



# Treatment Modalities of Muscle Invasive Transitional Cell Carcinoma of Bladder

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## Abstract:

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*The treatment of muscle invasive bladder cancer (MIBC) is complex. This review describes the available therapies for invasive urothelial carcinoma. Neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) and lymph node dissection has been considered the standard treatment for MIBC. Many patients those are unfit for surgery or cisplatin ineligible, bladder sparing strategies are considered in highly selected patients. Even though there are no level I data, the treatment outcomes for highly select patients given bladder sparing therapy appear promising, with many patients retaining a functional bladder. So it can be concluded that treatment of MIBC is a multidisciplinary collaborative program of surgery, radiation and medical oncology.*

## Introduction

The majority of bladder neoplasm is diagnosed as superficial bladder cancer, 20 to 30% of patients have muscle invasion at diagnosis and many with non-invasive disease will eventually progress to muscle invasion<sup>1</sup>. Muscle invasive bladder cancer (MIBC) is an aggressive disease and treatment is associated with significant morbidity and mortality in all age groups. Although radical cystectomy has historically been the cornerstone of treatment for MIBC, optimizing outcomes with neoadjuvant chemotherapy and alternative options for bladder preservation strategies have also emerged as treatment options.

## Epidemiology

Bladder cancer has a complex pathogenesis and its predilection for development in the elderly is likely caused by a combination of tumor biology, alterations in host defense and cumulative exposures. Both aging and the development of bladder cancer share many of the same mechanisms involving genes of DNA replication and repair, intruding and association with

TP53 mutations, oxidative stress, telomere shortening and DNA methylation<sup>2</sup>. Age has been associated with epigenetic silencing via promoter methylation of tumor suppressor genes, correlating with higher stage, grade and lower survival, suggesting a possible mechanism for increased tumor aggression<sup>3</sup>.

## Key Points

- A comprehensive assessment can be used for treatment decisions.
- Radical cystectomy has a survival benefit even in elderly patients and should be considered in all eligible patients.
- Neoadjuvant chemotherapy prior to radical cystectomy is well tolerated and effective in selected elderly patients with MIBC.
- Adjuvant chemotherapy after radical cystectomy should be considered in high- risk (lymph node positive or extra-vesical tumor extension), cisplatin-eligible patients who did not receive neoadjuvant chemotherapy.

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- Trimodality therapy (TMT) is a well-tolerated, effective, and potentially curative alternative to radical cystectomy in selected patients with MIBC.
- Increasing knowledge regarding biomarkers of response to chemotherapy, radiation or cystectomy may pave the way for selecting patients for different modalities.
- Multidisciplinary collaboration between surgery, radiation oncology, and medical oncology brings about the best outcomes for MIBC.

### Timely diagnosis and assessment of the patient

Bladder cancer diagnosis and management begins with a high quality transurethral resection of bladder tumor (TURBT). Inadequate resection can lead to considerable under staging and misdiagnosis. American Urological Association (AUA) and European Association of Urology (EAU) guidelines strongly recommend repeat TURBT in patients with high-grade T1 or high volume, high grade Ta. When performing a repeat TURBT, approximately 70% of patients have remaining visible tumors, with the majority away from the resection site [4]. These findings have been attributed to lack of detection of tumors using substandard or standard white light cystoscopy. More recently blue light cystoscopy (BLC) is being used in the initial diagnosis and staging of bladder cancer. Photodynamic diagnosis uses the photodynamic properties of hexaminole vulinate (HAL). Following intra-vesical instillation the HAL binds to photoporphyrin IX, which preferentially accumulates in neoplastic cells. The blue light causes the HAL bound to protoporphyrin IX to fluoresce red. The use of BLC with HAL has shown clinical benefit in five prospective international clinical studies involving more than 1800 patients. The main benefit is seen in the detection of carcinoma in situ, where BLC compared with white light cystoscopy detected around 40% more cases and at least one additional papillary tumor in 25% of cases<sup>5</sup>. With the improvement in staging with BLC the hope is to more accurately diagnose patients and provide the optimal treatment regimen.

### Use of neoadjuvant chemotherapy (NAC)

Large randomized clinical trials and a meta-analysis have established neoadjuvant cisplatin based combination chemotherapy as the standard of care prior to radical cystectomy in patients with MIBC<sup>6-8</sup>. NAC with methotrexate, vinblastine, adriamycin and cisplatin (MVAC) followed by surgery offered

significant disease free survival benefit. If patients are eligible for cisplatin, the combination of gemcitabine and cisplatin is widely used based on similar efficacy and improved tolerability when compared with MVAC. 40% of patients aged 70 and older are not eligible for cisplatin due to inadequate renal function and this proportion increases with age<sup>9</sup>. Several recent analysis show that NAC remains underutilized in the elderly population<sup>10,11</sup>. It may be related to increased comorbidities, frailty and decrease performance status and thus more efforts are focused on increasing NAC used in the fit patients.

### Use of adjuvant chemotherapy

Most trials evaluating adjuvant chemotherapy in patients with MIBC are small and underpowered making extrapolation to the elderly difficult<sup>12-14</sup>. Although the evidence supporting adjuvant chemotherapy is less compelling than that of neoadjuvant chemotherapy, some patients may benefit from adjuvant chemotherapy, such as those who underwent up-front radical cystectomy and have extensive tumor invasion of the bladder wall or lymph node involvement<sup>15</sup>. However, patients who received immediate adjuvant chemotherapy had significantly longer progression-free survival (PFS): 5 years PFS was 47.6% in immediate cisplatin based chemotherapy arm versus 31.8% in the deferred treatment arm (P<0.0001)<sup>16</sup>.

### Surgery

#### Radical Cystectomy:

The criterion standard for the treatment of patients with stage T2-T4 disease is radical cystoprostatectomy for men and anterior pelvic exenteration for women.

Cystoprostatectomy involves removal of the bladder, peritoneal covering, perivesical fat, distal ureters, prostate, seminal vesicles, vas deferentia and sometimes the membranous or entire urethra. Anterior pelvic exenteration consists of cystectomy, urethrectomy, hysterectomy, salpingo-oophorectomy and partial anterior vaginectomy. Both procedures also include regional lymph node dissection.

Although radical cystectomy is typically reserved for muscle invasive disease, it is also appropriately used to treat some patients with high-risk non-muscle invasive bladder cancer including CIS. Indications in non-muscle-invasive disease include the following:

- Tumor bulk so substantial that complete eradication of tumor is not feasible endoscopically.
- Prostatic urethra involvement

- CIS or T1 high- grade tumor persistence despite adequate intravesical management.

From 35 to 50% of patients who undergo cystectomy for Ta, T-1 or CIS are discovered to have muscle-invasive disease, with 10 to 15% demonstrating microscopic lymph node metastasis. According to the NCCN guidelines, cystectomy should involve at least bilateral node dissection, including iliac and obturator nodes<sup>17</sup>.

Robotic-assisted cystectomy is becoming more common nowadays. However, it is important to note that robotic cystectomy has not shown a benefit in terms of length of stay, oncology outcomes, or lymph node yield. In a recent publication, robotic cystectomy was associated with higher rates of peritoneal carcinomatosis (21% vs. 8%) when compared with open radical cystectomy<sup>22</sup>. The higher cost associated with robotic radical cystectomy has been well documented and must be weighed when considering using this technology in the treatment of MIBC without any notable clinical benefit<sup>23,24</sup>. Pelvic lymphadenectomy:

Approximately 25% of patients undergoing radical cystectomy have lymph node metastases at the time of surgery. Bilateral pelvic lymphadenectomy (PLND) adds prognostic information by appropriately staging the patient and may confer a therapeutic benefit. PLND can be performed in a standard or an extended version. The boundaries of a standard PLND include the bifurcation of the common iliac artery and vein superiorly, the genitofemoral nerve laterally, the obturator fossa posteriorly, and the circumflex iliac vein inferiorly. Extended PLND includes the lymph nodes in the presacral region and those surrounding the common iliac vessels to the level of the aortic bifurcation. For a supra-extended PLND, dissection can be continued to the level of the inferior mesenteric artery. Patients with lymph node metastases really have no 'skip lesion'. The additional benefit of an extended PLND is controversial and no randomized trial to date has proved its superiority to standard PLND.

Urinary diversion: After cystectomy is performed a urinary diversion must be created. Diversions can be incontinent or continent. Ileal or colonic conduit is the common incontinent diversion, ileal conduit has minimal morbidity and has been attaining more than 40 years excellent reliability. Continent urinary diversions have some contraindications:

- Multiple comorbid health problems
- Chronic renal insufficiency
- Hepatic dysfunction
- Advanced disease stage

The most commonly used continent cutaneous diversion is the Indiana pouch. The orthotopic neobladder is another form of continent urinary diversion. In neobladder diversions, various segments of intestine, including the ileum, ileum and colon, and sigmoid colon, can be used to construct a reservoir. The ureters are implanted to the reservoir and the reservoir is anastomosed to the urethra.

### Systemic regimens for metastatic bladder cancer

First line, platinum-based combinations, methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) is a standard combination regimen for treatment of metastatic bladder cancer. MVAC has an objective response rate of 57 - 70% and a complete response rate of 15 to 20%. Median overall patient survival with this regimen is typically 13 - 15 months and the two years survival rate is 15 to 20%<sup>(18,19,20)</sup>. Gemcitabine and cisplatin (GC) is a newer regimen that has been shown to be as effective as MVAC but with less toxicity<sup>21</sup>. There is second-line therapy for metastatic urothelial carcinoma is present in clinical practice on the patients who are not candidates for cisplatin chemotherapy. Agents in this category include atezolizumab, nivolumab, durvalumab, avelumab and pembrolizumab. They inhibit programmed cell death 1 (PD-1) protein and its ligands PD-L1 and PD-L2, which are part of immune checkpoint pathways that regulate T-cell activation to escape antitumor immunity.

Excepting these, fibroblast growth factor receptor inhibitors e.g. Erdafitib and Anti- Nectin-4 Monoclonal antibodies e.g. Enfortumab vedotin are approved by FDA for locally advanced or metastatic urothelial cancer.

### Radiation therapy

External beam radiation therapy has been shown to be inferior to radical cystectomy for the treatment of bladder cancer. The overall 5 year survival rate after treatment with external beam radiation is 20 to 40%, compared with a 90% 5 year survival after cystectomy for organ confined disease. Nevertheless, external beam radiation therapy is used in various countries for patients with comorbidities precluding treatment with modalities such as radical surgery or

chemotherapy<sup>25-27</sup>. Neoadjuvant external beam radiation therapy has been attempted for muscle invasive bladder cancer. However, no improvement in survival rate has been demonstrated.

Bladder preservation in muscle invasive bladder cancer

Interest in bladder preservation techniques has grown significantly over recent years as technological advancements improve bladder preservation therapy outcomes and the focus on improving quality of life heightens. Patients of two distinct categories have historically undertaken bladder preservation therapy: those who are medically inoperable (unfit for surgery) and those with organ-confined disease who have a strong preference to avoid radical surgery. The National Comprehensive Cancer Network (NCCN) recommends bladder preservation over radical cystectomy be reserved for patients whose tumors are small and solitary, lack lymph node metastases, lack carcinoma in situ (CIS), are without tumor-related hydronephrosis and have favorable baseline bladder function [28]. Single and multi-modality therapies are available for bladder preservation. Experts generally agree that single modality therapies such as maximal transurethral resection, chemotherapy and radiotherapy are less effective alone than in combination. Modern multi-modal bladder preservation typically involves some variation of maximal TUR with chemo-radiation therapy. This is followed by regular cystoscopic evaluation to determine response to therapy; with prompt salvage radical cystectomy (RC) should the patient not respond or have a muscle-invasive recurrence. Different retrospective studies show the use of bimodal or trimodal therapy in categorised patients preserved the bladder with the 5 year overall survival rate in more than 70% patients<sup>29,30</sup>.

Finally, a comparative effectiveness analysis developed a Markov model to compare trimodal therapy (TMT) with RC. This study found an increase in 0.59 quality-adjusted life years (QALYs) when undergoing TMT as compared to RC<sup>31</sup>. This study puts quality of life into the measure of QALYs, which is important when considering the use of TMT versus RC at a population-level perspective.

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