

RE: Revision of **22584**

Column: Original article

Retrospective Study

Title: Updated experiences of minimally invasive McKeown esophagectomy for esophageal cancer

Dear Editor-in-chief

Thank you very much for providing us with an opportunity to improve our manuscript. We have carefully read all the comments made by the reviewers and revised the manuscript according to their suggestions. We believe that we have responded to all the comments and now the manuscript has been satisfactorily improved. I would appreciate your proceeding with the publication.

Sincerely yours,

Jie He

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Reply to reviewer 1

1. Could the authors outline a little more clearly the selection criteria for patients to either MIE, Hybrid or open procedure

Reply: *The selection criteria for patients to either total MIE, hybrid MIE or open esophagectomy were mainly on the clinical staging and the experiences of surgeons. Patients with early staged esophageal cancer received more minimal invasive esophagectomies than open esophagectomies, and surgeons who received training in minimal invasive thoracic surgery performed more minimal invasive esophagectomies than open esophagectomies. Patients received more hybrid minimal invasive*

esophagectomies than total minimal invasive esophagectomies in the early period of this study, and patients.

We added the above information to the manuscript in line 4 Page 8.

2. Could the the authors outline more clearly the criteria used for giving neoadjuvant therapy and discuss whether the neoadjuvant therapy may have influenced outcomes

Reply: *Randomized, controlled trial of neoadjuvant treatment has shown a survival benefit in local advanced esophageal carcinoma as compared with esophagectomy alone in 2012 . And since then, we adopted neoadjuvant treatment as an alternative for local advanced esophageal carcinoma.*

The results of a large randomized, controlled trial of neoadjuvant treatment demonstratd a survival benefit in local advanced esophageal carcinoma as compared with esophagectomy alone, with a five-year survival of 47% in neoadjuvant treatment compared with 34% in the surgery group. And since then, some surgeons in our hospital adopted neoadjuvant treatment as an alternative for local advanced esophageal carcinoma to surgery alone. The rate of neoadjuvant treatment for local advanced esophageal carcinoma was only 20% in our hospital. Low fraction of patients with esophagecl squamous cell carcinoma in the study of van Hagen et al (around 20%) may preclude the application of neoadjuvant treatment in our hospital. Several meta analyses demonstrated consistent results of survival advantage of neoadjuvant treatment plus surgery over surgery alone for resectable esophageal adenocarcinoma. However, there were limited data regarding the survival advantage of neoadjuvant treatment plus surgery over surgery alone for resectable esophageal squamous cell carcinoma. More studies of neoadjuvant treatment on esophagecl squamous cell carcinoma are needed to define the role of neoadjuvant treatment in local advanced esophageal squamous cell carcinoma.

We added the above information to the manuscript in line 17 page 7 and line 23 Page 15 respectively.

3. Could the authors discuss more clearly any reason why respiratory and lung

complications were equal between the two groups as most studies have indicated an advantage for MIE

Reply: *We did not observe any reduction of incidence of morbidity or mortality in MIE group compared with open esophagectomy group. However, there was a trend in our study that the rate of pulmonary complication decreased in total minimal invasive group and hybrid minimal invasive group compared with open group, with the pulmonary complications rate of 2.9%, 2.9% and 5.8% respectively. Relatively small number of samples in our study may account for the reason.*

We added the above information to the manuscript in line 14page 15.

4. Apart from periop morbidity and long term survival were any other measures of quality of life used to determine difference between the procedures.

Reply: *Apart from perioperative morbidity and long term survival, other measures including quality of life questionnaires such as European Organization for Research on Treatment of Cancer quality of life questionnaire-C30 (EORTC QLQ-C30) and QLQ-0ES18 and cost analysis were used to assess the difference between minimal invasive and open esophagectomy.*

We added the above information to the manuscript in line 8 page 17.

5. In general, this study suggests no advantage of MIE over traditional open procedures, merely that it is comparable. As such, there should be discussion of the utility of this procedure in terms of cost or other advantages or disadvantages between the 2 procedures, and also illustrates why longer term QOL data may be very important. These issues should be discussed

Reply: *Apart from perioperative morbidity and long term survival, other measures including quality of life questionnaires such as European Organization for Research on Treatment of Cancer quality of life questionnaire-C30 (EORTC QLQ-C30) and QLQ-0ES18 and cost analysis were used to assess the difference between minimal invasive and open esophagectomy. More importantly, quality of life (QOL) measures could be a tool to provide clinical information from patients' perspective suggesting*

cancer recurrence^[21]. Indeed, an ongoing multicenter prospective study organized and led by our hospital are being performed which aimed to compare the effects between minimal invasive McKeown esophagectomy and open McKeown esophagectomy in China. The measures included perioperative morbidity, mortality and long term survival. Also, quality of life questionnaires (EORTC QLQ-C30 and QLQ-0ES18) are included in this ongoing study. Owing to the retrospective nature of this study, we did not included the quality of life questionnaires in the analysis. Reduced cost of minimal invasive esophagectomy compared with open esophagectomy has been demonstrated in our early study. Therefore, minimal invasive esophagectomy had the advantages of decreased intraoperative blood and reduced cost compared with open esophagectomy, with comparable perioperative morbidity and mortality, and long term survival. Although minimal invasive esophagectomy is technically changing, it is a valuable procedure for the surgical treatment of esophageal cancer patients in specialized center.

We added the above information to the manuscript in line 8 Page 17.

6. Minor grammar polishing needed, particularly in the introduction

Reply: We had invite native speaker to review the paper again.

Reply to reviewer 2

S1: I am not sure what this sentence means.

Answer: We corrected the sentence in line 10 Page 6.

S2: These are not good objectives of a scientific publication. You would be better to focus on oncological and clinical safety in terms of lymph node yield, survival, blood loss operating time and post operative mortality and morbidity. You can also focus on “feasibility” by focusing on conversion rate for either the thoracic phase, abdominal phase or both in the hybrid procedures.

Answer: We correct the objective as the reviewer pointed out in line 20 Page 6.

S 3: In clinical manuscripts, it is better to refer to this as Patients and Methods.

Answer: We correct the materials to patients in line 1 page 7.

S 4: Unless these patients were randomized into the larger study, then it is inappropriate to use them as controls because they were selected for open surgery. My advice would be to leave this group altogether. This also applies to the hybrid procedures. I realize that you want to show all your cases. However, unless you list your selection criteria, then it is difficult to conclude that the patients who had the procedures were equivalent in all other characteristics (as a group) other than the method of surgery.

Answer: Our study was a controlled study, so we included all patients who underwent McKeown esophagectomy. We correct the above information in line 7 Page 7.

S 5: You need to separate this group from the totally minimal invasive surgery group.

Answer: We separated total group and hybrid and compared clinical and perioperative data in Table 3 and Table 4.

S 6: I don't think you mean this. What exactly do you mean?

Answer: It is the first step to isolate the vessels of the stomach.

S 7: What is the difference between the harmonic scalpel and the ultrasonic coagulating shears. They are both ultrasonic. If they come from different manufacturers then you need to specify the manufacturers for both pieces of equipment.

Answer: We used the same equipment. We correct the information in line 19 Page 9.

S 8: There is a typographical error here: either it was created or not created.

Answer: we do not creat feeding jejunostomy. We correct the information in line 4

Page 10.

S 9: What does this mean? If you mean time line according to the learning curve, you need to explain this more thoroughly.

Answer: We added the exact time of 180 patients who received MIE for the study of learning curve in line 1 Page 12.

S 10: Not clear

Answer: We correct it as Fisher exact test in line 11 Page 12.

S11: These figures are summarized in a table labeled “patients characteristics”. Please refer to the table and condense this paragraph.

Answer: we condensed this paragraph to Table 1.

S 12: These figures could also be summarized in a table: reasons for conversion.

Answer: We summarized these figures in Table 2.

S 13: You will need to specify why patients were treated by one method or another. Is it because of surgeon’s preference or patients preference or other selection criteria.

Answer: The selection of which approach was based on the opinion of surgeon. We added the above information to the manuscript in line 8 Page 13.

S 14: Are these parts of your selection criteria? If this is the case, is there an age cut off that you have used or is it just in the opinion of the operating surgeon? This information is very useful for surgeons and patients in the future who look at your study.

Answer: These contents are the descriptive of the results of comparison of three approaches.

S 15: This is such a crude way to measure the learning curve. You would be better to plot the operating time for each procedure and then statistically determine the point

when the operating time plateaus. You will then need to do a similar plot for each surgeon and see whether a particular surgeon influences the group in either direction during each of the three phases.

Answer: First, we focus on minimal invasive McKeown esophagectomy and we found that about 12 cases are needed to reach the plateau of operation. Second, we analyzed the mean duration of operation of each surgeon, and displayed the result in Figure 2.

S 15: “are similar to” but not corroborate.

Answer: we correct it to “are similar to” in line 20 Page 16.

S 16: This point is not proven.

Answer: we delete this sentence.

We have highlighted all of those revisions in the updated version of the manuscript.

Thank you.