Radical cystectomy *vs* trimodality therapy for muscle-invasive bladder cancer: further extensive evaluation needed

We read the Article by Alexandre R Zlotta and colleagues[1] with great interest and would like to congratulate the authors and acknowledge their hard work in conducting this comparative analysis. This study provides a one-of-its-kind comparison of radical cystectomy and trimodality therapy for muscle-invasive bladder cancer. The study shows similar oncological outcomes between the two, in carefully chosen patients in the setting of a multidisciplinary team, opening up the horizon for trimodality therapy.

At the outset, it is important to point out that this study deals with a situation that is probably the best-case scenario for radiotherapy—ie, this study is likely to have selected patients in whom radiotherapy would excel. Out of the total of 1492 patients who underwent radical cystectomy at the participating institutions, only just over a quarter (440 [29%]) were found matching to the trimodality therapy group. The authors did propensity score matching for both groups of patients. 218 (77%) of the 282 patients in the trimodality therapy group had an Eastern Cooperative Oncology Group performance status of 0. It would appear odd that so many apparently fit patients would choose or were counselled for trimodality therapy in an era when most urologists in North America tended to recommend radical cystectomy for muscle-invasive bladder cancer. It is possible that patients who had trimodality therapy were at potentially high risk of morbidity and mortality from radical cystectomy, leading to selection bias. To do propensity score matching for this group, it is natural that those patients from the radical cystectomy group chosen to be matched were also at a higher risk of morbidity and mortality. The fact that overall survival was better in the trimodality therapy group but not metastasis-free survival, cancer-specific survival, or disease-free survival suggests that the groups might not be similar, which the authors have accepted and attempted to explain. The estimate of disease-free survival, as defined in this study, is a very conservative one as it did not include nearly a third (87 [31%] of 282) of the patients in the trimodality therapy group who had muscle-invasive or non-muscle-invasive disease recurrence in the bladder within 3 years.

Patients with variant histology were also included in both the groups, but it is unclear whether propensity score matching was performed for this, and a higher proportion of patients with variant histology undergoing radical cystectomy in this cohort could have possibly skewed the results. In both groups, recurrences in the ureter were considered as a second primary and the recurrence rates between groups were not commented upon, thus omitting potential insight into upper tract recurrences after trimodality therapy and radical cystectomy. A previous history of, and treatment for, urothelial carcinoma was not considered in this analysis; such patients are likely to have different survival statistics. Other factors not controlled for that might risk leaving residual confounders include tumours in a diverticulum, involvement of the urethra (especially the prostatic urethra) or ureteric orifices, tumour size distribution, and response status after neoadjuvant chemotherapy. The pathological staging for the radical cystectomy patients suggest that all of them had either residual muscle-invasive or node-positive disease, which could mean that patients who did not respond to neoadjuvant chemotherapy were preferentially selected for surgery. Again, the authors acknowledged the possibility of unknown residual confounders.

At 2·5 years of follow-up, 28% of patients in the trimodality therapy group were not being followed up compared with 41% in the radical cystectomy group. Is it possible that those patients with better outcomes after radical cystectomy were subjected to less stringent follow-up and hence dropped out of the follow-up schedule?

Traditionally urologists in the UK have been very accepting of radiotherapy as a treatment option for select patients with muscle-invasive bladder cancer and we do agree with the results of this trial. However, we find the enthusiasm expressed for this study a little surprising and worry that this enthusiasm might lead to losing the very important finesse needed when recommending treatments for patients with muscle-invasive bladder cancer.

We declare no competing interests.

*Rahul Jena, *Rami Issa, Matthew Perry*
rami.issa@nhs.net

Urology Surgery, The Royal Marsden Hospital, London, UK (RJ); Department of Urology, St George's University Hospital, London SW17 0QT, UK (RI); Royal Surrey NHS Trust and Faculty of Health and Medical Sciences, University of Surrey, Surrey, UK (MP)

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.