

52460 Response to the referee

We would like to thank the reviewers for their considerate review of our manuscript and helpful comments, which substantially improved the quality of our manuscript. We have addressed the points raised by the reviewers and have accordingly revised our manuscript with revisions indicated in red font. Our point-by-point responses are as follows:

Reviewer #1: 02468626 (Major revision)

I have read with pleasure this manuscript comparing robotic surgery to laparoscopic surgery for the treatment of gastric cancer. The paper is well written and the methods are robust due to the high number of patients included.

We thank the reviewer for his/her favorable comments on our manuscript.

Major remarks;

1) At multivariate analysis, the stage of gastric cancer appeared to be the third most important determinant of post-operative morbidity. Therefore, accurate preoperative staging is crucial. However, there is no mention on how the patients were diagnosed and staged (EGD, EUS, CT scan, etc.).

Thank you for raising an important thing. As we previously reported [20], cancer staging was performed based on the findings of contrast-enhanced computed tomography, gastrography, endoscopic study, and endosonography before the beginning of any treatment and, when applicable, after the completion of chemotherapy. These descriptions were added in the Methods section as follows;

"In the present study, the stage of the cancer was described according to the 15th edition of the Japanese Classification of Gastric Carcinoma [24]. Cancer staging was performed based on the findings of contrast-enhanced computed tomography, gastrography, endoscopic study, and endosonography before the beginning of any treatment and, when applicable, after the completion of chemotherapy, as we previously described [20]." (Please see Page 6, Line 20-26)

2) In particular, the critical role of EUS in gastric cancer staging should be briefly emphasized. In case of early cancer, selection between endoscopic resection and surgery should be discussed.

The clinical T-stage was determined by endoscopic ultrasonography as previously reported (Yanai H, et al. *Gastrointest Endosc* 1997;46(3):212-216, as new ref#25), and the indication of endoscopic resection was determined according to the 4th JGCA guidelines (2014). These descriptions were added in the Methods section as follows; "Tumor invasion depth was measured ultrasonographically [25]. The gastric wall was assessed based on the standard five-layer sonographic structure. On the EUS image, the mucosal layer is visualized as a combination of the first and second hypoechoic layers, and the submucosal layer corresponds to the third hyperechoic layer. The layer of the muscularis propria is visualized as the fourth hypoechoic layer, and the fifth hyperechoic layer is the serosa, including the subserosa. Initial endoscopic diagnosis regarding invasion depth was confirmed based on the agreement by expert endoscopists at the medical conference prior to therapy. The indication of endoscopic treatment and radical gastrectomy including the extent of systematic lymph node dissection was determined based on the 2014 Japanese Gastric Cancer Treatment Guidelines [3]." (Please see Page 6, Line 26-Page 7, Line 10)

(References)

25. Yanai H, Matsumoto Y, Harada T, Nishiaki M, Tokiyama H, Shibemitsu T, Tada M, Okita K. Endoscopic ultrasonography and endoscopy for staging depth of invasion in early gastric cancer: a pilot study. *Gastrointest Endosc* 1997; 46: 212-216 [PMID: 9378206 DOI: 10.1016/s0016-5107(97)70088-9]

3) There is no mention whether the patients were diagnosed after they became symptomatic or as a result of a screening program, or both.

In reality, mass cancer screening programs, which contribute to earlier detection of gastric cancer, have been executed nationwide. Accordingly, this study included not only symptomatic patients but also those who were diagnosed as a result of the mass cancer screening programs. "This study included not only symptomatic patients but also those who were diagnosed as a result of the mass cancer screening programs, which have been executed nationwide and have contributed to earlier detection of gastric cancer." was added to the **Methods** section (Page 6, Line 18-20).

4) Did the authors look for *Helicobacter pylori* infection? On the other hand, was it systematically eradicated before surgery? Please comment

No, we did not. But *Helicobacter pylori* was examined and systemically eradicated in a considerable number of the enrolled patients at each hospital or clinic at which

gastric cancer of those patients was diagnosed, although the exact details are beyond the scope of this study. Thus, "In a considerable number of the enrolled patients, *Helicobacter pylori* was examined and systemically eradicated before surgery at each hospital or clinic at which gastric cancer of those patients was diagnosed." was added to the **Methods** section (Please see Page 7, Line 14-16).

5) Overall, open gastrectomy seems an issue of the past while reading this manuscript. In fact, while only 25 patients were referred to upfront open gastrectomy (OG) (and excluded from the protocol), the rate of conversion to OG seems very low (0.1 %). Please explain the reasons for this choice in Japan, while in other areas of the world open surgery for gastric cancer is still widely adopted.

Laparoscopic gastrectomy (LG) had long been recognized as an investigational treatment even for early gastric cancer (EGC) but not as a standard procedure in Japan, as previously described in the **Japanese Gastric Cancer Treatment Guidelines 2010 (ver. 3)**. However, based on the results of the multicenter phase II trial conducted by the Japanese Clinical Oncology Group (JCOG) (JCOG0703) [6], the Japanese Gastric Cancer Treatment Guidelines ver. 4 (issued in 2014) has turned to allow laparoscopic distal gastrectomy (LDG) for clinical stage I disease as a standard treatment option as described in the **Japanese Gastric Cancer Treatment Guidelines 2014 (ver 4)**. In the meantime, we introduced laparoscopic assistance into moderate to advanced GI surgery in 1995 as an investigational treatment, and developed techniques for LDG and laparoscopic total gastrectomy (LTG) with D2 dissection for advanced gastric cancer (AGC), which were published for the first time in the world [Uyama I, et al. *Gastric Cancer* 1999; **2**: 230-2342, Uyama I, et al. *Gastric Cancer* 2000; **3**: 50-55]. The short-term and long-term outcomes of LG for AGC at our institute have been satisfactory from both technical and oncological point of view (LG vs. OG: morbidity, 1.1% vs. 0%, $p=0.519$; mortality, 24.2% vs. 28.5%, $p=0.402$; 5-year disease free survival, 65.8% vs. 62.0%, $p=0.737$; overall survival, 68.1% vs. 63.7%, $p=0.968$). Details are demonstrated in our previous reports [8,9]. Thus, since 2009, the standard type of operation for curable GC at our institute has been totally laparoscopic D2 gastrectomy [10]. So far, we have performed more than 2,000 LGs.

The following descriptions were added in the **Methods** section:

"Since we had previously demonstrated the comparability of the laparoscopic D2 gastrectomy over the open D2 gastrectomy in the short- and long-term outcomes [8,9], the standard type of operation for curable GC has been laparoscopic gastrectomy since 2009 [10]." (Please see Page 5, Line 8-11)

6) Although the paper was mainly addressed at complications, It would be interesting to have a short notice about the margins of resection (R0 vs R1 resection) with the two techniques. Microscopic margins of resection are indeed important for the oncological outcomes.

In this study, we routinely confirmed tumor-negative status in the cut end by intraoperative frozen section diagnosis as previously reported (Nakauchi M, et al. *Surg Endosc* 2017; 31: 4631-4640, as new ref#27). As a result, all patients completed successfully R0 resection. These descriptions were added in the Methods section in the **Methods** and **Results** section as follows;

(Methods)

"The microscopic tumor-negative status in the cut end was routinely confirmed by intraoperative frozen section diagnosis as previously reported [27], and margins of resection (R0 or R1 resection) was pathologically diagnosed by permanent section diagnosis." (Please see Page 7, Line 10-14)

(Results)

"All patients completed successfully R0 resection." (Please see Page 11, Line 23)

(References)

27. **Nakauchi M**, Suda K, Nakamura K, Shibasaki S, Kikuchi K, Nakamura T, Kadoya S, Ishida Y, Inaba K, Taniguchi K, Uyama I. Laparoscopic subtotal gastrectomy for advanced gastric cancer: technical aspects and surgical, nutritional and oncological outcomes. *Surg Endosc* 2017; 31: 4631-4640 [PMID: 28389797 DOI: 10.1007/s00464-017-5526-9]

Minor remarks; In view of the comments, a few references need to be added:

As the reviewer indicated, we have added a few references into this manuscript.

4. **Sasako M**. Progress in the treatment of gastric cancer in Japan over the last 50 years. *Ann Gastroenterol Surg* 2020; 4: 21-29 [PMID: 32021955 DOI: 10.1002/ags3.12306]

26. **Fusaroli P**, Kypraios D, Eloubeidi MA, Caletti G. Levels of evidence in endoscopic ultrasonography: A systematic review. *Digestive Diseases and Sciences* 2012; 57(3), pp. 602-609 [PMID: 22057240 DOI: 10.1007/s10620-011-1961-y]

43. **Aurello P**, Cinquepalmi M, Petrucciani N, Moschetta G, Antolino L, Felli F, Giulitti D, Nigri G, D'Angelo F, Valabrega S, Ramacciato G. Impact of Anastomotic Leakage on Overall and Disease-free Survival After Surgery for Gastric Carcinoma:

A Systematic Review. *Anticancer Res* 2020; 40(2): 619–624 [PMID: 32014902 DOI: 10.21873/anticancer.13991]

28. **Catena F**, Di Battista M, Ansaloni L, Pantaleo M, Fusaroli P, Di Scioscio V, Santini D, Nannini M, Saponara M, Ponti G, Persiani R, Delrio P, Coccolini F, Di Saverio S, Biasco G, Lazzareschi D, Pinna A. Microscopic margins of resection influence primary gastrointestinal stromal tumor survival. *Onkologie* 2012; 35 (11): pp. 645-648 [PMID: 23147540 DOI: 10.1159/000343585]

Reviewer #2: 02841708 (Minor revision)

Author should explain his results in Discussion section, and unnecessary introduction should be deleted.

According to the other reviewers' comments, we have modified the **Discussion** section. Please see our answers.

Reviewer #3: 03017156 (Minor revision)

The study is remarkable, for the number of included patients, the methodology, the large experience of the authors in minimally invasive gastrectomy. The rates of complications and mortality demonstrate the quality of the activity of this referral center. The article is well written and the methodology well explained and well conducted.

We appreciate the reviewer's favorable comment on our study.

(1) **Background:** for gastric cancer, the current randomized and/or prospective evidence supports the non-inferiority of laparoscopic surgery especially for the management of early GC located in the distal stomach, while the definitive efficacy of the laparoscopic approach for more surgically challenging situations remains largely explorative and investigative. In my opinion it would be better to "mitigate" the sentence "Recently, laparoscopic gastrectomy (LG) has been extensively used provided that it is a minimally invasive and safe curative procedure for GC".

According to the reviewer's suggestion, we have modified the description in the **Backgrounds** section as follows;

"Recently, laparoscopic gastrectomy (LG) has **gained widespread use as it is a minimally invasive and safe curative procedure especially for early gastric cancer** [5-7]." (Please see Page 5, Line 6-8)

(2) Introduction, line 5: same remark concerning the role of minimally invasive surgery for gastric cancer.

Also, we have modified the description as follows; "Minimally invasive surgery for gastric cancer has **gained widespread use** as a safe curative procedure **especially for early gastric cancer**." (Please see Page 3, Line 3-4)

(3) Introduction, line 2: I would say: "surgical resection with or without perioperative chemotherapy".

According to the suggestion, we have modified the sentence as follows:

"Surgical resection **with or without perioperative chemotherapy** has remained the only curative treatment option, with regional lymphadenectomy being recommended as part of radical gastrectomy." (Please see Page 5, Line 3-5)

(4) Results: the authors founded lower intra-abdominal infections for robotic gastrectomy versus laparoscopic. Eight surgeon performed the robotic gastrectomies (44.8 for each surgeon) whereas 33 surgeons performed the laparoscopic procedures (31.6 for each surgeon). Moreover, 100% of the RG cases and only 56.5% (572/1042) of the LG cases (p < 0.001) were handled by qualified surgeons. Don't you think that the lower volume of surgeons performing the laparoscopic procedures and the lower percentage of procedures performed by qualified surgeons may explain the difference in postoperative morbidity? Did you analyze the volume per surgeon as a potential predictive factor of postoperative morbidity? How do you explain the lower rate of intra-abdominal infections after robotic surgery? Do you really have a less precise dissection with laparoscopy? What is the cause of intra-abdominal infections? Where they related to hematomas, or small leaks? I would like to better understand your hypothesis on your findings.

We understand the point the reviewer has raised very well. The difference in the incidence of intra-abdominal infectious complications between RG and LG may be partly because of that in the skill of the operating surgeons of each group, because even in the matched cohort, there remained a significant difference in the volume of patients who were operated by the qualified surgeons (Table 4). This must be one of the major biases and limitations of this manuscript. Therefore, we made our best efforts to control for this bias and conducted the multivariate analysis in the matched cohort to

determine the risk factors for intra-abdominal infectious complications (Table 6). Then, non-qualified has turned out not to be one of the risk factors, at least in this study design. Furthermore, as mentioned in the Discussion section, the following limitations are being disclosed: "this study has concerns regarding operator bias given that almost half of the LG cases were performed by non-qualified surgeons, while all RG procedures were performed by qualified surgeons. Accordingly, it remains largely unclear whether the protective effects of RG on morbidity observed herein could be extrapolated to RG conducted by a non-qualified surgeon." In addition, there were no significant differences in morbidity rate of LG between the qualified and non-qualified surgeons (data not shown). We have added this remark in the **Discussion** section (Please see Page 16, Line 20-22). Regarding this point, we are writing another paper right now. In terms of the reasons why use of the robot attenuated intra-abdominal infectious complications, we assume that pancreas-protective lymph node dissection may be the key. Because we consider that this hypothesis is informative, the following descriptions were added in the **Discussion** section:

"Actually, according to Table 5, there is a trend towards decrease in intraperitoneal abscess as well as pancreatic fistula in the RG group. Since intraperitoneal abscess could be induced by subclinical pancreatic fistula, the following speculation has taken place considering the results of our previous study in which RG significantly reduced pancreatic fistula: Robotic articulating forceps in combination with the magnified vivid three dimensional image enable operating surgeons to conduct radical lymph node dissection with little touch on the pancreas, leading to reduction in postoperative intra-abdominal infectious complications including clinical and subclinical pancreatic fistula. In addition, the "double bipolar" method characterized by simultaneous use of Maryland bipolar forceps (bipolar forced coagulation, 420172, Intuitive) with the right hand and Fenestrated bipolar forceps (bipolar soft coagulation, 420205, Intuitive) with the left hand might also facilitate pancreas-protective dissection in RG [20, 23]." (Please see Page 15, Line 18-Page 16, Line 5)

(5) Why do you say "non-robotic surgery" instead of "laparoscopic surgery"?

This study compared between laparoscopic and robotic gastrectomy. We consider that when we use "laparoscopic surgery", the readers may misunderstand the laparoscopic gastrectomy has a risk factor as compared to open gastrectomy. However, "non-robotic surgery" also may be misunderstanding. Therefore, we have changed "non-robotic surgery" into "non-robotic **minimally invasive** surgery (MIS)".

(6) I congratulate the authors for this work and encourage them to perform also a

RCT on the topic.

Thanks very much again. We will plan a RCT on this topic in the near future.

Reviewer #4: 02839900 (Rejection)

Non-robotic gastrectomy is popular in world. May be non-robotic gastrectomy is an independent risk factor. The ratio of intra-abdominal infectious complications is low. The value of the paper is small.

We are afraid, we do not agree with this reviewer.

Reviewer #5: 03258070 (Major revision)

Dear Editor, Thanks for the opportunity to revise this manuscript, which I read with keen interest. Overall, I found the manuscript well written and interesting, especially due to the relatively paucity of evidences upon the matter.

We thank the reviewer for his/her favorable comments on our study.

(1) The authors state that "All LG procedures were performed by ESSQS-qualified surgeons who were involved as either the operating surgeon or assistant surgeon. Meanwhile, RG was performed by surgeons certified to operate a DVSS console, qualified by the ESSQS, and certified by the Japanese Society of Gastroenterological Surgery" At the same time the authors state in the results section that 100% of the RG cases while only 56.5% of the LG cases were handled by qualified surgeons. This is not clear? Do the authors mean that only 56% of the laparoscopic cases were operated on by qualified surgeons as first operating surgeon? Please clarify -

We are sorry for our confusing descriptions. Yes, you are correct. What we meant was that **"All LG procedures were performed or guided by the ESSQS-qualified surgeons."** Therefore, as you mentioned, only 56.5% of the LG cases were operated on by qualified surgeons as first operating surgeon. The remaining LGs were conducted by non-qualified surgeons, and for these cases, qualified surgeons did an assistant. Therefore, we have corrected these sentences in the Method section as follows;

"All LG procedures were performed or guided by the ESSQS-qualified surgeons."
(Please see Page 8, Line 20)

(2) The study of post-gastrectomy pancreatic fistula is gaining interest during the

last years. I found the results provided by the authors useful to the global knowledge. However, there is no mention on how PF was diagnosed during the postoperative course. Were drain-amylases routinely measured or only in the presence of clinical suspicion? Was the diagnosis made according to the ISGPF definition? These findings on PF are important but should be better defined.

In this study, drain-amylases levels were routinely measured at least on postoperative day 1 and 3. All postoperative complications, including postoperative pancreatic fistula (POPF), were classified and graded according to the Japan Clinical Oncology Group Postoperative Complications Criteria based on the Clavien-Dindo (CD) classification ver. 2.0 [31,32]. Therefore, the diagnosis and grading of pancreatic fistula was not made according to the ISGPF definition in this study. Regarding the correspondence between the CD classification and the ISGPF definition, please refer to our review article focused on the pancreatic fistula after minimally invasive gastrectomy (Suda K, et al. *Transl Gastrointest Cancer* 2015;4(6):461-467, as new ref #33). Our perioperative management for POPF was previously reported as follows: although pancreatic fistula is defined as output via an operatively placed drain (or a subsequently placed percutaneous drain) of any measurable volume of drain fluid on or after postoperative day 3, with an amylase level at least over 3 times as high as the upper normal range of the serum level, it was comprehensively diagnosed according to not only drain amylase levels, but also changes in the properties of the drain and the clinical, laboratory, and imaging findings including computed tomographic scans. Patients with high drain amylase level and no abnormal physical and laboratory findings were observed without any treatment (CD Grade I, corresponding to ISGPF Grade A). The abdominal drainage tube was removed basically after the drain amylase level was sufficiently recovered. Patients with high drain amylase level accompanied by abnormal findings such as fever, abdominal pain and high inflammatory markers, were intensively treated with antibiotics, octreotide acetate and parenteral nutrition while the drainage tube position was urgently confirmed using computed tomographic scans and radiographic contrast study (CD Grade II, corresponding to ISGPF Grade B). When the drainage tube position was not appropriate, an additional or alternative drainage tube was placed into the fluid cavity using percutaneous computed tomography or ultrasonography-guided technique (CD Grade IIIa, corresponding to ISGPF Grade C), and irrigation and drainage with saline was performed. Parenteral nutrition was gradually switched to enteral nutrition without delay, once pancreatic fistula had been confined to a certain space and inflammatory response had settled.

Because we consider that these descriptions are important for the readers to understand the relationship between CD classification and ISGPF definition, we have added these sentences into the **Methods** section as follows:

"Perioperative management of postoperative pancreatic fistula (POPF)

Diagnosis and grading of pancreatic fistula were determined according to CD classification [31] as mentioned above. Our perioperative management for POPF was conducted as follows [20, 33]: although pancreatic fistula is defined as output via an operatively placed drain (or a subsequently placed percutaneous drain) of any measurable volume of drain fluid on or after postoperative day 3, with an amylase level at least over 3 times as high as the upper normal range of the serum level, it was comprehensively diagnosed according to not only drain amylase levels, but also changes in the properties of the drain and the clinical, laboratory, and imaging findings including computed tomographic scans. Patients with high drain amylase level and no abnormal physical and laboratory findings were observed without any treatment (CD Grade I). The abdominal drainage tube was removed basically after the drain amylase level was sufficiently recovered. Patients with high drain amylase level accompanied by abnormal findings such as fever, abdominal pain and high inflammatory markers, were intensively treated with antibiotics, octreotide acetate and parenteral nutrition while the drainage tube position was urgently confirmed using computed tomographic scans and radiographic contrast study (CD Grade II). When the drainage tube position was not appropriate, an additional or alternative drainage tube was placed into the fluid cavity using percutaneous computed tomography or ultrasonography-guided technique (CD Grade IIIa), and irrigation and drainage with saline was performed. Parenteral nutrition was gradually switched to enteral nutrition without delay, once pancreatic fistula had been confined to a certain space and inflammatory response had settled." (Please See Page 9, Line 16-Page 10, Line 13)

(References)

33. **Suda K**, Nakauchi M, Inaba K, Ishida Y, Uyama I. Revising robotic surgery for stomach, potential benefits revised II: prevention of pancreatic fistula. *Transl Gastrointest Cancer* 2015; 4: 461-467 [PMID: none DOI: 10.3978/j.issn.2224-4778.2015.10.05]

(4) Also, there are at least two systematic reviews with meta-analysis investigating on the incidence of PF after gastrectomy (open vs. minimally invasive, Surg Endosc 2017, and Lap vs. Robot, J Laparoendos Adv Surg Tech 2018), whose main findings should be commented while analyzing the current evidence upon the argument.

We have added the into the **Discussion** section as follows:

"However, there has been little evidence that minimally invasive gastrectomy is contributed to the reduction in postoperative pancreatic fistula (POPF), as shown in previous meta-analyses based on retrospective studies [38,39]. Therefore, further studies including multi-center randomized controlled trial are desired to establish solid evidence on RG." (Please see Page 16, Line 5-9)

(References)

38. **Guerra F**, Giuliani G, Iacobone M, Bianchi PP, Coratti A. Pancreas-related complications following gastrectomy: systematic review and meta-analysis of open versus minimally invasive surgery. *Surg Endosc* 2017; 31: 4346-4356 [PMID: 28378074 DOI: 10.1007/s00464-017-5507-z]
39. **Guerra F**, Giuliani G, Formisano G, Bianchi PP, Patriiti A, Coratti A. Pancreatic complications after conventional laparoscopic radical gastrectomy versus robotic radical gastrectomy: Systematic Review and Meta-Analysis. *J Laparoendos Adv Surg Tech* 2018; 28: 1207-1215 [PMID: 29733241 DOI: 10.1089/lap.2018.0159]