Author’s response to reviews

Title: Predictive factors for major postoperative complications related to gastric conduit reconstruction in thoracoscopic esophagectomy for esophageal cancer: A case control study

Authors:
Shincihiro Kobayashi (shinichirokobayashi@nagasaki-u.ac.jp)
Kengo Kanetaka (kanetaka@nagasaki-u.ac.jp)
Yasuhiro Nagata (ynagata1961@nagasaki-u.ac.jp)
Masahiko Nakayama (insomniac-g.d.0830@hotmail.co.jp)
Ryo Matsumoto (f073eb@gmail.com)
Mitsuhisa Takatsuki (takapon@nagasaki-u.ac.jp)
Susumu Eguchi (sueguchi@nagasaki-u.ac.jp)

Version: 1 Date: 31 Oct 2017

Author’s response to reviews:

The full-version of authors’ response letter has been included as a supplementary file.

(Reviewer 1):

Q: It is mentioned that a total of 105 patients underwent oesophagectomy during this period. 20 were excluded as these were performed as open surgeries. Seventy five patients were included- this leaves 10 patients unaccounted for. Can the authors advise as to why these were excluded.

A: As the reviewer suggests, I reconfirmed the number of patients with open esophagsectomy and excluded 30 patients who were performed as open esophagectomy. This comments was added in the main document.

Q: The choice for the route of reconstruction may have some influence on the outcomes. Can the Authors advise why the post sternal route was chosen in the vast majority of cases rather than the posterior mediastinal route? The post sternal route is longer and can have the potential to place tension on the gastric conduit.
A: We usually apply the retrosternal route to the gastric conduit of reconstruction after esophagectomy. There are several advantages in the retrosternal route of reconstruction although the posterior mediastinal route to the gastric conduit is the original anatomic location. First, the radiation therapy for intrathoracic local recurrence in the posterior mediastinal route of reconstruction is sometimes hard because the site of recurrence is close to the gastric conduit. Second, surgery for second primary cancer in the gastric conduit in the retrosternal route of reconstruction after esophagectomy is easier than in the posterior mediastinal route. Third, the management of anastomotic leakage and total necrosis of gastric conduit in the retrosternal route of reconstruction is easier than the posterior mediastinal route. Fourth, the retrosternal route is the shorter passage than the posterior mediastinal route for the reconstruction of the gastric conduit after esophagectomy. In RCT studies, both posterior and anterior mediastinal routes of reconstruction are associated with similar outcomes after esophagectomy for cancer. Actually, in Japanese registry, retrosternal route of reconstruction was selected in 34% of patients, although posterior mediastinal route was used in 41.3%. Thus, the route of reconstruction remains controversial. These comments were added in the main document.

Q: The overall anastomotic leak rates are high as compared to world literature. Can the authors provide any explanation for this as well as the long length of stay overall?

A: As the reviewer suggests, the rate of anastomotic leakage might be slightly high. Many cases of advanced cancer (62.7%) and preoperative chemotherapy (68%) might affect the incidence of leakage. Of course, our data about anastomotic leakage were acceptable comparing with systematic reviews, that reported anastomotic leakage of the patients with esophagectomy is about 0 to 35%. There also is no significant difference between our data and Japanese nationwide web-based database about anastomotic leakage (P > 0.05).

The length of postoperative stay is no significantly different with Japanese nationwide web-based database. (P > 0.05). Transthoracic extended radical esophagectomy with 3-field lymph node dissection to esophageal squamous cell carcinoma is included in our data. The invasive procedure caused delayed recovery of the patients and seemed relatively long postoperative stay. The difference of health insurance system and lifestyle between Japan and western countries might also be associated with postoperative stay. These comments were added in the main document.

Q: The overall surgical time appears quite long as well. Can the authors elaborate on single lung ventilation time?

A: As reviewers suggested, we add the operation time in the chest part. The length of postoperative stay is no significantly different with Japanese nationwide web-based database.
Transthoracic extended radical esophagectomy with 3-field lymph node dissection is included in our data because differences in pathology may result in differences in surgical procedures between Japan and western countries. In operation time, 88% of esophagectomy in Japan is more than 6h. Our data of operation time are similar to the operation time in other articles from Japan (526 to 655 min). These comments were added in the main document and tables.

Q: Was delayed emptying of the gastric conduit studied?
A: As reviewers suggested, about 10 – 50% of patients after esophagectomy developed delayed emptying of the gastric conduit. However, delayed emptying of the gastric conduit was eliminated from complications because preventive medication, such as PPI, Mosapride, and Camostat mesilate, was performed in most cases and there were no patients with endoscopic pyloric dilation and surgical intervention, which is defined as Clavien-Dindo classification of grade III and more [13]. Jejunostomy tube was inserted in all cases and oral intakes were limited for preventing delayed emptying and continuing enteral nutrition in a month. Early enteral nutrition within 24 h was performed to prevent postoperative complications.

Q: Was there a multi and univariate analysis performed to see which factors may be predictive or was CRP on POD 1 and CPK chosen empirically based on some prior studies? were other factors such as postoperative development of new AF or inotrope requirement post op looked at?
A: As reviewers suggested, we added the data of Paf requiring treatments and vasopressor agents at the postoperative days. CRP and CPK were empirically chosen because CRP and CPK often elevate after esophagostomy. CPK was also reported as a biomarker of ischemic small bowel disease and animal models. These comments were added in the main document and tables.

(Reviewer 2): Major comments

1. In defining "major postoperative complications related to gastric conduit reconstruction", the authors are combining acute perioperative complications of leak and conduit necrosis, and medium/long-term complications of refractory strictures. Although ischaemia may be common to both, they are different pathologies with different implications and it is confusing to identify the same predictive factors for acute and long-term complications.

Perhaps a subgroup analysis of only leaks/necrosis may be useful for example?
A: As reviewers suggested, we add the tables of anastomotic leakage and refractory strictures.
Simple stricture formation is different pathological implication from ischemic formation. For example, technical failure of anastomosis, mismatching circular size, mucosal injury, and foreign body reaction to sampler may be related. Strictures are usually improved within usually less than 4 sessions of dilatation. These stricture may be short length of strictures. On the other hand, long strictures cause refractory strictures. Thus, severe ischemic change may cause large ulcer formation and long stricture formation even if leakage is avoided. In this study, all patient with refractory strictures developed within 2 month after esophagectomy. In cervical anastomotic complication several studies also showed relationships with graft ischemia and stricture formation. These comments were added in the main document and tables.

2. Patient/operation/outcome characteristics - There are various features of the study population and procedure which are different to general worldwide experience and therefore affects whether the results are applicable to most surgeons' practice or the correct conclusions can be made.

Patient BMI = 21.3 - This is significantly lower than most experiences.

Gastric conduit pulled up in the "post-sternal" route - This is relatively unusual with many surgeons using the mediastinal route.

Operating time = 605 minutes (Over 10 hrs) - This is significantly longer than other published series of MIE (approximately 330-400 minutes).

Length of stay = 27 days (22 days in those without conduit problems) - Again this is significantly longer than other published series of MIO AND open esophagectomy (around 11-16 days usually).

A: As reviewers suggested, we recognize that 2-field lymphadenectomy using the Ivor Lewis procedure or transhiatal esophagectomy is more commonly performed for esophageal adenocarcinoma in Western countries. Because differences in pathology may result in differences in surgical procedures, it remains unclear whether the risk models developed in this study are applicable to assess patients in western countries. In length of stay and BMI, there also is no different about our data and Japanese nationwide web-based database. In operation time, 88% of esophagectomy in japan is more than 6h. Our data of operation time are similar to the operation time in other articles from japan (526 to 655 min). We usually apply the retrosternal route to the gastric conduit of reconstruction after esophagectomy. There are several advantage in the retrosternal route of reconstruction although the posterior mediastinal route to the gastric conduit of reconstruction is original anatomic location. First, the radiation therapy for intrathoracic local recurrence in the posterior mediastinal route of reconstruction is sometimes hard because the site of recurrence is closed to the gastric conduit. Second, surgery for second primary cancer in the gastric conduit in the retrosternal route of reconstruction after
esophagectomy is easier than in the posterior mediastinal route. Third, the management of anastomotic leakage and total necrosis of gastric conduit in the retrosternal route of reconstruction is easier than the posterior mediastinal route. Fourth, the retrosternal route is the shorter passage than the posterior mediastinal route for the reconstruction of the gastric conduit after esophagectomy. In RCT studies, both posterior and anterior mediastinal routes of reconstruction are associated with similar outcomes after esophagectomy for cancer. Actually, in Japanese registry, retrosternal route of reconstruction was selected in 34% of patients, although posterior mediastinal route was used of reconstruction in 41.3%. Thus, the route of reconstruction remains controversial. These comments were added in the main document.

3. Statistics

The AUC number for CRP and CPK accuracy for detecting complications was 0.68 and 0.67 and there was no accompanying confidence intervals or p-values.

AUC between 0.6 to 0.7 is considered to show 'poor' discrimination for test accuracy. I suspect the p value would be > 0.05. Although this weak correlation is acknowledged by the authors it still means the predictive ability of CRP/CPK is very low.

Also, is Student t-test applicable (Page 8) - this assumes parametric data but I would consider those variables to be non-parametric.

Statistician input would be useful to clarify these issues.

A: As reviewers suggested, we discussed about statistics and calculated about ROC curve analysis.

AUC about CRP is 0.684 (95%CI; 0.546 – 0.796) is to. AUC about CPK is 0.670 (95%CI; 0.514 – 0.796). 95%CI of AUC about CRP and CPK is significantly greater than 0.5 although the accuracy of CPK and CRP is poor. These comments were added in the main document.

4. Conclusion

CRP and CPK are general markers of traumatic, inflammatory and infective insult and the authors even acknowledge that high levels are seen for other reasons other than conduit problems. But then they go on to say they would be useful to predict gastric conduit problems specifically and intervene early with endoscopy etc. Given the aforementioned poor predictive ability it is difficult to say if this is true or this would change practice.

A: As reviewers suggested, CPK, CRP, were poor predictive ability in the ROC analysis. However, The Odds ratios of CPK, CRP, and 3-field lymphadenectomy were more than 5.
Moreover, when the number of these factors increased, the incidence of major complications of the gastric conduits increased. The accuracy of 2 or more factors for major complications related to gastric conduit after TE was 0.800. On the other hand, the accuracy of 1 or more factors for major complications related to gastric conduit after TE was 0.533. Thus, we recommend 2 or more factors are likely to predict major complications related to gastric conduit after TE. The risk models, which we developed, presumably contribute to improvements in the quality control in the short-term follow-up for TE.

Minor comments

1. Repeated comments in 'Introduction / Discussion' that esophagectomy (including minimally invasive approach) has "high incidences of morbidity and mortality", "post-operative complications related to gastric conduit are common", "morbidity after TE remains high" etc. This is arguably not true with most published operative mortality rates <5% and anastomotic leak rates around 10-12%. Also the references supporting this are outdated - Refs 1 and 11 published 2009

Update morbidity/mortality data from more recent series.

A: As reviewers suggested, we quoted the several large data from recent articles. A systematic review of 57,299 esophagectomies from 2005 to 2009 showed the rate of morbidity was 0 to 35% and the rate of mortality was 0 to 15.4%. From 2005 to 2010, 7502 patients in the United Kingdom underwent esophagectomy and were recorded in the database. The rate of morbidity was 45.2% and the rate of mortality was 4.3%. From 2005 to 2008, 1032 patients in the United States underwent esophagectomy and were recorded in the database. The rate of morbidity was 50% and the rate of mortality was 3%. From 2010 to 2012 4266 patients in the United States underwent esophagectomy and were recorded in the database. The rate of mortality was 3.4%. A total 5354 patients in Japan underwent esophagectomy in 2011 and were recorded in the database. The rate of morbidity was 42% and the rate of mortality was 3.4% [7]. From 2011 to 2012, 9584 patients in Japan underwent esophagectomy and were recorded in the database. The rate of morbidity was 42% and the rate of mortality was 2.8%. We edited morbidity and mortality data in the main document.

2. Please clarify why "20 patients required open esophagectomy" - this could lead to selection bias of the TE group.
A: As the reviewer suggests, I reconfirmed the number of patients with open esophagesectomy and excluded 30 patients who were performed as open esophagectomy. We decided open esophagectomy to the patients with severe adhesion in the chest or the invasion of neoplasm or lymph node to the organs suspected. These comments were added in the main document.

3. Language accuracy - Example: Page 5, line 54/57 - "...a gastric conduit was created by cutting the proximal stomach", possibly change to "...a gastric conduit was created by resecting/dividing the lesser curve of the stomach"?

A: As reviewers suggested, we edited the sentence.