Dear editors and reviews

Thank you for your suggestions. In the revised article, we had made corrections and add data. We hope our article will be accepted and be published. Thank you again for everything.

Responses for the reviewers' suggestion are as follow.

Reviewer's code: 03766580
Reviewer's country: Greece
Comments: The present review article summarizes in an excellent way the surgical approach of this group of tumors

Answer: We would thank the suggestions from the reviewer.

Reviewer's code: 00182891
Reviewer's country: France
Comments:
1) Did the authors mean "is not greater than 5 cm" instead of "is greater than 5 cm" in the "LN metastases in Type II EGJ cancer" section?
Answer: We would thank the suggestions from the reviewer. We want to mean "is not greater than 5cm". We have corrected the mistake in the revised version.

2) "Is" is wrongly repeated at the beginning of the "Lymphadenectomy with prognosis" section.
Answer: I have corrected the mistake in the revised version.

3) Authors should not use "meta-analysis" term for reviews of literature.
Answer: We have changed the "meta-analysis" term in the revised version.

Reviewer's code: 02554808

Reviewer's country: Romania

Comments:

The results showed that the incidence of metastasis or recurrence was 4%,7%, and 11% in the upper, middle, and lower mediastinal LNs respectively. It also revealed the length of esophageal invasion correlated with the number and location of mediastinal LN metastases. The incidence of metastasis was much higher when the length of esophageal invasion was >3 cm for the upper or middle mediastinal nodes and >2 cm for the lower mediastinal nodes[1]. In practice, this result means that if esophageal invasion of >3cm is noted, the upper and middle mediastinal LNs should be harvested

11% lower mediastinal lymh node metastases for pT2-4 Siewert Type II is a figure that is difficult to accept. The authors should be more cautious and discuss there hard-to-be-true values.

Answer: We would thank the suggestions from the reviewer. We added discussion in the reversed article. Among 315 patients in Kurokawa et.al study, there are 176 patients underwent LNs dissection in the lower mediastinal region, and the metastasis rate in the lower mediastinal nodes was 17.6%. In other 139 patients who didn't undergo dissection, the researchers did a long follow-up period. The recurrence rate among these 139 patients was 3.6%. So, the researchers combined the metastasis with recurrence to the final overall rates of metastasis or recurrence that was 11.4%. We should recognize that recurrence didn't always reflect metastasis at the time of surgery. This point was the limitation of their study.

The incidence of metastasis was much higher when the length of esophageal invasion was >3 cm for the upper or middle mediastinal nodes and >2 cm for the lower mediastinal nodes[1]

Is is also difficult to explain a significant difference in lymph node metastases on a difference of 1 cm esophageal invasion. It does not correlate with the later statements of the authors that the proximal resection margin o the sophagus may be as low as 2-3 cm.

Answer: In this section, we just want to express that the length of esophageal invasion has a relationship with LNs metastasis. About proximal resection margin, we also agreed with the views from the reviewer. In operation a negative proximal margin should be firstly affirmed. There are different views about the distance of proximal margin and no agreement. Mine et.al reported an improved survival with a proximal resection margin of 3.0 cm in vivo. Some surgeons suggested longer margin to prevent recurrence. However, other researchers thought that a negative proximal margin may be sufficient.

These results may indicate that harvest of the peri gastric nodes of the lower half of the stomach is not beneficial if the distance from the EGJ to the anal edge of the tumoris greater than 5cm. - this is a false statement

Answer: We want to mean "is not greater than 5cm". We have corrected the mistake in the revised version.

Esophagectomy with proximal gastrectomy might be enough in type II cancer, however it is better that the lower mediastinal compartment be routinely sampled during the operation – what type of esophagectomy, Ivor-Lewis or McKeown? Why mediastinal lymphadenectomy if the authors state that *there is still an uncertain incidence of metastasis to the lower mediastinal compartment?* It seems that even the authors do not have a clear idea of the operation recommended for the Siewert II type cancers and therefore they are not able to send a message to the reader.

Answer: We add some discussion about surgery type in the section "Surgery choice according to Siewert classification". We also modified our conclusion based on these literatures.

The length of esophageal invasion is a reference point in a surgical strategy of whether a transthoracic or a transabdominal approach is used? Does it mean that is the esophagus is invaded 3.1 cm a different operation is performed compared with a 1.9 cm invasion? What happens with a patient with 2.6 cm invasion of the esophagus? The data in the literature does not fully support such strategy and the authors should be more careful when advocating it.

Answer: We modified our conclusion based on the literature in the revised article. Accurate preoperative evaluation of the length of esophageal invasion is therefore essential, as it can be as a reference point for mediastinal LN metastases.

Although the incidence of Nos 10 LN metastasis ranged from 10-20%, there was no survival benefit associated with adding splenectomy to carry out a D2 lymphadenectomy[2, 3]. Itis recommended that splenectomy is done only to get an R0 resection[4, 5] – The authors do not mention about the possibility to retrieve the No 10 lymph nodes with preservation of the spleen.

Answer: We mentioned the difficulty of No 10 lymph nodes with preservation of the spleen. Obviously, splenic hilar lymphadenectomy is technically difficult and quite sophisticated due to the deeply located operative field, limited space, and tortuous and variant vessels at this site. With Accumulation of experience, new technological emergences and new surgical energy instruments, this procedure has gradually become possible.

LNs metastasis is also an indicator of prognosis. The highest risk factor is the number of metastatic LN≥7[6, 7] A multicenter retrospective study from the USA indicated that

the number of LNs harvested was an independent predictor for survival after surgery. They concluded that a minimum of 23 regional LNs harvested can offer a survival benefit[8] The authors do not mention the ration metastased/total LN as prognostic factor.

Answer: We add the information of metastatic LNs as prognostic factor in the revised article. The number of metastatic LNs and distant metastatic nodes such as para-aortal sometimes indicates very poor prognosis. In a systematic review including 2252 type II cancer patients, ≥7 metastatic LNs (N3) indicate much worse survival (2.0%-17.4%) compared to no LN metastasis (up to 82.7%).

The researchers indicated that more than 15 LNs were recommended for patients undergoing curative resection.[9]*. However,a Dutch study found thatthere is no benefit from an extended lymphadenectomy for type II disease*[10] The authors imply that removing more than 15 LN represents extended surgery which is actually not. Removing at least 15 LN is a prerequisite for correct oncological surgery

Answer: We don't want to imply that removing more than 15 LNs means extended surgery. In order that to make expression much more clearly, we made modification in the revised article. Whether more extensive lymphadenectomy in EGJ cancer can provide more survival benefit has been recently challenged.

A LN harvest of at least 23 nodes is enough for maximizing the outcomes after EGJ cancer surgery. The present day bench mark for oncological gastric surgery is to remove 15 LN. The authors extrapolate the conclusion of a single study which is not scientifically correct. To date there is no standardized rule to remove more that 23 LN.

Answer: We modified and make expression more accurately in the revised article. A moderately extensive lymph node removal may be enough for maximizing the outcomes after EGJ cancer surgery.

Barbour et al. identified that 5 cm of grossly normal in vivo (approximately 3.8cm ex vivo) proximal esophagus was associated with improved survival for patients (≥T2 and≤6 positive lymph nodes) with Siewert types I/II/III[11] – improved versus what? What happens with tumors with more than 6 LN invaded?

Answer: Barbour et al. reported that patients with grossly normal proximal margin lengths greater than 3.8 cm experienced significantly improved survival (median OS, 54 months; 5-year OS, 47%) compared with patients whose proximal margin length was less than or equal to 3.8 cm

(median OS, 29 months; 5-year OS, 29%) using Kaplan-Meier survival analysis.

There were 58 patients with more than 6 positive LNs. However, both univariate and multivariable analyses showed proximal margin carried no prognostic significance for these patients. Their results only showed a potential benefit for esophageal resection beyond the minimum length required to avoid a positive margin in R0 patients. The benefit associated with a grossly negative margin of 3.8 cm ex vivo appeared limited to patients with ≤6 LNs.

Esophagogastrectomy with moderate lymphadenectomy is still considered the standard surgical strategy to EGJ cancer – what is moderate lymhdenectomy? This parameter is new to the surgical community. Lymphadenectomy is either 2 field or 3 field and should involve at least the LN from the inferior mediastinum and stations 1,2,3,7,8,9,10p. Is that moderate? The authors should be more exact in the expression of their ideas.

Answer: We would thank the suggestions from the reviewer. We modified the lymphadenectomy in the revised article.

For type II cancers, some recommend esophagectomy with proximal gastrectomy, which allows for dissection of both abdominal and mediastinal LNs –what type of esophegctomy, Ivor-Lewis or McKeown? Which is the extent of lymphadenectomy, should the carinal lymph nodes be removed, should the recurrent lymph nodes be evaluated as sentinel nodes? The information provided by the authors is too vague and general.

Answer: We would thank the suggestions from the reviewer. We add some information about surgery.

Surgerychoiceaccording to Siewert classification – is just an enumeration of some of the surgical techniques available. There is no critical discussion related to their indications and pitfalls. *allowing exposure to the entire mediastinum to harvest even the upper mediastinal LNs.* – previously the authors showed data that the upper mediastinal LN are invaded in 4% of cases. There is no discussion as to whether such lymphadenectomy is necessary.

Answer: In this section, we just to list the potential advantages of the right transthoracic (RT) approach. We add some discussion about the RT procedure. RT allows exposure to the entire mediastinum to harvest even the upper mediastinal LNs which can make benefit especially for advanced stage patients with long esophageal invasion. Due to low rate of invaded upper mediastinal LNs, the Ivor Lewis approach without upper mediastinal LN dissection is usually performed in western countries.

Based on these results, the researchers suggested that LTA should be avoided as a surgical therapy for adenocarcinoma of the EGJ or gastric cardia – This statement may be true for the Siewert type II and II cancers. Siewert Type I cancer benefits from an Ivor Lewis procedure

Answer: We agreed with the opinion of the review. There is general agreement on the optimal surgical approach (a two-field Ivor Lewis operation) for Siewert types I. The Japanese JCOG9502 phase III trial (n=67) only compare oncologic outcomes between LTA and TH in patients with type II or type III EGJ cancers. Combination the first interim analysis and 10-years follow-up, the researchers only get the conclusion that LTA may be not suitable for type II or type III EGI cancers. Because no consensus on which technique is most suitable. We think future large RCTs are still needed to examine these techniques on the result of long-term OS.

Transthoracic vs transhiatal esophagectomy – the authors ignore the papers that show a trend for a higher survival in patients operated by a transthoracic technique with adequate lymphadenectomy starting 3 years postoperatively. This is significant in those with less than 8 LN metastasized. The role of neoadjuvant chemoradiotherapy followed by radical surgery is also ignored.

Answer: We added another literature in the revised article to show improved medium survival in transthoracic technique. Omloo et.al compared transthoracic and transhiatal approach for esophagectomy. They found that transhiatal was associated with a lower morbidity, however better medium-term survival with the transthoracic esophagectomy were shown in two subgroups: patients with type I AEG and those with ≤8 metastatic nodes.

Both minimally invasive surgeries show similar surgical and oncological outcomes compared with open surgeries – this statements should be more cautious. MIS s generally reserved for less advanced cases and patients with better performance status, hence there is a selection bias.

Answer: We agreed with the opinion of reviewer. We modified the expression sentences in our revised article.

Usually, the minimally invasive Ivor-Lewis technique is the main choice, although the intrathoracic anastomosis is sometimes difficult - the anastomosis is especially difficult, the double stapling techniques has a higher risk of insufficiency, introduction of the circular stapler is cumbersome, newer approaches use a linear stapler for the anastomosis - all these details are forgotten by the authors.

Answer: In our article, we have some information about anastomosis methods about minimally invasive Ivor-Lewis technique. The anastomosis

methods include end-to-side anastomosis by manual or circular stapler (with or without Orvil device), and side-to-side anastomosis by linear stapler (with or without barbed suture).

Favorable oncological results were also reported in several studies. A meta-analysis analyzed 359 early EGJ adenocarcinoma patients who received ESD treatment. More than 20% of tumors were reported to have deep submucosal invasion – which is the criteria for deep submucosal invasion? *Why was ESD performed in these cases?*

Answer: The criteria for deep submucosal invasion was>500 mm from the muscularis mucosa, the rate of invasion was 8.6–24.5%. We added the information in the revised article.

According to the above-mentioned risk factor for LN metastasis, there were 277 patients in the low risk group and 95 in the high risk group - the authors provide no definition of low risk and high risk features.

Answer: In this study, patients were classified into 2 groups based on the risk of metastasis according to the histologic features. Patients at low risk for metastasis were defined as those with mucosal cancer without both LVI and a poorly differentiated component or those with a cancer with SM depth ≤500 μm without LVI, without a poorly differentiated component, and measuring ≤30 mm. High-risk patients were all patients with mucosal and SM EGJ who did not meet the low-risk criteria.

Taken together, ER may be a good therapy for early EGJ cancer – this statement may be confusing for those that do not have a good knowledge on the indications of EMR – which are not stated in this paper. Can all patients with early EGJ cancer treated with ER? Of course not but the authors give this impression.

Answer: We agreed with opinions of reviewer. We modified the submitted article. Taken together, ER may be a good therapy for some early stage (intra-mucosal) EGJ cancer. Not all patients with early EGJ cancer can be treated with ER. Doctor should understand of the incidence of metastasis and confirm the indication to maximize the benefits of ER for early EGJ cancer.