BJU Int 2026; **138:** 798–800 doi:10.1111/bju.70441

Check for updates

BJUI
BJU International

Comment

Bladder preservation with systemic therapy alone: are we losing sight of survival?

Alec Zhu, Pierre-Etienne Gabriel and John P. Sfakianos

The Milton and Carroll Petrie Department of Urology, Icahn School of Medicine at Mount Sinai, New York City, NY, USA

The contemporary management of muscle-invasive bladder cancer (MIBC) is evolving rapidly, driven by advances in systemic therapy and novel biomarkers. These developments have justifiably generated enthusiasm for bladder-sparing approaches that rely heavily, or in some cases exclusively, on systemic therapy. However, should this enthusiasm be tempered with caution? In pursuing organ preservation and reduced perioperative morbidity, we risk losing sight of the primary objectives of durable oncologic control and survival and the secondary goal of preserving quality of life.

Interest in bladder-preserving strategies for MIBC is driven largely by the morbidity of radical cystectomy (RC) and urinary diversion. Currently, trimodal therapy (TMT) is the most effective bladder-sparing approach, offering select patients organ preservation without compromising cancer control [1]. Expert consensus now recommends that appropriately selected patients with MIBC be evaluated for bladder preservation in a multidisciplinary setting. Multiple phase II trials (HCRN GU16-257, SURE-02, RETAIN) have evaluated systemic therapy-only bladder-sparing strategies, and a growing number of trials are testing this approach with newer agents (Table 1). Although clinical complete response (cCR) rates of around 40% have been observed in early-phase trials, long-term survival data remain immature, and not all patients who achieve cCR remain disease free. In RETAIN-1, at a median follow-up of 40 months, 2-year metastasis-free survival (MFS) was 73% overall, but only 48% of patients managed with active surveillance after cCR remained metastasis free with an intact bladder [2]. By comparison, 5-year MFS after RC or TMT in well-selected patients was 74–75% [1]. Although not directly comparable given differences in patient selection and follow-up, these findings underscore that bladder-intact survival and MFS are not equivalent endpoints and that cCR remains an imperfect surrogate for durable disease control.

Bladder preservation is often equated with improved quality of life, but this assumption is overly simplistic; avoiding cystectomy preserves the native bladder without necessarily preserving normal function or eliminating treatment-related morbidity. Advancements in minimally invasive surgery and 'enhanced recovery after surgery' protocols have reduced severe RC complications: contemporary series report Clavien–Dindo grade ≥III complication rates of 15–20% at 90 days [3], with a long-term reoperation risk around 6%. By comparison, neoadjuvant systemic therapy carries grade III–V adverse event rates of 10–50%, rising as regimens intensify in pursuit of higher complete response rates. Single-agent immune checkpoint inhibitors carry the lowest rates of grade ≥III events (~10%), whereas dual checkpoint inhibition and antibody–drug conjugate (ADC)/platinum-based regimens approach 25–50%. The key disparity is longevity of adverse effects: platinum-induced neuropathy and nephrotoxicity, immune-related endocrinopathies, and ADC-related neuropathy may persist indefinitely, whereas surgical morbidity is concentrated in the perioperative period. Surgery and systemic therapy should be framed not as a choice of morbidity versus normalcy but as a trade-off between different adverse event profiles with a focus on long-term consequences. Notably, most agents now used for bladder-sparing approaches have shown survival benefit only when paired with radical cystectomy in phase III trials.

Financial toxicity further complicates this choice. Joyce et al. modelled the cost effectiveness of RC and TMT for MIBC and found that, although TMT yielded slightly improved quality-adjusted life-years, it was substantially more expensive and not cost effective relative to RC at 5 or 10 years [4]. Bladder preservation may avoid a major operation, but downstream treatment demands and costs continue to burden patients and health systems. Immunotherapy and ADC agents are also substantially more expensive than chemotherapy and radiation, so drug-acquisition costs may offset any savings from avoiding surgery. However, cost-effectiveness data specific to systemic therapy-only bladder preservation remain lacking.

The burden of RC may also be less severe than commonly portrayed. Historically, the narrative around cystectomy relied on anecdotal opinion emphasizing durable quality-of-life impairment. We now have prospective health-related quality-of-life data suggesting a more nuanced recovery. In a large prospective cohort, Clements et al. found that most health-related quality-of-life domains stabilized or returned toward baseline over time, with global quality of life exceeding baseline by 6 months and psychosocial domains generally stable or improved; notable exceptions were body image and sexual function, which remained adversely affected [5]. Prospective patient-centered data challenge the assumption

© 2026 BJU International.
Published by John Wiley & Sons Ltd. www.bjui.org
All rights reserved, including rights for text and data mining and training of artificial intelligence technologies or similar technologies.

Table 1 Ongoing or completed clinical trials evaluating the efficacy of neoadjuvant systemic therapies followed by bladder-sparing protocols.

Trial (year)	Neoadjuvant type	Neoadjuvant regimen	Primary outcomes
HCRN GU16-257 NCT03558087 (2023)	CTX + ICI	G/C + NIV	Median follow-up 30 months 43% (33/76 pts) had cCR PPV of cCR was 97% 2-year MFS cCR: 97% No cCR: 75%
RETAIN-1 NCT02710734 (2025)	CTX	AMVAC ➔AS for cT0 after NAC and ≥1 mutation (*ATM, ERCC2, FANCC, RB1*) ➔RC, CRT, or intravesical therapy for cT > 0 or without mutation (*ATM, ERCC2, FANCC, RB1*)	Median follow-up 40 months 2-year MFS All: 73% AS: 76% 2-year OS All: 84% AS: 82% 48% were metastasis free with intact bladder in AS group
RETAIN-2 NCT04506554 (2025)	CTX + ICI	AMVAC+ NIV ➔ AS for cT0 after NAC and ≥1 mutation (*ATM, ERCC2, RB1*) ➔RC, CRT, or intravesical therapy for cT > 0 or without mutation (*ATM, ERCC2, FANCC, RB1*)	*Interim results* Median follow-up 18 months All patients: 86% are metastasis-free In AS group: 78% were metastasis-free with intact bladder
SURE-02 NCT05535218 (2026)	ADC + ICI	SG + PEM	Median follow-up 14 months 39% (19/49 pts) had cCR All pts with cCR were metastasis free
Alliance A031701 NCT03609216	CTX	GC ➔ AS in cT < 1 after NAC and DDR gene alteration ➔ RC or CRT in cT ≥ 1 or without DDR gene alteration	Ongoing
NeoSTOP-IT NCT06571708	CTX + ICI	GC + CEM with or without FIA ➔ AS for cCR ➔ RC for those without cCR	Ongoing
HCRN GU22-598 NCT06809140	ADC + ICI	EV + PEM	Ongoing
NCT07475806	ADC + ICI	EV + PEM	Ongoing

All trials are phase II trials. ADC, antibody–drug conjugate; AMVAC, accelerated methotrexate, vinblastine, doxorubicin, and cisplatin; AS, active surveillance; cCR, clinical complete response; CEM, cemiplimab; CRT, chemoradiation; CTX, chemotherapy; DDR, DNA damage repair; FIA, fianlimab; GC, gemcitabine/cisplatin; ICI, immune checkpoint inhibitor; MFS, metastasis-free survival; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; NAC, neoadjuvant chemotherapy; NIV, nivolumab; OS, overall survival; PEM, pembrolizumab; PPV, positive predictive value; pt(s), patient(s); RC, radical cystectomy; SG, sacituzumab govitecan.

that bladder preservation yields superior quality of life. In the CISTO study of recurrent high-grade non-muscle-invasive bladder cancer, RC was associated with worse physical function early on, but this difference resolved by 12 months; RC was also associated with better emotional well-being, general quality of life, and lower financial burden, whereas bladder-sparing therapy offered better bowel and sexual health [6]. Although not an MIBC cohort, these trial data underscore that treatment burdens are multifactorial and domain specific. Persistent deficits in body image and sexual function after RC are real and should be central to preoperative counselling, but they do not outweigh the broader pattern of functional recovery across most other domains.

So, are we losing sight of survival? At present, we are at risk of doing so. The rapid expansion of systemic therapy-only bladder-sparing protocols reflects genuine optimism and a real desire to reduce surgical morbidity, but we are extrapolating from single-centre phase II data to justify widespread adoption of novel therapeutic options. This optimism must be disciplined by evidence, and the evidence base for this approach, regarding long-term oncologic control, quality of life, and cost effectiveness, remains immature. We should resist framing bladder-sparing systemic therapy as inherently less burdensome than surgery; rather, RC and bladder-sparing strategies distribute morbidity differently. RC concentrates the burden in the perioperative period and in the permanent consequences of urinary diversion, whereas bladder-sparing treatments avoid upfront surgery at the cost of systemic therapy-related toxicity that often lasts longer than surgical morbidity. Bladder preservation with systemic therapy remains one of the most important advances in modern bladder cancer care, but patients considering this

1464410x, 2026, 5, Downloaded from https://bjui-journals.onlinelibrary.wiley.com/doi/10.1111/bju.70441 by University Of Cape Town, Wiley Online Library on [06/11/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

option must be grounded in its uncertainty. Cancer control data are not yet mature, and quality-of-life advantages remain unproven prospectively. Shared decision-making in MIBC must not conflate organ preservation with treatment success until survival equivalence is established. We must move beyond the binary consideration of bladder removal versus preservation and, instead, consider which treatment burdens patients are most willing to bear.

Disclosure of Interests

None declared.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

References

1 **Zlotta AR, Ballas LK, Niemierko A et al.** Radical cystectomy versus trimodality therapy for muscle-invasive bladder cancer: a multi-institutional propensity score matched and weighted analysis. *Lancet Oncol* 2023; 24: 669–81

2 **Geynisman DM, Abbosh PH, Ross E et al.** Phase II trial of risk-enabled therapy after neoadjuvant chemotherapy for muscle-invasive bladder cancer (RETAIN 1). *J Clin Oncol* 2025; 43: 1113–22

3 **Catto JWF, Khetrapal P, Ricciardi F et al.** Effect of robot-assisted radical cystectomy with intracorporeal urinary diversion vs open radical cystectomy on 90-day morbidity and mortality among patients with bladder cancer: a randomized clinical trial. *JAMA* 2022; 327: 2092–103

4 **Joyce DD, Wymer KM, Graves JA et al.** Cost-effectiveness of trimodal therapy and radical cystectomy for muscle-invasive bladder cancer. *JAMA Netw Open* 2025; 8: e2517056

5 **Clements MB, Atkinson TM, Dalbagni GM et al.** Health-related quality of life for patients undergoing radical cystectomy: results of a large prospective cohort. *Eur Urol* 2022; 81: 294–304

6 **Gore JL, Wolff EM, Nash MG et al.** Twelve-month results from the CISTO study comparing radical cystectomy versus bladder-sparing therapy for recurrent high-grade non-muscle-invasive bladder cancer. *J Clin Oncol* 2026; 44: 274–85

Correspondence: John P. Sfakianos, Department of Urology, Icahn School of Medicine at Mount Sinai, 5 East 98th Street, 6th Floor, New York, NY 10029, USA.
e-mail: john.sfakianos@mountsinai.org

 © 2026 BJU International.

1464410x, 2026, 5, Downloaded from https://bjui-journals.onlinelibrary.wiley.com/doi/10.1111/bju.70441 by University Of Cape Town, Wiley Online Library on [06/11/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License