

REVIEW

Bladder-sparing treatment in MIBC: where do we stand?

Srikanth MURALI-KRISHNAN ¹*, Karl H. PANG ², Francesco GRECO ³,
Cristian FIORI ⁴, James W. CATTO ^{1,2}, Vittorio L. VAVASSORI ⁵, Francesco ESPERTO ¹, on behalf of
EAU-ESRU (European Associations of Urology-European Society of Residents Urologist)

¹Department of Urology, Royal Hallamshire Hospital, Sheffield Teaching Hospital, Sheffield, UK; ²Unit of Academic, University of Sheffield, Sheffield, UK; ³Department of Urology, Humanitas Gavazzeni Hospital, Bergamo, Italy; ⁴Department of Urology, University of Turin, San Luigi Gonzaga Hospital, Orbassano, Turin, Italy; ⁵Department of Radiation Oncology, Humanitas Gavazzeni, Bergamo, Italy

*Corresponding author: Srikanth Murali-Krishnan, Department of Urology, Royal Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF UK. E-mail: Srikanth@hotmail.co.uk

ABSTRACT

INTRODUCTION: The gold-standard treatment of muscle-invasive bladder cancer is radical cystectomy (RC), but this can be associated with morbidity and perioperative risks. Patients may not be fit for RC or choose to preserve their bladders. There are evolving bladder-sparing treatments that are often delivered in a multimodal approach. Here, we aim to review recent advances in bladder-sparing treatments.

EVIDENCE ACQUISITION: We undertook a narrative review informed by a Medline/PubMed literature search using a combination of terms for recent (5 years) articles in English. Relevant studies from authors' bibliographies were retrieved. **EVIDENCE SYNTHESIS:** Bladder-sparing treatment consists of transurethral resection of bladder tumour (TURBT), radiotherapy and chemotherapy. Experimental approaches with immunotherapy and using gene signatures for radiation therapy and chemotherapy response are being explored.

CONCLUSIONS: Bladder-sparing treatment is an option for patients with bladder cancer. Those who may benefit most are those with solitary invasive cancers, those with good bladder capacity and compliance, those who choose to preserve their bladder and sexual function and who are not fit for RC. Multimodal bladder-sparing approaches may have comparable oncological outcomes to RC and so appear an attractive alternative in suitable patients.

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Introduction

Bladder cancer (BC) is the 9th most common cancer worldwide and is more common in males.¹ In Europe, the age-standardized incidence rate (per 100,000 person-years) for men is 17.1 and 3.5 for females.¹ The age-standardized mortality in Europe for men is 5.2 and 1.1 for females.¹

The most common form of BC is urothelial cell carcinoma (UCC) occurring in approximately 80% of cases with 15-25% of cases presenting

as non-urothelial or "variant" histology, such as micropapillary, plasmacytoid and sarcomatoid disease.² Variant histology is usually considered as a high-risk disease.³ BC is classified into non-muscle invasive BC (NMIBC) and muscle invasive BC (MIBC).⁴ In order to increase an early diagnosis of progression from NMIBC to MIBC, EORTC Genito-urinary cancer group has developed a scoring system.⁵ The scoring system is based on a number of clinical (previous recurrence rate, tumor number, size and Ta or T1) and

pathological factors (tumor grade and presence of CIS), which are scored to give a 1-year recurrence probability of between 15-61%.⁵ Treatment of BC depends on the stage of disease, variant histology, patient fitness and patient preferences.^{6, 7} In NMIBC, tumors are treated according to risk stratification with low risk tumors being treated with TURBT and a single instillation of intravesical chemotherapy to high risk tumors being offered TURBT and intravesical immunotherapy (Bacillus Calmette-Guerin, BCG) or RC.⁷

The gold-standard treatment of MIBC is RC, however many patients with BC have competing diseases and have considerable risks of mortality from other causes.^{6, 8, 9} For those who are unfit for RC and who prefer to not have their bladder removed, then bladder-sparing options with multimodal approaches have been developed. There is increasing quality of data comparing bladder-sparing treatment with RC, and here we discuss the components and outcomes of bladder-sparing treatment.¹⁰⁻¹²

Evidence acquisition

A non-systematic Medline/PubMed literature search was performed with different combination of terms including “bladder cancer treatment,” “muscle-invasive bladder cancer treatment,” “radiotherapy,” “chemotherapy,” “cystectomy,” “trimodal,” “multimodal,” “immunotherapy” and “bladder sparing.” Only articles in English language from the last 5 years were obtained. Relevant meta-analyses and original articles were reviewed and retrieved from authors’ bibliographies.

Muscle-invasive bladder cancer

Approximately 25% of BCs at presentation are found to be muscle invasive or metastatic.¹³ MIBC is much more aggressive than NMIBC with a 5-year survival of less than 15% when left untreated.¹⁴ MIBC is always considered high grade therefore prognostic information is limited from the histological grading and is predominately ascertained from the TNM staging.¹⁵ However, emerging research demonstrates more targeted treatment can be provided on the basis of histological subtypes of MIBC.^{16, 17} An example

of this includes p53-like MIBCs being resistant to neoadjuvant chemotherapy (NAC).¹⁷ This remains an area with slightly conflicting evidence and more research is needed.^{16, 18}

Surgical treatment of MIBC

The management of MIBC can involve removing the bladder with adjacent structures (RC) or bladder-sparing modalities (Figure 1). The gold-standard treatment for localized MIBC is RC with pelvic lymph node dissection (PLND).⁶ However, recurrence develops in around 32% of patients 5 years following the procedure and RC can be a morbid procedure.¹⁹ Early complications related to RC include bleeding, bowel injury, infection, collection (urine leak/lymphocele) and ileus. Long-term complications include ureteric stricture, herniation and disease recurrence.

Efforts to reduce the trauma of surgery have been developed, such as enhanced recovery after surgery and the use of minimal invasive approaches.²⁰⁻²⁵ When compared with open RC, robot-assisted radical cystectomy (RARC) has been shown to reduce blood loss and length of stay.^{23, 25-28}

Despite radical treatment with RC, approximately half of all patients with MIBC have a mortality associated with local recurrence or pre-existing metastatic disease.⁸ As a result neoadjuvant treatment options have been sought after with major trials exploring the use of NAC being performed between 1991 and 2003.²⁷ Similar studies were performed for neoadjuvant radiotherapy (RT) however a 2018 meta-analysis of 10 RCTs by McAlpine *et al.* of preoperative RT concluded there was no significant survival benefit at 5 years with an odds ratio (OR) of 1.26 (95% CI 0.76-2.09).²⁹

MIBC bladder preservation treatment

Why bladder preserving treatments?

Patients may choose to avoid RC as they wish to keep their bladder in situ (for quality of life [QOL], body image reasons etc.), for sexual preservation or they are of high anesthetic risk.³⁰ Feuerstein *et al.* compared QOL in MIBC patients treated with bladder-sparing options against RC patients and there appeared to be a

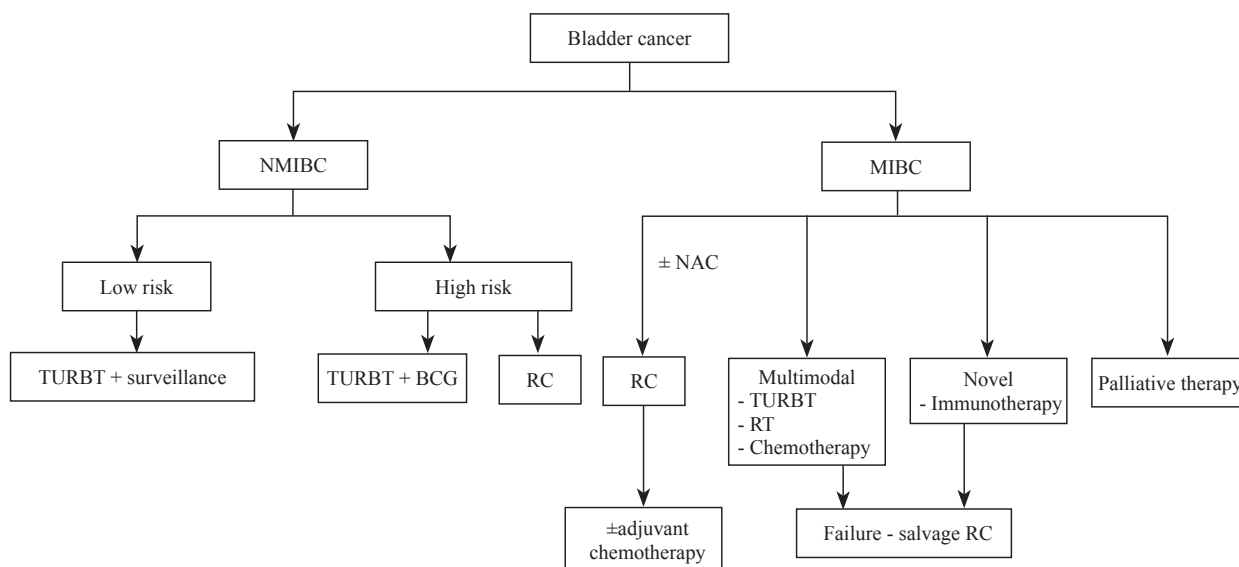


Figure 1.—Overview of treatment options available for bladder cancer. The management of MIBC can be RC or bladder-sparing options. These options include TURBT, RT and chemotherapy, often delivered through a multimodal route. There are evolving immunotherapies which have also shown to be effective. NMBIC: non-muscle-invasive bladder cancer; MBIC: muscle-invasive bladder cancer; TURBT: transurethral resection of bladder tumor; BCG: Bacillus Calmette-Guerin; RC: radical cystectomy; RT: radiotherapy.

similar or better QOL in those receiving bladder-sparing treatment, with satisfactory sexual and urinary function but with gastrointestinal side effects.³¹ These data supported findings by a cross-sectional study looking at health related QOL markers in patients treated with bladder-sparing therapy (trimodal therapy [TMT] in this case) against RC. The study used six validated QOL instruments to score the patients and then a multivariate analysis of the mean QOL scores was performed to assess different aspects of the patients' QOL. The patients undergoing TMT had a better general QOL (average points difference 9.7, 95% CI 4.1-15.3, P=0.001), better bowel function (average points difference 4.5, P=0.02), fewer problems to get or maintain an erection (average points difference 32.1, P<0.001), and also showed less concern about body image (average points difference 15.9, P<0.001).³²

A study of Canadian urologists, medical oncologists and radiation oncologists identified a number of barriers and enabling factors to the use of bladder-sparing therapy in their practice.³³ Data showed that there was a perception that bladder-sparing treatment resulted in an inferior survival compared to RC (mean estimates of survival at 5 years of bladder-sparing treatment 54.9% and

65% for RC) and that a lack of referral systems existed between urology and radiation oncology.³³ The study demonstrated that these barriers often led to patients not being routinely offered bladder-sparing options. In practices that enabled bladder-sparing therapy, presence of “champions” (one who believes in bladder-sparing treatment and is an advocate for its adoption) was a key factor and all options should be presented and undergo multidisciplinary reviews.³³

Patient selection

The most widely accepted bladder-preserving strategy is TMT.³⁴ This involves an attempted complete TURBT, RT and chemotherapy.³⁴

Bladder-preserving therapy is offered to patients with MIBC stage c(linical)T2N0M0 who are either unfit for RC or they have chosen to preserve their bladder, understanding the risks involved in this approach.³⁴

Higher tumor stages appear less responsive to chemotherapy and RT. For example, in an observational study of 415 patients treated with bladder-sparing therapy for MIBC, a reduced response rate was demonstrated as the tumor stage worsened (metastases-free survival at 5 years T2, 85%; T3, 63%; and T4, 34%).³⁵ No effect

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was seen in response when comparing multifocal lesions to single lesions, however multifocal lesions were associated with a greater risk of local recurrence following complete response to bladder-sparing treatment.³⁵

Since T3 tumors invade perivesical tissue and T4 tumours invades prostate stroma, seminal vesicles, uterus, vagina, pelvic wall and/or the abdominal wall there is a preference to managing them surgically in suitable patients, even though this may be palliative, due to their poorer response to chemotherapy and RT.³⁶

MIBC patients with associated hydronephrosis show reduced complete response rates to bladder-sparing therapy and therefore should not be routinely offered, however it is not an absolute contraindication.^{37, 38}

Very limited data has been produced regarding BC with variant histology; therefore, the use of bladder-sparing therapy in these patients does not have a strong evidence base. A retrospective analysis of 66 patients with UCC and variant histology treated with bladder-sparing therapy showed no statistically significant difference in 10-year disease-specific survival rates (UCC, 64% and variant histology, 64%; hazard ratio (HR), 1.30; 95% CI 0.77-2.20, P=0.33).¹⁸

Surgical therapy

TMT

TMT is composed of three different stages, TURBT, RT and chemotherapy.

TURBT is a crucial element of the TMT model and should be as complete as possible. Even in patients undergoing RC, complete TURBT has been show to increase overall and disease specific survival rates.³⁹⁻⁴¹ A single center retrospective analysis of patients showed a statistically significant difference in complete response rates to bladder-sparing therapy.⁴² Complete response was achieved in 79% of those whom had undergone a complete TURBT against 57% of those whom had undergone an incomplete resection (P<0.001).⁴²

There are two methods of bladder-sparing treatment that have been outlined following maximal transurethral resection, split course chemoradiation and single course chemoradiation. The split course regime involves induction radiation

therapy given at approximately 40Gy with concurrent chemotherapy following TURBT.⁴³ This is followed by cystoscopic assessment with biopsies. If there is an incomplete response, patients will be offered a salvage RC, however if a complete response is achieved, consolidation radiotherapy (usually to 60-65Gy) with concurrent chemotherapy will be given followed by cystoscopic surveillance.⁴²

Single course chemoradiation (or as its also known, continuous course) consists of giving full dose radiotherapy at approximately 65Gy with concurrent chemotherapy after TURBT.⁴³ Cystoscopic assessment and biopsies are then performed 1-3 months following TMT. In patients with good response, cystoscopic surveillance is commenced. Salvage RC will be offered if there is an incomplete response.⁴³

TURBT

An area of interest for TURBT is the fluorescence based photodynamic technique of blue light cystoscopy. This works on the preferential uptake and subsequent accrual of protoporphyrins in BC cells.⁴⁴ Protoporphyrins emit a red fluorescence when blue light (360-450nm wavelengths) touches it as it is converted to photoactive porphyrins.⁴⁴ There are currently 2 agents that have been investigated, namely hexaminolevulinate and 5-aminolevulinic acid, however the former is a more potent agent and is the only one that has Food and Drug Administration and European Medicines Agency approval.⁴⁴

The technology has mainly been used in NMIBC and a meta-analysis comparing hexaminolevulinate cystoscopy against standard white light cystoscopy showed improved detection with 24.9% of patients having at least one additional Ta/T1 tumor seen (P<0.001).⁴⁵ Furthermore, the recurrence rates were significantly lower overall using hexaminolevulinate cystoscopy with a relative risk of 0.761 (95% CI 0.62-0.92, P=0.006).⁴⁵

A more recent meta-analysis investigated the effects of the technology on progression of NMIBC. With a median follow-up of approximately 28 months, progression was seen in 44 out of 644 (6.8%) patients who underwent hexaminolevulinate cystoscopy and 70 out of 657

(10.7%) who underwent standard white light cystoscopy.⁴⁶ The OR for progression in white light TURBT was 1.64, when compared to hexaminolevulinate cystoscopy (95% CI 1.10-2.45, P=0.01).⁴⁶

In the context of bladder sparing treatments for MIBC, fluorescence-based cystoscopy may show multifocal lesions which may be missed, such as CIS or smaller Ta/T1 tumors, when focusing on a T2 tumor, thereby reducing recurrence rates. This is an area that has not yet been researched as the technology is not yet widely used but may be a line of enquiry in the future.

Cryotherapy

For those patients who have unresectable tumors, such as those who have difficulty to reach tumors cystoscopically or grossly adherent bladder for which cystectomy may be abandoned, an alternative treatment has been devised but is still not verified in large studies. Cryotherapy in MIBC has been trialed in small patient cohorts.

A preliminary study of 7 patients with T4b unresectable cancer (RC was abandoned in these patients) underwent transrectal ultrasound guided transperineal cryosurgery.⁴⁷ Out of the 7 patients, 2 died due to pulmonary metastasis and 2 died due to extensive abdominal and pelvic metastasis.⁴⁷ At 43 months after cryosurgery, the remaining 3 patients were alive with no evidence of progression.⁴⁷

An earlier study of 32 patients with MIBC was performed to evaluate the feasibility of CT guided cryoablation of the tumor performed with local anesthetic. With an average follow-up of 33 months, 29 patients had no evidence of tumor recurrence.⁴⁸ This procedure might be an option in patients who are unsuitable for general or regional anesthesia.

Radiotherapy

Radiotherapy has been used as a treatment for BC since 1926, with radical radiotherapy only being used for those who have inoperable tumors or are unfit for RC.²⁷ RT alone has been shown to have poorer outcomes when compared to chemoradiotherapy.^{49, 50}

A phase 3 RCT compared 360 patients with

MIBC treated using radiotherapy with or without synchronous chemotherapy (fluorouracil and mitomycin).⁴⁹ In addition, patients were also randomized to either receive whole-bladder radiotherapy of modified-volume, in which the volume of the bladder receiving full dose radiation was reduced. The primary end point was survival-free of locoregional disease and secondary end points were overall survival and toxicity.⁴⁹ At 2 years patients undergoing RT alone had a locoregional disease-free survival rate of 54% compared to the chemoradiotherapy group, 67%.⁴⁹ The median follow-up for the study was 69.9 months and at this stage, the chemoradiotherapy group was approximately 1.47 times more likely to be locoregional disease free compared to RT alone (HR, 0.68; 95% CI 0.48-0.96, P=0.03).⁴⁹

The precise technique, fractionation and doses has not been standardized for bladder-sparing treatment but as described above, the regimes are usually split course or continuous. The most frequently used technique is to target the whole pelvis and pelvic lymph nodes at a dose of 40Gy using conventional fractionation, followed by a boost dose of radiation to the whole bladder at a dose of 20Gy with conventional fractionation.⁵¹

A recent RCT compared 60 patients having reduced volume RT (group 1) and standard RT (group 2) as part of single course TMT.⁵² They found no significant difference in disease recurrence (group 1, 7.1% vs. group 2, 10.3%), metastases (group 1, 17.9% vs. group 2, 13.8%) or overall survival (group 1, 75% vs. group 2, 79.3%) but decreased radiation toxicity (group 1, 93.3% vs. group 2, 16.7%).⁵² An earlier similar RCT showed similar results but both studies had relatively small patient numbers.⁵³

Chemotherapy

Chemotherapy can be delivered preoperatively (NAC) in MIBC prior to RC to improve outcomes. In addition, it can be given post-operatively in the form of adjuvant or palliative therapy. In bladder sparing treatments for MIBC, chemotherapy makes up a key component of TMT, aiming to increase the radio-sensitivity of the tumor.

BC is associated with complex genetic and epi-

genetic alterations. In order to understand the molecular basis of NMIBC progression, treatment responses and recurrence and metastasis following radical treatment, The Cancer Genome Atlas (TCGA) project which begun in 2005 aimed at identifying genetic mutations in cancer. The genomic mutation of 131 chemotherapy-naive MIBC (T2-4, Nx, Mx) samples have been reported and recurrent mutations in 32 genes involved in cell-cycle and chromatic regulation, and kinase signaling pathways have been identified.^{54, 55}

As discussed previously outcomes are improved with radio-sensitizing chemotherapy prior to RT when compared to RT alone.^{49, 50} The most frequently used and studied radio-sensitising agents used are, cisplatin-based and fluorouracil with mitomycin C.^{49, 56-58}

Cisplatin was shown to be safe and feasible in 1987 in those who were deemed unsuitable for RC in a small study of patients undergoing radiotherapy with 70 mg/m² of cisplatin (given intravenously every three weeks for eight courses).⁵⁹

A RCT comparing RT with or without 100mg/m² of cisplatin in patients with T2-T4b BC showed that pelvic recurrence was significantly reduced in those receiving cisplatin at 40% compared to 59% of the control group after 5 years (P=0.036).⁶⁰ Overall survival was not significantly affected by the addition of cisplatin but the study was inadequately powered for this.⁶⁰

A 2-step meta-analysis of 15 RCT (N.=3285) compared platinum-based NAC with local treatment compared to local treatment alone.⁶¹ Local treatment was defined as RC or RT, with 9 out of the 15 studies including RT.⁶¹ The use of cisplatin-based NAC was found to have a significant survival benefit (with NAC, 53% vs. without NAC, 45%; HR, 0.87; 95% CI, 0.79-0.96, P=0.004).⁶¹ In the second step of the study, retrospective data (N.=1766) on pathological response and overall survival was compared between methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) against gemcitabine and cisplatin/carboplatin (GC).⁶¹ No significant difference in pathological response between MVAC and GC (OR, 1.17; 95% CI 0.92-1.50, P=0.37) was found, however, overall survival was found to be significantly higher with the use of GC (HR, 1.26; 95% CI 1.01-1.57, P=0.94).⁶¹

Approximately 30% of patients with MIBC are unsuitable for cisplatin-based chemotherapy, with the proportion climbing to greater than 65% in the above 80-year age bracket.⁶²

There are no studies that specifically look at specific thresholds for cisplatin usage. However, a consensus for patients with metastatic BC was formulated to exclude patients who are unfit for cisplatin-based chemotherapy. This was based on the most commonly used standard criteria used in clinical trials.⁶³ These include patients meeting any one of the following criteria: WHO/ECOG (World Health Organization/Eastern Cooperative Oncology Group) performance status of 2, Creatinine clearance of less than 60mL/min, NYHA (New York Heart Association) class 3 heart failure, CTCAE (Common Terminology Criteria for Adverse Events) version 4, grade 2 audiometric hearing loss or peripheral neuropathy.⁶³

In patients that are eligible for cisplatin-based chemotherapy, the most commonly used regime is fluorouracil with mitomycin C. As previously discussed James *et al.* were able to demonstrate significant radiosensitization using fluorouracil with mitomycin C.⁴⁹

Other alternatives include carbogen and nicotinamide (CON) for hypoxic modification prior to RT. A RCT of 333 MIBC/high grade T1 patients compared RT against RT with CON with cystoscopic control at 6 months as the primary end point with secondary end points of overall survival and local relapse-free survival over 3 years.⁶⁴ There was no significant improvement of cystoscopic control between the two groups however the addition of CON was favorable in terms of overall survival (RT, 46% vs. RT+CON, 59%; HR, 0.87; 95% CI 0.80-0.95, P= 0.003) and local relapse-free survival (RT, 43% vs. RT+CON, 54%; HR, 0.88; 95% CI 0.80-0.96, P=0.003).⁶⁴

Immunotherapy

Immunotherapy was first used in BC in 1976 in the form of BCG.⁶⁵ The mechanism of action of BCG is not fully understood however there are two modes of actions that have been demonstrated: direct interaction with the urothelium and BCG internalization.⁶⁶ It is indicated in NMIBC patients who are high risk for progression.^{7, 67}

Since then our understanding for the immunogenic basis for BC has grown and interest has been shown for immunotherapy especially since the long lasting response rates of immune checkpoint blockade seen in patients with metastatic BC.⁶⁸ The programmed cell death ligand-1 (PD-L1) receptor and programmed death-1 (PD-1) regulates T cell activity and when they are targeted and are blocked by monoclonal antibodies, such as durvalumab (PD-L1) or pembrolizumab (PD-1), T cell antitumor activity can increase.⁶⁸

In an open label phase-3 trial for metastatic BC patients who had recurred or had progressive disease following platinum-based chemotherapy were treated with pembrolizumab or the investigators choice of chemotherapy (paclitaxel, docetaxel or vinflunine).⁶⁹ The median overall survival in the pembrolizumab group was 10.3 months *versus* 7.4 months in the chemotherapy group, giving a significantly longer overall survival time (HR, 0.73; 95% CI 0.59-0.91, P=0.002).⁶⁹

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4; otherwise known as CD152) is another receptor of interest in urological malignancies. CTLA-4 is only found on T cells and regulates the amplitude of T cell activity at the early stage.⁶⁸ CTLA-4 is blocked by anti-CTLA-4 antibodies, such as ipilimumab, which results in a broad enhancement of the immune response by up regulating CD4+ T cell activity and inhibiting T cell-dependent immunosuppression.⁶⁸ In 2010 a phase I clinical trial investigating the anti-CTLA-4 therapy, found it to have a tolerable safety profile in the presurgical setting.⁷⁰ Currently a trial using tremelimumab (an anti-CTLA-4 agent), is being assessed in combination with durvalumab prior to RC in non-metastatic MIBC patients.⁷¹

To our knowledge, there are currently no studies identifying the role of immunotherapy in MIBC patients and bladder preservation therapy. There are however a number of registered trials that are currently in the recruiting phase, which may address these questions (NCT02662062 - Pembrolizumab With Chemoradiotherapy as Treatment for Muscle Invasive Bladder Cancer, NCT02621151 - Pembrolizumab [MK3475], Gemcitabine, and Concurrent Hypofractionated Radiation Therapy for Muscle-Invasive Urothe-

lial Cancer of the Bladder, NCT02845323 - Neoadjuvant Nivolumab With and Without Urelumab in Patients With Cisplatin-Ineligible Muscle-Invasive Urothelial Carcinoma of the Bladder).⁷²

Predictive gene signatures for response to chemotherapy and radiotherapy

Advances in molecular subtyping have allowed MIBC to be divided into distinct subgroups with varying characteristics. There are four widely used published classification methods: University of North Carolina (UNC), MD Anderson Cancer Center (MDA), The Cancer Genome Atlas (TCGA), and Lund University (Lund) (Figure 2).^{17, 54, 73, 74} 1) UNC classifies MIBC into two broad subgroups, luminal (cells exhibit markers of terminal urothelial differentiation) and basal (express genes of basal urothelial cells). In addition, a subset of basal tumors can be classified as claudin-low;⁷³ 2) MDA divides MIBC into three groups: luminal, p53-like and basal tumors;¹⁷ 3) TCGA divides MIBC into four groups: Cluster I (luminal/papillary-like with HER2), II (luminal-like with HER2), III (basal/squamous-like) and IV (basal/squamous-like with stroma and muscle features);⁵⁴ 4) Lund divides MIBC into five groups based on gene expression profiles: urobasal A, genomically unstable, infiltrated, squamous cell carcinoma (SCC) like and urobasal B.⁷⁴

The significance of the groups are observed in survival outcomes and in response rates to NAC.¹⁷ Seiler *et al.* found that basal tumors (N.=158) had significantly worse overall survival over 8 years compared to luminal tumors

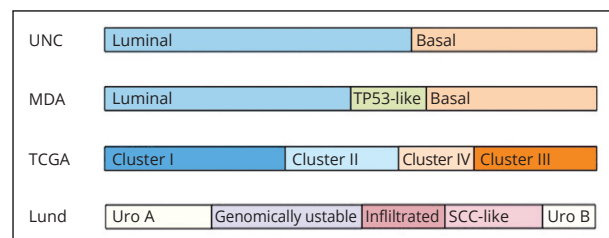


Figure 2.—Molecular subtypes of bladder cancer and the overlaps in classification. There are four classifications of BC molecular subtypes. Subtypes of BC predict response to neoadjuvant chemotherapy. UNA: University of North Carolina; MDA; MD Anderson Cancer Center; TCGA: The Cancer Genome Atlas; Lund: Lund University; Uro: urobasal; SCC: squamous cell carcinoma like; BC: bladder cancer.

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(N.=195) when using the UNC classification system in non-NAC-treated patients (P=0.009).¹⁶ These results were contrasted by those receiving NAC and the luminal subgroup (N.=107) showed significantly better survival in the basal subgroup (N.=52) (P=0.014) with particularly poor response rates seen in claudin-low patients (N.=41).¹⁶

Tanaka *et al.* used the Lund classification and investigated 92 post RC patients' response to chemoradiotherapy.⁷⁵ Those with urobasal cancers had a 15% complete clinical response rate to chemoradiotherapy, which was significantly lower than the genomically unstable (52%, P<0.001) or the SCC-like (45%, P=0.01).⁷⁵

Specific protein expression has also been shown to have an effect on survival in MIBC patients. For example, low MRE11 expression was associated with a poor 3-year cancer-specific survival following RT when compared to high MRE11 expression patients (low 43.1% vs. high 68.7%, P=0.012).⁷⁶ This effect was not seen in RC patients (low 62.2% vs. high 53.8%, P=0.46).⁷⁶

In solid tumors, areas of hypoxia have been found to have increased radioresistance.⁷⁷ Carbogen and nicotinamide (CON) are used to modify hypoxia in tumors, to improve oxygenation and reduced hypoxic cell radioresistance.⁷⁸

Yang *et al.* investigated the predictive effect of hypoxia gene signatures in 151 BC patients to determine if RT+CON gives better survival outcomes than RT alone.⁷⁹ In patients who had high-hypoxia expression, RT+CON resulted in a greater local progression-free survival at 5 years when compared to RT alone (HR, 0.47; 95% CI 0.26-0.86, P=0.015).⁷⁹ There was no significant difference between RT+CON and RT in the low-hypoxia group.⁷⁹

Molecular subtypes have not yet been used as predictive markers bladder-sparing approaches but given the increased survival rates in basal subgroups with NAC and improved clinical response rates in urobasal cancers to chemoradiotherapy post RC, these groups may have more benefit from bladder sparing approaches.^{16, 75}

Comparison of outcomes

Outcomes for bladder preservation strategies are largely dependent on retrospective analyses, with

the exception of a few small RCTs. Comparisons of bladder preservations strategies to RC have often been limited to cancer registries or single centers, which can result in heavy selection bias.

A recent large systematic review and meta-analysis was performed in effort to gain more robust data on the effectiveness of bladder-sparing therapy *versus* RC plus PLND. In the study 11 studies were included, with 2 RCTs (N.=205) and the rest were cohort studies (N.=43,829).¹⁰ A total of 39,836 were in the RC group and 4198 in the bladder-sparing therapy group with overall survival, cancer-specific survival and progression-free survival being the main outcomes assessed.¹⁰ In terms of overall survival and progression-free survival, no significant difference was seen between the groups (overall survival: HR, 1.06; 95% CI 0.85-1.31) (progression-free survival: HR, 1.11; 95% CI 0.63-1.95).¹⁰ A significant difference was seen favoring RC with regards to cancer-specific survival (HR, 1.23; 95% CI 1.04-1.46).¹⁰ However, caution should be taken in giving credence to the results of the study, as they themselves grade the certainty of evidence as "very low" in accordance to the GRADE Working Group grade of evidence due to the high reliance of prospective data collection and bias attributable to this.¹⁰

Pooled analysis of prospective bladder preserving protocols gave evidence of efficacy and safety of multimodal therapy. In this study, rates (5-year, 71% and 10-year, 65%) and disease-free survival (5-year, 57% and 10-year, 36%) were comparable to equivalently staged RC patients.¹¹

A recent retrospective analysis comparing the costs associated with bladder-sparing therapy *versus* RC in US (based on data between 2011 and 2013) showed a greater median total cost for bladder-sparing therapy.¹² The median difference at 90 days was \$8964 and \$63771 at 180 days.¹² This study also demonstrated a significantly decreased overall survival and cancer-specific survival in the bladder-sparing group (overall survival: HR, 1.49; 95% CI 1.31-1.69) (cancer-specific survival: HR, 1.55; 95% CI 1.32-1.83).¹²

In a recent study evaluating health-related QOL markers in BC patients showed a statistically significant negative impact when compar-

ing patients who have undergone RC against those who have had conservative treatment.⁸⁰ This was across nearly all of the physical and mental domains tested.

Salvage cystectomy

For those who fail bladder-sparing therapy, salvage RC is offered. This is often considered a more difficult undertaking due to the desmoplastic reaction following radiotherapy, making it harder to identify planes for dissection.⁸¹

In a report of 91 patients treated with salvage RC following bladder-sparing therapy failure, an acceptable morbidity was found with slightly higher complication rate when comparing to standard RC case series.⁸²

Salvage RC rates have varied from center to center with no high-level data to quote precise rates. Gorfit *et al.* described a rate of 6%, Kulkarni *et al.* found a rate of 10% and Kim *et al.* showed a rate of 12%.⁸³⁻⁸⁵ As previously discussed, many patients elect to avoid RC for QOL reasons.

Conclusions

RC is the gold-standard treatment for MIBC and is an option for high-risk NMIBC. Those who are unfit, or do not want to undergo such high morbid procedure resulting in bladder removal and urinary diversion may be offered bladder-sparing treatment. This takes the form of TURBT, radiotherapy, chemotherapy or immunotherapy and is often used in a multimodal approach to improve outcomes. Molecular subtypes of BC help to predict response to NAC. There are increasing data on outcomes of multimodal therapy and appear to be comparable to outcomes from RC.^{10, 11, 86} The data that is currently available is generally not high powered and often have numerous biases. There are ongoing trials to evaluate novel systemic therapies, which may act alone or form part of a multimodal model.

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