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Review – Bladder Cancer – Editor's choice

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Bladder Preservation Strategies in Muscle-invasive Bladder Cancer: Recommendations from the International Bladder Cancer Group

Shilpa Gupta [a], ***Patrick J. Hensley*** [b], ***Roger Li*** [c], ***Ananya Choudhury*** [d], ***Siamak Daneshmand*** [e], ***Bishoy M. Faltas*** [f], ***Thomas W. Flaig*** [g], ***G. Daniel Grass*** [h], ***Petros Grivas*** [i], ***Donna E. Hansel*** [j], ***Comron Hassanzadeh*** [k], ***Wassim Kassouf*** [l], ***Janet Kukreja*** [m], ***Arturo Mendoza-Valdés*** [n], ***Marco Moschini*** [o], ***Kent W. Mouw*** [p], ***Neema Navai*** [q], ***Andrea Necchi*** [r], ***Jonathan E. Rosenberg*** [s], ***Jeffrey S. Ross*** [t,u], ***Arlene O. Siefker-Radtke*** [v], ***John Taylor*** [w], ***Stephen B. Willliams*** [x], ***Alexandre R. Zlotta*** [y,z], ***Roger Buckley*** [aa], ***Ashish M. Kamat*** [q,*]

[a] *Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA;* [b] *Department of Urology, University of Kentucky College of Medicine, Lexington, KY, USA;* [c] *Department of Genitourinary Oncology, H. Lee Moffitt Cancer Center, Tampa, FL, USA;* [d] *Division of Cancer Sciences, University of Manchester, Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester, England, UK;* [e] *Department of Urology, University of Southern California Keck School of Medicine, Norris Comprehensive Cancer Center, Los Angeles, CA, USA;* [f] *Division of Hematology & Medical Oncology, Weill Cornell Medical College, New York City, NY, USA;* [g] *Department of Medicine, Division of Medical Oncology, University of Colorado School of Medicine, Aurora, CO, USA;* [h] *Department of Radiation Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA;* [i] *Division of Hematology Oncology, Department of Medicine, University of Washington School of Medicine, Fred Hutchinson Cancer Center, Seattle, WA, USA;* [j] *Division of Pathology and Laboratory Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [k] *Department of Genitourinary Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [l] *Division of Urology, McGill University, Montreal, Quebec, Canada;* [m] *University of Colorado Anschutz Medical Campus, Denver, CO, USA;* [n] *Urology Department, Hospital Medica Sur, Mexico City, Mexico;* [o] *Division of Oncology/Unit of Urology, URI IRCCS Ospedale San Raffaele, Milan, Italy;* [p] *Department of Radiation Oncology, Dana-Farber Cancer Institute & Brigham and Women's Hospital & Harvard Medical School, Boston, MA, USA;* [q] *Division of Urology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [r] *Vita-Salute San Raffaele University, Milan Italy, Department of Medical Oncology, IRCC San Raffaele Hospital, Milan, Italy;* [s] *Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA;* [t] *Urology and Medicine (Oncology), Upstate Medical University, Syracuse, NY, USA;* [u] *Foundation Medicine, Boston, MA USA;* [v] *Department of Genitourinary Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [w] *University of Kansas Cancer Center, Kansas City, KS, USA;* [x] *Division of Urology, The University of Texas Medical Branch (UTMB), Galveston, TX, USA;* [y] *Division of Urology, Department of Surgery, Sinai Health System, University of Toronto, Toronto, Ontario, Canada;* [z] *Department of Surgical Oncology, Princess Margaret Cancer Centre, University Heath Network, University of Toronto, Toronto, Ontario, Canada;* [aa] *North York General Hospital, Toronto, Ontario, Canada*

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Abstract

Background and objective: Patient-centric management necessitates providing care aligned with patients' values, preferences, and expressed needs. Therefore, critical assessment of bladder preservation therapies (BPTs) as alternatives to radical cystectomy (RC) for muscle-invasive bladder cancer (MIBC) and practical recommendations on the optimal selection of patients for BPTs are needed urgently.
Methods: A global committee of bladder cancer experts was assembled to develop BPT recommendations for MIBC. Working groups reviewed the literature and drafted

* Corresponding author. Department of Urology, The UT MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 1343 Houston, TX 77030, USA. Tel. +1-713-792-3250; Fax: +1-713-792-3474.
E-mail address: akamat@mdanderson.org (A.M. Kamat).

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recommendations, which were voted on by International Bladder Cancer Group (IBCG) members using a modified Delphi process. During a live meeting in August 2023, voting results and supporting evidence were presented, and recommendations were refined based on discussions. Final recommendations achieved ≥75% agreement during the meeting, with further refinements through web conferences and e-mail discussions.

Key findings and limitations: Patients with newly diagnosed MIBC should be offered evaluation in a multidisciplinary setting for consideration of BPTs. The main alternative to RC is trimodal therapy (TMT), and favorable prognostic factors for TMT include unifocal cT2 stage, lack of hydronephrosis, and no multifocal carcinoma in situ (CIS). Other options should be reserved for very select patients who are ineligible for or who decline TMT or RC after thorough consideration of benefits versus risks. These include partial cystectomy (PC) for urachal adenocarcinoma and PC or radical transurethral resection alone for solitary tumors amenable to resection with adequate margins and without concomitant CIS or histologic subtypes.

Conclusions and clinical implications: The IBCG consensus recommendations provide practical guidance on BPTs for MIBC.

ADVANCING PRACTICE

What does this study add?
This study provides consensus-based recommendations for bladder preservation therapies for muscle-invasive bladder cancer, emphasizing a multidisciplinary approach and trimodal therapy as the primary alternatives to radical cystectomy. The recommendations offer clinicians practical guidance on patient selection for bladder preservation strategies based on prognostic factors and individual patient needs.

Clinical Relevance
This manuscript presents comprehensive evidence-based best-practices regarding bladder-preserving strategies for patients with muscle-invasive bladder cancer, spanning evaluation and patient selection, to delivery of trimodality therapy, and subsequent surveillance, while presenting a balanced discussion of key selection criteria for alternative bladder sparing options. The guidelines underscore the critical involvement of a multidisciplinary team with expertise in the management of muscle-invasive bladder cancer from diagnosis onward, and provide insights into critical knowledge gaps regarding optimal bladder sparing strategies. Associate Editor: Sarah P. Psutka.

Patient Summary
We developed recommendations on therapies to preserve the bladder as alternatives to bladder removal for people with muscle-invasive bladder cancer. For newly diagnosed patients, we recommend evaluation by a multidisciplinary team of specialists to consider these bladder-preserving treatments. The main alternative to bladder removal is a combination therapy called trimodal therapy, while other options are recommended only for specific situations.

1. Introduction

Radical cystectomy (RC) with cisplatin-based neoadjuvant chemotherapy (NAC) in fit patients is currently the most common treatment for muscle-invasive bladder cancer (MIBC) worldwide. However, RC is associated with long-term, life-altering physiologic, psychological, and sexual ramifications, and clinicians and patient advocates continue to lobby for alternative, effective bladder preservation therapies (BPTs) [1–3]. Trimodal therapy (TMT) has emerged as a guideline-recommended BPT option for select MIBC patients, and other options such as partial cystectomy (PC), radical transurethral resection (TUR), and bladder preservation following a complete clinical response (cCR) to systemic NAC have also been proposed [4–6]. However, given the lack of direct prospective randomized clinical trial (RCT) comparisons, in addition to limitations in contemporary clinical staging, heterogeneously proposed patient selection criteria, and a lack of conclusive comparative effectiveness data, BPTs are underutilized in real-world settings [7,8]. The International Bladder Cancer Group (IBCG) developed consensus recommendations to provide guidance for clinicians and patients on BPTs and to define more precisely the optimal patient selection criteria and benchmarks for future clinical trial designs.

2. Methods

A multidisciplinary steering committee of global bladder cancer experts (urologic oncologists, medical oncologists,

radiation oncologists as well as genitourinary pathologists, research scientists, and patient advocates) was assembled to develop consensus recommendations on BPTs for MIBC. Recommendations were based on literature evidence, where possible, and clinical experience, where appropriate. Literature searches in relevant databases were performed, and publications were screened for inclusion in the evidence base. Working groups employed a system of literature review and expert opinion–based recommendation statement synthesis, open communication, and scientific debate. Specifically, panel members participated in a modified Delphi process. Recommendation statements were initially circulated via an anonymized online voting system for premeeting voting from the IBCG membership (see the Supplementary material).

On August 25–26, 2023, during a live, in-person consensus meeting, working groups presented the results of this voting, and the recommendation statements were subsequently discussed along with summarized evidence supporting the draft recommendations. Bladder cancer patient advocates also provided their perspectives on the recommendations.

Recommendation statements were revised based on feedback, and final statements underwent further live voting (restricted to bladder cancer experts and patient advocates); consensus was defined as $\geq$75% agreement. These recommendations then formed the basis of this manuscript, refined via subsequent web conferences and e-mail discussions. In some cases, when additional practice-changing data or clinical trial results became available in the time between the live meeting and manuscript submission date, the authors considered and incorporated new evidence into the recommendations. All authors reviewed, edited, and agreed upon the final recommendations put forth in this manuscript.

3. Results

The IBCG's consensus recommendations for BPTs in MIBC are presented in Table 1, and supporting evidence for these recommendations is discussed in the text below.

3.1. General recommendations

Patients with newly diagnosed MIBC should be offered evaluation in a multidisciplinary setting that includes urologic oncologists, medical oncologists, radiation oncologists, pathologists, and radiologists (as appropriate) for consideration of BPTs.

Variations in histologic interpretation can significantly affect both proposed management strategies and prognosis in patients with high-risk tumors [9,10]. Traboulsi et al [9] found that review of TUR specimens by a genitourinary pathology specialist led to significant management changes in 35% of patients with T1-T2 bladder cancer. Therefore, the IBCG recommends that, when feasible, all MIBC cases, including those being considered for BPTs, be reviewed by a pathologist with experience and expertise in urothelial carcinoma [11].

3.2. Trimodal therapy

The goal of TMT is to preserve the bladder and patient quality of life (QoL) without compromising oncologic outcomes. Despite the growing body of evidence supporting its safety and efficacy, and its endorsement in appropriately selected patients in current guidelines [4–6], TMT is still underutilized [12]. The IBCG's consensus recommendations aim to address this discordance and identify best practices in patient selection, treatment, and follow-up.

3.2.1. Patient selection

A laudable attempt at a randomized controlled trial (RCT) comparing TMT and RC for MIBC closed early due to lack of accrual [13], indicating that future RCTs in this space are unlikely to succeed. In the absence of such data, a recent large, multi-institutional, retrospective study compared TMT and RC in matched cohorts of patients with clinical stage T2–T4N0M0 MIBC (n = 722; 440 RC and 282 TMT cases) [14]. All patients had solitary tumors of <7 cm, no or unilateral hydronephrosis, and no diffuse or multifocal carcinoma in situ (CIS; tumor-associated CIS was allowed), and the decision for TMT or RC was based on patient preference following multidisciplinary counseling. Notably, the 440 RC cases represented 29% of all RCs performed during the study period at the contributing institutions. No significant difference emerged between the TMT and RC groups in 5-yr metastasis-free survival (MFS; 74% vs 74%; p = 0.64), cancer-specific survival (CSS; 85% vs 83%; p = 0.06), or disease-free survival (76% vs 76%; p = 0.37), while the 5-yr overall survival (OS) was higher with TMT than with RC (77% vs 72%; p = 0.008). In the TMT cohort, 13% of patients underwent salvage cystectomy; the 5-yr CSS rate of these patients (83%) was similar to that in patients who did not require salvage cystectomy (84%; p = 0.77), indicating that a window of opportunity may exist to cure such patients with timely cystectomy for recurrence. Similar results have been shown by other contemporary series [15]. However, it should be noted that a major limitation of propensity comparisons between TMT and RC is that completeness of the pretreatment resection is unknown, which introduces a potential selection bias (eg, patients with unresectable tumors may have been more likely to undergo RC).

There are limited data on the outcomes of TMT in patients with tumors exhibiting histologic subtypes/variants. In a large retrospective analysis, there were no significant differences in outcomes (complete response [CR], salvage cystectomy, DSS, or OS rates) after TMT between patients with MIBC with pure urothelial carcinoma (n = 237) and those with histology subtypes (n = 66) [16]. This finding was also observed in a more recent large, multicenter retrospective study of 864 patients with MIBC who underwent curative-intent radiotherapy (RT) to the bladder for MIBC (clinical T2-T4aN0-2M0) between 2001 and 2018 [17].

Historically, patients with cT3-4a stage, hydronephrosis, or CIS were excluded from or highly under-represented in bladder preservation trials. However, the BC2001 and Bladder Carbogen Nicotinamide (BCON) trials [18] and large

Table 1 – IBCG consensus recommendations for BPT in MIBC

General recommendations:

1. Patients with newly diagnosed MIBC should be offered evaluation in a multidisciplinary setting that includes visits with urologic oncology, medical oncology, and radiation oncology providers (as appropriate) as well as input from experts in bladder cancer radiology and pathology.
2. When feasible, all MIBC cases, including those being considered for BPT, should be reviewed by a pathologist with experience and expertise in urothelial carcinoma.

Trimodal therapy:

Patient selection:

1. Ideal candidates for TMT include patients with unifocal cT2 stage without hydronephrosis or concomitant multifocal CIS, and who have good baseline bladder function.
2. While cT3-4a stage, hydronephrosis, and CIS are poor prognostic factors, their presence is not an absolute contraindication to TMT.

Technique:

3. When feasible, maximally safe TURBT should be performed prior to the initiation of TMT.
4. A radiosensitizing agent should be delivered concurrently with bladder RT. Reasonable options include 5FU + MMC, cisplatin, gemcitabine, or carbogen + nicotinamide.
5. Induction systemic chemotherapy (eg, cisplatin-based chemotherapy) prior to RT with a concurrent radiosensitizer can be offered, particularly for patients with high-risk features, including cT3–4 stage, hydronephrosis, and/or cN+ disease in the pelvis (strongly recommended for cN+).
6. The tumor bed, as well as any gross residual tumor remaining after TURBT, should receive the highest radiation dose. Uninvolved portions of the bladder may be treated with full or reduced radiation doses. The role of pelvic nodal radiation remains uncertain and should be discussed with patients (on a case-by-case basis) based on benefits versus risks.

Follow-up and surveillance:

7. Follow-up after TMT should be patient-specific and include the following:
   (a) Cross-sectional imaging of the chest, abdomen, and pelvis every 3–6 mo for 2–3 yr (based on risk factors and time from the end of TMT), then at least annually for at least 5 yr.
   (b) Surveillance cystoscopy and urine cytology every 3–4 mo for the first 2 yr, then every 6 mo for 5 yr. Lifelong annual cystoscopy thereafter should strongly be considered.
8. Patients who develop locally recurrent MIBC (with no metastasis) after TMT should undergo prompt RC and pelvic lymphadenectomy, if eligible (with cisplatin-based NAC, where appropriate).
9. Patients who develop NMIBC after TMT may be eligible for further BPT.

Partial cystectomy:

Patient selection:

1. PC is not considered a standard option in MIBC, and this should be discussed with patients. PC can be discussed as an alternative to TMT or RC in very carefully selected patients with MIBC and small, solitary tumors amenable to resection with adequate margins that do not exhibit concomitant CIS or histologic subtype (excluding pure adenocarcinoma of the urachus) after adequate consultation about risks versus benefits of this approach.
2. PC should be offered to patients with urachal adenocarcinomas that are amenable for resection with adequate margins.
3. Prior to PC, random bladder or directed biopsies with blue light cystoscopy, if available, along with prostatic urethral biopsies should be considered to rule out concomitant CIS.

Technique:

4. Cisplatin-based NAC should be offered to eligible patients with MIBC prior to PC. Risk-stratified adjuvant therapy should be offered based on PC pathology and available data.
5. Owing to the high rate of pathologic upstaging and frequent identification of squamous (variant) histology subtype of cT1 high-grade tumors in bladder diverticuli, fit patients with a high suspicion of more advanced-stage disease on imaging/examination and/or large volume in a bladder diverticulum should be offered cisplatin-based NAC prior to PC (a multidisciplinary review is important).
6. Standard bilateral pelvic lymphadenectomy should be performed in patients undergoing PC for MIBC.
7. Preventing intraoperative tumor and urine spillage during PC is critical to ensure optimal outcomes.

Follow-up and surveillance:

8. Follow-up after PC for MIBC should be patient-specific and include the following:
   (a) Cross-sectional imaging of the chest, abdomen, and pelvis every 3–6 mo for 2–3 yr, then at least annually for up to at least 5 yr.
   (b) Surveillance cystoscopy and urine cytology every 3–4 mo for the first 2 yr, then every 6–12 mo for up to 10 yr. Thereafter, lifelong annual cystoscopy should strongly be considered.

Radical TUR:

1. Radical TUR alone is not a standard of care and should be considered only in patients who are not eligible for or who refuse RC and TMT.
2. The ideal candidate for radical TUR alone is a patient with a single, small, T2 lesion; no CIS; no histologic subtype; and no hydronephrosis.
3. A repeat TUR (when feasible/safe) should be performed to ensure maximal tumor removal.
4. Radical TUR is a highly skilled procedure and should be performed by those who are comfortable with maximal tumor resection, including removal of all tumors up to the perivesical fat, while trying to avoid perforation.

Bladder preservation after neoadjuvant therapy:

1. Omission of RC or RT after neoadjuvant therapy remains experimental at this time.
2. A cCR should be defined, at a minimum, as negative cystoscopy, negative cytology, no evidence of residual viable cancer at biopsy or TURBT, and negative cross-sectional imaging (CT or MRI of the abdomen and pelvis).

Biomarkers for BPT in MIBC:

1. The role of tumor tissue, plasma, and urine biomarkers to select patients for bladder preservation after a cCR to neoadjuvant/induction systemic therapy remains unclear and should be investigated further in properly designed clinical trials before use in clinical practice.
2. The following biomarkers have promising emerging data to warrant potential consideration for use in the clinic, but formal recommendations will need to wait for prospective trial data:
   (a) Serum ctDNA: Detection of minimal residual disease/recurrence after BPT.
   (b) Somatic/tumor NGS testing on TURBT tissue sample: Profiling actionable genomic alterations as potential biomarkers for available systemic therapies.
3. Germline genetic testing and genetic counseling should be considered in patients with MIBC at a high risk for inheritable mutations, including early-onset (<50–55 yr) disease and a personal or broader family history of cancer or hereditary cancer syndromes, and those with upper tract urothelial carcinoma or multifocal urothelial tumors (among other considerations).

BPT = bladder preservation therapy; cCR = clinical complete response; CIS = carcinoma in situ; CT = computed tomography; ctDNA = circulating tumor deoxyribonucleic acid; 5FU + MMC = 5-fluorouracil and mitomycin C; IBCG = International Bladder Cancer Group; MIBC = muscle-invasive bladder cancer; MRI = magnetic resonance imaging; NAC = neoadjuvant chemotherapy; NGS = next-generation sequencing; NMIBC = non–muscle-invasive bladder cancer; PC = partial cystectomy; RC = radical cystectomy; RT = radiation therapy; TMT = trimodal therapy; TUR = transurethral resection; TURBT = transurethral resection of bladder tumor.

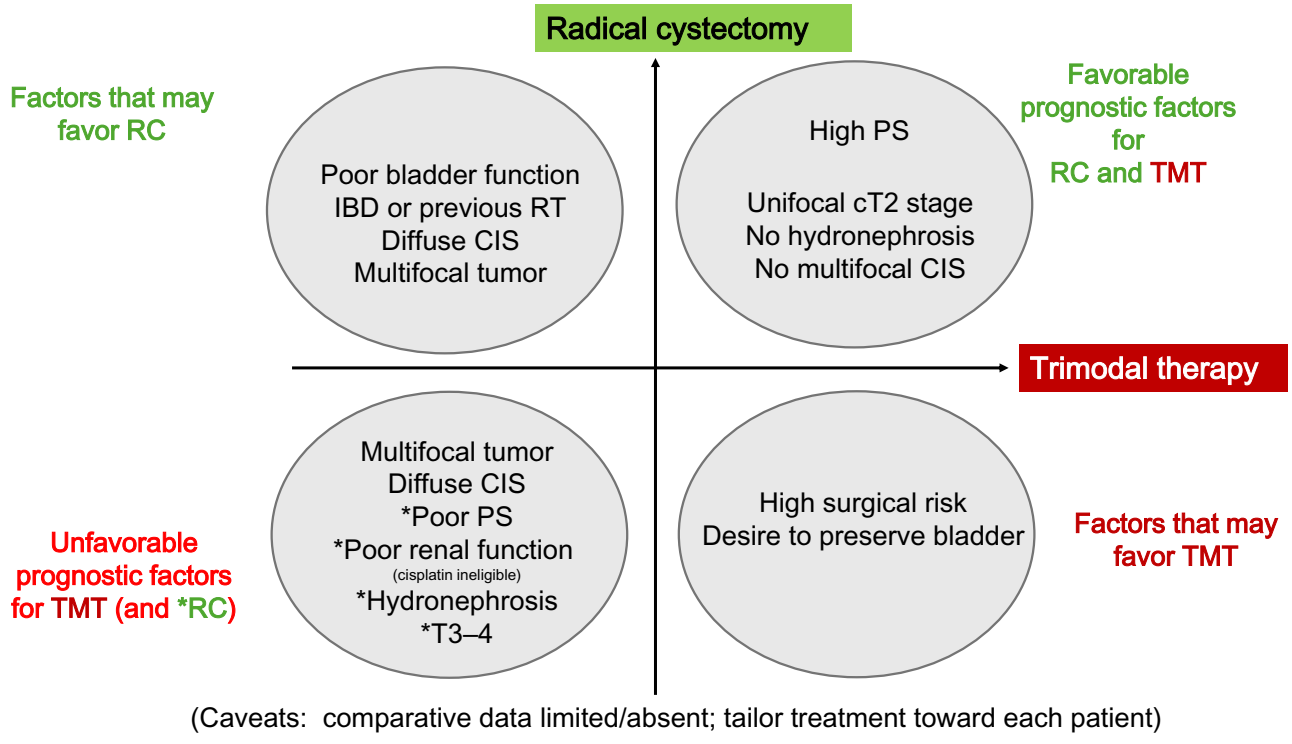

Fig. 1 – Factors that may impact the choice of TMT or RC in patients with MIBC. CIS = carcinoma in situ; IBD = inflammatory bowel disease; MIBC = muscle-invasive bladder cancer; PS = performance status; RC = radical cystectomy; RT = radiation therapy; TMT = trimodal therapy.

retrospective series of TMT-treated patients [14,19] included small numbers of patients with T3 and T4 stages and unilateral hydronephrosis, allowing for some inferences to be made. Based on this, the IBCG agreed that while patients with histologic subtypes, cT3-T4 stage, hydronephrosis, and multifocal CIS have worse outcomes after TMT, these are generally poor prognostic factors and hence should not be considered as absolute contraindications. Fig. 1 outlines factors that may inform treatment recommendations when counseling MIBC patients on TMT and RC.

3.2.2. Technique

3.2.2.1. Maximally safe transurethral resection of bladder tumor. The goal of "maximal transurethral resection of bladder tumor (TURBT)" is to resect all tumors, and visibly complete TURBT is associated with a higher CR to TMT and improved survival [18,20,21]. Although maximal TURBT is ideal and preferred (when feasible), trials have demonstrated acceptable CR rates with RT even in those patients with incomplete resections [18,20,21].

3.2.2.2. Chemotherapy considerations: radiosensitizers. Compared with RT alone, cisplatin, gemcitabine, 5-fluorouracil + mitomycin C, and carbogen + nicotinamide have all been found to improve clinical outcomes when used concurrently with RT [21–29]. Given the strength of evidence across studies, use of a concurrent radiosensitizer is recommended in all eligible patients. There are no data that clearly support the use of one radiosensitizing regimen over another; therefore, the choice of radiosensitizer should be tailored to the clinical scenario and patient preferences/characteristics.

3.2.2.3. Chemotherapy considerations: neoadjuvant therapy. Given the positive impact of NAC prior to RC on oncologic outcomes in MIBC, the rationale for its use prior to bladder preservation with TMT is logical. The international, phase 3 BA06 30894 trial randomized 976 patients treated with either RC or RT to NAC or no NAC [30]. After a median follow-up of 8 yr, there was a significant increase in OS favoring the NAC arm (hazard ratio [HR]: 0.84; 95% confidence interval [CI]: 0.72–0.99; $p = 0.037$), and NAC reduced the risk of death by 26% (HR: 0.74; 95% CI: 0.57–0.96; $p = 0.022$) and 20% (HR: 0.80; 95% CI: 0.63–1.02; $p = 0.070$) compared with that in patients treated with RC and RT alone, respectively. Notably, these patients were not treated with a radiosensitizer concurrently with RT, making these results difficult to interpret in a modern TMT setting. In the BC2001 trial, where 33% of participants ($n = 117$) received NAC prior to RT or chemoradiation, even in those patients who received NAC, concurrent chemoradiation showed a trend toward improved locoregional disease control over RT alone [31]. Recent retrospective data corroborated these findings [32]. In contrast, prospective evidence from the RTOG 89-03 trial suggests no improvement in pathologic response or OS with two cycles of neoadjuvant methotrexate, vinblastine, adriamycin, and cisplatin prior to TMT [33].

With regard to N+ disease, a recent multicenter retrospective analysis of 287 patients with cN+ M0 MIBC treated with either RC or RT following induction cisplatin-based chemotherapy showed no significant difference in OS (HR: 0.94; 95% CI: 0.63–1.41; $p = 0.76$) or progression-free survival (PFS; HR: 0.74; 95% CI: 0.50–1.08; $p = 0.12$) in those

undergoing RC or RT [34], suggesting that bladder preservation is feasible for select patients with clinically node-positive MIBC.

Taken together, the IBCG recommends that induction systemic chemotherapy (eg, cisplatin-based chemotherapy) prior to RT with a concurrent radiosensitizer be considered, particularly for patients with high-risk features such as cT3–4 stage and/or hydronephrosis, and cN+ disease in the pelvis (strongly recommended for the latter).

3.2.3. Radiation considerations

While dosing and template considerations for RT have been described in evidence-based guidelines [35], there remains heterogeneity in the technique. A meta-analysis of individual patient data from the BC2001 and BCON trials found a lower risk of invasive locoregional recurrence and similar toxicity profiles in patients with locally advanced bladder cancer who received moderately hypofractionated RT (55 Gy in 20 fractions over 4 wk) compared with those who received conventional fractionation (64 Gy in 32 fractions over 6.5 wk) to the bladder (neither regimen included elective pelvic nodal treatment) [18]. As was concluded by the study investigators, the IBCG recommends that 55 Gy in 20 fractions be adopted as a standard-of-care option for bladder preservation given the numerous socioeconomic and logistical advantages of shorter treatment schedules.

Historically, TMT trials from the RTOG/NRG Cooperative Group included treatment of uninvolved pelvic lymph nodes, whereas trials such as BC2001 and BCON did not include pelvic lymph node treatment. Recent data from a large retrospective series collected over 20 yr suggest that there is a benefit of pelvic nodal irradiation [36], although a large prospective study found that pelvic nodal recurrence with modern bladder-only RT is 7% [37]. Without contemporary prospective randomized data, the IBCG agreed that the role of pelvic nodal irradiation remains uncertain and should be discussed case by case with patients.

Lastly, the IBCG recommends that the tumor bed as well as any gross residual tumor remaining after TURBT should receive the highest radiation dose. Uninvolved portions of the bladder may be treated to full or reduced radiation dose [38,39].

3.2.4. Follow-up and surveillance

The follow-up of patients after TMT should be tailored to their specific clinical scenario/situation. This includes cross-sectional imaging of the chest, abdomen, and pelvis every 3–6 mo for 2–3 yr, then at least annually up to at least 5 yr. Surveillance cystoscopy with urine cytology should be performed every 3–4 mo for the first 2 yr, then every 6 mo for 5 yr. The IBCG agreed that there is no role for TUR of the prior tumor site in the setting of normal cystoscopy. Lifelong annual cystoscopy thereafter should strongly be considered. Patients who develop locally recurrent MIBC after TMT should undergo prompt RC and pelvic lymphadenectomy with cisplatin-based NAC, where appropriate. Patients who develop non–muscle-invasive bladder cancer after TMT may be eligible for further BPTs (eg, intravesical therapy).

Contemporary TMT trials are incorporating novel composite endpoints such as bladder-intact event-free survival, which includes muscle-invasive recurrence in the bladder, regional pelvic soft tissue or nodal recurrence, distant metastases, cystectomy, or death due to any cause.

In summary, in the setting of multidisciplinary shared and informed decision-making, the IBCG recommends that TMT should be offered to all eligible candidates with MIBC (see the criteria in Table 1).

3.3. Partial cystectomy

3.3.1. Patient selection

Similar to TMT, there are no RCTs comparing PC with RC; however, a number of retrospective studies and case series suggest that, in highly selected patients, PC may provide adequate cancer control, with 5-yr OS rates ranging from 57% to 79% (Table 2) [40–49]. The majority of these series used PC in patients with small, solitary, first-occurrence MIBC without CIS in the bladder and without histologic subtypes, which were amenable to resection with negative margins.

Based on the evidence reviewed, and in agreement with current MIBC clinical practice guidelines [4,6], the IBCG agreed that PC should not be offered as a standard of care and that it should be discussed only as an alternative to RC or TMT in appropriately and carefully selected patients (ie, for pure adenocarcinoma of the urachus or for small, solitary urothelial tumors amenable to resection with adequate margins, and which do not exhibit concomitant CIS or histologic subtype).

3.3.2. Technique

If PC is being considered for BPTs in patients with MIBC, the IBCG recommends that the same principles for use of NAC/adjuvant chemotherapy in those treated with RC be followed [4–6]. The IBCG also highlighted the importance of preventing intraoperative tumor and urine spillage during PC to ensure optimal outcomes [40]. Since it is known that blue light cystoscopy increases the detection of CIS over white light cystoscopy by up to 43% [50], the IBCG recommends its use (if available), along with prostatic urethral biopsies, to rule out concomitant CIS prior to PC. Standard bilateral pelvic lymphadenectomy should be performed in patients undergoing PC for MIBC.

3.3.3. Special considerations

The incidence of bladder cancer in diverticuli ranges from 1% to 14% [40]. Given the high rate of pathologic upstaging of cT1 high-grade tumors in bladder diverticuli [51], the IBCG recommends that fit patients with a high suspicion of more advanced stage disease on imaging/examination and/or large-volume disease in a bladder diverticulum should be offered cisplatin-based NAC prior to PC, when feasible (multidisciplinary review is important).

3.3.4. Follow-up and surveillance

Given that late recurrences can occur after PC [42], the IBCG recommends surveillance cystoscopy and urine cytology for at least 10 yr in PC-treated patients. Cross-sectional imaging

Table 2 – Summary of retrospective data evaluating the oncologic efficacy of PC

Retrospective study/case series	No. of patients	Study design	Oncologic outcomes	Mean follow-up (mo)
Holzbeierlein et al [41]	58 PC	Inclusion criteria: primary bladder tumor of nonurachal origin	5-yr advanced RFS: 67%; 5-yr OS: 69%	33.4
Kassouf et al [42]	37 PC	Inclusion criteria: (1) solitary tumor; (2) absence of CIS; (3) 2 cm surgical margin; (4) not requiring ureteral reimplant	5-yr RFS: 39%; 5-yr DSS: 87%; 5-yr OS: 67%	72.6
Smaldone et al [43]	25 PC	Inclusion criteria: (1) solitary, urothelial tumor; (2) absence of CIS; (3) negative surgical margin. Protocol: (1) preoperative radiation (25 Gy); (2) 6 wk of BCG postoperatively	5-yr RFS: 62%; 5-yr DSS: 84%; 5-yr OS: 70%	45.3
Golombos et al [44]	29 PC	Included urothelial and variant histology (adenocarcinoma, squamous, neuroendocrine, micropapillary, myxoid)	5-yr RFS: 68%; 5-yr OS: 79%	37.0
Koga et al [45]	46 PC	Inclusion criteria: (1) intravesically circumscribed tumor; (2) bladder neck and trigone uninvolved; (3) no residual tumor or only NMIBC at restaging after chemoradiation. Protocol: (1) preoperative radiation (40 Gy); (2) preoperative cisplatin (2 cycles)	5-yr MFS: 100%; 5-yr DSS: 100%	45 (median)
Knoedler et al [46]	167 RC; 86 PC	1:2 matched case-control study comparing PC with RC	RC: 10-yr MFS: 66%; 10-yr DSS: 63%; 10-yr OS: 36% PC: 10-yr MFS: 61%; 10-yr DSS: 58%; 10-yr OS: 36%	74.4
Capitanio et al [47]	5670 RC; 1573 PC	Matched case-control study from the SEER database comparing PC with RC in patients with T1–4, N0–2, M0 disease	RC: 5-yr DSS: 65.8%; 5-yr OS: 50.2% PC: 5-yr DSS: 76.4%; 5-yr OS: 57.2%	77.0; 64.0
Herr et al [48]	17 RC; 15 PC	(1) Patients underwent 4 cycles of neoadjuvant MVAC; (2) case-control study comparing RC with PC for those patients who were rendered T0 after chemotherapy	RC: 10-yr MFS: 65% PC: 10-yr MFS: 73%	120 (median)
Sternberg et al [49]	39 RC; 13 PC	(1) Patients underwent 3 cycles of neoadjuvant MVAC; (2) inclusion criteria for PC: complete or partial response to MVAC, solitary lesions, no CIS, good capacity bladder; (3) RC selected based on the lack of a chemotherapy response	RC: 5-yr OS: 46% PC: 5-yr OS: 69%	45 (median); 88 (median)

CIS = carcinoma in situ; DSS = disease-specific survival; MFS = metastasis-free survival; MVAC = methotrexate, vincristine, doxorubicin, cisplatin; NMIBC = non–muscle-invasive bladder cancer; OS = overall survival; PC = partial cystectomy; RC = radical cystectomy; RFS = recurrence-free survival.
The table was adapted from the study of Peak and Hemal [40].

of the chest, abdomen, and pelvis every 3–6 mo for 2–3 yr, and then at least annually for at least 5 yr, is also recommended.

3.4. Radical TUR

Radical TUR implies a maximal TUR of all visible tumors and beyond, to the level of perivesical fat. In a retrospective series of 151 patients with MIBC treated by standard RC (n = 52) or by radical TUR (n = 99), the 10-yr DSS rates in the TUR alone (76%) and RC (71%) groups were similar (p = 0.3), and 57% of those managed with TUR alone survived with their bladders intact [52]. A prospective, nonrandomized, phase 2 trial of 133 patients with MIBC managed with radical TUR alone demonstrated 10-yr rates of DSS and PFS with bladders intact of 79.5% and 64.9%, respectively [53]. The key inclusion criteria for this trial were no residual tumor (cT0) upon repeat biopsy of the tumor bed and absence of hydronephrosis. Furthermore, the majority of patients had primary unifocal disease without CIS.

The IBCG agreed that radical TUR alone is not a standard of care and should be offered only in select patients who decline or are ineligible for RC or TMT and who have a single, small, cT2 lesion with no CIS, no variant histologic subtype, and no hydronephrosis [52–56]. Repeat resection within 6 wk of the initial TUR is recommended to help identify the residual tumor and potentially improve oncologic outcomes [52,57]. Furthermore, since radical TUR is a highly skilled procedure, it should be performed only by those who are comfortable with maximal tumor resection, including removal of all tumors up to the perivesical fat, while avoiding frank perforation.

3.5. Bladder preservation after cCR following NAC/immunotherapy

The potential to avoid consolidative surgery in patients who achieve a cCR is of great clinical interest since it has the potential to improve QoL and mitigate treatment-related morbidity. Clinical restaging after NAC often disagrees with the final pathology after RC, making it unreliable for predicting residual disease. While achieving a pathologic CR after NAC is associated with good outcomes, current restaging methods such as biopsies and imaging miss invasive disease in a significant proportion of patients. Multiparametric magnetic resonance imaging shows promise but needs further validation. Standardized protocols are crucial for bladder preservation trials after neoadjuvant therapy. The IBCG recommends that strict criteria be used for defining a cCR, including negative cytology, cystoscopy, and imaging that is reliable and reproducible, and emphasizes correlating this with long-term outcomes. Within the caveats of this approach, the IBCG considers bladder preservation after systemic therapy a rapidly evolving field ripe for research protocols as shown in Fig. 2. Indeed, using one such approach to define a cCR in patients treated with gemcitabine/cisplatin with nivolumab in the HCRN GU16-257 trial, 33/76 (43%) patients achieved a cCR (32 patients elected to forgo RC or TMT; the positive predictive value of a cCR for 2-yr MFS was 0.97 [95% CI: 0.91, 1]) [58]. Please

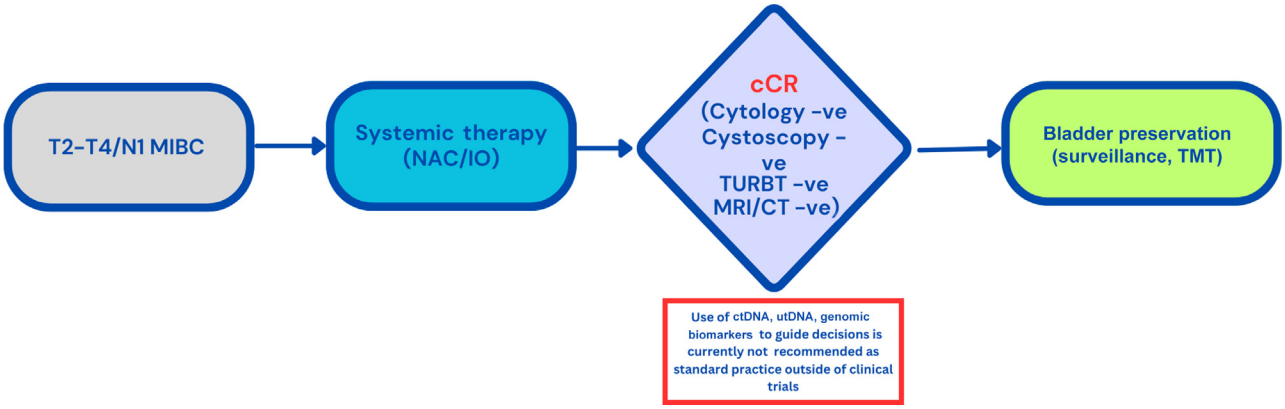

Fig. 2 – Bladder preservation in MIBC patients after systemic therapy: research opportunities. cCR = complete clinical response; CT = computed tomography; ctDNA = circulating tumor deoxyribonucleic acid; IO = immunotherapy; MIBC = muscle-invasive bladder cancer; MRI = magnetic resonance imaging; NAC = neoadjuvant chemotherapy; TMT = trimodal therapy; TURBT = transurethral resection of the bladder tumor; utDNA = urine tumor deoxyribonucleic acid; -ve = negative.

see the Supplementary material for a more detailed discussion and evidence review on this topic.

3.6. Biomarkers for BPTs in MIBC

The role of tumor tissue, plasma, and urine biomarkers to select patients for bladder preservation remains unclear and requires further investigation in prospective clinical trials prior to use in clinical practice. For a detailed discussion on this topic, please see the Supplementary material.

4. Discussion

Patients with newly diagnosed MIBC should be offered evaluation in a multidisciplinary setting for consideration of BPTs. The main alternative to RC is TMT, and favorable prognostic factors for TMT include unifocal cT2 stage, a lack of hydronephrosis, and no multifocal CIS and good bladder function at baseline. Other options should be reserved for select patients who are ineligible for or who decline TMT or RC after thorough consideration of the benefits and risks. These include PC for urachal adenocarcinoma and PC or radical TUR alone for solitary tumors amenable to resection with adequate margins and without concomitant CIS or histologic subtypes.

5. Conclusions

While there have been no head-to-head comparisons of RC versus BPTs, retrospective series suggest similar outcomes in select patients. Identifying factors that may influence outcomes after RC or BPTs is critical to optimizing disease outcomes and patient QoL. The IBCG consensus recommendations represent an important step toward providing useful guidance for clinicians, patients, and other stakeholders worldwide on available BPTs for MIBC. It is expected that these consensus recommendations, in conjunction with existing clinical practice guidelines, will provide MIBC patients and clinicians with useful considerations regarding viable bladder-preserving alternatives to RC with acceptable oncologic outcomes, at least until additional evidence and novel biomarkers become available to further guide our future approach.

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Conception and design: Kamat, Gupta, Hensley, Buckley, Li.
Acquisition of data: All authors.
Analyses and interpretation of data: All authors.
Drafting of manuscript: Kamat, Gupta, Hensley.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analyses: All authors.
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Supplementary data

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