Peer Review File

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Review comments

This is a commentary article on the clinical trial by Tang et al. 2023. The manuscript is well-written and clinically relevant. The authors also reviewed up-to-date knowledge on this research focus. I have a few minor comments for the authors to improve this paper.

First, the authors may consider to have a brief summary of the challenges in the clinical management of locally advanced esophageal carcinoma, analyzed the unaddressed clinical questions and knowledge gaps in the clinical guidelines, analyzed why the optimal strategy remains unclear, and clearly indicate the strengths of this study, including the knowledge gaps filled by the current data.

Reply: *Thank you for this suggestion to include a brief summary of the clinical challenges in the management of locally advanced esophageal cancer and the current knowledge gaps in the best strategy for treating this complex disease process. We began this discussion in the first paragraph in which we establish that CROSS-style nCRT is the standard of care, but the challenges lie in the impact of preoperative radiation on perioperative complications and the concerns of systemic toxicity with chemotherapy (**Page 1, Lines 2-3).** We solidify this summary by adding the NCCN guidelines in the introduction itself and begin our commentary by acknowledging that the study by Tang et al. seeks to address the critical knowledge gap in the optimal strategy for neoadjuvant therapy for ESCC (**Page 1, Lines 18-23)** below:*

Page 1, Lines 18-23:

"Despite these conflicting findings, the National Comprehensive Cancer Network (NCCN) guidelines suggest definitive or neoadjuvant chemoradiation for locally advanced ESCC (T2N0 (+LVI, ≥3cm, poorly differentiated), T1b-T2N+, or T3-T4a). (5) Therefore, this randomized controlled trial published by Tang et al. is particularly timely, as it aims to address this knowledge gap in the optimal strategy for neoadjuvant therapy for ESCC."

*We also clearly indicate the strengths of the study now in **Page 2-3, Lines 43-48:***

Page 2-3, Lines 43-48:

"This is a well-designed study with several strengths. First, it is reasonably high-powered with appropriate randomization of patients with an intention-to-treat approach into both the nCRT and nCT arms. The authors standardized the operative approach (MIE) for both arms, which strengthens their comparisons of postoperative complications. In their investigation of nCRT vs nCT, the authors directly address the key knowledge gap in the optimal strategy for the management of locally advanced ESCC."

Second, the authors may consider to have comments on the limitations and unanswered clinical questions in Tang's study and suggest possible research focuses to facilitate the development of the optimal treatment of locally advanced esophageal carcinoma.

Reply: *We are grateful for the reviewer's suggestion to discuss the limitations and yet unanswered questions raised by this study. We have done so in detail as the preamble to our formal discussion in* ***Page 3, Lines 48-56****.*

Page 3, Lines 48-56:

"There are several limitations to this study, however. The chemotherapy regimen used in this trial was based on cisplatin, while most chemotherapy alone regimens in the Western hemisphere use fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) which has an acceptable toxicity profile.(9) To this end, retrospective investigation has suggested that cisplatin-based regimen may be associated with higher incidence of grade 3 or higher febrile neutropenia in locally advanced ESCC. (7) The major contribution of this study's findings is that it raises fundamental, yet unanswered questions about the utility of pCR for prognostication and the utility of dual-local therapy (surgery and radiation) for the management of ESCC."

Third, the authors may need to cite some relevant studies that focusing the pathophysiological of esophageal carcinoma to explain the findings from the study by Tang and colleagues.

Reply: *Thank you to the reviewer for this important suggestion to discuss the pathophysiology of esophageal cancer to explain the findings of Tang et al.'s study. We first discuss the biochemical principle behind chemoradiation a core tenet of the management for tumors like esophageal cancer and why a comparison of neoadjuvant chemoradiation was considered compared to chemotherapy alone. We also discuss the anatomic reason why T2+ esophageal cancer is at such high risk for nodal or micro-metastasis in* ***Page 1, Lines 3-11.***

Page 1, Lines 3-11:

The biologic principle behind nCRT lies in the dual effect of both locoregional disease control (radiation) and ablation of micrometastatic disease (chemotherapy), putatively enhancing the efficacy of surgical resection in resecting all possible tumor burden. (2) At the same time, both therapies may also work synergistically at the tumor site itself with chemotherapy providing both direct cytotoxicity and promoting radiosensitization of tumor cells. (2)In esophageal cancer, tumors that are T2 and beyond are at high risk for nodal metastasis or micrometastatic disease, as these lesions have either invaded through submucosa (which contains a rich network of lymphatics) or involve the muscularis propria to regional lymph nodes or surrounding structures. (3)