Reply to: Dose-escalation of radiation may improve outcomes of squamous cell carcinoma of bladder

Dear Editors,

We would like to thank Karmakar et al. for their interest and comments regarding our study which compared definitive chemoradiation therapy for patients with urothelial carcinoma (UC) versus squamous cell carcinoma (SqCC) of the urinary bladder [1].

In our brief report, we proposed that given the worse overall survival outcomes for patients with SqCC in comparison to UC, methods to intensify therapy are reasonable. We suggested that treatment intensification could be accomplished with dose escalation of conventional chemotherapy, the use of novel systemic agents, and/or dose escalation of radiotherapy. As Dr. Karmakar and colleagues point out, intensification of conventional chemotherapy is a challenge, given the older age and multiple comorbidities common in this patient cohort (median age of 78 in our study) [1]. In addition, the National Cancer Database that we used for our analysis is not a useful resource to evaluate the potential benefit of dose escalated chemotherapy, since details on chemotherapy administration (agent, dose, number of cycles) are notably absent. The newer systemic therapy agents, particularly immunotherapy, are promising, as recent prospective early-phase trials of neoadjuvant immunotherapy with atezolizumab and pembrolizumab combined with radical cystectomy revealed pathologic complete response rates of 30–40% [2]. These early results suggest that immunotherapy may be a powerful tool in future treatment intensification, but its role is not yet defined for patients undergoing chemoradiation for bladder cancer. Less than 5% of our study population received immunotherapy and we decided to exclude them from the analysis.

Given the potential challenges with systemic therapy intensification strategies, XX and colleagues suggest that dose-escalated RT may improve local control in bladder cancer, which could in turn improve survival [3,4]. Their institutional data, published in 2016, proposed a method of adaptive image-guided radiotherapy using a plan-of-the-day approach in which multiple treatment plans are generated assuming different degrees of bladder filling and the plan that best conforms to the patient’s anatomy on that given day is chosen, to help ensure optimal coverage of the clinical target volume while minimizing excess radiation dose to normal organs-at-risk (e.g. small bowel) [3]. This plan-of-the-day approach proved to be clinically feasible with relatively low rates of acute and late adverse events [3]. Using this approach, they were able to deliver dose-escalated treatment to nearly 70 Gy to the bladder tumor in 55% of the patients, compared to the standard dose of ~64–65 Gy [3]. Dose-escalated radiotherapy was associated with better oncologic outcomes in their relatively small patient cohort, although the differences were not statistically significant [3]. Another method to escalate radiation dose is with online-adaptive MR-image guided radiation therapy, which we have employed at Washington University in St. Louis [5]. The improved soft-tissue visualization of onboard MRI enhances the daily visualization of the primary tumor, allowing for a more focused tumor-directed treatment. The inherent online adaption capabilities also allow for rapid re-contouring of the anatomy on the day of treatment and re-planning with the patient in the treatment position. This adaptive technology is already being used for other disease sites such as gastrointestinal, thoracic, and breast malignancies and is particularly useful for patients receiving short-course radiation delivered using stereotactic body radiotherapy (SBRT) techniques [5]. Limitations of this method include the additional physician time required to do daily adaptive treatment planning, machine downtime during adaptive planning, and a lack of clinically relevant metrics to guide decision-making on plan adaptation.

We think additional clinical trials aimed at intensifying systemic therapy and/or radiotherapy are needed to improve outcomes for these patients.

Regards,
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