

Peer Review File

Article Information: <http://dx.doi.org/10.21037/jgo-20-530>

Reviewer A:

Comment 1: This is a retrospective cohort study with a title of “A population-based analysis of chemoradiation versus radiation alone in the definitive treatment of patients with stage I-II squamous cell carcinoma of the anus”. The authors analyzed 4288 patients with stage I-II anal squamous cell carcinoma. Although the data is an interesting reflection of the practice pattern for management of Anal SCC in the US, the study simply confirms that omission of concurrent chemotherapy is associated with inferior overall survival in patients with stage II SCC. The EORTC and the UKCCCR anal cancer (ACT I) trials have already shown the superiority of CRT over RT alone. (1,2) The authors also acknowledged the superiority of the CRT standard in their introduction. Perhaps the authors original intention was to focus on T1 lesions only as it is known to have similar outcomes using RT alone based on recent case series.

The research design is appropriate, the methods are adequately described, and the conclusions are supported by the results. The authors criticized both the strengths and limitations of their article. The main limitation of this paper is that randomized trials have already shown the superiority of CRT over RT. I do have a few comments though.

Reply 1: We thank the reviewer for their insightful comments. We agree that pre-existing data suggests that patients with stage II SCC should be treated with combined chemoradiation. The study was undertaken principally to assess the need for combined chemoradiation in patients with stage I SCC, which is less well-defined in the literature, while confirming the findings from the EORTC and UKCCCR studies for stage II patients. We have altered some of the language to make our intentions clearer.

Changes in the text: We have modified our text as advised (see page 2, lines 47-49; page 12, line 265).

Comment 2: The current study identified 3982 (93%) who underwent CRT and only 306 (7%) who underwent RT. The study focused on the patients getting CRT and RT alone. Since only 306 underwent RT and 30.8% were T1 patients and 69.2% has T2-T3 disease putting a figure around 203 patients that are stage 2, these patients may have significant co-morbidities such as advanced age that precluded CRT. This seems to be reflected in the age groups in the unadjusted data set. This needs to be emphasized in the discussion.

Reply 2: We agree that the patients who underwent RT likely had co-morbidities precluding the administration of combined modality therapy, and these may potentially serve as confounding variables. We have emphasized this as an additional weakness of our analysis in the discussion.

Changes in the text: We have modified our text as advised (see page 11, lines 248-249).

Comment 3: The role of chemotherapy is to enhance radiation treatment. Based on the UKCCCR Anal cancer trial, although patients had more early morbidity with the addition of chemotherapy, late morbidity rates were similar. Furthermore, updated 13-year follow-up results showed there is a reduction in risk of dying from anal cancer. This needs to be addressed in the discussion even for stage I patients who had similar outcomes with CRT vs RT.

Reply 3: We thank the reviewer for this insightful comment. Indeed, the UKCCCR study suggests that with late follow-up, there is a clear oncological benefit to chemoradiation that outlasts the higher rates of early non-anal cancer deaths with this approach. It is possible that even with stage I patients, chemoradiation may be superior with very late follow-up as oncological improvements outlast early non-anal cancer deaths (potentially from treatment toxicity).

Changes in the text: We have modified our text as advised (see page 9, lines 201-208).

Comment 4: During the study, the authors used propensity score matching with IPTW to show that overall Kaplan meier survial is the same with stage I anal SCC using CRT vs RT but inferior with stage II anal SCC. This does support the hypothesis that a subset of T1 patients can benefit from RT alone. Can the authors be more explicit in terms of which group of patients are best treated with RT alone, such as those of the tumor size group 1-1.5cm, or female gender, etc.

Reply 4: We thank the reviewer for their insight. We do hesitate to make definitive treatment recommendations based on this hypothesis-generating analysis. That being said, we have added a statement suggesting RT alone may be most prudent in patients with very small, <1.5 cm, well-differentiated tumors.

Changes in the text: We have modified our text as advised (see page 11, lines 241-242).

Comment 5: I would like to see a survival curve relationship between Tumor size and survival, perhaps as supplement.

Reply 5: We thank the reviewer for this suggestion. We have added Figure 1A (Appendix), which includes Kaplan-Meier comparisons between CRT and RT for various size groupings.

Changes in the text: We have added Figure 1A to the Appendix. We have modified our text as advised (see pages 7-8, lines 171-173).

Reviewer B:

Comment 1: The manuscript is very well-written with nice statistics description as well as a complete discussion. I would only suggest to the authors to add a sentence in the discussion section (when describing the limitations of the study) about the possibility of understaging of the patients included (since it was not described how the patients were staged in terms of imaging). The database used comprised pts from 2004 to 2016 and, more recently, we have been incorporating PET-CT scan as a staging method. PET-CT scan may change nodal staging in up to 28% of pts with anal cancer (The Role of FDG-PET in the Initial Staging and Response Assessment of Anal Cancer: A Systematic Review and Meta-analysis - PubMed (nih.gov))

I would publish this nice manuscript after this minor suggestion.

Reply 1: We thank the reviewer for their important insights and agree that methods of staging have evolved with time. We have added the possibility that patients were understaged to our limitations section along with the recommended citation.

Changes in the text: We have modified our text as advised (see page 11, lines 254-258).