Peer review file

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Reviewer A

Comment 1: Can you use a pattern for some columns instead of solid colors to make the figures easier to interpret?

Reply 1: We have modified our figures as advised.

Changes in the text: See figures 1,2,3,4.

Comment 2: Add more details regarding statistical analysis for example, numeric values were presented as median with 25-75 IQR

Reply 2: The changes were made as suggested.

Changes in the text: See page 6 and 7, lines 140-142.
"Chi square test was used when comparing categorical variables. Continuous variables were compared by T-test and Mann-Whitney U test as appropriate. Numeric values are presented and mean (standard deviation) and median (interquartile range)."

Comment 3: Consider talking about limitations at the end of the discussion

Reply 3: Limitations are obviously important and according to our group policy, we prefer strengths and limitations -chapter as the second one in the Discussion section, please see page 11, paragraph 2.

Changes in the text: No changes in the text.

Comment 4: Figure 1 d: why there was a period of decreased neoadjuvant therapy between 2005 and 2009?

Reply 4: This is an important point and should be addressed in the manuscript. Especially in Western countries, incidence of esophageal cancer has rised due to increase in adenocarcinoma, which is by far the most prevalent histology nowadays. However, SCC was more or as common as adenocarcinoma up to 2004 (see Figure 2a). Early trials evaluating role of neoadjuvant treatment mostly included SCCs with findings suggesting improvement outcomes after neoadjuvant treatment (Urschel et al. Am J Surg 2002, ref 26 in the manuscript). The neoadjuvant chemoradiotherapy in patients with squamous cell carcinoma was used especially during years 1999-2004. This however gradually decreased until MAGIC trial (Cunningham et al. NEJM 2006, ref 27 in the manuscript) followed by CROSS-trial where neoadjuvant chemotherapy was gradually adopted as a standard of care. We included discussion regarding this topic.

Changes in the text: See page 13, lines 260-264.
"Some variation was seen in neoadjuvant treatment over time. During 1999-2004, where SCC was prevalent histology type, treatment was given according to early trials (26). However, neoadjuvant treatment rate decreased until MAGIC-trial (27) involving adenocarcinoma patients followed by CROSS-trial (28) (adenocarcinoma and SCC) when treatment gradually became the standard of care."

Comment 5: Can the earlier year period and learning curve explain why Transhiatal had higher positive margins and lower LN yield

Reply 5: There are possibly many reasons why transhiatal had higher positive margins. Due to the cervical anastomosis longer conduit was needed compared to intrathoracic anastomosis possibly affecting distal resection margin. Furthermore, when transhiatal procedure was used, frozen sections on resection margins were not routinely used. Also, neoadjuvant treatment was rare, which has been shown to affect R0 rates (van Hagen et al. N Engl J Med 2012, ref 28 in the manuscript, Shapiro et al. Lancet Oncol 2015, ref 12). Lower LN yield compared to transthoracic approach is in line with previous reports (Kutup et al. Ann Surg 2014, ref 6). Due to technical reasons, the lymph nodes of the thorax are not dissected in the transhiatal approach, resulting in lower LN yield.

Changes in the text: See page 13, lines 265-266.
"Lower lymph node yield in transhiatal approach is in line with previous reports (6)."
See page 13, lines 269-273.

“There may be some reasons for higher positive margins related to transhiatal approach. Due to the cervical anastomosis longer conduit was needed compared to intrathoracic anastomosis possibly affecting distal resection margin. Also at the time, frozen sections on resection margins were not routinely used and neoadjuvant treatment was rare (28),(12).”
See page 14, lines 292-293.
“Low preoperative use of PET-CT may explain higher positive resection margins.”

Comment 6: Not a necessity, but consideration can be given to do a regression analysis to assess predictors of some of the complications. The tumor histology and location can affect the surgeon choice about surgical approach driving higher rates of complications with a certain approach that’s driven by the disease pathology more than the surgery itself

Reply 6: We appreciate the comment. Regression analysis could be of interest recarding many outcomes. However, since the study design is retrospective over long period of time, we consider it not suitable after consulting a statistician. The purpose is to look at the change that has taken place over time.

Changes in the text: No changes in the text.

Minor Changes:
Line 54: cancer-related – modified text as advised, see line 69.
Line 100: should tumor free or tumor-free – Changes in the text: “R0 resection was defined as complete resection with at least 1 mm resection margin.” See lines 116-117.
Line 113/116: add “a” to be a circular stapler - modified text as advised, see line 130 and 133.
Line 137: figure should be figures - modified text as advised, see line 155.
Line 178: performed on 65 - modified text as advised, see line 201.
Line 195: in September 2017- modified text as advised, see line 218.
Line 203: pulmonary complications - modified text as advised, see line 226.
Line 213: prevented the inclusion - modified text as advised, see line 236.
Line 251: an incidence - modified text as advised, see line 284.
Line 257: In our study, - modified text as advised, see line 290.

Reviewer B

Comment 1: One of the main objectives of the study was to analyze the introduction of minimally invasive techniques. Unfortunately, only recently (2017) MIE was introduced in the institution and just 14.5% of the patients underwent MIE. Therefore, we are just at the beginning of the learning curve and is hard to compare the results with the open approach. Discussing challenges of the embracement of MIE and how to adopt a MIS program for a complex procedure like an esophagectomy in a low/intermediate volume center will be helpful for the readership.

Reply 1: We thank the Reviewer for these comments. The main objective of the study was to assess changes in esophageal cancer treatment including surgical therapy. Learning curve has taken place when changing primary approach from transhiatal to transthoracal procedure, and as the Reviewer mentions, especially when changing from open to minimally invasive approach. Although the rate of MIE in the whole cohort is 14.5%, since introducing MIE nearly all patients have been operated with minimally invasive approach. Length of the learning curve varies depending on the study from 25 to 175 patients (Claassen et al. J Thorac Dis 2019, ref 37 in the manuscript). In any case, the learning curve has been included in the study and affects outcomes. This is visible in lymph node yield, anastomosis leaks and hospital stay (Figure 2 and 3). Learning curve has been discussed in page xx, but as suggested, we have now included discussion regarding learning curve with emphasis on these parameters where learning related additional morbidity was seen.

Changes in the text: See page 15, lines 300-304.
“Length of the learning curve varies depending on the study from 25 to 175 patients (37). Learning curve has taken place when changing primary approach from transhiatal to transthoracic procedure and when changing from open to minimally invasive approach. The learning curve has been included in the study and affects outcomes. This is visible in decreased lymph node yield, increased anastomosis leaks and hospital stay despite minor tissue trauma.”

Comment 2: Considering the number of patients with locally advanced disease in your series, I am surprised with the low number of patients receiving neoadjuvant therapy (around 30%). In addition, VERY few patients were adequately studied before the operation (very few PET-TC and EUS). This partially explains your high rates of upstaging. Although some of these issues are mentioned in the discussion, this should be further explained.

Reply 2: We agree that the neoadjuvant rate is low throughout the dataset. However, in recent years the neoadjuvant rate has been in line with the guidelines, (80%), while the data have about 80% locally advanced diseases. Please see reply 4 for the reasons for variation in neoadjuvant treatment over time. According to guidelines, PET should be used in patients who are candidates for esophagectomy if availability is not an issue. PET-CT scan was selectively done in cases of suspected distant metastases and possible lymph node spread.

We agree that in modern practice, all patients should undergo preoperative PET when considering esophagectomy, and actions have been made to include PET-CT as a routine practice, instead of selective use.

Changes in the text: See page 13, lines 257-259.
"… explaining high upstaging. The use of PET-CT is improving, and actions have been made to include PET-CT as a routine practice, instead of selective use."

Comment 3: Around 15% of the patients had positive margins in the surgical specimen (Table 1 with 84.4% of R0 resections). The authors should explain and discuss this.

Reply 3: R0 resection rate was lower in previous time periods and changed as follows: 81.8%, 71.4%, 95.5%, 91.7%, 71.9%, 74.5%, 88.0%, 84.8% and 93.0% in years 1987-1995, 1996-1998, 1999-2001, 2002-2004, 2005-2007, 2008-2010, 2011-2013, 2014-2016, 2017-2020. In earlier time periods the use of frozen sections on resection margins was not established and transhiatal approach with cervical anastomosis due to the need for longer conduit compared to the transthoracic approach can be reasons for variation. Time periods also include at least two learning curves, please see Reply 7. Positive margins may be explained by operated T4 tumors, which were often observed intraoperatively, in 3.9% (n 13) of all patients and in time periods 0%, 0%, 0%, 0%, 6.3%, 3.9%, 10%, 2.2% and 5.4% (1987-1995, 1996-1998, 1999-2001, 2002-2004, 2005-2007, 2008-2010, 2011-2013, 2014-2016, 2017-2020). As the reviewer commented above, there was a lot of upstaging in our study, please see reply 8. One likely reason for this is the inadequate use of PET-CT.

Changes in the text: Please see reply 8 (See page 13, lines 257-259) and 5 (See page 13, lines 265-266, See page 13, lines 269-273, See page 14, lines 292-293).

Comment 4: Figure 3 is interesting. Why do you think anastomotic leak rates are increasing over time?

Reply 4: The increase in the anastomotic leak rate in recent years is likely a result of the MIE learning curve. Please see our response to comment 7. There is no definite reason for the increase in the anastomotic leak rates since 2000. Because hospital stay did not increase at that time, possibly more Grade 1 anastomotic leaks have been diagnosed, which may have previously been treated empirically with antibiotic therapy.

Changes in the text: No changes in the text.

Comment 5: Have you compared the outcomes between different anastomotic techniques?

Reply 5: We have the data (see Table below). Overall numbers are relatively small and therefore strict conclusions based on these incidences cannot be made. However, it seems that in our data no major differences exist, or possibly handsewn anastomoses have been associated with slightly increased leak rate, which can also be associated with technical difficulties. Also confounding can occur related to other simultaneous changes over time. We added a small insertion of leak rates after handsewn and stapler assisted anastomosis in the Results section.

Type of anastomosis	Leak rate % (n)
Handsewn	
end to end	16.7 (9)
end to side	27.3 (6)
side to side	16.7 (5)
Stapled	
end to end	0 (6)
end to side	11.3 (11)
side to side	15.4 (2)

Changes in the text: See page 10, lines 194-195.
“Anastomotic leak rate after handsewn and stapler assisted anastomosis was 14% (n=22) and 12.2% (n=20).”

Comment 6: Median hospital stay remained stable. Why do you think LOS did not decrease with the adoption of MIS?

Reply 6: There may be a few reasons why hospital stay did not decrease with the adoption of MIS. Although MIE is associated with minor tissue trauma and thus decreased hospital stay, there were slightly more complications with the adoption of MIS and the ongoing learning curve which may have extended the hospital stay. Please see our response to comment 7.

Changes in the text: Please see reply 7 (See page 15, lines 300-304).

Comment 7: A figure showing the percentage of patients undergoing open and MIE since 2017 might be interesting.

Reply 7: Since September 2017, only two patients underwent open esophagectomy, the rest were MIE, therefore no proper figure can be presented.

Changes in the text: No changes in the text.