

-Article Type: Review Article

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Title: Is there an oncological benefit to extended lymphadenectomy for muscle-invasive bladder cancer?

Reviewer #1

This is a review article on the role of extended lymphadenectomy in patients with muscle-invasive bladder cancer. It is an excellent review article – very impressed and I feel honoured to review this article. The authors must be very dedicated to this area.

Comment 1: From the LEA trial, seem the differences in CSS and OS are higher than RFS. Yet both LEA and SWOG trials have primary outcomes of RFS. In my opinion, CSS and OS are perhaps more clinically important than RFS. What do you think and is it something worthwhile to discuss, maybe in the future direction section?

Response #1: We thank the reviewer for their comments and analysis of the prospective LEA and SWOG trials. Both of these trials were powered for RFS due to developing enough power in the trials to show a difference, which may be nearly impossible for CSS and OS. Unfortunately, review of the retrospective studies does not provide a clear CSS or OS benefit to eLND. We have added a line in the future direction section to acknowledge that CSS and OS would provide even more meaningful clinical endpoints.

Reviewer #2

Comment 1: A very abbreviated attempt to do a meta-analysis of this topic. Needs more coverage and discussion into techniques to improve node dissection eg. Tehcnium, ICG etc. to add more depth and perspective to this topic. There is an attempt to look at the recent trials focusing on node dissection, which is good.

Response #1: We thank the reviewer for their comments and insights to improve this review. We agree with expanding the discussion into technologies to improve nodal dissection. We have added a new section titled “Intraoperative Technology for Lymph Node Dissection” to discuss these techniques including Tc-99m and ICG. While the use of ICG with robotic cystectomy has become easier than dynamic lymphoscintigraphy, the utility is very limited given high false-negative rates. There have also been studies looking at the routine use of PET/CT preoperatively to better identify nodal

metastasis, which we have added as well.

Comment 2: There is also a need to discuss the role of immune-oncology in bladder cancer especially in the context of node positive disease and neoadjuvant therapy.

Response #2: We agree with the reviewer that the role of immunotherapy in bladder cancer, especially neoadjuvant therapy is becoming more important. While we had included the initial results of PURE-01 trial of neoadjuvant pembrolizumab we have included an expanded paragraph discussing the use of immunotherapy in those with node-positive disease. We specifically highlight the three adjuvant trials as well, with the recent report that adjuvant atezolizumab did not reach its primary endpoint.