

19. Shipley WU, Winter KA, Kaufman DS, et al. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. *J Clin Oncol*. 1998;16:3576–3583.
20. Nichols RC, Sweetser MG, Mahmood SK, et al. Radiation therapy and concomitant paclitaxel/carboplatin chemotherapy for muscle invasive transitional cell carcinoma of the bladder: a well-tolerated combination. *Int J Cancer*. 2000;90:281–286.
21. Sangar VK, McBain CA, Lyons J, et al. Phase I study of conformal radiotherapy with concurrent gemcitabine in locally advanced bladder cancer. *Int J Radiat Oncol*. 2005;61:420–425.
22. Zietman AL, Grocela J, Zehr E, et al. Selective bladder conservation using transurethral resection, chemotherapy, and radiation: management and consequences of T_a, T₁, and T_{is} recurrence within the retained bladder. *Urology*. 2001;58:380–385.
23. Weiss C, Wittlinger M, Engehausen DG, et al. Management of superficial recurrences in an irradiated bladder after combined-modality organ-preserving therapy. *Int J Radiat Oncol*. 2008;70:1502–1506.
24. Sapre N, Anderson P, Foroudi F. Management of local recurrences in the irradiated bladder: a systematic review. *BJU Int*. 2012;110:51–57.
25. Zietman AL, Sacco D, Skowronski U, et al. Organ conservation in invasive bladder cancer by transurethral resection, chemotherapy and radiation: results of a urodynamic and quality of life study on long-term survivors. *J Urol*. 2003;170:1772–1776.
26. Efsthathiou JA, Bae K, Shipley WU, et al. Late pelvic toxicity after bladder-sparing therapy in patients with invasive bladder cancer: RTOG 89-03, 95-06, 97-06, 99-06. *J Clin Oncol*. 2009;27:4055–4061.
27. Henningsohn L, Wijkström H, Dickman PW, Bergmark K, Steineck G. Distressful symptoms after radical radiotherapy for urinary bladder cancer. *Radiother Oncol*. 2002;62:215–225.
28. Shabsigh A, Korets R, Vora KC, et al. Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. *Eur Urol*. 2009;55:164–176.
29. Knollman H, Godwin JL, Jain R, Wong Y-N, Plimack ER, Geynisman DM. Muscle-invasive urothelial bladder cancer: an update on systemic therapy. *Ther Adv Urol*. 2015;7:312–330.
30. Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. *Lancet*. 2017;389:67–76.
31. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2017;18:312–322.
32. Tsai Y-C, Ho P-Y, Tzen K-Y, et al. Synergistic Blockade of EGFR and HER2 by new-generation EGFR tyrosine kinase inhibitor enhances radiation effect in bladder cancer cells. *Mol Cancer Ther*. 2015;14:810–820.

10 years in surviving patients, they report 10-year bladder preservation rates of 79% and cause-specific survival of 76%. These results complement the long-term experience of other institutions.³

While their relatively small cohort over 3 decades raises the possibility of selection bias, their mature TMT results contribute to a growing body of literature demonstrating comparable long-term outcomes to upfront RC for MIBC in appropriately selected patients. With the randomized selective bladder preservation against radical excision trial closing early due to poor accrual (partly explained by patient preference for TMT),⁴ alternative analyses have compared the 2 treatments. A recent propensity-score analysis matching RC and TMT patients treated in a multidisciplinary setting found no survival difference, nor did a systematic review and meta-analysis.^{5,6} Two retrospective large database studies using the National Cancer Database and the Surveillance, Epidemiology and End Results-Medicare database found inferior survival for patients treated with TMT vs RC.^{7,8} However, in such analyses using population-level data, many important confounders go unaccounted for making results hard to interpret, such as the validity of chemoradiation data (adequate dose, etc), and whether patients undergoing TMT fit the recommended selection criteria or were simply unfit for surgery.

If survival data are equivalent in appropriately selected patients, the different morbidity profiles of TMT and RC become essential to consider. With over 80% of patients undergoing TMT retaining their native bladder nowadays, there are potential quality-adjusted life year gains with TMT and the quality-of-life (QOL) implications of the strategies need further investigation. One study using validated QOL instruments from 226 patients found that TMT was associated with superior general and sexual QOL.⁹ At the least, respect for patient autonomy dictates that they can be made aware of acceptable alternative treatments options during the supported decision-making process.¹⁰

The key to successful TMT is well-coordinated multidisciplinary care and the careful selection of appropriate candidates. The urologist is essential to introducing and leading patients through a bladder-sparing approach, highlighted by a maximal transurethral resection being a strong predictor of success,³ the importance of salvage cystectomy, and the need for lifelong cystoscopic surveillance. With TMT ready for "prime-time," it is being investigated in the immunotherapy era through SWOG/NRG 1806, a phase III randomized trial of TMT +/- the PD-L1 inhibitor atezolizumab. Those eligible may stand to benefit in certain QOL domains and, as shown by Büchser et al, 80% may preserve their bladder. After all, a functioning bladder is a bladder well worth saving.

Trevor J. Royce, M.D., M.S., M.P.H., Jason A. Efsthathiou, M.D., D.Phil., Department of Radiation Oncology, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC; Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

References

1. Chang SS, et al. Treatment of non-metastatic muscle-invasive bladder cancer: AUA/ASCO/ASTRO/SUO guideline. *J Urol*. 2017;198:552–559.
2. Alfred Witjes J, et al. Updated 2016 EAU guidelines on muscle-invasive and metastatic bladder cancer. *Eur Urol*. 2017;71:462–475.

EDITORIAL COMMENT



Bladder-sparing trimodality therapy (TMT) as an acceptable alternative to radical cystectomy (RC) for the treatment of muscle invasive bladder cancer (MIBC) is the product of consecutive institutional and national protocols over decades and across continents. RC and TMT are now recognized as bona fide treatment options for MIBC by multiple international guidelines.^{1,2}

In this issue, Büchser et al contribute their institution's experience with TMT. Having treated 90 MIBC patients eligible for RC from 1990 to 2016, with a median follow-up of almost

3. Giacalone NJ, et al. Long-term outcomes after bladder-preserving tri-modality therapy for patients with muscle-invasive bladder cancer: an updated analysis of the Massachusetts General Hospital experience. *Eur Urol* 2017;1–9. <http://dx.doi.org/10.1016/j.eururo.2016.12.020>.
4. Huddart RA, Hall E, Lewis R, Birtle A. Life and death of spare (selective bladder preservation against radical excision): reflections on why the spare trial closed. *BJU Int*. 2010;106:753–755.
5. Kulkarni GS, et al. Propensity score analysis of radical cystectomy versus bladder-sparing trimodal therapy in the setting of a multidisciplinary bladder cancer clinic. *J Clin Oncol*. 2017;35. JCO2016692327.
6. Vashistha V, et al. Radical cystectomy compared to combined modality treatment for muscle-invasive bladder cancer: a systematic review and meta-analysis of over 12,000 patients. *Int J Radiat Oncol*. 2016;97:1002–1020.
7. Seisen T, et al. Comparative effectiveness of trimodal therapy versus radical cystectomy for localized muscle-invasive urothelial carcinoma of the bladder. *Eur Urol*. 2017;72.
8. Williams SB, et al. Comparing survival outcomes and costs associated with radical cystectomy and trimodal therapy for older adults with muscle-invasive bladder cancer. *JAMA Surg*. 2018;77555:1–9.
9. Mak KS, et al. Quality of life in long-term survivors of muscle-invasive bladder cancer. *Int J Radiat Oncol Biol Phys*. 2016;96:1028–1036.
10. The Royal College of Surgeons of England. Consent: supported decision-making a guide to good practice. *RCS Prof Clin Stand* 2016.

<https://doi.org/10.1016/j.urology.2018.07.060>
UROLOGY 124: 189–190, 2019. © 2018 Elsevier Inc.



AUTHOR REPLY

As has been discussed in our work and the related Editorial Comment, there is now a mounting evidence supporting combined modality treatments in the management of muscle invasive bladder cancer as an acceptable alternative to radical cystectomy.¹⁻³ In this context, patient selection acquires particular significance.

The results of our study with a median FU of 115 months showed a 10-year bladder preservation rate of 79% and 10-year OS, CSS, and MFS rates were 43.2%, 76.3%, and 79.2%, respectively. These data are particularly relevant in a clinical scenario where randomized information is nonexistent and there is little hope of having it in the medium or long term. In this setting, we should make a special effort in producing high-quality observational studies intending to identify predictive and prognostic factors associated with each treatment. This will allow professionals to assign each patient to the most appropriate treatment and provide accurate information, so a fully informed decision can be made.

Although our data is subjected to some limitations given the small sample size, we could not observe significant

differences in survival between treatment protocols. However, from our point of view, the data seem to support the use of a more convenient scheme (transurethral resection and chemoradiation: 64.8 Gy with 6 cycles of concomitant weekly cisplatin) for both patients and physicians. This protocol entails a shorter period of treatment, less complications (ie, toxicity) and slightly better bladder preservation rate (90% vs 81% and 74% in the other 2 protocols). In this setting we should underline the relevant role of urologists' expertise in performing successful salvage radical cystectomies after full-course of radiochemotherapy.

We can only agree with the editorial comment on the utter importance of the multidisciplinary approach in the management of muscle invasive bladder cancer. Considering the impact on quality of life of each treatment^{4,5} and the high likelihood of retaining a functional bladder after combined modality treatments in well selected and informed patients, it is our opinion that organ sparing approaches should be always discussed in a multidisciplinary team, where the need for an intensive cystoscopic FU and the possibility of a salvage cystectomy should be considered as well.

Finally, we cannot obviate the high expectations derived from emerging role of immunotherapy in bladder preserving approaches.

D. Büchser, M.D., A. Zapatero, M.D., Ph.D., R. Arellano, M.D., Department of Radiation Oncology, Hospital Universitario de La Princesa, Madrid, Spain; Department of Urology, Hospital Universitario de La Princesa, Madrid, Spain

References

1. Seisen T, Sun M, Lipsitz SR, et al. Comparative effectiveness of trimodal therapy versus radical cystectomy for localized muscle-invasive urothelial carcinoma of the bladder. *Eur Urol*. 2017;72:483–487.
2. Vashistha V, Wang H, Mazzone A, et al. Radical cystectomy compared to combined modality treatment for muscle-invasive bladder cancer: a systematic review and meta-analysis. *Int J Radiat Oncol*. 2017;97:1002–1020.
3. Zapatero A, Martin De Vidales C, Arellano R, et al. Long-term results of two prospective bladder-sparing trimodality approaches for invasive bladder cancer: neoadjuvant chemotherapy and concurrent radiochemotherapy. *Urology*. 2012;80:1056–1062.
4. Mak KS, Smith AB, Eidelman A, et al. Quality of life in long-term survivors of muscle-invasive bladder cancer. *Int J Radiat Oncol*. 2016;96:1028–1036.
5. Efstathiou JA, Bae K, Shipley WU, et al. Late pelvic toxicity after bladder-sparing therapy in patients with invasive bladder cancer: RTOG 89-03, 95-06, 97-06, 99-06. *J Clin Oncol*. 2009;27:4055–4061.

<https://doi.org/10.1016/j.urology.2018.07.061>
UROLOGY 124: 190, 2019. © 2018 Elsevier Inc.