

Peer Review File

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Reviewer A

This is a study that tries to shed light on an issue that is still unclear at present, and for this an innovative methodology is used in this type of article.

The structure of the article and its wording are adequate.

I would like to contribute the following observations to the authors:

Comment 1: I think the PSM should be explained in more detail in the methodology section.

Reply 1: Thank you very much for your pertinent advices. We have modified our text as advised.

Changes in the text: (1) line93-100: Because the patients were not randomly assigned in this retrospective study, the baseline covariates of the 2 groups might have been unbalanced which could have affected the evaluation of treatment results. Thus, propensity score matching (PSM) was used to minimize differences in baseline characteristics between the 2 groups with the “Nonrandom” R package. The propensity score (PS) of each patient was calculated with a logistic regression model that included the following variables: age, sex, race, insurance status, pathological grade, T stage, marital status, and diagnosis time. Each patient in the surgery group was matched 1:1 with a corresponding patient in the radiotherapy group using a nearest-neighbor PS matching algorithm with a caliper size of $x = 0.05$.

(2) line102-103: Chi-square tests were used to compare baseline characteristics between the treatment groups before and after PSM.

Comment 2: Authors should pay attention to grammar and check punctuation marks, for example on lines 163 to 165.

Reply 2: Thank you very much for your pertinent advices. We have modified our text as advised.

Changes in the text: line159-161: To explore whether the therapeutic effects of the 2 treatment modalities are consistent in patients with early glottic laryngeal cancer but with different clinical features, subgroup analyses were conducted.

Comment 3: Perhaps the notable difference between the proportion of patients in the treatment groups should be included as a study limitation.

Reply 3: We sincerely thank the reviewer for the pertinent question. We have added discussion in our revised manuscript.

Changes in the text: line 254-259: This study has several limitations. First, there was an inherent patient selection bias in retrospective studies. Patients in the surgery group had a better T stage, were more likely to be diagnosed between 2005 and 2009, and were less likely to be Black, which might have led to a better prognosis. Despite improvements in methods balancing the baseline covariates,

bias could not be completely overcome considering that a number of variables significantly related to survival, such as comorbidities and performance status, were not available from the database.

Reviewer B

This is a well-written manuscript which discusses long term survival for patients with early glottic cancer using SEER database. However, some changes are recommended.

Comment 1: It seems like there are too many figures and tables in the manuscript. I would recommend the authors to move some of the less important figures and tables to supplementary material (thus focusing on the data after propensity matching).

Reply 1: We sincerely thank the reviewer for the pertinent question. We have modified our figures and tables as advised.

Changes in the text: We have moved original figure 2, figure 6, and table 2 to supplementary materials as supplementary figure 1, supplementary figure 2, and supplementary table 2.

Comment 2: In the figures, does the survival graphs need to show until 250 months? It seems very long and cutting the graph at around 120 months seems reasonable unless the authors have any intention. At the end of the graph, the lines for surgery and RT groups cross and it may confuse the readers.

Reply 2: We sincerely thank the reviewer for the pertinent question. We have modified our figures as advised.

Changes in the text: We have modified the graphs to show only the first 120 months of survival curves in Figure 1, Figure 3, Figure 4, Supplementary Figure 1, and Supplementary Figure 2.

We have also added words “Dashed and solid lines indicate survival rates, with shaded areas indicating 95% CIs” in each of the above-mentioned figure legends.

Comment 3: I would recommend including the univariate analysis also along with the multivariate analysis in the tables. If it makes the tables too complicated, please organize the figures and tables as recommended in comment #1.

Reply 3: We sincerely thank the reviewer for the pertinent question.

Changes in the text: We have added univariate analyses for patients with early glottic cancer before propensity score matching (PSM), after PSM, and patients aged ≥ 70 years after PSM in Supplementary Table 1, Supplementary Table 3, and Supplementary Table 4, respectively.

Line 127-128: We also performed univariate survival analysis (Supplementary Table 1) and further multivariate regression analysis in the overall cohort

(Supplementary Table 2).

Line 152-153: Univariate analysis was conducted to preliminarily screen prognostic factors for survival (Supplementary Table 3).

Line 167-168: We next performed univariate survival analysis (Supplementary Table 4) and further multivariate survival analysis (Table 4) in patients aged ≥ 70 years after PSM.

Comment 4: I would recommend updating the statistic numbers for line 49 (the data is updated on the website).

Reply 4: We sincerely thank the reviewer for the pertinent question. We have modified our text as advised.

Changes in the text: line 42-44: It is estimated that, in 2021, there will be approximately 12,620 new cases of laryngeal cancer and 3770 deaths in the United States

Comment 5: Between line 123 and 124, I would recommend the authors to include a sentence for characteristics that significantly differed between the two groups. For example, there were more T2 patients in the RT group.

Reply 5: We sincerely thank the reviewer for the pertinent question. We have modified our text as advised.

Changes in the text: line 120: There were more T2 patients in the radiotherapy than surgery group.

Comment 6: I would recommend deleting line 137-138, since this is the results section, and it should be moved to the discussion section with additional discussion.

Reply 6: We sincerely thank the reviewer for the pertinent question. We have moved the sentence to the discussion section in the revised manuscript. When we used the word "seems", we tried to convey the meaning that the preliminary analysis seems to indicate a superiority of surgery compared with radiotherapy, thus paving the way for the reversal of results after PSM. We have discussed the logic of our analyses and this reversal of conclusion in the revised manuscript (line 213-221).

Changes in the text: line 213-221: Similar to previous reports (12,17), our analyses performed without PSM indicated that patients treated with surgery had better OS and CSS outcomes than did patients treated with radiotherapy. Furthermore, this survival trend favoring surgery was also evident in the T1a, male, well/moderately differentiated grade, and all age subgroups. **Surgery seems to improve the survival of patients with early glottic cancer better than radiotherapy based on our preliminary analyses.** However, after PSM, there was no significant difference in OS and CSS between the surgery and radiotherapy groups for patients with early glottic cancer. Further subgroup analyses stratified by T stage, sex, and pathological grade also revealed comparable survival

outcomes between the 2 treatment methods.

Comment 7: Line 164, the period (.) needs to be changed to a comma (,).

Reply 7: We sincerely thank the reviewer for the comments. We have modified our text in the revised manuscript.

Changes in the text: line 159-161: To explore whether the therapeutic effects of the 2 treatment modalities are consistent in patients with early glottic laryngeal cancer but with different clinical features, subgroup analyses were conducted.

Comment 8: For line 254-257: The radiation dose for early glottic cancer is not lower compared to other cancers. For early glottic cancer, the RT field is smaller than other H&N cancers: RT field for other H&N cancers or advanced laryngeal cancer include bilateral elective neck LNs whereas the RT field for early glottic cancer is confined to the laryngeal box. Also, due to the advance of RT technology, IMRT allows to reduce the dose to the carotid artery and other structures.

Reply 8: We sincerely thank the reviewer for the comments. We have modified our text in the revised manuscript.

Change in the text: line 246-251: Radiotherapy is relatively safe in early glottic carcinoma, and this may be related to the smaller field of radiotherapy. The radiotherapy field for other head and neck cancers or advanced laryngeal cancers includes the bilateral elective cervical lymph nodes (30,31), whereas the radiotherapy field of early glottic cancer is limited to the laryngeal box (32). Currently, more advanced intensity-modulated radiation therapy technology allows for a reduced dose to other important structures, such as the carotid artery (33).

Comment 9: Is there any OS or CSS differences for transoral laser microsurgery vs open surgery previously reported? Currently, it would be likely that transoral laser microsurgery is preferred due to its less invasiveness and it would have been best if RT and transoral laser microsurgery (+/- partial laryngectomy) were compared. Since all types of surgeries were included in this study from 2005 to 2015, it may have affected the results. Although it is simply written as a limitation, additional discussion could be helpful.

Reply 9: We sincerely thank the reviewer for the comments. We have modified our text in the revised manuscript.

Change in the text: line 261-266: Currently, TLM has largely replaced open surgery in early-stage laryngeal cancer due to its minimal invasiveness. Many studies have demonstrated similar OS and local control rates between the 2 methods for early laryngeal cancer (34,35). However, open surgery may be better for lesions with deep infiltration (34). In the present study, both open surgery and TLM were categorized as part of the single "surgery" group. It would have been more meaningful if the analysis had been performed comparing just TLM and

radiotherapy.