

Peer review file

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Reviewer A

Comment 1: “by this technique, an anastomosis region is already defined in advance and cannot be adjusted during surgery, should the frozen section not reach tumor-free resection margins.... At the same time, the interposition can also become too long with functional disturbances.”

Reply 1: Thanks for your valuable comment. Transecting the gastric tube at the sternal angle could usually satisfy the anastomosis at the top of thoracic cavity. For some patients who cannot ensure tumor-free resection even creating the anastomosis at the top of thoracic cavity, we would place a titanium clip to mark the upper edge of the tumor through the preoperative gastroscopy, and then review the chest radiograph. According to the position of the upper edge of the tumor marked by the titanium clip on the chest radiograph, we would determine whether the anastomosis at the top of thoracic cavity could reach tumor-free resection margins. If not, we would perform Meckown esophagectomy with cervical esophago-gastric anastomosis(EGA). What’s more, we would tailor the proximal esophageal stump and send removed esophageal tissue as the upper resection margin for intraoperative frozen inspection to further confirm the resection margin was tumor-free before anastomosis. As for the problem of too long interposition time, we continued to optimize the surgical procedure and accumulate experience, and the current interposition time had been greatly reduced, which was basically close to the traditional Ivor Lewis esophagectomy.

Changes in the text: we have modified our text (see Page 4, line 85-86; Page 7, line 145-147).

Comment 2: “Due to the actual side-to-side anastomosis with 2 additional staple lines of the stapled ends, there is a risk of ischemia. IN the report is described from a distance of 1,5-2cm. This appears unrealistic in the figures and carries the risk of an ischemic zone. This will not be discussed further.”

Reply 2: Thanks for your valuable comment. This was an error of our expression. Actually, what we want to express was making the gastrostomy 1.5cm -2cm from the poorly vascularized gastric fundus. In addition, we would tailor the esophagus stump and the gastrostomy separately before the anastomosis. While tailoring, we would detect the color and state of the mucosa. In our previous cases, all the mucosa were in good condition and there was no manifestations of ischemic necrosis.

Changes in the text: we have modified our text (see Page 5, line 110).

Comment 3: “Hand sutures generally have a high risk for strictures - this information is completely missing in the follow up.”

Reply 3: Thanks for your kind comment. In our series, there were 2 cases developed postoperative anastomotic stricture, which had been listed in Table 2. By placing the duodenal feeding tube and one endoscopic balloon dilatation, the patients gradually returned to normal diet. Our center once reported 1024 consecutive patients completed by this layered anastomosis method in open surgery⁽¹⁾, and the incidence of anastomotic stricture was only 0.6%. In our opinion, the good blood supply and the layer to layer anastomosis (esophageal mucosal layer to gastric mucosal layer, esophageal muscular layer to the gastric seromuscular layer) reduced the scar formation at the anastomotic region; the use of 4/0 Vicryl plus antibacterial suture to close the mucosal layer reduced inflammatory reaction at the anastomotic region, which were both conducive to reducing the occurrence of anastomotic stricture.

Changes in the text: we added the data and have modified our text (see Page 10, line200-202 and Page12 , line 247-249).

Comment 4: “Authors report a leakage rate of 0%. How is the occurrence of leakage defined? How was this controlled. Considering the known problems with this type of surgery, these data seem unacceptable - especially in view of the fact that this work represents the implementation phase.”

Reply 4: Thanks for your valuable comment. In this article, anastomotic leakage was defined according to the Esophagectomy Complications Consensus Group: “Full

thickness GI defect involving esophagus, anastomosis, staple line, or conduit irrespective of presentation or method of identification”.⁽²⁾

In fact, this new anastomosis technique was developed on the basis of our previous extensive experience of three-leaf clipper-assisted hand-sewn layered anastomosis. Our center once reported that there were no anastomotic leakage in 1024 consecutive patients completed by this layered anastomosis method in open surgery⁽¹⁾. Now we used the da Vinci surgical system to complete this layered anastomosis in minimally invasive esophagectomy.

Changes in the text: we added the definition of anastomotic fistula (see Page 9, line 177-178).

Comment 5: “In the discussion, many reports are mentioned that describe exactly this technique of hand-sewn anastomosis. The only difference is that no mucosa suture was used. This is not correct, because a two-row anastomosis is also created in other described technique.”

Reply 5: Thanks for your valuable comment. This was an error of our expression.

Changes in the text: we have modified our text (see Page 11, line 231).

Reference

1. Zhu ZJ, Zhao YF, Chen LQ, et al: Clinical application of layered anastomosis during esophagogastrostomy. World journal of surgery 2008, 32(4):583-588.
2. ölscher AH, Hofstetter WL, Jobe BA et al: International Consensus on Standardization of Data Collection for Complications Associated With Esophagectomy: Esophagectomy Complications Consensus Group (ECCG). Annals of surgery 2015, 262(2):286-294.

Reviewer B

Comment 1: “The word “pretreatment-facilitated” is ambiguous and hard to understand. Actually, the tips of their “preparation for anastomosis” are adjustment of the length of the conduit before pull-up, gauze wrapping of conduit to prevent manipulation trauma and the use of non-damage clamp for hemostasis during anastomosis. The title needs to be reconsidered and the description needs to be

altered.”

Reply 1: Thanks for your valuable comment. It was difficult to complete some surgical steps directly using the robot under existing conditions. We adopted a series of measures (including adjustment of the length of the conduit before pull-up, gauze wrapping of conduit to prevent manipulation trauma, the use of non-damage clamp and saline irrigation, etc.) to overcome potential interference factors that may affected the anastomosis process, making the anastomosis could be completed in the shortest time and realizing the effective combination of robot and human hands. We call this series of measures ‘pretreatment’. Now we have changed "pretreatment-facilitated" to "pretreatment-assisted" and hope to express our meaning clearly. Thank you again for your suggestions.

Changes in the text: we have modified the title and the text.

Comment 2: “I assume the rate of anastomotic stricture may be relatively high using this method. What is the rate of the balloon dilation? Usually the side to side esophagogastrostomy using the linear stapler has less anastomotic stenosis than the end to side esophagogastrostomy.”

Reply 2: Thanks for your kind comment. In our series, there are 2 cases developed postoperative anastomotic stricture, one patient had severe dysphagia. We firstly inserted a duodenal nutrition tube and performed one endoscopic balloon dilatation. The patient gradually returned to normal. Another patient had mild symptoms and we did not insert a duodenal feeding tube, the patient returned to normal after one endoscopic balloon dilation. Our center once reported 1024 consecutive patients completed by this layered anastomosis method in open surgery⁽¹⁾, and the incidence of anastomotic stricture was only 0.6%. In our opinion, the good blood supply and the layer to layer anastomosis (esophageal mucosal layer to gastric mucosal layer, esophageal muscular layer to the gastric seromuscular layer) reduced the scar formation at the anastomotic region; the use of 4/0 Vicryl plus antibacterial suture to close the mucosal layer reduced inflammatory reaction at the anastomotic region, which were both conducive to reducing the occurrence of anastomotic stricture.

Changes in the text: (see Page 10, line200-202 and Page12, line 247-249).

Comment 3: “7-0 silk sounds too thin to tie the gauze. Is it correct? The thread in fig1c seems thicker.”

Reply 3: Thanks for your kind comment. This was an error of our expression. Actually, what we use was “0” silk thread (we usually called it 7# silk thread).

Changes in the text: we have modified our text (see Page 6, line 115).

Reviewer C

Comment 1: “In line 53 - circular stapler with diameter greater than 25mm are associated with lower stricture rates postoperatively, and lower leak rates than hand sewn EGA. In line 57 - Re linear stapler EGA: I have never heard of ischemia of the proximal esophageal stump due to mobilisation. The submucosa blood supply is usually very good. In line 275: do you mean linear stapled anastomosis?”

Reply 1: Thanks for your valuable comment. In our previous studies, we found that the circular-stapler anastomosis had a higher incidence of anastomotic stricture and anastomotic leakage compared with hand-sewn layered anastomosis^(1,2). Studies from other medical centers also had reached the same conclusion^(3,4). Therefore, hand-sewn layered anastomosis had become the mainstream in our center and satisfactory postoperative results had been achieved. In another study investigating the association between circular stapler size and the incidence of anastomotic stricture, the incidence of anastomotic stricture was still as high as 23% using a 28mm or 29mm circular stapler⁽⁵⁾. Of course, each surgeon choosed the most suitable anastomosis method according to his own habits and experience was also the key to reducing anastomotic complications. We still had a lot to learn and improve on the circular-stapler anastomosis.

We agree with your valuable comment on line 57, we have corrected it in the manuscript.

Regarding in line 275, we meant not only linear-stapled anastomosis, but also circular-stapler anastomosis. Due to the limitation of the intercostal space, inserting the anvil into the esophagus at the top of the thoracic cavity was very complicated under thoracoscopy.

Changes in the text: we have modified our text (see Page 4, line 67-69; Page 14, line 289).

Comment 2: “Why is the gastric conduit transected at the sternal angle? You could easily open the staple line at the tip of the gastric conduit to inspect the ischemic purple mucosa before transecting the ischemic tip.”

Reply 2: Thanks for your kind comment. In our operation, the sternal angle was selected as the marker for tailoring the gastric conduit outside the body, mainly to ensure the precise tailoring to meet the length of the gastric conduit required for intrathoracic anastomosis. In addition, this tailoring method removed the poorly vascularized gastric fundus, getting a highly vascularized gastric conduit.

Changes in the text: we have modified our text (see Page 5, line 106-108).

Comment 3: “Why do you use a vicryl suture for the anastomosis? Why didn’t you use the same type of suture? What was the reason for changing?”

Reply 3: Thanks for your kind comment. When we suture the mucosal layer, we chose the 4/0 Vicryl plus antibacterial suture (J&J Co. U.S.A.), which was mainly based on this kind of suture might inhibit bacterial growth and consequently prevent postoperative infection and further reduce the occurrence of postoperative anastomotic stricture⁽⁶⁾.

Changes in the text: we have modified our text (see Page 12, line 244-245).

Comment 4: “I cannot appreciate how the use of a gauze to cover the gastric conduit can prevent conduit necrosis; it can only prevent trauma to the gastric conduit wall. Ischaemic necrosis of the conduit can happen due to other factors like perfusion.”

Reply 4: Thanks for your kind comment. I totally agree with your opinion that the blood perfusion is the key of conduit necrosis, and also is the basis for anastomotic healing. The use of gauze to wrap the gastric conduit was mainly due to the lack of sensitive tactile feedback during robotic surgery. During the operation, we could pull the gastric conduit into the thoracic cavity by pulling the gauze, avoiding the potential damage caused by the robot surgical instrument directly pulling the gastric conduit and even the gastroepiploic arterial arcade.

Changes in the text: we have modified our text (see Page 13, line 269-274).

Comment 5: “I cannot understand the use of atraumatic clamps, especially on the proximal oesophagus. Can you explain please? It looks like you have to do more mobilisation of the proximal oesophagus?”

Reply 5: Thanks for your kind comment. The main reason for using the atraumatic clamps was that the blood supply of the submucosa was sufficient. After we tailored the mucosa with cold scissors, the bleeding of small blood vessels in the submucosa was often serious, which would interfere with the precise layer to layer anastomosis. As for the need to do more mobilisation of the proximal oesophagus, we routinely perform upper mediastinal lymph node dissection before anastomosis. After completing the upper mediastinal lymph node dissection, placing the atraumatic clamp at the proximal esophagus was always unobstructed.

Changes in the text: we have modified our text (see Page 6, line 128-130).

Comment 6: “Do you use an mental flap at the end to cover the EGA”

Reply 6: In our operation, there was no any form of mental flap to cover anastomosis.

Comment 7: “Do you insert a nasogastric tube to decompress the conduit at the end? ”

Reply 7: In our operation, we routinely didn’t place nasogastric tube and duodenal feeding tube, there was only one thoracic drainage tube placed in the posterior mediastinum at the end of the operation.

Changes in the text: we have modified our text (see Page 8, line 161-162).

Comment 8: “Is there a pyloroplasty to help with emptying?”

Reply 8: In our operation, we didn’t routinely perform pyloroplasty.

Comment 9: “Some Spelling Errors to consider please:

“mucous” should be changed to “mucosa”

“non damage” clamp should be “atraumatic” clamp

Table 5 should be Italy.”

Reply 9: Thanks for your kind comment. We have corrected these errors in the manuscript.

Changes in the text: we have modified our text (see Page 7, line 147; Page 8, line 158 and so on).

Comment 10: “Have you consider an RCT between stapled and hand sewn anastomosis in robotic MIE?”

Reply 10: Yes, we believe further multi-center RCT studies will get more convincing conclusions when comparing stapled and hand sewn anastomosis in robotic MIE.

References

1. Luo J, Zhuo ZG, Zhu YK, et al: Fixed in the neck or pushed back into the thorax?-Impact of cervical anastomosis position on anastomosis healing. Journal of

thoracic disease 2020, 12(5):2153-2160.

2. Zhu ZJ, Zhao YF, Chen LQ, et al: Clinical application of layered anastomosis during esophagostomy. World journal of surgery 2008, 32(4):583-588.
3. Honda M, Kuriyama A, Noma H et al: Hand-sewn versus mechanical esophagogastric anastomosis after esophagectomy: a systematic review and meta-analysis. Ann Surg 2013, 257:238-248.
4. Kim RH, Takabe K: Methods of esophagogastric anastomoses following esophagectomy for cancer: A systematic review. Journal of surgical oncology 2010, 101(6):527-533.
5. Hosoi T, Abe T, Uemura N, Higaki E, Kawai R, Kawakami J, An B, Nagino M, Shimizu Y: The Impact of Circular Stapler Size on the Incidence of Cervical Anastomotic Stricture After Esophagectomy. World journal of surgery 2019, 43(7):1746-1755
6. Suárez Grau JM, De Toro Crespo M, Docobo Durántez F, et al: [Prevention of surgical infection using reabsorbable antibacterial suture (Vicryl Plus) versus reabsorbable conventional suture in hernioplasty. An experimental study in animals]. Cirugia española 2007, 81(6):324-329.

Reviewer D

Comment 1: “Before anastomosis, they created hole of muscular layer of the anterior side of the gastric tube. The authors should show how to make it. Did they Just cut the muscular layer linearly? Or did they actually make hole of the muscular layer?”

Reply 1: Thanks for your kind comment. During abdominal phase, we first cut the muscular layer of the gastric tube linearly and sew a marking thread on the muscular layer to be removed. After the gastric conduit was pulled into the thoracic cavity and ready for anastomosis, we cut open the mucosa below the muscularis, and finally removed the mucosa and the seromuscular together.

Changes in the text: we have modified our text (see Page 6, line 113-114).

Comment 2: “If a patient has the esophagogastric junctional cancer, do the authors create the gastric tube under the laparoscopic procedure like this article? Is there any possibility that the distal margin would be very close?”

Reply 2: Thanks for your valuable comment. For esophagogastric junction cancer, we would divide the stomach at the lower edge of the tumor. When making the gastric conduit, we would sacrifice a certain length to ensure that the margin is negative. At the same time, the level of intrathoracic anastomosis would be lower.

Comment 3: “In the text, they described that “Incise the esophageal muscular layer at a level 1.0cm proximal to its margin” on page 5, line 128. How about the mucosal layer of the esophagus?”

Reply 3: After completing the posterior wall muscle layer suture, we would tailor the proximal esophageal mucosa and remove excess esophageal mucosal and muscular tissue together.

Changes in the text: we have modified our text (see Page 7, line 145-147).

Reviewer E

Comment 1: “extensive English editing of title, abstract and main text is necessary.”

Reply 1: Thanks for your valuable comment. We have edited this manuscript with the help of Mr. Shi-De Wu from the High School Attached to Northeast Normal University.

Changes in the text: we have modified our text.

Comment 2: “the authors have divided in the series in two groups. They found the that the late group was associated with better intraop outcomes. Since the number of patients is limited, I suggest not to perform such comparison.”

Reply 2: Thanks for your kind comment. We were constantly improving and optimizing the surgical procedure. Although the total number of cases in this study was small, compared to the first year, we had made significant improvements in terms of operation time and other aspects. Moreover, as far as we know, the number of cases included in this study was the largest among the articles published so far on robotic intrathoracic hand-sewn anastomosis. Of course, if more patients were included in the future, the conclusion would be more convincing.

Comment 3: “did the authors check the anastomotic viability with indocyanine green test?”

Reply 3: Thanks for your kind comment. Up to now, we have not performed the indocyanine green test. It is undeniable that the indocyanine green test is an intuitive and accurate method to check the blood supply of the gastric tube. We plan to use this test to check the anastomotic viability in the future.

Comment 4: “the authors conclude that this technique simplifies a complicated procedure, is safe, effective and reproducible. I suggest to modify this statement (also in the abstract) since there is no evidence that it is easier and more reproducibile than standard esophagectomy.”

Reply 4: Thanks for your kind comment. We have modified this in the text.

Changes in the text: we have modified our text (see Page14, line 299-301; Page2, line 36-37).