Review Article

Bladder sparing management for muscle-invasive bladder cancer after a complete clinical response: ready for prime time?—a narrative review

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Background and Objective: A standard of care for muscle-invasive bladder cancer (MIBC) is cisplatin-based neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC). Given recent improvements in NAC and the morbidity associated with RC, bladder-sparing therapy has been investigated as a promising treatment for patients with MIBC who experience a complete clinical response (CCR) to systemic therapy. However, clinical staging is unreliable, making it challenging to determine ideal candidates for bladder-sparing therapy. Our primary objective is to review the efficacy of NAC, strategies for determining a CCR as a surrogate for a complete pathologic response, and the emerging role of imaging, tumor genomics, and biomarkers in selecting candidates for bladder-sparing therapy.

Methods: We surveyed the literature for studies investigating the outcomes of current treatment modalities for MIBC and methods for determining a CCR following systemic therapy as well as the impact this has on pathologic staging. Studies employing imaging, tumor biomarkers, and genomics were included.

Key Content and Findings: Clinical staging with cystoscopy or transurethral resection shows significant discordance with final pathology, with high rates of understaging. Multiparametric magnetic resonance imaging (mpMRI) has shown strong utility in determining the presence of MIBC, but it has yet to reliably identify CCR. Meanwhile, somatic DNA damage repair mutations and biomarkers such as circulating and urinary tumor DNA are strong predictors of recurrence, showing promise in predicting and monitoring a CCR to systemic therapy. Multiple ongoing trials are currently assessing the use of biomarkers and genomic analyses in determining eligibility for bladder-sparing therapy.

Conclusions: While no one method has reliably demonstrated the ability to detect a true CCR, a multimodal approach involving imaging, biomarkers, and genomic analyses holds promise. We eagerly await the results of clinical trials investigating these tools, which may allow for the safe recommendation of bladder-sparing therapy.

Keywords: Muscle-invasive bladder cancer (MIBC); bladder-sparing therapy; neoadjuvant chemotherapy (NAC); complete clinical response (CCR); tumor biomarker

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Introduction

Background

Bladder cancer remains the 7th most prevalent cancer globally, with over 500,000 new cases annually (1,2). While most patients initially manifest with non-muscle invasive bladder cancer (NMIBC), approximately 25–30% present as, and 10% will progress to, muscle-invasive bladder cancer (MIBC) (1,3,4).

According to both the American Urological Association and the National Comprehensive Cancer Network, the standard of care for MIBC is neoadjuvant cisplatin-based chemotherapy (NAC) followed by radical cystectomy (RC) or trimodal therapy, which consists of maximal transurethral resection of bladder tumor (TURBT) followed by chemotherapy combined with external beam radiotherapy (3). RC leads to a 5-year overall survival (OS) rate ranging from 40–60%, while the adoption of NAC has led to nearly an 8% survival benefit (5). Survival is greatest among patients with a complete pathologic response following NAC (ypT0), defined as the absence of disease in the bladder specimen at the time of cystectomy. This occurs in up to 38–42% of patients (6,7). A complete clinical response (CCR) to NAC, defined as the absence of disease on cystoscopic, radiographic, and/or genomic analyses, has been proposed as a surrogate for ypT0. This, along with the significant morbidity associated with undergoing RC, has led many to question whether certain patients can safely forego a RC after a CCR to NAC (8).

Rationale and knowledge gap

As such, there is a contemporary interest in bladder-sparing treatment for patients with MIBC deemed to have had a CCR to NAC. Due to limited evidence, the efficacy of chemotherapy alone in achieving a CCR is not well understood. Numerous retrospective, prospective, and ongoing randomized controlled trials (RCTs) have and are currently addressing this challenge by investigating survival outcomes after CCR with chemotherapy alone, clinical predictors of NAC response, and proposed management strategies (3,9,10).

Objective

Herein, we aim to provide a contemporary review on the effectiveness of NAC, methods for determining a CCR and its potential as a surrogate for ypT0, and the role of imaging, tumor genomics, and biomarkers in selecting candidates for bladder-sparing therapy. We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-726/rc).

Methods

Using PubMed, Google Scholar, and Wiley Online Library, we reviewed relevant articles published between 2000–2024. Search terms included “muscle invasive bladder cancer”, “neoadjuvant chemotherapy”, “complete clinical response”, “bladder sparing therapy”, and “genomic biomarkers”. Articles included were original articles published in English. Unpublished works, works not in English, and news articles were not included. Information on clinical trials was collected from clinicaltrials.gov, which was last accessed in August 2024. The search strategy is detailed in *Table 1*.

Investigation into neoadjuvant chemotherapy (NAC)

Establishment of cisplatin-based NAC

Over the last two decades, NAC combined with RC has established itself as a standard of care for MIBC, with trimodal therapy being appropriate for certain patients. In 2003, SWOG-8710 was among the first and largest trials supporting cisplatin-based NAC, using methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) (6). In this trial, 307 patients were randomized to RC with or without NAC. The use of NAC led to an improved median survival of 77 months, compared to 46 months with RC alone. Five-year OS was 57% in the NAC group compared to 43% with RC alone (P=0.06), with significantly fewer bladder cancer-specific deaths. Of particular interest, a complete pathologic response was achieved in 38% of patients with NAC (ypT0), compared to only 15% with RC alone (pT0)

Table 1 The search strategy summary

Items	Specification
Date of search	08/11/2024
Databases and other sources searched	PubMed, Google Scholar, and Wiley Online Library
Search terms used	Search terms included "muscle invasive bladder cancer", "neoadjuvant chemotherapy", "complete clinical response", "bladder sparing therapy", and "genomic biomarkers"
Timeframe	01/01/2000–08/11/2024
Inclusion and exclusion criteria	Inclusion: all articles, including systematic reviews, original articles, and case reports/series, published in English. Exclusion: unpublished works, commentaries and news articles, works not in English, and news articles
Selection process	Authors collectively conducted the study selection, and all full-text articles meeting inclusion and exclusion criteria were then also independently reviewed by all authors

(P<0.001). Patients with ypT0 had an 85% 5-year OS, with an improved OS of 11 years compared to 3.4 years in those > ypT0. In addition, patients with ypT0 had a 26% and 51% lower risk of mortality and recurrence, respectively (6). These findings suggest a complete pathologic response is a favorable prognostic factor, which is better achieved using NAC.

Similarly, the international phase III trial BA06-30894 assessed the efficacy of NAC with cisplatin, methotrexate, and vinblastine, with 976 patients randomized to either radiotherapy (40%) or RC (60%) with or without NAC. The use of NAC led to a 16% reduction in mortality risk (P=0.04) and a 10-year survival increase from 30% to 36% (P=0.04). Similar to SWOG-8710, 32.5% of patients achieved ypT0 compared to only 12.3% achieving pT0 (11). A meta-analysis by Vale *et al.* consolidated findings on NAC with either RC or radiotherapy from 11 RCTs (6 involving RC) and 3,005 patients (12). They reported 5% and 9% improvements in 5-year absolute and disease-free survival, respectively. The smaller benefit of NAC compared to the aforementioned clinical trials may be due to the inclusion of heterogeneous study designs, NAC regimens, and treatment modalities (12).

Recent studies have looked to broaden the options for NAC due to the side effect profile associated with MVAC and the various contraindications precluding certain patients from receiving this treatment. The phase III VESPER trial compared dose-dense (dd) MVAC with gemcitabine/cisplatin, showing NAC with dd-MVAC led to significantly better 5-year OS (P=0.08) and disease-specific survival (P=0.004) with a 3-year higher local control rate (complete pathological response, downstaging, or organ confinement) (P=0.02). Nonetheless, 42% of patients on dd-MVAC and 36% on gemcitabine/cisplatin achieved ypT0 (P=0.20) (13,14). Furthermore, retrospective studies and phase III trials have reported a beneficial toxicity profile with gemcitabine/cisplatin compared to MVAC, with lower rates of grade 3 or 4 anemia, neutropenic fever, infections, sepsis, alopecia, and grade 3 or 4 mucositis (15-17).

Investigations into neoadjuvant immunotherapy

Two phase II RCTs also investigated pathological response to NAC with accelerated MVAC alone and with immunotherapy in the form of bevacizumab, with both reporting a 38% achievement of ypT0 status. Uniquely, using gene expression, McConkey *et al.* reported improved response to chemotherapy in basal subtype urothelial carcinoma (18,19). Beyond platinum-based NAC, the phase II study PURE-01 investigating single-agent pembrolizumab reported that 42% of patients achieved ypT0 at the time of cystectomy (20). Interestingly, patients with higher programmed death ligand 1 (PD-L1) positivity exhibited an improved ypT0 rate of 53.4% compared to only 13.3% in those with lower levels of PD-L1 positivity (20). These reported ypT0 rates mirror those observed with MVAC and reported by SWOG-8710 (6,11). Equivocal survival outcomes, together with the genomic analyses by PURE-01 and McConkey *et al.*, suggest newer neoadjuvant regimens offer safe alternatives and may allow for targeted selection of systemic therapy (19,20).

Despite level 1 recommendations supporting its use, the National Cancer Database reveals that only 21% of patients receive NAC with an optimistic rise from 9.7% in 2006 to

32.2% in 2014 (21). Popularization of NAC will help more patients achieve ypT0, which will be imperative as we look towards improving oncologic outcomes and considering bladder preservation for patients with MIBC.

Outcomes and adverse effects of RC

In addition to NAC, recent guidelines strongly recommend RC and pelvic lymph node dissection (PLND) for non-metastatic MIBC within 12 weeks of systemic therapy (3,6,22). While NAC options have improved significantly over recent years, RC continues to be a major abdominopelvic surgery with significant peri- and postoperative morbidity in an older and comorbid population (8).

One of the largest prospective databases comprising 1,142 RC patients revealed a 64% 90-day complication rate and 2.7% 90-day mortality rate (23). Among reported complications, 67% occurred during the initial hospitalization and 53% after discharge. Of these, 79% had grade 1–2, and 13% had grade 3–5 complications based on the Memorial Sloan-Kettering Cancer Center complication grading system. They were predominantly gastrointestinal (29%), infectious (25%), wound-related (15%), cardiac (11%), and genitourinary (11%). Consequently, 34% required an emergency department visit, of whom 78% required readmission. They also reported a 26% overall readmission rate, similar to other reported data (8,23,24). Undoubtedly, the growing acceptance of Enhanced Recovery After Surgery (ERAS) protocols has led to improved survival outcomes over the last decade, with decreased perioperative complications, length of stay, 30-day readmission, and medical costs (25-28).

Analysis of this trend using the NSQIP database, which is limited to 30 days postoperatively but includes 11,351 cases, observed a decline in 30-day overall complication rates from 2006–2011 to 2015–2018 (56.5% *vs.* 50.6%), along with a decreased rate of any or minor complications (P<0.01) and length of stay (P<0.001) (8). This coincides with the introduction of ERAS around 2013 and its subsequent widespread adoption (8,27,28). Moreover, RC performed at high-volume centers has been shown to preserve health-related quality of life, further cementing it as a standard of care (29). However, the potential for excellent survival in patients with a CCR has made bladder-preserving therapy with systemic therapy alone an alluring therapeutic alternative.

Clinical response as a surrogate for ypT0

Before bladder preservation therapy can become standard of care, a method to accurately assess a CCR to NAC must be established. Currently, the clinical response to NAC is best determined by pathology after RC, necessitating a surrogate marker for ypT0 if opting for bladder preservation. Herein, the assessment of a CCR to NAC may serve this purpose. However, methods for staging bladder cancer and determining a CCR are heterogeneous. These typically include a combination of cystoscopy, cytology, and radiological imaging (30-33). Even imaging modalities vary considerably, including computed tomography (CT), magnetic resonance imaging (MRI), and/or positron emission tomography (PET) scans (30,32,34). More recently, genomic and biomarker analyses have also been investigated as adjuncts to these methods for active surveillance after achieving a CCR.

Importantly, differing staging protocols may yield varied efficacy in assessing CCR and predicting pathological response. This warrants further exploration because there is a well-documented discordance between clinical and pathologic staging in high-risk bladder cancer. A recent review of the National Cancer Database found that among 47.8% of patients undergoing RC, 35.2% initially staged with cT0 disease were found to have upstaging (> ypT0) (35). However, they could not comment on clinical staging modality.

TURBT-based methods to assess CCR

The use of TURBT with imaging to determine CCR reveals similar discrepancy rates (*Table 2*). Notably, a retrospective study by Kukreja *et al.* reported on 78 patients who received NAC and were staged cT0 based on pathology from TURBT with cross-sectional imaging and chest X-ray or CT prior to RC. They found that 53.6% of these patients still had evidence of residual disease at the time of cystectomy (30). However, they were unable to explicitly assess CCR after NAC due to the lack of restaging data following chemotherapy and instead required only cT0 prior to RC. Conversely, Becker *et al.* utilized a similar restaging protocol post-NAC, which included cross-sectional imaging (chest, abdomen, pelvis), examination under anesthesia, and cystoscopic evaluation with or without TURBT They found that 53% of patients who had no evidence of disease on cystoscopy or TURBT still

Table 2 Studies assessing the efficacies of TURBT-based methods to assess CCR

Study	Method of assessing CCR	Cohort	Outcome(s)
Kukreja *et al.* (30)	TURBT with cross-sectional imaging	157 with ≤ T4 disease staged cT0. 78 (49.7%) received NAC	RC after CCR (cT0) - 35.7% (n=56) were pT0 - 53.6% (n=30) post-NAC patients were pT0 - 25.5% (n=50) ≥ pT2 (muscle invasive disease)
Becker *et al.* (36)	TURBT, cystoscopy with cross-sectional imaging	114 with MIBC re-staged post-NAC. 53 (46.5%) staged rT0 post-NAC	RC after CCR (rT0) - 47% (n=25) were ypT0 - 25% (n=13) had residual CIS; 23% (n=12) were ≥ ypT2 - 32% (n=36) falsely downstaged; 12 staged < rT2 had microscopic lymph node-positive disease - 27% sensitivity and 95% specificity of ≥ rT2 on TURBT to predict ≥ ypT2
	Tumor genomic sequencing	49 patients screened for RETAIN or Alliance trial gene panels	- Mutations in 22/49 (45%) or 26/49 (53%) with RETAIN or Alliance trials gene panel, respectively - Tumor mutational burden and status not associated with NAC response - 18% (4/22) RETAIN(+) falsely downstaged, not significant from RETAIN(–) - 19% (5/26) Alliance(+) falsely downstaged, including 4/7 staged rT0, not significant from Alliance(–) - In favorable patients (< rT2 + tumor mutation), rate of missed MIBC (> ypT2) was 36% for both panels
SWOG S0219 trial (31)	TURBT	10 staged cT0 post-NAC	RC after CCR (cT0) - 4/10 had no residual disease on RC (pT0) - 60% had > ypT2 disease (resulted in study termination)
Zibelman *et al.* (32)	SEE	61 patients undergoing SEE. 68.9% (n=42) had MIBC and 62.3% (n=38) were post-NAC. 31 patients (50.8%) were SEET0	SEE showing cT0 - 51.6% (16/31) had residual disease (> pT0) - 25.8% (8/31) had residual ≥ pT2 disease - Overall, NPV of SEET0 for pT0 is 48.4%, and 57.1% among patients post-NAC - PPV for any disease on SEE is 96.7%

TURBT, transurethral resection of bladder tumor; CCR, complete clinical response; SEE, systematic endoscopic evaluation; NAC, neoadjuvant chemotherapy; MIBC, muscle-invasive bladder cancer; SEET0, no tumor was detected at SEE; RC, radical cystectomy; CIS, carcinoma in situ; NPV, negative predictive value; PPV, positive predictive value.

had residual disease on cystectomy (36). Alarmingly, 25% and 23% had residual CIS or ≥ ypT2 disease, respectively, with 32% being falsely downstaged to NMIBC (36,37). Nonetheless, given their retrospective nature, both studies faced a significant lack of standardization for restaging protocols.

Alternatively, using only TURBT, the 2009 phase II SWOG S0219 trial assessed CCR to NAC with paclitaxel, carboplatin, and gemcitabine (31). It allowed patients with a CCR, based on a re-staging TURBT, to choose from immediate cystectomy or cystoscopic surveillance. Of 74 patients, 46% achieved a CCR. Of the ten who chose immediate cystectomy, an alarming 60% had residual > ypT2 disease. With a notably higher discrepancy rate than previously reported, a criticism of the study was the use of carboplatin instead of cisplatin, as it is not considered the

optimal peri-operative chemotherapy. Still, it is unclear if this affected outcomes (31).

Systematic endoscopic evaluation (SEE), involving cystoscopy and tissue sampling, reveals a similar discordance with final pathology to TURBT (32). In a prospective trial, 61 patients with NMIBC or MIBC underwent SEE before RC. Among patients with MIBC, 90.5% were post-NAC. Of the 50.8% (n=31) who had no visible disease or a negative biopsy, 51.6% (n=16) had > pT0 disease, and 25.8% (n=8) had ≥ pT2 disease, showing a negative predictive value of only 48.4% (32). A limitation to consider is institution-specific standardized cystoscopy evaluations may limit generalizability and exhibit discordance with clinical practice. Moreover, given these results, clinical staging with cystoscopy and TURBT cannot be safely used as the only surrogate for ypT0. However, showing some success, it may hold value in a multimodal approach to assessing CCR.

Observation after a CCR

TURBT-based staging methods alone may be insufficient to determine a CCR. However, since CCR has been shown to be a favorable prognostic factor, many have questioned that if CCR can be accurately assessed, could these patients then safely be observed with a plan to intervene at the first signs of recurrence. Prior literature suggests that delays to RC beyond the suggested 12 weeks may lead to worse final pathologic staging, upstaging, and disease-specific survival and OS, with few retrospective findings of non-inferiority (3,38-42). Nonetheless, these studies do not assess the impact of treatment delay in clinically staged ypT0 patients.

Active surveillance after varying methods to determine CCR

RCTs and retrospective studies have investigated the utility of observation following a CCR determined by a multimodal approach involving TURBT, cytology, and imaging (*Table 3*). A retrospective study by Mazza *et al.* looked at 148 patients with MIBC who achieved a CCR after NAC and pursued surveillance (43). CCR in this study was defined as no evidence of disease on final TURBT alongside negative urine cytology and cross-sectional abdominal imaging, generally by CT. Active surveillance entailed regular physical exams, cystoscopies, cytology every 2–3 months, and cross-sectional abdominal imaging at specified intervals for 2 years. Over a median follow-up of 55 months, recurrence occurred in 48% of cases, with 11% being MIBC. The 5-year recurrence-free survival and OS rates were 64% and 90%, respectively. The 5-year cystectomy-free survival rate was 76%. Of the 26 patients who underwent RC, four died of bladder cancer. Of the 15 patients who died of bladder cancer, 11 experienced local disease before metastases (43). Following a similar determination of CCR and active surveillance protocols, a retrospective study by Robins *et al.* reported 5-year cancer-specific and cystectomy-free survival rates of 87% and 79%, respectively. They also reported a 46% (n=16) recurrence rate, with only 23% as > cT1 (44). While indicating durable survival with conservative management, they are limited by retrospective design with restrictive selection criteria, as well as non-standardized protocols for surveillance and indication for RC.

On the other hand, the phase II RETAIN trial investigated a risk-stratified approach utilizing biomarker selection with clinical staging to identify patients for surveillance or definitive treatment (45). Again, CCR was determined by no clinical evidence of disease after restaging TURBT, negative urine cytology, and no evidence of disease on imaging. Patients with at least one DNA repair gene mutation (*ATM*, *ERCC2*, *FANCC*, or *RB1*) and a CCR were assigned to surveillance. Initial stage was cT2 in 79% of patients, making it a relatively favorable population. Among 37% (n=26) who pursued surveillance, the 2-year metastasis-free survival was 65% compared to 76% with definitive treatment. Still, 69% experienced urothelial recurrence with surveillance. Of the patients who developed metastases on surveillance, 9 out of 10 had a urothelial recurrence prior. Furthermore, no association was found between mutation presence and metastasis-free survival or disease recurrence. While similar genomic analyses have been shown to predict tumor response, they have yet to show a definitive benefit when incorporated as part of a structured treatment algorithm (45).

Other retrospective studies shared similar results with observation, but with CCR determined by only TURBT and imaging. Herr *et al.* reported on 63 patients who had a CCR and declined RC (34). CCR was defined as the absence of disease on cystoscopy +/– TURBT and CT scan, whereafter patients were followed prospectively with repeat CT, cystoscopies, and TURBTs every 3–6 months over a median of 86 months. The 5-year metastasis-free survival was 64% at last follow-up, with 36% (n=23) of the cohort dying of bladder cancer. Recurrence occurred in 64% (n=40), with 38% (n=24) as MIBC. Of the 14 patients who

Table 3 Studies evaluating outcomes of active surveillance following CCR

Study	Cohort	Definition of CCR	Active surveillance protocol	Survival outcomes
Mazza *et al.* (43)	148 patients with nmMIBC staged cT0 post-NAC	Negative TURBT, urine cytology, cross-sectional imaging	Physical exam, cystoscopies, and cytology every 2–3 months. Cross-sectional abdominal imaging at specified intervals for 2 years	- 5-year recurrence-free survival: 64% - Median follow-up of 55 months, 48% had recurrence with 11% MIBC - 5-year DSS: 90% - 5-year overall survival: 90% - 5-year cystectomy-free survival: 76%, with 4/26 bladder cancer deaths after RC
Robins *et al.* (44)	48 patients with MIBC staged cT0 post-NAC	Negative TURBT, urine cytology, cross-sectional imaging	Cytology and cystoscopy with or without biopsy every 2–3 months + abdominal CT every 4 months for 2 years. Repeat every 6 months for 2 years with annual follow-up	- 5-year DFS: 58% - 46% had disease recurrence (23% ≤ cT1) with a median of 5 months - 5-year cancer-specific survival: 87% - 5-year cystectomy-free survival: 79%, with 2/9 bladder cancer deaths after RC
RETAIN trial (45)	26 patients with MIBC with CCR and >1 DNA tumor mutation post-NAC	≥1 mutation + negative restaging TUR, urine cytology, and imaging	Not stated	- 2-year overall survival: 89% with AS *vs.* 83% with definitive treatment - 2-year metastasis-free survival: 65% with AS *vs.* 76% with definitive treatment - 69% (n=18) had UC recurrence; 8/26 underwent RC - 9/10 with later metastatic disease had initial localized disease recurrence - No association between mutation and MFS or UC recurrence
Herr *et al.* (34)	63 patients with MIBC staged cT0 post-NAC	Negative cystoscopy +/– TURBT and CT scan	Repeat CT, cystoscopies, and TURBTs every 3–6 months over median of 86 months	- 64% (n=40) had recurrence, with 38% (n=24) as MIBC - 5-year metastasis-free survival: 64% at last follow-up - 36% (n=23) died of bladder cancer; 19/23 had initial localized disease recurrence - Mean survival of 108 *vs.* 32 months for disease-specific death - 14 patients underwent RC, with 8/14 bladder cancer deaths after RC - 54% with intact, normally functioning bladder

CCR, complete clinical response; nmMIBC, non-metastatic muscle-invasive bladder cancer; NAC, neoadjuvant chemotherapy; MIBC, muscle-invasive bladder cancer; TURBT, transurethral resection of bladder tumor; TUR, transurethral resection; CT, computed tomography; DSS, disease-specific survival; RC, radical cystectomy; DFS, disease-free survival; AS, active surveillance; UC, urothelial carcinoma; MFS, metastasis-free survival.

underwent a salvage RC, 8 died of bladder cancer. Notably, 19 had a local recurrence prior to metastases, suggesting up to a 30% added mortality risk with surveillance (34). Following the same CCR determination and similar surveillance protocols, a retrospective study by Sternberg *et al.* also reported a comparable 5-year OS of 67.5% (46). Notably, Herr *et al.* found that survival outcomes in patients undergoing active surveillance are also influenced by clinical and pathological factors, such as tumor focality and size. These factors may worsen survival outcomes, highlighting the need to consider aspects beyond the specific active surveillance protocols when evaluating bladder-sparing

management.

Risk of active surveillance with T understaging

Further, while active surveillance has shown moderate success, it is also limited by a heavy reliance on clinical staging to determine CCR. As previously stated, this is not an accurate marker, and misclassification can have severe consequences. Kurtzman *et al.* investigated survival outcomes of patients misclassified after a CCR (47). Misclassification was defined as the discovery of intravesical MIBC within 6 months of meeting CCR criteria. CCR was determined by negative findings across cytology, benign TURBT pathology, and negative cross-sectional imaging. Of 54 patients who had a CCR, 6 patients were misclassified. These patients had a significantly lower 5-year overall (63% *vs.* 80%, P=0.03) and metastasis-free survival (63% *vs.* 93%, P=0.05) (47).

Risk of observation with undetected nodal or micrometastatic disease

Another concern is the use of clinical staging as a marker for nodal or micrometastatic disease (37,48). Analysis of the National Cancer Database by Nassiri *et al.* revealed that among patients who underwent NAC and RC for MIBC, 4.3% of patients who achieved ypT0 disease still had node-positive disease on final pathology, suggesting that there is often discordance between bladder and nodal pathology. Of note, only 13.1% were found to be ypT0, deviating significantly from what has been seen in the established literature (48). Even if we could identify who truly had a complete response to NAC, identifying those with nodal disease poses a significant concern. In a study of 130 patients with clinically node-positive bladder cancer, preoperative CT imaging could not accurately predict pathologic nodal status. When using the most stringent imagining criteria, a median nodal size of 8 mm as a cut-off for positivity, sensitivity and specificity were only 72% and 80%, respectively (49).

Alternative imaging approaches to determine nodal status have also been studied. Notably, in a study of 199 patients with bladder cancer, preoperative assessment of nodal status with fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET/CT revealed per-patient sensitivity and specificity of 0.30 and 0.91 in predicting pathologic nodal status, respectively. Interestingly, among a subgroup receiving NAC or immunotherapy, the sensitivity and specificity were found to be only 36% and 91%, respectively, with an accuracy of 77% (50). Ultimately, PLND has shown significant oncologic benefit and correlation with improved cancer-specific survival (51). As of now, it may be the only method to accurately assess nodal staging and determine the necessity for adjuvant therapy (51).

Imaging to identify CCR

While TURBT-based staging and clinical assessment alone are insufficient in identifying patients who are truly ypT0, a multimodal approach may provide an avenue toward reliably determining a CCR. This multimodal approach is made possible in part by recent advancements in imaging, particularly multiparametric magnetic resonance imaging (mpMRI).

mpMRI and establishment of the VI-RADS score

Particularly, mpMRI may identify patients with a CCR. A prospective study by Huele *et al.* lends credence to mpMRI use (33). Their analysis of 37 patients who underwent mpMRI before RC revealed a promising 88% sensitivity, 58% specificity, and 78% diagnostic accuracy in differentiating NMIBC and MIBC (33). Of note, this study's limited sample size, particularly its inclusion of only 10 patients with NMIBC, may have contributed to a reduced specificity of mpMRI compared to previous studies. In 2018, Panebianco *et al.* first described using mpMRI to develop the Vesical Imaging-Reporting And Data System (VI-RADS) score, a five-point scoring system incorporating size, location, and morphology to quantify the risk of MIBC (52). A retrospective study by Ahn *et al.* evaluated the validity of VI-RADS using two radiologists to independently assess mpMRI scans of 82 patients before TURBT or RC. They reported strong inter-reader agreement and a significant association between VI-RADS score and muscle layer invasion (53). However, the study did not evaluate intra-reader agreement, limiting the assessment of VI-RADS scoring reproducibility. A meta-analysis by Woo *et al.* of 6 studies and 1,770 patients similarly reported an 83% sensitivity and 90% specificity in detecting muscle invasion (54). Nonetheless, anatomic changes following TURBT may decrease VI-RADS accuracy, with the creators pushing for a separate criterion to assess treatment response (33,55).

Table 4 Studies investigating tumor biomarkers and their relationships with oncological outcomes

Study	Cohort	Biomarker	Baseline prevalence	Important findings
Powles *et al.* (57)	406 patients treated with adjuvant atezolizumab *vs.* 403 with observation	ctDNA	37%	- ctDNA positivity associated with shorter OS in observed patients - Reductions in ctDNA by <50%, 50–99%, and 100% associated with graded improvements in median OS of 19.9, 34.2, and 60 months, respectively - ctDNA positivity at C1D1 + C3D1 associated with 68% sensitivity for relapse compared to 57% for C1D1 alone
Szabados *et al.* (58)	95 patients treated with neoadjuvant atezolizumab (40 tested for ctDNA)	ctDNA	63%	- ctDNA status after NAC significantly correlated with lymph node status and T stage at surgery - ctDNA(+) patients exhibited a significantly higher rate of relapse than ctDNA(–) patients - No relapse events observed in ctDNA(–) patients at baseline or after NAC
Plimack *et al.* and Miron *et al.* (59,60)	34 patients treated with MVAC and 24 patients treated with gemcitabine/cisplatin	*ATM, RB1*, and *FANCC* genes	38% of patients with at least one mutation	- Alteration in ≥1 DNA repair genes predicted pathologic response in the discovery set (87% sensitivity, 100% specificity) and validation set - 5-year OS 85% in patients with ≥1 mutation *vs.* 46% in those without any mutation - DSS 90% in patients with ≥1 mutation *vs.* 49% in those without any mutation

ctDNA, circulating tumor DNA; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; OS, overall survival; NAC, neoadjuvant chemotherapy; DSS, disease-specific survival.

Clinical efficacy of mpMRI

To this end, the aforementioned phase II PURE-01 study investigated the association between mpMRI findings post-NAC and final pathology (20). Images were defined by three binary parameters: residual disease on T1 and T2-weighted images, hyperintense spots within the bladder wall on diffusion-weighted images, and pathological contrast enhancement. Across 82 patients, a complete radiographic response was significantly associated with pT0. Of 37 patients with negative findings on all three criteria, 62% (n=23) were pT0, and 94–96% were pT ≤1, suggesting utility in ruling out MIBC. On the other hand, 4–8% of patients with presumed radiographic disease were pT0, suggesting they underwent unnecessary RC (20,56). However, similar to the VI-RADS system, this protocol is limited by subjectivity and inter-reader disagreement, as internal assessments only identified pT0 in 62% of patients with no evidence of disease on final pathology compared to 73% for externally evaluated patients.

While objective frameworks show moderate success in evaluating mpMRI, they alone cannot determine CCR.

Tumor biomarkers in response to NAC

Analyzing tumor genomics and identifying surrogate biomarkers can provide a clearer image of tumor response to systemic therapy (*Table 4*).

Circulating tumor DNA (ctDNA)

One such biomarker is ctDNA, which has shown a significant association with poor outcomes in MIBC (57,58,61). A recent prospective study by Ben-David *et al.* reported on 112 patients undergoing RC, finding ctDNA-positive patients (53%) had higher rates of upstaging and node-positivity with worse pathological staging and prognosis (61). ctDNA positivity before or within 90 days following RC was associated with a decreased recurrence-free survival from 100% to 33% at 6 months and to 16% at 12 months. However, ctDNA is not an infallible prognostic marker, as

21% and 10% of ctDNA-negative patients still had residual ≥ pT3 or nodal-positive disease, respectively (61).

Recently, the phase III IMvigor010 trial investigated adjuvant atezolizumab versus observation for MIBC and simultaneously trended ctDNA levels throughout treatment (57). ctDNA was collected at the initiation of cycle 1 and cycle 3 of adjuvant chemotherapy. They found ctDNA-positivity was associated with a significantly shorter OS in patients undergoing observation alone [hazard ratio (HR) 6.3, 95% confidence interval (CI): 4.3–9.3]. Although not significant, a similar trend was seen in the atezolizumab arm. Persistent ctDNA positivity was also associated with an increased risk of relapse. On the other hand, reductions in ctDNA by <50%, 50–99%, and 100% led to graded improvements in median OS of 19.9, 34.2, and 60 months, respectively. These findings highlight the utility of trending ctDNA to gauge tumor response (57). Meanwhile, the phase II ABACUS trial characterized trends in ctDNA in patients receiving neoadjuvant atezolizumab (58). The authors found that 63% (25/40) of patients were ctDNA positive at baseline, compared to 47% (14/30) after NAC and 14% (5/36) after RC. Of these ctDNA-positive patients, three became ctDNA-negative after NAC, all of whom achieved ypT0. Positive ctDNA post-NAC was significantly associated with positive nodal status and pathologic T stage (P=0.02 and P<0.001, respectively). ctDNA-positivity after RC led to higher rates of recurrence, while ctDNA-negative patients at baseline or after NAC did not experience any relapse (58). However, this was a single-arm study with patients not on NAC and largely exploratory in nature, providing limited guidance on using ctDNA to guide therapy. Still, in the neoadjuvant setting, given its significant association with disease status, ctDNA may have substantial predictive value in identifying patients who can safely pursue surveillance after CCR.

DNA damage repair genes

To this end, the phase II RCT by Plimack *et al.* investigated additional molecular biomarkers to predict treatment response, particularly to accelerated MVAC (59). Mutations in the DNA damage repair genes *ATM*, *RB1*, and *FANCC* have been found in 11%, 14%, and 2% of urothelial carcinomas, respectively. Mutation in one or more genes was associated with increased rates of ypT0 and improved OS. Among NAC responders (downstaged to ≤ T1), 87% had at least one mutation (18). Miron *et al.* published long-term survival data for this cohort, reporting a mutation in either gene was associated with an improved 5-year overall and disease-specific survival from 45% for both measures to 85% and 90%, respectively (P=0.004, 0.002) (60). Interestingly, the aforementioned retrospective study by Becker *et al.* performed DNA sequencing on their cohort before NAC using gene panels based on ongoing RETAIN and Alliance RCTs (36). At least one mutation of interest was found in 32 patients, but mutation status was not associated with CCR, ypT0, false downstaging, or survival outcomes. Limited by low power and heterogeneous NAC, it still underscores skepticism on using tumor mutational status for clinical decision-making as we await the results of ongoing trials (36).

Urine biomarkers to assess treatment response

Urine-based tumor DNA (utDNA) analysis, or "liquid biopsies", may offer a non-invasive alternative to tissue biomarkers (62-64). Numerous utDNA sequencing technologies have been developed, including uCAPP-Seq, TAm-Seq, ddPCR, sWGS, and UroSEEK. UroSEEK, which consists of mutational analysis, TERT promotor assay, and aneuploidy detection applied to urine sediment, is one of the most studied. UroSEEk demonstrated up to 80% and 68% sensitivity in detecting either the presence or recurrence of bladder cancer, respectively. However, the utility of utDNA sequencing in assessing CCR after NAC in MIBC remains unclear (62,65,66).

Recently, a prospective study by Chauhan *et al.* utilized Urine Cancer Personalized Profiling by Deep Sequencing (uCAPP-Seq), an assay of genomic regions from 460 genes whose mutations are associated with MIBC, to detect utDNA in 42 patients with localized bladder cancer (76% MIBC, 59% with NAC) (63,67). utDNA levels were quantified as the highest variant allele fraction among non-silent mutations detected by CAPP-Seq. They reported a median utDNA level of 0% in healthy adults and an 85% concordance between mutations present in utDNA and tumor, validating it as a surrogate marker for tumor response. A median utDNA level of 0% at RC was associated with pT0 versus 4.3% with residual disease (P=0.002), noting a sensitivity and specificity of 81% in predicting incomplete response. Elevated levels were associated with reduced progression-free survival (P=0.02) (67). A follow-up study by the same authors also incorporated ultra-low-pass whole genome sequencing, reporting an 87% sensitivity in predicting residual disease (68).

Using alternative sequencing, a recent prospective

study combined tagged-amplicon sequencing (TAm-Seq) and shallow whole-genome sequencing (sWGS) to detect mutant DNA (muDNA) in patients undergoing NAC (69). Tracking urine muDNA over 83 days, they noted positivity during the 2nd cycle of NAC predicted disease recurrence with 83% sensitivity and 100% specificity. Hence, negativity during NAC may suggest a positive response, while persistent positivity may warrant investigation into a modified treatment (69). Another sequencing technique is digital droplet PCR (ddPCR), which analyzes single droplets of oil containing DNA molecules to allow for targeted querying of specific mutations. In retrospective analyses, it has been used to detect utDNA in patients with recurrent NMIBC and who have advanced to metastatic disease and to monitor changes in cell-free tumor DNA following RC. However, it has yet to be incorporated into protocols for determining response to NAC from urine samples prior to RC (70,71). With closer proximity to the tumor and comparable efficacy to ctDNA, urinary biomarkers may be another tool in bridging the gap between CCR and a true complete pathologic response.

The urinary microbiome

In addition to genomic markers, characterizing the urobiome may provide yet another noninvasive tool for both assessment of bladder cancer risk and response to therapy, enabled by recent advancements in sequencing technologies like 16S rRNA and WGS (72-74). Despite conflicting data, preclinical and clinical studies have illustrated an interplay between the urinary microbiome and bladder cancer. Specific bacteria, such as Fusobacterium and Streptococcus, are overrepresented in bladder cancer urine samples (75). These have been found to contribute to the chronic inflammatory environment, aiding the recruitment of tumor-infiltrating immune cells and tumor progression (76).

A recent study by Nardelli *et al.* used 16S rRNA sequencing to profile the urobiome of 48 patients undergoing TURBT, comparing them to prostate cancer or cancer-free controls (72). The authors found that males over age 50 with confirmed bladder cancer had significantly different bacterial communities compared to controls (P=0.001), with larger components of *Aerococcus urinae* (3.08% *vs.* 0.25%), *Porphyromonas asaccharolytica* (1.20% *vs.* 0.09%), and *P. somerae* (2.21% *vs.* 0.02%). Porphyromonas and P. somerae were also significantly increased in all bladder cancer patients compared to prostate cancer (P<0.01 and P<0.001, respectively) and cancer-free controls (P<0.0001). However, generalizability was difficult due to the limited study cohort and further investigations with larger cohorts may determine the utility of the urobiome in predicting a CCR and tracking disease progression during active surveillance (72).

Ongoing clinical trials

Nonetheless, multiple ongoing clinical trials are investigating the use of biomarkers to identify patients with MIBC who may benefit from bladder-sparing therapy (*Table 5*).

Tumor genomics

The phase II trial HCRN-GU16-257 (NCT03558087) by Galsky *et al.* is investigating NAC with gemcitabine, cisplatin, and nivolumab (77). It aims to characterize the positive predictive value of a CCR in predicting both a 2-year metastasis-free survival in patients forgoing immediate cystectomy and rate of < ypT1N0 in patients electing immediate RC. CCR was defined as benign biopsy (low-grade Ta allowed) and negative urine cytology with no local or metastatic disease on imaging. With a median follow-up of 30 months, they reported a positive predictive value of 97% for 2-year metastasis-free survival (95% CI: 0.91–1) and a significantly longer OS on post hoc analysis (P=0.003). Interestingly, mutations in DNA repair genes (*ATM*, *RB1*, *FANCC*, or *ERCC2*) or an increased tumor mutational burden were not associated with an improved positive predictive value of CCR. However, a restaging VI-RADS score of ≤2 versus >2 was associated with significantly longer metastasis-free survival (P<0.001) (77).

In an ongoing trial sponsored by the Alliance for Clinical Trials in Oncology (NCT03609216), Iyer *et al.* are investigating a different panel of somatic DNA damage response gene alterations (*ATM*, *ATR*, *BRCA1*, *BRCA2*, *ERCC2*, and *FANCC*) on TURBT specimens to determine eligibility for bladder-sparing treatment (78). Patients with a somatic DNA damage response gene mutation and < yT1 on clinical restaging will forego RC and instead undergo cystoscopic and radiographic surveillance. The primary outcome will be 3-year event-free survival, defined as the proportion of patients without invasive or metastatic recurrence (78). While results are still pending, a prior study by Iyer *et al.* found that these mutations were associated with chemosensitivity (positive predictive value of 89% for < pT2N0) and a favorable prognosis (no recurrences over a median follow-up of 2 years) (79).

Table 5 Ongoing trials involving tumor biomarkers in the context of bladder-preserving therapy for patients with MIBC

Study name	Trial number	Status	Primary endpoint	Intervention
Gemcitabine, cisplatin, plus nivolumab in patients with muscle-invasive bladder cancer with selective bladder sparing	NCT03558087	Active, not recruiting	Complete response rate and its ability to predict treatment benefit	Nivolumab, gemcitabine, and cisplatin
Risk enabled therapy after initiating neoadjuvant chemotherapy for bladder cancer (RETAIN)	NCT02710734	Active, not recruiting	Time to recurrence	Active surveillance
Gemcitabine and cisplatin without cystectomy for patients with muscle invasive bladder urothelial cancer and select genetic alterations	NCT03609216	Recruiting	3-year event free survival	Gemcitabine, cisplatin, bladder sparing
Bladder sparing treatment of tislelizumab, gemcitabine and cisplatin for patients with PD-L1 positive muscle invasive bladder cancer	NCT05401279	Recruiting	2-year bladder-intact disease-free survival	Tislelizumab, gemcitabine, and cisplatin
Risk-stratification based bladder-sparing modalities for muscle-invasive bladder cancer	NCT05531123	Recruiting	1-year bladder-intact disease-free survival	Tislelizumab or tislelizumab, gemcitabine, cisplatin and radiation

MIBC, muscle-invasive bladder cancer; PD-L1, programmed death ligand 1.

Meanwhile, the aforementioned and ongoing RETAIN trial (NCT02710734) is investigating a similar gene panel to determine eligibility for bladder-sparing treatment in MIBC (45). Preliminary results have found no significant association between tumor mutational status and survival outcomes. Nonetheless, these studies serve as important tests for using biomarkers as part of a structured treatment algorithm.

Immunotherapy biomarkers

Another potential biomarker for directing bladder-sparing therapy is PD-L1. In the ongoing phase II study NCT05401279, patients with PD-L1 positive MIBC who refuse or are not candidates for RC will undergo TURBT or partial cystectomy before receiving tislelizumab and gemcitabine/cisplatin (80). The primary outcome is 2-year bladder-intact disease-free survival, with secondary outcomes assessing adverse events as well as overall and metastasis-free survival. While PD-L1 has been considered a negative prognostic indicator for urothelial carcinoma, this trial will serve as an intriguing example of its use in bladder-sparing eligibility (80,81).

Limitations

This review provides an overview of recent cohort studies and clinical trials, introducing several limitations to consider.

Current methods for assessing CCR to NAC, such as clinical staging with TURBT or SEE, are often discordant with final pathology and inadequately assess nodal or micrometastatic disease. This also questions the survival benefit of active surveillance, which is dependent on clinical staging. This may be confounded by variability among cohort studies including heterogeneous definitions of CCR, staging and surveillance protocols, and cohort selection.

Advanced imaging techniques, such as mpMRI, offer alternatives for assessing CCR. While promising for identifying muscle invasion, they are sensitive to anatomical changes, increasing the risk for false positives. Meanwhile, standardized scoring systems like VI-RADS are untested for assessing CCR to NAC. Tumor genomics and biomarkers such as ctDNA and utDNA also offer the potential for predicting tumor response and identifying candidates for bladder-sparing treatment but have shown unclear benefits to date or have yet to be studied with traditional NAC. Further, pending RCTs, these newer modalities have not been tested with structured treatment algorithms. In addition, bladder cancer remains one of the most expensive malignancies to treat, underscoring the challenge of implementation and the necessity for cost-benefit analysis as the efficacy of these new methods are investigated. Overall, research in this area is relatively new, consisting of observational studies with significant heterogeneity and ongoing RCTs with limited power and follow-up. Still, they

provide guarded optimism for bladder-sparing management.

Future directions

While awaiting the results of ongoing RCTs, there are several future directions to consider for bladder-sparing management. A significant limitation of current studies has been a lack of power. Utilizing large tissue banks may enable better molecular profiling of MIBC, helping elucidate biomarker relationships to immune infiltration, disease recurrence, and progression. Consequently, this may help to identify subtypes that could benefit from observation versus immediate surgery. Additionally, other future directions include establishing a graded approach to assessing clinical response to NAC. Beyond looking for a CCR or cT0, understanding the prognostic value of a partial response could guide decisions regarding the need for delayed intervention, limited resection, or RC. Further, there is also a need to explore the feasibility of establishing the aforementioned new technologies and methodology, considering their accessibility, cost, and impact on quality of life through more structured treatment protocols.

Conclusions

RC with NAC is the standard of care in the management of MIBC. However, RC is associated with notable morbidity and mortality. NAC has improved complete pathological response rates and survival outcomes, questioning the necessity of RC in favor of bladder-sparing treatment with systemic therapy. However, accurately identifying CCR remains challenging. Various approaches, including traditional TURBT and SEE, advanced imaging techniques, or tissue and urine biomarkers and microbiomes, are being explored to assess CCR and the feasibility of active surveillance. Though research in this area is still emerging, there is cautious optimism for bladder-sparing strategies, possibly utilizing a multi-modal approach. Thus, high-quality trials, such as those highlighted in this review, are eagerly anticipated to establish guidelines for bladder preservation.

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