Clinics in Surgery

Short Communication
Published: 12 Aug, 2019

Bladder-Sparing and Immediate Radical Cystectomy Treatment Options for High-Risk Non-Muscle Invasive Bladder Cancer

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Introduction

Bladder Cancer (BC) has a high morbidity in patients worldwide, where it is the seventh most common malignancy in men and the eleventh most common in both sexes [1]. It is one of the more expensive malignancies to manage, as patients with Non-Muscle Invasive Bladder Cancer (NMIBC) who are managed with bladder-sparing approaches, go on to require long-term follow-up with flexible cystoscopy, and often require further repeated treatment for recurrences [2-4]. Approximately 75% of newly diagnosed BC are NMIBC, which include mucosal lesions (pTa), lamina propria invasion (pT1) or Carcinoma In Situ (CIS) [5]. Currently treatment options for high-risk (HR) NMIBC include Transurethral Resection Of Bladder Tumour (TURBT) with intravesical Bacillus Chalmette-Guerin (BCG), with the European Association of Urology (EAU) guidelines recommending immediate or delayed Radical Cystectomy (RC) for high-risk and a subgroup of "highest risk" NMIBC. The management of HR-NMIBC is aimed at preventing both recurrence and Progression to Muscle Invasive (pT2+) Bladder Cancer (MIBC). Unfortunately, due to the high recurrence rate seen in HR-NMIBC, there is significant associated 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 maintenance Bacillus Chalmette-Guerin (mCBT), as recommended by the EAU guidelines. 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 [6].

Bladder-Sparing Treatment for HR-NMIBC

The disease-specific mortality of patients with HR-NMIBC is approximately 20% to 25% [7]. The use of bladder-sparing treatment options such as intravesical immunotherapy post TURBT has been the gold-standard over the last 40 years and has been known to reduce both recurrence and progression. These include BCG, mitomycin C (MMC) or epirubicin [8]. Although mCBT is a bladder-sparing treatment option, it can subject patients to risk of disease recurrence and progression in cases of BCG failure [9]. It can also impact Quality of Life (QOL) through local symptoms and potential severe BCG-toxicity, such as BCG sepsis with tuberculosis infection [10,11]. In addition, as a consequence of BCG failure, such bladder preservation treatment options may affect survival outcome due to the delay in performing RC. The delay in RC can increase the risk of lymph node metastases and BC-specific mortality. Patients with NMIBC who experience disease progression to MIBC have a 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 [12].

Radical Cystectomy

The EAU guidelines recommend immediate or delayed RC for HR- and a subgroup of "highest-risk" NMIBC, which include G3pT1, CIS, multiple and/or large G3pT1 and/or recurrent G3pT1, lymphovascular invasion, G3pT1 with prostatic urethra CIS or variant histology (micropapillary, plasmacytoid, sarcomatoid) [13]. RC includes surgically removing the whole bladder and adjacent organ removal, pelvic lymphadenectomy and reconstruction of urinary drainage through an ileal

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Received Date: *01 Jun 2019*
Accepted Date: *02 Aug 2019*
Published Date: *12 Aug 2019*

Citation:
Bhadra A, Esperto F, Krishnan J, Pang KH. Bladder-Sparing and Immediate Radical Cystectomy Treatment Options for High-Risk Non-Muscle Invasive Bladder Cancer. Clin Surg. 2019; 4: 2544.

conduit. Having a RC eliminates the risk of local progression and may provide the best oncological outcome. However, it may also be associated with over-treatment for non-progressing disease, short- and long-term post-operative complications and reduction in QOL. Studies have reported that many patients, unfortunately, suffer from short-term complications which can take up to 6 months for their QOL to return back to their preoperative levels [14]. The 5-year progression-free survival exceeds 75% in those that have a RC for HR-NMIBC, and the recurrence-free survival of ~79% at 10 years following immediate RC for HR-NMIBC exceeds BCG [15]. Post-operative complications which require intervention occurs in around 20% of cases. Moreover, with the introduction of Enhanced Recovery after Surgery (ERAS) protocols, patients have shorter hospital length of stay, reduced time-to-bowel function and experience lower rate of post-operative complications when compared with standard care [16,17]. In younger patients, it is important to note that urinary incontinence and sexual function may be of concern following radical surgery, highlighting the importance of QOL discussions when counseling for immediate RC [18]. Immediate RC is recommended for patients with HR-NMIBC who are fit for surgery, 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. In addition, it is also important to note that 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 with having had initial BCG and surveillance. This may be the case for the elderly cohort. And should be considered when discussing immediate RC versus intravesical BCG [19,20].

Conclusion

BC is an expensive malignancy to manage due to the need for active surveillance following treatment of NMIBC. Treatment options for HR-NMIBC include immediate RC or bladder-sparing approaches with TURBT and intravesical agents. Patients who undergo RC for MIBC progressed from HR-NMIBC have a worse prognosis than those who receive immediate RC for HR-NMIBC, highlighting the importance of disease progression and early radical treatment. Immediate RC is now a much safer and less morbid operation 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 BCG treatment and offer this group of patients immediate RC to provide the best survival outcomes. Moreover, patient demographics should be taken into account whereby, those with an expected longer life expectancy should be offered a RC. Innovations in bladder-sparing approaches such as thermo chemotherapy immunotherapy and gene therapy may offer alternatives for patients who are not fit for RC or who fail BCG.

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