Peer Review File

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Reviewer A

The manuscript "Surgical Outcomes of Oro-Intestinal Continuity Reconstruction after Total Esophagectomy in Patients with Cervicothoracic Malignancy: A Thoracic Surgeon's Perspective" represents an accurate descriptive case series of advanced radical Esophagectomy with laryngectomy and hypopharyngectomy. There are currently few updated articles addressing this very complex issue and I think the authors should be complemented both for their clinical achievement and the stringent article describing it. Of course sample size is small and this small case series does not represent any high grade evidence, but nevertheless it proves the feasibility of the described surgery. My only complaint is that the two first paragraphs of the Discussion is too wordy and largely redundant. Please reduce the general background information considerably in this part of the manuscript. Also, the previous literature specifically regarding this procedure and the alternative treatments need to be more thoroughly discussed.

Reply 1: Thank you for your good suggestion. We revised our text in accordance with your comments.

Change 1: In advanced HNSCCs and cervical esophageal cancers (CECs) that are generally considered unresectable (4,5), definitive chemoradiotherapy is currently favored as a treatment method (1,2,6) and shows 3-year overall survival rates of 29% to 66.5% (7). However, up to 60% of locoregional recurrence after definitive chemotherapy has been reported (7-11). From this perspective, total esophagectomy followed by oro-intestinal continuity reconstruction could be considered to achieve complete resection in selected patients with advanced HNSCCs and CECs. Although the surgery might lower the quality of life of the patients, it might be the only treatment option as a salvage therapy for patients who want the life-saving option following the failure of definitive regimens (1,2). However, owing to serious morbidity and mortality, surgical treatment for these patients is limited in the clinical field (1-3) and there are few reports on surgery in these patients. In this study, we evaluated the treatment outcomes of patients, who underwent oro-intestinal reconstruction surgery in our center, from a thoracic surgeon's perspective.

In this study, postoperative patient mortality within 30 days, 90 days, and 1 year was 7.1%, 28.6%, and 42.8% of, respectively. Operative complications occurred in half of the overall patients. The most common complication was prolonged ventilation over 24 hours. There were three cases of reoperation, two of conduit necrosis, and one of anastomosis leakage. Regarding oncological outcomes, the rate of complete resection was 71.4%, although most of the patients had stage III or IV cancer. Furthermore, 1-year and 2-year overall survival was 57.14% and 42.86%, respectively. These outcomes are comparable to those of previous studies (10, 11), although those results were obtained from patients with middle and lower esophageal cancer without pharyngolaryngectomy or with less aggressive tumor stage compared to our study.

In terms of treatment modality, the prognoses of patients who underwent surgical resection in this study were relatively inferior to those who received definitive chemoradiation therapy for CECs and advanced-stage HNSCC (12, 13). However, the patients in this study had more aggressive cancer, such as tracheal or esophageal invasion, compared with those in previous studies (12,13). In addition, some patients in this study underwent salvage operation due to cancer recurrence. Thus, we believe that reconstruction of oral-intestinal continuity after total esophageal resection is sufficiently beneficial if the tumor seems to be completely resectable and the patient can tolerate the surgery. (See page 12-13, Discussion section, paragraph 1-3)

Reviewer B

This retrospective study, from a high-volume center in Korea, aimed at clarifying clinical implication of total esophagectomy followed by oro-intestinal continuity reconstruction for advanced-stage head/neck or esophageal carcinoma. They thoroughly reviewed the clinicopathological characteristics and the perioperative profiles of 14 patients and suggested that this surgical procedure was feasible with acceptable rate of morbidity and mortality. Their clinical experiences are invaluable and this paper would hence serve as a prominent reference for thoracic surgeons. However, this investigation harbors some concerns reducing its significance.

Comment 1: Among the 14 subjects, postoperative mortality within 30 days, 90 days, and 1 year was 7.1%, 28.6%, and 42.8%, respectively. Is it acceptable? As the authors mentioned, these results were not equally comparable to those regarding definitive chemoradiation. Moreover, this markedly complicated surgical procedures could only be performed in highly experienced institutions. Therefore, application of their results is entirely limited. This weakness should be explicitly mentioned.

Reply 1: Thank you for your valuable comment. As we mentioned in the discussion section, patients in our study had more aggressive cancer, such as tracheal or esophageal invasion, whose prognosis is extremely poor even in patients with definitive CRTx (1-3). In addition, this study included some patients who had cancer recurrence after definitive CRTx and had no choice but surgical resection. The main message of this study is not to recommend surgical resection as a first choice for patients with advanced HNSCCs and cervical esophageal cancers, but to present surgical results as an alternative treatment in selected patients. Thus, we think it is possible to conclude that our results showed acceptable prognosis and care selection of surgical candidates are mandatory to minimize the surgical risk.

(1) Conti M, Benhamed L, Mortuaire G, et al. Indications and results of anterior mediastinal tracheostomy for malignancies. Ann Thorac Surg 2010;89:1588-95.
(2) Al-Mamgani A, Navran A, Walraven I, et al. Organ-preservation (chemo)radiotherapy for T4 laryngeal and hypopharyngeal cancer: is the effort worth? Eur Arch Otorhinolaryngol. 2019;276(2):575-83.
(3) Makino T, Doki Y. Treatment of T4 esophageal cancer. Definitive chemo-radiotherapy vs chemo-radiotherapy followed by surgery. Ann Thorac Cardiovasc Surg.

2011;17(3):221-8.
In addition, we acknowledge these results are obtained from multidisplinary team with highly experienced surgeons. According to your comment, we added these points in the Limitation section.
Change 1: The current study has some limitations. Selection bias is inherent in a retrospective study from a single institution. Analyzing the long-term outcomes was not feasible due to the small number of patients and the relatively short follow-up period. Our results cannot be generalized to other settings as the study was performed at a tertiary, high-volume, and experienced center. A cumulative analysis of these surgical cases and a multicenter study are warranted to further evaluate the actual survival outcomes and prognosis. (See page 14, line 368-371)

Comment 2: The authors concluded "careful selection of surgical candidates and multidisciplinary collaboration of experienced specialists are essential." The readers would be interested in how we can select such candidates. This point should be discussed in further depth.
Reply 2: We focused on the point whether patient could tolerate the surgery. Age, ECOG performance score, and pulmonary function test were used to determine the tolerance for this extensive surgery. Resectability of the tumor was assessed by multidisplinary team including thoracic and neck surgeon with full experience.
Change 2: The surgical indication of patients with cervicothoracic malignancy and esophageal invasion was not definite, but patients of advanced age (>75 years), or in poor physical condition (Eastern Cooperative Oncology Group performance ≥ 2), with decreased pulmonary function test (FEV1 % < 60% of predicted), were generally contraindicated. (See page 6, line 109-110)

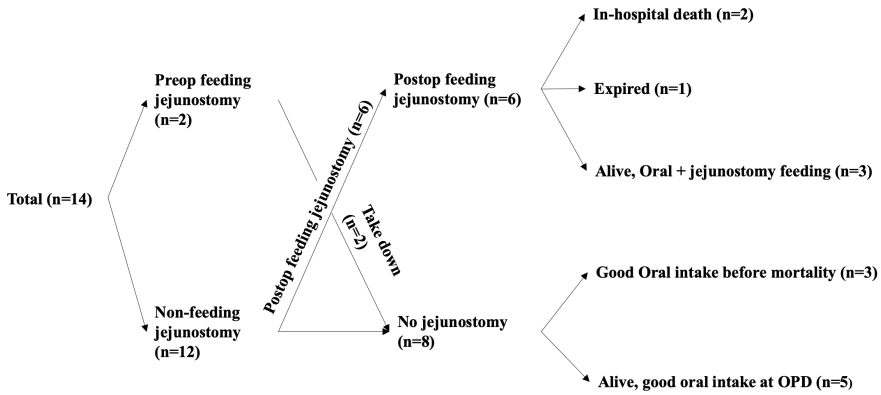
Comment 3: English is somewhat poor, thus needs editing.
Reply 3: Thank you for pointing this out. To improve the quality of the manuscript, we additionally performed English editing.

Reviewer C
Major comment:
The manuscript is well written, and the results are clearly presented. My only concern is that 14 cases may not be enough if you state the prognosis. Since this study included cases of advanced cancer, it would be a worthwhile case series if this point is emphasized in abstract.
Reply: Thank you for your critical comment. We revised the abstract according to your comment.
Change:
Background: Oro-intestinal continuity reconstruction following total esophagectomy in patients with head-neck or esophageal cancer is rare and results in high operative morbidity and mortality. This case series aimed to investigate the perioperative surgical outcomes of oro-intestinal continuity reconstruction after total esophagectomy in

selected patients with advanced head/neck or esophageal cancer.
Methods: From 2011 to 2018, 14 patients who underwent oro-intestinal reconstruction after total esophagectomy were assessed. We analyzed perioperative mortality, postoperative complications, oncologic outcomes, and recovery of dietary function.
Results: The median age of the patients was 61 years old (range: 42–72) and median follow-up time was 18.6 months (range: 0–52.9). For conduit selection, 11 cases of oro-gastrostomy (78.6%), 2 of oro-colo-gastrostomy (14.3%), and 1 of oro-jejuno-gastrostomy (7.1%) were performed. Complete resection was pathologically confirmed in 10 patients (71.4%). Anastomosis site leakage was observed in three patients (21.4%) and conduit necrosis in two (14.3%). Postoperative mortality within 30 days, 90 days, and 1 year was 7.1%, 28.6%, and 42.8%, respectively.
Conclusion: Oro-intestinal continuity reconstruction following total esophagectomy showed acceptable morbidity and mortality in selected patients with advanced head/neck cancer or esophageal cancer. Careful selection of surgical candidates and multidisciplinary collaboration of experienced surgical teams are essential to minimize the surgical risk.
(See page3, line 38-40 and 54-56)

Minor comment 1:
Title and Abstract
Overall, the data are clearly presented. However, it is questionable whether Oro-intestinal continuity reconstruction following total esophagectomy is a rare or not.
Reply 1: Thank you for pointing this out. As we described in the text, previous studies have reported high rates of morbidity and mortality following this surgery. However, those studies included small number of patients due to the rarity of the disease itself and the preference of definitive CRTx. In addition, recent study describing detailed surgical methods from the perspective of thoracic surgeon and reporting the surgical outcomes are particularly rare.Thus, we think it is enough to comment that “few studies have analyzed the feasibility and safety of this surgery and number of patients enrolled in these studies was relatively small.”

Minor comment 2:
Where is the “Recovery of dietary function” listed?
Reply 2: We simply presented the diagram showing changes of dietary function before and after the surgery as figure 4.



Minor comment 3:
Table and Figure
Table1: Does the FEV1(%) exceed 100%?
Reply 3: We used the value of FEV1(%) of predicted. We changed the term as 'FEV1(%) of predicted' in Table 1.
Change 3:

Variable	Value
Age (year)	61 (range; 42-72)
Sex (male)	10 (71.4)
BMI, kg/m^2	21.3 (range; 14.0-29.0)
Smoking history	10 (71.4)
Charlson comorbidity index	
≤3	3 (21.4)
4-6	4 (28.6)
≥7	7 (50)
ECOG Performance status	
0	2 (14.3)
1	10 (71.4)
2	2 (14.3)
Pulmonary function	
FEV1 (%) of predicted	72.5 (range; 45-120)
Primary Cancer	10 (71.4)
Esophageal cancer	5 (35.7)
Head and neck cancer	3 (21.4)
Double primary cancer	2 (14.3)
Salvage Operation	4 (28.6)
Esophageal cancer	1 (7.1)
Head and neck cancer	2 (14.3)
Double primary cancer	1 (7.1)

(See Table 1)

Reviewer D
It is a very well written paper on one of the most difficult patient populations – patients with cervicothoracic malignancies, requiring cervicomediastinal exenteration. The paper focuses on the technique of oro- intestinal continuity reconstruction and its types – gastric and colonic pedicled flaps and jejunal free flap. The group of patients in the analysis is small – only 14, further subdivided into groups by the type of reconstruction. However, it is important to acknowledge unique and challenging nature of these patient and it is probably one of the largest series in the world nevertheless.

The paper is well written. Surgical technique is described with clarity for esophageal surgeon to understand the thought process and fine surgical details. Choice of the conduit and the route likewise are well elucidated. Outcomes are described honestly

and with humility to the postoperative complications.

Discussed section is likewise written with logical flow of the though process in the management of this desperate group of patients.
The criticism of the paper is a limited study material, retrospective nature fo the study and single center experience. However, it is unlikely that randomized trial can be performed in this group of patient due to unique nature of the advanced malignancy, few surgeons would be brave enough to tackle. Only true masters can take on this challenge.
Additionally, the only one intraoperative image is insufficient to adequately represent the nature of the procedure performed. We would like to request more images, focusing specifically on the cervical anatomy and lay out of the oro-intestinal anastomosis.

Reply: Thank you for your valuable comment. We added the figure of the surgical field performing cervical anastomosis at reconstruction phase as Figure 1 and 2.

Change:

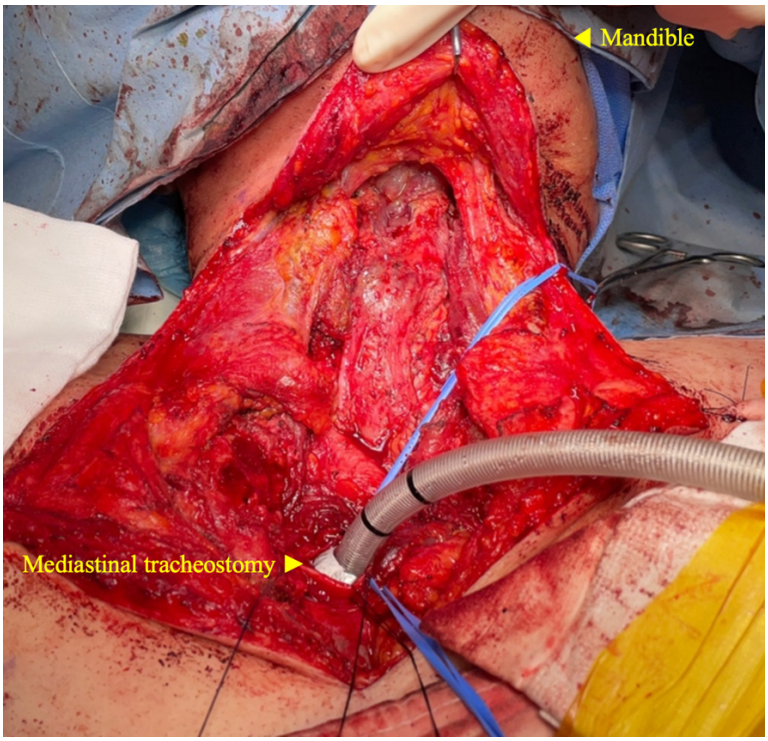


Fig. 1. Operative field finding showing the status post total pharyngolaryngectomy before the reconstruction phase. Mediastinal tracheostomy was performed. The image was approved by the Asan Medical Center Ethics Committee/Review Board, which waived the need for informed consent.

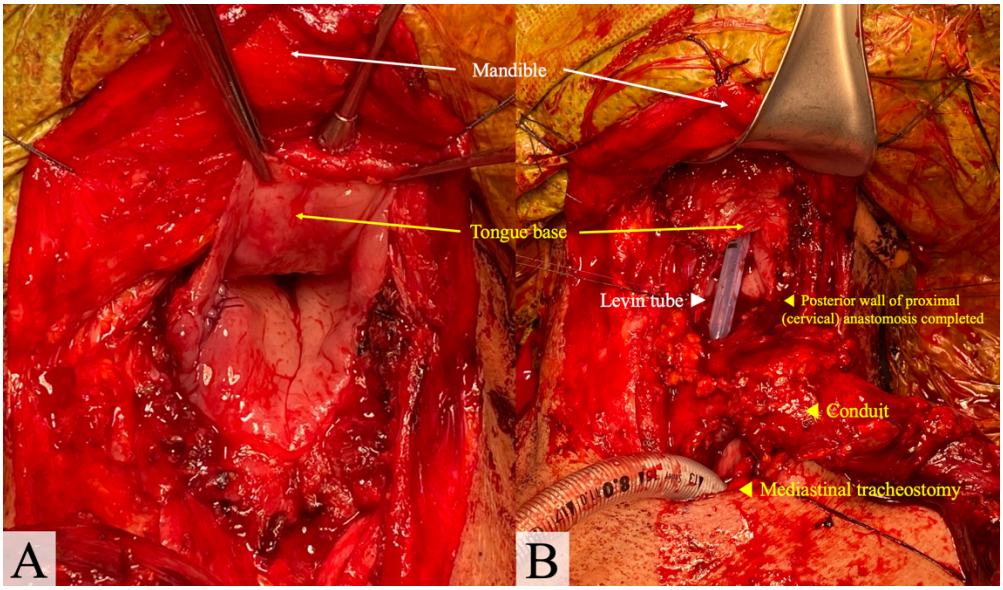


Fig. 2. Operative field finding showing the reconstruction phase of oro-intestinal continuity reconstruction. A) Tongue base was lifted up to identify the location of cervical (proximal) anastomosis site carefully. B) Posterior side of the cervical (proximal) anastomosis was completed. During the anastomosis, Levin tube was inserted to check the continuity. The image was approved by the Asan Medical Center Ethics Committee/Review Board which waived the need for informed consent
(See Figure 1, 2 and Page 18, figure Legends section).