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Neoadjuvant Chemotherapy With Transurethral Resection for Bladder Preservation: 15-Year Follow-Up of the Retained Bladder

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Study Need and Importance: Bladder preservation is a desired goal for most patients with muscle-invasive bladder cancer (MIBC), although select few are ideal candidates based on established criteria. Heterogenous cohorts with short follow-up in current bladder preservation literature hinder assessment of true risks/benefits for "ideal candidates." This unique study describes 15-year outcomes in select patients with MIBC meeting established ideal criteria for bladder preservation treated initially with systemic neoadjuvant chemotherapy (NAC) and transurethral resection (TUR) and provides important long-term outcome information useful for patient counseling.

What We Found: Fifteen-year risk of death from bladder cancer was 11% (95% CI: 5.8%, 18%), with the competing risk of death from other causes 44% (95% CI: 33%, 54%) and cystectomy risk of 11% (95% CI: 5.9%, 18%). Of 41 patients alive with their bladder intact, median (IQR) follow-up time was 14 (11, 20) years. Recurrence and survival status are shown in the Figure. Bladder relapse occurred in 38 patients, 29 of whom had nonmuscle-invasive cancer, and 25 were salvaged with either intravesical therapy (n = 20) or cystectomy (n = 5). The probability of relapse persisted beyond 10 years, necessitating lifetime surveillance.

Limitations: Because we are a high-volume tertiary cancer center, our findings may not be generalizable to other practice settings or to patients with MIBC not meeting "ideal" selection criteria (small ≤5 cm solitary organ-confined [cT2N0M0] disease, who achieve a complete clinical response to NAC with radical TUR), assessed by a negative bimanual examination under anesthesia, cross-sectional imaging, and radical restaging TUR.

Interpretation for Patient Care: NAC with TUR is a viable bladder preservation strategy with durable complete remissions and long-term bladder intact survival for select patients meeting established ideal selection criteria. Patients can be counseled that preservation outcomes are near 40:40:10:10 for death from another cause, alive with an intact bladder, cystectomy, and death from bladder cancer.

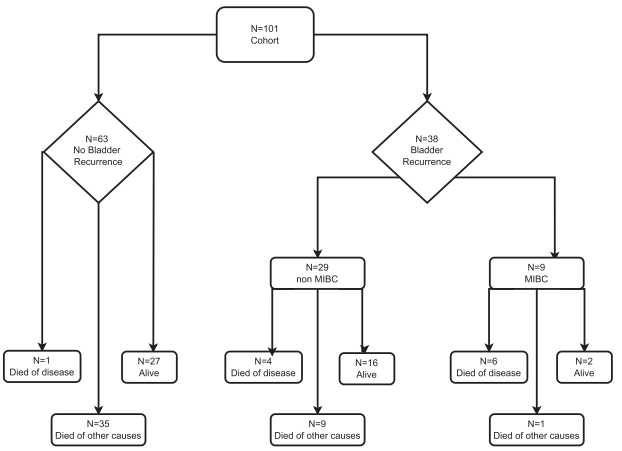

Figure. Flowchart of survival outcomes based on bladder recurrence status. MIBC indicates muscle-invasive bladder cancer.

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Neoadjuvant Chemotherapy With Transurethral Resection for Bladder Preservation: 15-Year Follow-Up of the Retained Bladder

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Ethics Statement: This study received Institutional Review Board approval (IRB No. 16-953).

Author Contributions:

Conception and design: Herr, Donat.
Data acquisition: Herr, Donat.
Data analysis and interpretation: Tin, Vickers, Herr, Donat.
Critical revision of the manuscript for scientific and factual content: Tin, Vickers, Herr, Donat.
Drafting the manuscript: Tin, Herr, Donat.
Supervision: Herr, Donat.
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Purpose: Bladder preservation is a desired goal for most patients with muscle-invasive bladder cancer, although select few are ideal candidates based on established criteria. Heterogenous cohorts with short follow-up hinder assessment of true risks/benefits for ideal candidates. We describe long-term outcomes in patients with muscle-invasive bladder cancer, meeting established ideal criteria for bladder preservation, treated initially with systemic therapy and transurethral resection (TUR).

Materials and Methods: We conducted an institutional retrospective review of 101 prospectively monitored patients meeting "ideal" criteria for bladder preservation achieving a clinical complete response to cisplatin-based chemotherapy and TUR from 1994 to 2015, with > 10 years of follow-up. Primary end points were bladder-intact survival, local recurrence-free survival, and cancer-specific survival.

Results: Fifteen-year risk of death from bladder cancer was 11% (95% CI: 5.8%, 18%), with the competing risk of death from other causes 44% (95% CI: 33%, 54%) and cystectomy risk of 11% (95% CI: 5.9%, 18%). Bladder preservation outcomes were near 40:40:10:10 for death from another cause, alive with an intact bladder, cystectomy, and death from bladder cancer. Of 41 patients alive with their bladder intact, median (IQR) follow-up time was 14 (11, 20) years. One-third relapsed locally, with the probability persisting beyond 10 years, necessitating lifetime surveillance. Our findings may not be generalizable to other settings or to patients not meeting "ideal" criteria.

Conclusions: Bladder preservation with neoadjuvant chemotherapy with TUR is a viable option for select patients meeting established selection criteria. Patients and physicians must consider the probabilities of long-term bladder preservation vs excess mortality when electing bladder-sparing.

Key Words: bladder cancer, neoadjuvant chemotherapy, organ preservation

Bladder preservation strategies are gaining traction as alternatives to cystectomy in selected patients with muscle-invasive bladder cancer (MIBC).[1] One option is surveillance (watch-and-wait) after clinical complete response (cCR) to cisplatin-based neoadjuvant chemotherapy (NAC) and transurethral resection (TUR).[2-4] Arguments against this approach include understaging of the primary tumor, inability to identify complete responses to NAC using clinical staging modalities, and possibility of reduced survival caused by bladder recurrences. Nonetheless, there are patients who are interested in a bladder-sparing approach for their MIBC.

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There is a paucity of long-term (>5 year) data on bladder-sparing outcomes in MIBC, mainly because this approach is rarely used in practice. In addition, most published series evaluating bladder preservation consist of heterogenous cohorts rather than limiting patient selection to the established criteria for "ideal" candidates and have very short follow-up, hindering assessment of the true risks and benefits for bladder preservation in ideal candidates.[5,6] Finally, the impact of local relapse on cancer-specific and bladder-intact survival has not been determined.[7,8] We aimed to describe our single institution experience with patients meeting established ideal selection criteria, who opted for NAC with TUR as initial treatment for their MIBC, reporting on the long-term outcomes among these patients.

MATERIALS AND METHODS

We evaluated patients referred with a MIBC who wished to preserve their bladder and met the established "ideal" criteria for bladder preservation between 1994 and 2015. The study cohort was stopped at 2015 to ensure a minimum of 10-year follow-up in all surviving patients. The "ideal" criteria included a visibly complete (R0) restaging TUR of a small (≤5 cm), solitary (no carcinoma in situ beyond the primary tumor), organ-confined (cT2N0M0) MIBC and had no mass or induration on bimanual examination under anesthesia, hydronephrosis related to tumor compression or invasion, or evidence of local, regional, or metastatic disease on cross-sectional imaging (CT/MRI) of the chest, abdomen, and pelvis. Mild nontumor-related hydronephrosis due to reflux, resection of the orifice, or tumor flopping over the orifice was not an exclusion factor and no patient with mild hydronephrosis required a stent or percutaneous nephrostomy. Patients received 4 cycles of a cisplatin-based chemotherapy regimen and achieved a cCR. A cCR was defined as absent tumor on post-NAC radical TUR of the bladder tumor site (showing only scar) to the level of perivesical fat, a normal urine cytology, and normal imaging.[2,9] All patients who elected surveillance after a discussion of the standards of care with radical cystectomy (RC) or trimodal therapy (TMT), including possible mortality from tumor recurrences in a retained bladder were included in the study. Patients underwent surveillance cystoscopy and imaging every 6 months for 5 years, then annually, and were highly motivated and compliant to keep their bladders. No patients were lost to follow-up. Primary end points were bladder-intact survival and incidence and impact of local recurrences on cancer-specific survival. Time was measured from start of NAC to last follow-up or death from any cause. Patients who did not have an event were censored at last follow-up or death from any cause. Patients' data were entered prospectively in a database approved by the Institutional Review Board.

We first report on the outcome of time to bladder recurrence by using Kaplan-Meier methods. Next, we aimed to estimate the risk of death from bladder cancer, accounting for death from other causes as a competing risk. Finally, we aimed to examine death according to whether patients had a bladder recurrence. We used a competing risk regression model with death from disease as the main outcome, with death from other causes as the competing risk, and whether patients experienced a bladder recurrence as the predictor. Because patients could experience bladder recurrence at any point after NAC, bladder recurrence was included in the model as a time-dependent covariate. Patients who did not die were censored at the date of last follow-up. All analyses were conducted using R version 4.3.2.

RESULTS

We identified 101 consecutive patients at our institution who met our eligibility criteria from 1994 to 2015 and who elected chemotherapy with TUR as a bladder preservation modality. No patients were excluded. The Table presents the characteristics of our cohort. Thirty-eight patients developed recurrence in the bladder (29 of these relapses were non-MIBC, and the remaining 9 were MIBC). The median follow-up among patients without recurrence was 10 (IQR 7, 16) years from NAC. Figure 1 shows the probability of bladder recurrence over time, with the 1-, 5-, and 15-year probabilities of 9.9% (95% CI: 3.9%, 16%), 28% (95% CI: 19%, 36%), and 44% (95% CI: 31%, 54%), respectively. Notably there were 3 patients who recurred in the bladder after 10 years, with events occurring at 11, 12, and 13 years after NAC.

Among our cohort, 11 patients died from disease (7 of whom had their bladder intact) and 45 patients died from other causes (42 of whom had their bladder intact). The median follow-up among the 45 patients who were alive at last follow-up was 14 (IQR 11, 20) years. Figure 2 presents the cumulative incidence plot which shows the probability of death from disease, where the 5-year and 15-year probability of death from disease is 5.9% (95% CI: 2.4%, 12%) and 11% (95% CI: 5.8%, 18%), respectively. Notably the last patient died from disease 7 years after NAC, with no other patients who died after

Table. *Patient Characteristics*

	N = 101
Age, median (IQR), y	67 (57, 73)
Male, No. (%)	74 (73)
T2 stage, No. (%)	101 (100)
Tumor size 5 cm or less, No. (%)	101 (100)
Variant histology, No. (%)	18 (18)
Prior history of noninvasive bladder tumor, No. (%)	28 (28)
Solid bladder tumor, No. (%)	61 (60)
Mild nontumor-related hydronephrosis, No. (%)	6 (5.9)
Carcinoma in situ (focal), No. (%)	26 (26)
Lymphovascular invasion, No. (%)	16 (16)
Type of neoadjuvant chemotherapy, No. (%)	
Etoposide, cisplatin	1 (1.0)
Gemcitabine, cisplatin	63 (62)
Ifosfamide, paclitaxel, cisplatin	3 (3.0)
Methotrexate, vinblastine, doxorubicin, cisplatin	34 (34)

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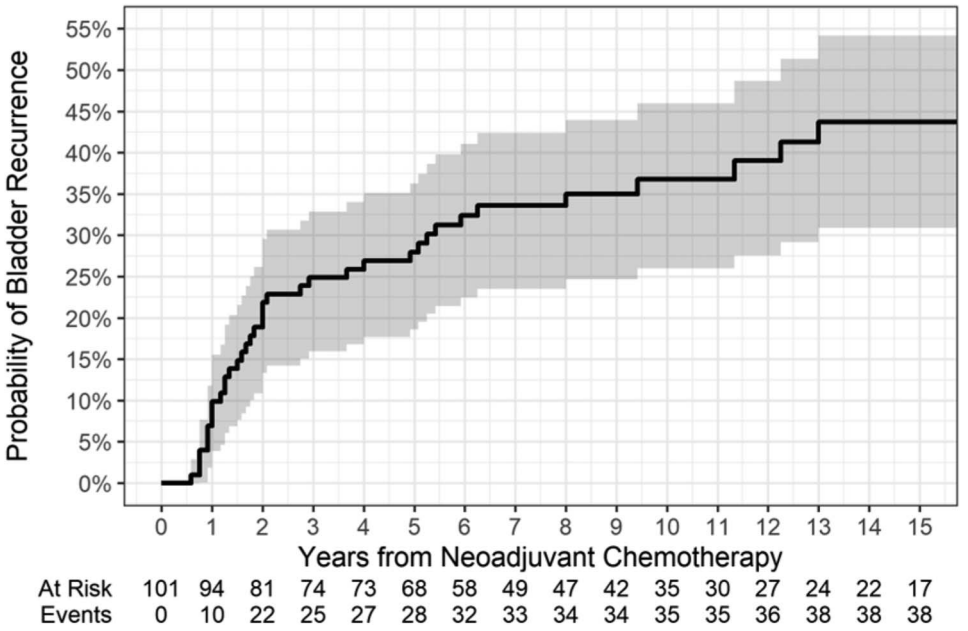

Figure 1. Kaplan-Meier plot for bladder recurrence after neoadjuvant chemotherapy. Shaded area corresponds to 95% CI.

this time point found to have metastatic bladder cancer.

Patients who develop a recurrence in the bladder were at increased risk of death from disease (HR: 2.35, 95% CI: 0.98, 5.59, $P = .054$), although this did not meet conventional levels of significance. However, the long-term risk of cystectomy was low, 11% (95% CI: 5.9%, 18%) at 15 years after accounting for competing risk of death from any cause (Figure 3). Eighty-three patients are alive (or died of other causes) with their bladder intact, and 7 survived after salvage cystectomy (among the 11 who underwent surgery). Among patients who relapsed in the bladder, the 5-year and 15-year cancer-specific mortality rate was 15% (95% CI: 4.7%, 26%) and 26% (95% CI: 14%, 41%), respectively.

Of the 29 patients who relapsed with noninvasive tumors, 4 died of disease, whereas 25 were salvaged with either intravesical bacillus Calmette-Guérin (20 cases) or cystectomy (5 cases) after failing

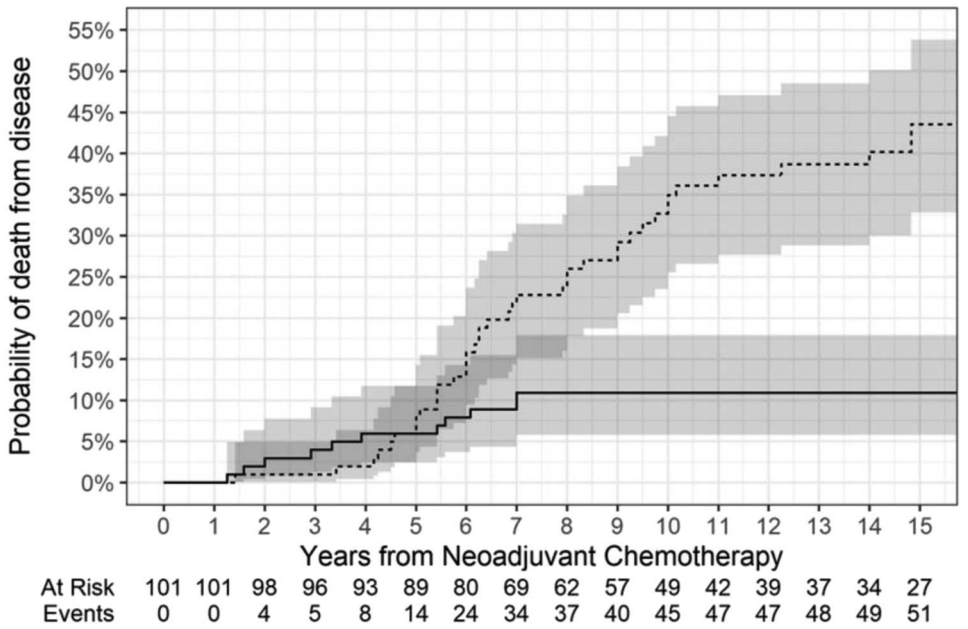

Figure 2. Cumulative incidence plot for death from disease (solid black line) and death from other causes (dashed line) after neoadjuvant chemotherapy. Shaded area corresponds to 95% CI.

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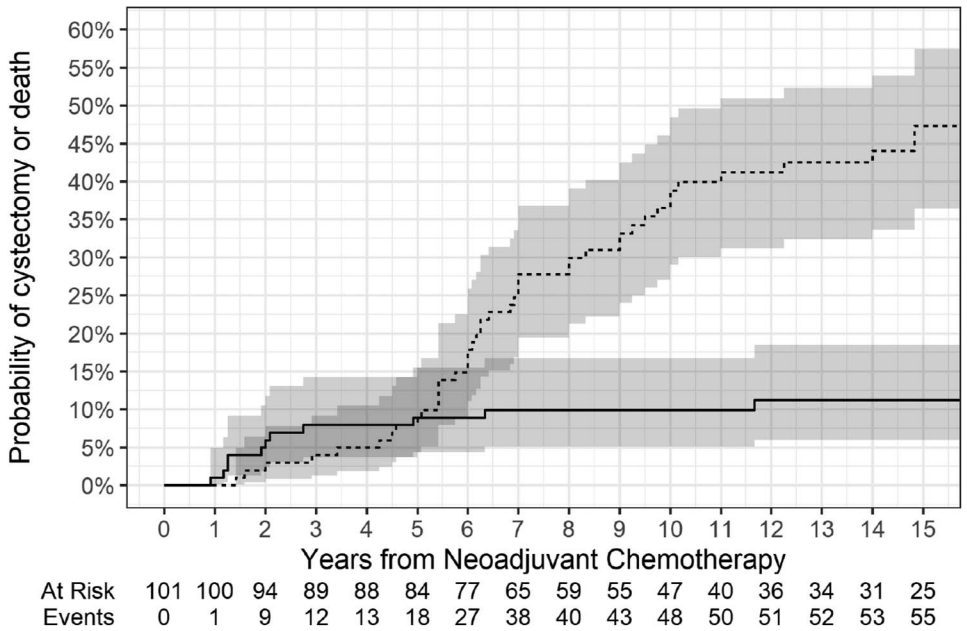

Figure 3. Cumulative incidence plot for cystectomy after neoadjuvant chemotherapy (solid black line), with competing risk of death from any cause (dashed line). Shaded area corresponds to 95% CI.

bacillus Calmette-Guérin therapy. Nine patients recurred with MIBC, and of those, 6 died of bladder cancer (including 2 who refused cystectomy), 1 died of other causes after cystectomy, 1 is alive without disease, and 1 died of metastatic bladder cancer absent a recurrence in the bladder. The 15-year probability of being alive and having an intact bladder was 41% (95% CI: 32%, 53%). Among the 41 patients alive with their bladder intact, the median (IQR) follow-up time was 14 (11, 20) years. Overall, the 15-year probability of cystectomy or bladder cancer-specific mortality was 18%. Figure 4 demonstrates the probability of cystectomy-free survival, presented based on the cumulative incidence plot for undergoing a cystectomy (the competing risk of death from any cause is not shown in this figure for clarity, though can be seen in Figure 3). Although not objectively measured, patients reported normal voiding during observation.

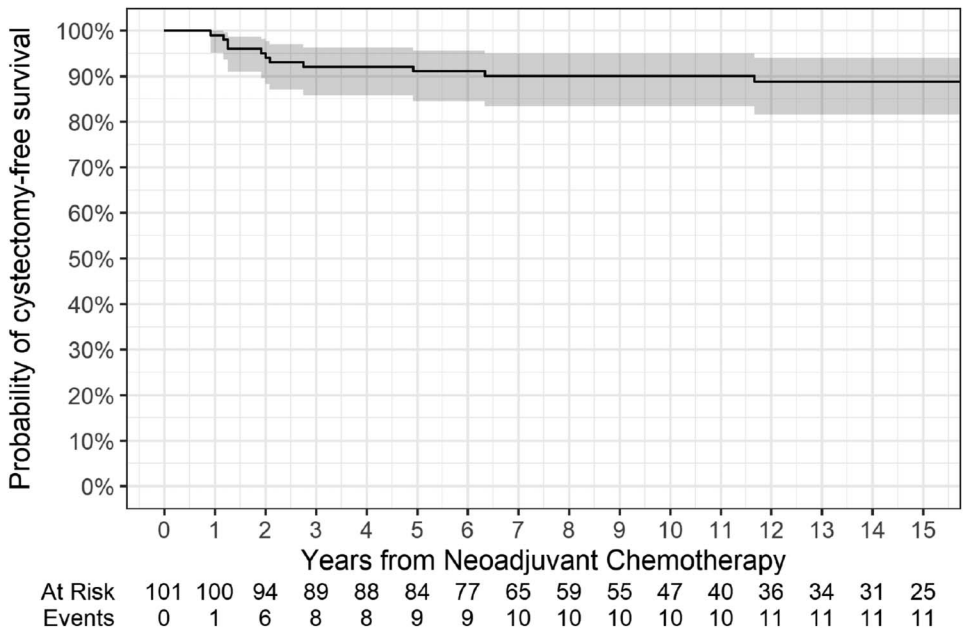

Figure 4. Probability of cystectomy-free survival, based on cumulative incidence plot for undergoing cystectomy, with competing risk of death from any cause (not shown). Shaded area corresponds to 95% CI.

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DISCUSSION

Most patients facing an RC for treatment of their bladder cancer, express a desire to preserve their bladder if there is a safe alternative that can maintain acceptable bladder function, while understanding that a delayed cystectomy at the time of recurrence could result in a diminished survival. TMT is a standard-of-care bladder-sparing option for patients who refuse or are unfit for RC. Multi-institutional experience suggests noninferior outcomes of TMT and RC.[8] Our prior prospective study with NAC showed similar 10-year survival rates for patients with cT2 and cT3-4 lesions who achieved a cCR to NAC and elected surveillance compared with those undergoing a planned post-NAC RC.[2] This provides rationale for avoiding radiation in selected patients with low-volume (cT2) MIBC who have no evidence of disease after chemotherapy.

This study demonstrates durable complete remissions and long-term bladder-intact survival in selected patients with small-volume clinically localized MIBC who achieve a complete clinical response to NAC and TUR. Bladder cancer-specific survival and cystectomy-free survival were both close to 90% at 10 years. Moreover, only a few later muscle-invasive bladder recurrences and long-term bladder preservation in this study demonstrates that significant early bladder under-staging was not a major factor with radical TUR before and after NAC in our hands. Local relapses occurred in a third of patients with the probability of recurrence persisting beyond 10 years, with a 44% risk of recurrence by 15 years. Most recurrences were noninvasive and can be treated successfully by intravesical therapy; however, the retained bladder remains at risk for tumor recurrence over a patient's lifetime and therefore warrants continued surveillance.

Cystectomy may salvage most, but not all patients with local recurrences. Overall, the cumulative probability of death from disease in our study, at 5 year and 15 year was 5.9% (95% CI: 2.4%, 12%) and 11% (95% CI: 5.8%, 18%) respectively. However, the 5-year and 15-year mortality rate for those who relapsed in the bladder (38 patients) in this study was 13% (95% CI: 4.7%, 26%) and 26% (95% CI: 14%, 41%), respectively. Furthermore, if we assume that all the patients who died of disease with or without a relapse in the bladder, would have been cured by a planned post-NAC cystectomy, then the estimated excess mortality risk at 15 years would be 11%, in line with other methods of bladder preservation.[2-4,7,8,10]

Taken altogether, this information is useful in counseling patients meeting ideal selection criteria and wishing to consider bladder preservation. Based on our findings, patients could be told that looking over the course of the next 15 years, for a set of 100 patients like them, 40 patients will have died from another cause, such as a heart problem and accordingly would have lived out their natural life with their bladder intact, 10 patients will have had to have a cystectomy, 10 patients will have died of bladder cancer, and the remaining 40 patients will be alive with their bladder intact.

The major limitation of the study is that it is an experience from a single high-volume comprehensive cancer center and may not be generalizable to other practice settings and patient populations not meeting established ideal selection criteria.[1,9] It is also important to emphasize optimal patients for surveillance after NAC with TUR are more highly selected to have low-volume (cT2) MIBC than those selected for trimodal (chemoradiation) therapy, which includes higher-volume cT2 and extravesical (cT3,4) MIBC patients, and therefore are not comparable populations to our cohort.[5,6] Further research, particularly genomic analysis, is warranted and being conducted to better identify complete responders to cisplatin and/or immunotherapy that can be managed by a bladder-sparing approach.[1,6,11,12] In addition, these studies may also help identify patients whom radiation therapy may not be necessary.

CONCLUSIONS

Bladder preservation with a durable complete remission and long-term bladder-intact survival can be achieved in highly selected patients (cT2) with small-volume clinically localized MIBC who achieve a complete clinical response to cisplatin-based NAC with TUR. However, the risk of bladder recurrence persists beyond 10 years (37% recurring by 10 years), requiring lifetime surveillance. Bladder preservation was associated with an excess mortality risk of 11% at 15 years, which the patient and physician must consider when electing bladder preservation.

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EDITORIAL COMMENT

Curative treatments with safe bladder preservation are the ultimate goal in patients with muscle-invasive bladder cancer. However, the standard of care remains neoadjuvant chemotherapy (NAC) or perioperative chemoimmunotherapy, followed by radical cystectomy (RC). RC is associated with significant morbidity and diminished quality of life, and understanding which patients require RC to achieve cure after NAC is an area of active investigation.

Donat et al[1] report 15-year outcomes of 101 patients with low-volume cT2 disease meeting strict complete response (CR) criteria after cisplatin-based NAC and transurethral resection. Eleven percent died of bladder cancer, 44% from other causes, and 41% were alive with an intact bladder at 15 years. Notably, no patients were lost to follow-up over this long study period, an extraordinary commitment to reporting long-term outcomes.

Key unanswered questions include the applicability of these findings to lower-volume or nonacademic centers and how to maintain excellent long-term outcomes in more heterogeneous and less strictly (eg, cT2-T3) selected patients. Recently published and ongoing work shows that transurethral resection, DNA damage response gene mutations, Vesical Imaging Reporting and Data System scoring, and even circulating tumor DNA are individually suboptimal to predict pathologic CR.[2-5] Urinary tumor DNA may be helpful, and likely a combination of all the above is necessary to optimize the bladder preservation approach.[6] How more modern systemic therapies may affect outcomes for patients with CR and how best to surveil the patient with a retained bladder after NAC remain undefined.

The findings by Donat et al provide an encouraging benchmark as we await overall survival results from modern risk-adapted bladder preservation studies, including RETAIN, RETAIN2, and HCRN GU16-257, for which the short-term event-free, metastasis-free, and overall survival results are encouraging.[7-9] Future successes in bladder preservation will depend on prospective validation, particularly with novel treatment approaches, such as enfortumab vedotin plus pembrolizumab, and refined techniques to detect minimal residual disease.

Gregory Hemenway,[1] Elizabeth R. Plimack,[1] and Daniel M. Geynisman[1]

[1]Fox Chase Cancer Center, Philadelphia, Pennsylvania

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REPLY BY AUTHORS

The authors appreciate the thoughtful editorial commentary[1] and agree that the standard of care for muscle-invasive cancer remains neoadjuvant chemotherapy (NAC) or perioperative chemo-immunotherapy, followed by radical cystectomy (RC); however, many patients understandably wish to preserve their bladders and are accepting of the risks associated with bladder preservation including local recurrence and disease-specific mortality that might be prevented by an immediate cystectomy.

Our findings[2] uniquely define the long-term risks of a retained bladder in this highly select group and are helpful for patient counselling, as well as verifying the continued importance that clinical staging and patient selection factors play in the success of bladder preservation. Based on our findings, patients could be counselled that looking over the course of the next 15 years, for a set of 100 patients like them, 40 patients will have died from another cause, such as a heart problem, and accordingly would have lived out their natural life with their bladder intact, 10 patients will have had to have a cystectomy, 10 patients will have died of bladder cancer, and the remaining 40 patients will be alive with their bladder intact.

It remains to be seen whether our findings can be reproduced in lower-volume or nonacademic centers, or if they may be extended to patients with higher volume or stage of disease who achieve a clinical complete response to systemic chemo/immune therapy, but they do set a benchmark for future comparisons.

The ongoing risk-adapted bladder preservation phase 2 studies evaluating various neoadjuvant chemoimmunotherapy combinations, those evaluating improvements in imaging for clinical staging, and those using molecular characterization and biomarkers to predict response to therapy are all promising, but they remain unproven, and the short-term results will need to be validated over time to assess the durability. The hope is they will improve our ability to successfully select patients for durable bladder preservation, and perhaps reduce the individual inaccuracies in clinical staging so bladder preservation may be reproducible in various practice settings. Until then the urologist is an integral component in clinical staging, patient selection, and shared decision-making with the patient.

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EDITORIAL COMMENT

Donat et al[1] report strikingly favorable long-term outcomes among highly selected patients with muscle-invasive bladder cancer treated solely with neoadjuvant cisplatin-based chemotherapy and transurethral resection.

Despite the nonstandard nature of this approach, only 11% of patients died from bladder cancer, and 45% remained alive including 40% with an intact bladder, of whom two-thirds never relapsed. These outcomes are remarkable given that this cohort was treated before the introduction of combination neoadjuvant chemoimmunotherapy or immune checkpoint blockade for metastatic disease, both of which may improve systemic control and survival.[2]

This study highlights that, in carefully selected patients, bladder preservation after chemotherapy alone is not only feasible but durable. However, this strategy remains suboptimal and investigational.

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In a study comparing radical cystectomy with trimodal therapy, bladder cancer–specific mortality approached one-quarter at 5 years, despite the use of combined modality treatment.[3] This suggests that outcomes with less intensive or single-modality approaches, such as chemotherapy with transurethral resection alone, are expected to be considerably worse and should be approached with caution outside of clinical trials.

The evolving utilization of biomarkers, multiparametric MRI, and circulating tumor DNA shows significant promise for improving risk stratification in this domain. Current studies have validated MRI response assessment scoring systems (eg, neoadjuvant chemotherapy Vesical Imaging Reporting and Data System) with strong correlation to pathologic response.[4] Concurrently, circulating tumor DNA detection after neoadjuvant therapy has been shown to independently predict complete response to neoadjuvant treatment, disease recurrence, and survival outcomes suggesting a role in guiding surveillance or adjuvant treatment intensification. Integrating these modalities could refine patient selection for bladder-sparing strategies in future protocols involving chemotherapy or chemoimmunotherapy combinations.

Although the results from Donat et al challenge historical assumptions about bladder preservation, they underscore the need to evolve beyond traditional criteria based on tumor location or resectability and toward a molecularly informed, personalized approach for disease management.

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REPLY BY AUTHORS

The authors very much appreciate the editorial commentary and would like to emphasize several salient points.[1] Our study[2] highlights the continued importance that clinical staging and patient selection factors play in the success of bladder preservation. Our study uniquely shows that durable preservation of a functioning bladder is feasible with systemic chemotherapy and surveillance after local transurethral resection alone.

We agree that our findings are based on a highly select group of patients meeting the "ideal selection criteria" for bladder preservation achieving a complete clinical response (cCR) to neoadjuvant chemotherapy and transurethral resection. They are not applicable to patients with higher stage or volume of tumor who achieve a cCR and are better candidates for trimodal therapy. It does, however, raise the question of what radiation therapy may be adding to those who achieve a cCR by any means (chemotherapy and/or immunotherapy) and whether de-escalation of therapy may be appropriate for some patients.

We look forward to improvements in imaging for clinical staging and molecular characterization and biomarkers to better predict response to therapy, thereby improving our ability to select patients for long-term bladder preservation. However, marker-driven studies are still ongoing and remain unproved. Until then, robust clinical evaluation by the urologist will remain paramount in selecting patient-centered approaches. Biomarkers may hopefully add to—but not replace—sound clinical evaluation selection factors. Participation in such studies is essential to moving the field forward, and we are currently participating in the multicenter Alliance A031701 genomic trial.[3]

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