at 3 months or during BCG treatment [recurrence rate of ~40.5%) (18)], and detection of CIS at both 3 and 6 months (6). Patients with late BCG relapse (>1–2 years after last BCG exposure) and who are reluctant or unfit for RC can have a trial of salvage intravesical treatment with repeat BCG, BCG with interferon alpha-2a, gemcitabine or valrubicin (20,21). Device-assisted therapies such as electromotive drug administration and thermochemotherapy are also treatment options following BCG-failure (22). There is a current worldwide shortage of BCG due to problems in manufacturing and alternative therapies are needed to manage this challenging group of patients with HR-NMIBC (23,24).

New immunotherapeutic agents are being tested. A new international randomised-controlled trial (RCT) started in May 2018 is comparing Durvalumab [monoclonal antibody directed against programmed cell death-1 ligand 1 (PD-L1)] plus BCG with BCG alone in managing NMIBC [Assessment of Efficacy and Safety of Durvalumab Plus BCG Compared to the Standard Therapy with BCG in NMIBC (POTOMAC)] (ClinicalTrials.gov, NCT03528694).

## Immediate RC for HR-NMIBC

Around 27–51% of pT1 tumours diagnosed through TURBT are upstaged to MIBC at RC (25-27). Patients with NMIBC who experience disease progression to MIBC have reduced 10-year recurrence-free survival (progression, 36% *vs.* MIBC, 43%, P=0.01), overall (progression, 28 *vs.* MIBC, 35%, P=0.03) and disease-specific survival (progression, 37% *vs.* MIBC, 43%, P=0.01) compared to those who present with MIBC (28). Patients with CIS have a progression rate to MIBC of ~54% if untreated (29) and ~41–100% if only managed by biopsy/fulguration (30).

RC includes bladder and adjacent organ removal, pelvic lymphadenectomy and reconstruction of urinary drainage through an ileal conduit or neobladder. A number of reports have evaluated robotic-assisted RC (RARC) as an alternative to open RC (ORC). RARC provides longer operative time (additional 1–1.5 hours), major costs, but shorter hospital length of stay (LOS) and less blood loss compared to ORC. The grade 3 90-day complication rate appears to be lower with RARC, but the intermediate-term oncological and QoL outcomes are not different between RARC and ORC (31-33). The US national RARC *vs.* ORC in patients with BC (RAZOR) RCT concluded that RARC was non-inferior to ORC for 2-year progression-free survival (RARC, 72.3% *vs.* ORC, 71.6%, non-inferiority P=0.001) (34). The ongoing UK robot-assisted radical cystectomy with intracorporeal urinary diversion versus open radical cystectomy (iROC) RCT aim to evaluate recovery times and complications (35).

RC eliminates the risk of local progression and may provide the best oncological outcomes but may be associated with over-treatment for non-progressing disease, short- and long-term post-operative complications and reduction in QoL. However, some patients are found to have extra-vesical (~43%) and metastatic regional lymph node disease (~23%) at the time of surgery (36). The 5-year progression-free survival exceeds 75% in HR-NMIBC (36). Post-operative complications requiring intervention occurs in around 20% of cases (37). With the introduction of enhanced recovery after surgery (ERAS) protocols, patients have shorter hospital LOS, reduced time-to-bowel function and experience lower rate of post-operative complications when compared with standard care (38,39). In younger patients, urinary incontinence and sexual function may be of concern following radical surgery and QoL discussion is important when counselling for immediate RC (40). Recurrence-free survival of ~79% at 10 years following immediate RC for HR-NMIBC appears superior when compared with mBCG (41).

The comparative risks and benefits of mBCG and immediate RC are unclear, therefore, clinicians and patients face the uncertainty of potential under- or over-treatment. An RCT would provide more data on QoL and oncological outcomes that could help clinicians make treatment

 

decisions. However, there are difficulties with conducting an RCT, such as eligibility and recruitment. The CRUK-SPARE trial comparing surgical and non-surgical treatments for BC is an example reflecting difficulties in recruitment (42).

The NICE guidelines highlighted that comparison of BCG with RC as one of the research priorities in BC (13). The BRAVO multicentre RCT aimed to compare RC and mBCG for HR-NMIBC. The BRAVO feasibility study planned to assess whether a target sample size of n=506 for the full RCT can be met by first randomising 60 patients. Unfortunately, the study failed to recruit and has been closed. Therefore, the comparative outcomes between RC and BCG are still unclear (14,43).

## Patient selection for immediate RC

Immediate RC is recommended for HR-NMIBC due to the risk of progression and BCG failure, and subsequent poor survival outcomes. Patients who have HR-NMIBC and who are fit for surgery should be offered immediate RC, but the potential benefits must be weighed against its potential risks, morbidity and impact on QoL. Immediate RC should also be considered in surgically fit patients with absolute and relative contraindications to BCG.

The clinicopathologic characteristics of HR disease such as grade 3, pathological stage 1, CIS, large tumours, histological variants increase the risk of progression with or without BCG. Recently there has been evolving evidence on molecular markers that may predict BCG-failure and progression. This knowledge may help clinicians identify those who may not respond to BCG and better select patients for immediate RC. Therefore, patients who are unable to have BCG or "predicted" to unlikely to benefit from BCG should be considered for immediate RC. In addition, patients who were deemed fit for RC at diagnosis of HR-NMIBC, may not be fit when found to have progression to MIBC following 3 years plus of initial mBCG and surveillance. This may be the case for the elderly cohort and should be considered when discussing immediate RC versus intravesical mBCG.

Cigarette smoking is a modifiable risk factor for urothelial BC development. Smoking status and lifetime smoking exposure at BC diagnosis and at different periods during treatment appear to affect disease recurrence, progression and survival. However, the evidence is heterogenous and further evaluation is needed (44). It may be important to emphasize to patient undergoing RC the importance of smoking cessation in order to maximise the benefits of RC.

## Molecular and clinicopathological factors in predicting BCG response

Next-generation sequencing (NGS) data have shown several genetic and epigenetic alterations that are associated with disease progression such as *FGFR3* mutation, high urinary tumour DNA levels and increased expression of long non-coding RNA H19 (45-48). *ARID1A* mutations were associated with an increased risk of recurrence after BCG (hazard ratio: 3.14, 95% CI: 1.51–6.51, P=0.002) when 105 NMIBC formalin-fixed paraffin-embedded (FFPE) samples were analysed (49).

A recent systematic review analysed "definitely useful", "probably useful" and "emerging" factors in predicting BCG response (50). Clinicopathologic features (stage, grade, recurrent tumours, multiplicity, CIS, female gender, age) were classified as "definitely useful" and remain the most effective predictors of BCG response in keeping with the EORTC risk scores. Urinary fluorescent in-situ hybridization (FISH, UroVysion) is a molecular cytogenetic test for detecting chromosomal abnormalities and is a "definitely useful" tool for predicting failure after BCG (51,52). There are numerous tumour molecular biomarkers that are "probably useful" in predicting BCG response. These include cell cycle regulator Rb; apoptosis inhibitors surviving, bcl-2; cell adhesion molecules E-cadherin, ezrin, sialyl-Tn, sialyl-6-T; proliferation index Ki-67; and growth factor FGFR3. Urinary cytokines such as TNF-α, IL-12 and TRALI (cytokine panel for response to intravesical therapy, CyPRIT nomogram) (53) and immunity markers such as leukocyturia (improved response), CD4+ and CD8+ T-cells are "probably useful" in predicting BCG response during treatment. There is currently no single molecular strategy that can predict BCG response. Identifying molecular subtypes of NMIBC have been proposed and the use of NGS has appeared to be important in developing 'emerging strategies' in predicting BCG response (50,54).

## Conclusions

BC is expensive to manage due to the need for active surveillance following treatment of NMIBC. Treatment options for HR-NMIBC include immediate RC or bladder-sparing intravesical agents. Innovations in bladder-sparing approaches such as thermochemotherapy immunotherapy

 

and gene therapy may offer alternatives for patients who are not fit for RC or who fail mBCG. Patients who undergo RC for MIBC progressed from HR-NMIBC have a worse prognosis than those who receive immediate RC for HR-NMIBC. Immediate RC is now a much safer and less morbid procedure that currently offers the best chance of preventing progression of disease. It is important to identify those with HR-NMIBC who are likely to progress or fail with mBCG treatment and offer this group of patients immediate RC to provide the best survival outcomes. There are Clinicopathologic features that may predict progression, and although research into molecular markers in this context appear promising, better strategies of identifying patients at risk of failure of bladder-sparing treatments are needed.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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