

Peer Review File

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Reviewer Comments

Background

Comment 1: In the sentence (Line 4/5): “According to whether the second primary cancer occurs at the same time, it can be divided into synchronous carcinoma (SC) and metachronous carcinoma (MC)” it is not clear what the definition of SC and MC is. SC is not only a second primary cancer that occurs at the same time. Please be more specific because this definition is very important in this study.

Reply 1: Synchronous cancers are defined as the occurrence of a second primitive cancer within the first six months following the detection of the first cancer, whereas metachronous cancers appear within more than six months

Changes in the text: We have modified our text as advised (see Page 3, line 4-7)

Materials and Methods

Comment 2: This section starts with a description of the results. Information such as male/female ratio and age belongs to the result section. Please move this information to the result section. Moreover, it would be more informative to provide this detailed information (e.g. 16 cases of 50-59 years old, 13 cases of 60-69 years old etc.) in a table rather than in the text. Is the age of the cohort normally distributed? If so, you are able to provide the average and standard deviation. If not, please provide the median and interquartile range.

Reply 2: We have moved this information to the result section. And we provided that in Table 1 and Table 2.

Changes in the text: We have modified our text as advised (see Results 1. Characteristics of patients included in the present study, Table 1 and Table 2),

Comment 3: Why are esophageal lesions only included when detected by white light upper gastrointestinal endoscopy? For the detection of esophageal second primary tumors, NBI and Lugol chromoendoscopy are very important tools and second primary tumors are easily overlooked with white light endoscopy (PMID: 33049006). I think the number of detected esophageal SPTs is underestimated when only white light endoscopy is used.

Reply 3: We have used NBI to detect esophageal lesions, we described that in methods, 3. Endoscopic examination and classification of esophageal cancer. Page 5, line 3.

Changes in the text: No changes.

Comment 4: Please remove the second exclusion criteria “Benign esophageal lesions, and esophageal cancer without the HNSCC history” because you repeat inclusion criteria 2 and 3 in this sentence.

Reply 4: We have removed the second exclusion criteria.

Changes in the text: We have modified our text as advised (see Page 4, line 10)

Comment 5: At part 2 “Endoscopic examination and classification of esophageal cancer” the authors describe that NBI is used during upper gastrointestinal endoscopy. This is confusing because esophageal second primary tumors were only included when detected with white light endoscopy according to the inclusion criteria. Please explain.

Reply 5: In the inclusion criteria, we wanted to express that “esophageal lesions were found by upper gastrointestinal endoscopy with NBI mode”.

Changes in the text: We have modified our text as advised (see Page 5, line 3)

Comment 6: Please explain the following sentence “Gastrointestinal endoscopy were carried out on initiation diagnosis of HNSCC, or postoperative follow-up”. Was the endoscopy only performed when patients had dysphagia or in every patient with HNSCC? And were there only two moments the endoscopy could be performed (initiation diagnosis of HSNCC or postoperative) and what was the time between HNSCC diagnosis and the postoperative follow-up endoscopy? Was this within 6 months or > 6 months after HNSCC diagnosis?

Reply 6: We retrospectively reviewed the medical records of 32 patients of esophageal cancer with HNSCC history, all esophageal cancers were diagnosed after undergoing upper gastrointestinal endoscopy because of progressive dysphagia or pain behind the sternum, no other endoscopy were performed.

Changes in the text: We have modified our text as advised (see Page 4, line 1-5)

Comment 7: Were patients only selected when they received surgery for HNSCC? Radiotherapy is a very common treatment strategy for patients with HNSCC.

Reply 7: All HNSCC patients underwent surgical treatment, some of them received postoperative radiotherapy, radiotherapy history is very important information for esophageal cancer patients with HNSCC. We have analyzed the radiotherapy history and there were no significant differences between the two groups.

Changes in the text: We have modified our text as advised (Page 4, line 23)

Comment 8: Statistical analysis: “comparison between two groups”, please explain which two groups were compared? Probably you mean the SC and MC group, but this is not clearly explained. Moreover, what are the endpoints of your study? Please provide this information in the method section. The authors do not clearly describe that they want to compare the SC and MC group.

Reply 8: This is a retrospective study, comparison between the SC and MC group were analyzed. The end point was 36 months after esophageal cancer diagnosis or death.

Changes in the text: We have modified our text as advised (Page 5, line 14)

Comment 9: How were survival analyses performed? Please provide this

information in the statistical analysis section.

Reply 9: Survival analyses of the SC and MC group was performed by GraphPad Prism 6, survival period was calculated from the time of esophageal cancer diagnosis, the end point was 36 months after esophageal cancer diagnosis or patient death.

Changes in the text: We have modified our text as advised (Page 5, line 16-18)

Results

Comment 10: Please provide a flow-chart of all patients with HNSCC in your center between 2007 and 2017 and how many patients were in- and excluded from this study.

Reply 10: In this retrospective study, between 2007 and 2017, we diagnosed 32 cases of esophageal cancer in 30 HNSCC patients, but we don't know the total number of HNSCC patients in our center between 2007 and 2017. We hope to carry out that in the next prospective study.

Changes in the text: No changes.

Comment 11: It would be interesting to show the cumulative incidence of esophageal SPTs with a cumulative incidence curve (including 95% confidence intervals).

Reply 11: Because the overall number of HNSCC cases was difficult to determine, we had not been able to find the specific incidence of esophageal cancer in HNSCC patients, however, in other previous studies, the incidence of occurrence esophageal cancer in HNSCC patients was about 5%-15%, which was significant higher than that in the general population. We hope to carry out that in the next prospective study.

Changes in the text: No changes.

Comment 12: First provide information of the total cohort and refer to Table 1, after this you can compare the two groups.

Reply 12: We don't think that is clearer than our Table, because we want to find the information how to detect esophageal SPTs in HNSCC, so we try to seek total characteristics of HNSCC, not only limited in the SC and MC group.

Changes in the text: No changes.

Comment 13: The information about HNSCC stages is not clearly described, it would be better to only provide this information in a table rather than in the text.

Reply 13: We provided HNSCC stages in Table 1.

Changes in the text: No changes.

Comment 14: As explained in the method section, all patients were treated by surgery. Why is only information provided about radiotherapy (yes or no) in Table 1 and not all treatment strategies?

Reply 14: All HNSCC patients were treated by surgery, and some of them received

postoperative radiotherapy, radiotherapy history is very important information for esophageal cancer patients with HNSCC. We have analyzed the radiotherapy history and there were no significant differences between the two groups.

Changes in the text: No changes.

Comment 15: The information about time interval between HNSCC and esophageal cancer is unclear. Please provide this information in a figure instead of summing up all the time intervals in one sentence (“In the 24 cases of the MC group, the interval time are 12, 12, 13, 15, 15, 17, 20, 24 etc.).

Reply 15: We showed that in Figure 1B

Changes in the text: No changes.

Comment 16: Please provide information about the Paris classification of endoscopic morphology of esophageal cancer.

Reply 16: Most of esophageal cancer diagnosed in this study were in developed stage. We described cases of early stage according to Paris classification.

Changes in the text: We have modified our text as advised (Page 7, line 17, 18, Table 2)

Comment 17: In the MC and SC groups together, there were 5 cases of early esophageal cancer. Why are these tumors not treated by endoscopic resection?

Reply 17: All the HNSCC patients underwent upper gastrointestinal endoscopy because of progressive dysphagia or pain behind the sternum, and the 5 cases of early esophageal cancers were not limited in SM1 evaluated by endoscopy, and were not suitable for EMR or ESD.

Changes in the text: No changes.

Comment 18: Survival analysis: is this the overall survival or disease specific survival? It would be more informative to show the disease specific survival instead of the overall survival. Figure 1 C suggest that no patient is alive after +/- 37 months. But there are patients in which a second primary tumor was detected after 180 months. Please explain.

Reply 18: This is disease specific survival of esophageal cancers, the survival time was calculated from the time of esophageal cancer diagnosis, the end point was 36 months after esophageal cancer diagnosis or patient’s death. 180 months was the longest time of interval time between HNSCC and esophageal cancer.

Changes in the text: No changes.

Discussion

Comment 19: Why was the overall number of HNSCC cases difficult to determine?

Reply 19: In this retrospective study, between 2007 and 2017, we diagnosed 32 cases of esophageal cancer in 30 HNSCC patients, but we don’t know the total number of HNSCC patients involved.

Changes in the text: No changes.

Comment 20: Based on this retrospective study with a very small sample size, the authors can not made the statement that male patients with HNSCC aged 50-69 years should be endoscopically screened for second primary tumors. The authors should be very careful with such statements about screening because this is not a screening study! Whether screening should be performed depends on several aspects such as patient survival, curative treatment of HNSCC, second primary tumor treatment etc. Please remove this sentence!!

Reply 20: Yes, we removed this sentence.

Changes in the text:We have modified our text as advised (Page 9, line 8)

Comment 21: “In terms of HNSCC characteristics to have esophageal recurrent cancers, previous studies had shown that esophageal cancers were not related to HNSCC location.[31]” This is not true, according to reference number 1 (Bugter et al. 2019 Head and Neck - doi: 10.1002/hed.25548), the prevalence of esophageal SPTs is related to HNSCC location (more SPTs are detected in patients with hypopharyngeal and oropharyngeal cancer).

Reply 21: There are inconsistencies about the relation.

Changes in the text:We have modified our text as advised (Page 9, line 9-12)

Comment 22: What are the strengths and limitations of this study? This information is not provided in the discussion section.

Reply 22: We added that at the end of discussion.

Changes in the text:We have modified our text as advised (Page 10, line 9-11)

Comment 23: Please downgrade the conclusions of this manuscript! You can not conclude, based on this retrospective study of only 32 patients, that regular gastroscopy should be performed to detect early metachronous esophageal cancers!! A prospective study is needed with NBI, Lugol chromoendoscopy and white light endoscopy. All patients with HNSCC should be screened and not only patients with dysphagia, because dysphagia is most often a symptom of high stage esophageal cancer. The authors can only provide information about the characteristics of patients with ESCC and HNSCC but are not able to make a statement about screening for esophageal second primary tumors. Moreover, because there is no data about patients with HNSCC who did not develop a second primary tumor in the esophagus the authors cannot conclude that male patients, aged 50-59, should be screened.

Reply 23: Yes, we downgraded the conclusions of this manuscript.

Changes in the text:We have modified our text as advised