



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 63371

Title: Health-related quality of life after curative resection for gastric adenocarcinoma

Reviewer's code: 03478004

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: Japan

Author's Country/Territory: Slovenia

Manuscript submission date: 2021-01-31

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-02-01 06:11

Reviewer performed review: 2021-02-01 12:23

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

The authors investigated the QOL among gastrectomized patients. The results were of interests. However, I have some questions. 1. As you mentioned in the Discussion session, QOL changes over time. The current results may be affected by the time interval from the surgery to the questionnaire. I wonder differences of the time intervals existed between the groups. You should describe the time interval for each group. 2. Why don' t you perform Billroth-I reconstruction after distal gastrectomy?



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 63371

Title: Health-related quality of life after curative resection for gastric adenocarcinoma

Reviewer's code: 03767650

Position: Editorial Board

Academic degree: MD

Professional title: Director, Professor

Reviewer's Country/Territory: Japan

Author's Country/Territory: Slovenia

Manuscript submission date: 2021-01-31

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-02-01 10:42

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

Jan Grosek et al studied QOL after gastrectomy. This article is well written. In particular, the comparison between the Billroth II and the Roux-en-Y reconstruction and that between total and subtotal resection were interesting. They concluded that subtotal distal gastrectomy with Roux-en-Y reconstruction should be preferred over subtotal distal gastrectomy with Billroth II reconstruction. However, when adjusted for demographic data, no statistically significant differences were obtained among surgical procedures but in disease stages. There some issues raised. Major 1. Please explain whether it is ethically correct to include the data of declined participants in Table 1 in this paper. Minor 1. In Table 2, is Role function median 91.5 correct? Line 401. Period behind "life" is missing.



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 63371

Title: Health-related quality of life after curative resection for gastric adenocarcinoma

Reviewer's code: 05127894

Position: Peer Reviewer

Academic degree: MD, MSc

Professional title: Attending Doctor, Professor, Surgeon

Reviewer's Country/Territory: Peru

Author's Country/Territory: Slovenia

Manuscript submission date: 2021-01-31

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-02-01 16:28

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Review time: 15 Days and 5 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

The submitted manuscript is interesting and correctly written. Properly evaluate by an English expert, since some spelling errors are observed. I strongly suggest that the comparison with the general population is not placed in the study, since the data does not seem to correspond to the same study.



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 63371

Title: Health-related quality of life after curative resection for gastric adenocarcinoma

Reviewer's code: 03822338

Position: Editorial Board

Academic degree: MBBS, MNAMS, MS

Professional title: Professor

Reviewer's Country/Territory: India

Author's Country/Territory: Slovenia

Manuscript submission date: 2021-01-31

Reviewer chosen by: Jia-Ping Yan

Reviewer accepted review: 2021-02-03 19:46

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

Dear Authors, The article is a fairly written. There are some statements which have not been referenced which have been highlighted on track changes.

- 1 Title. Does the title reflect the main subject/hypothesis of the manuscript? YES
- 2 Abstract. Does the abstract summarize and reflect the work described in the manuscript? YES
- 3 Key words. Do the key words reflect the focus of the manuscript? YES
- 4 Background. Does the manuscript adequately describe the background, present status and significance of the study? YES
- 5 Methods. Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail? YES
- 6 Results. Are the research objectives achieved by the experiments used in this study? What are the contributions that the study has made for research progress in this field? YES. It comments on the Health-related Quality of Life after patients have undergone gastrectomy. There is limited literature on this aspect of post-operative QoL in Gastrectomy for cancer stomach.
- 7 Discussion. Does the manuscript interpret the findings adequately and appropriately, highlighting the key points concisely, clearly and logically? Are the findings and their applicability/relevance to the literature stated in a clear and definite manner? Is the discussion accurate and does it discuss the paper's scientific significance and/or relevance to clinical practice sufficiently? YES
- 8 Illustrations and tables. Are the figures, diagrams and tables sufficient, good quality and appropriately illustrative of the paper contents? Do figures require labeling with arrows, asterisks etc., better legends? YES
- 9 Biostatistics. Does the manuscript meet the requirements of biostatistics? YES
- 10 Units. Does the manuscript meet the requirements of use of SI units? YES
- 11 References. Does the manuscript cite appropriately the latest, important and authoritative references in the introduction and discussion sections? Does the author self-cite, omit, incorrectly cite and/or over-cite references? Some references are missing, which is highlighted on track changes.
- 12



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Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? Is the style, language and grammar accurate and appropriate? YES 13 Research methods and reporting. Authors should have prepared their manuscripts according to manuscript type and the appropriate categories, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study, Prospective study, Randomized Controlled trial, Randomized Clinical trial; (3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4) STROBE Statement - Case Control study, Observational study, Retrospective Cohort study; and (5) The ARRIVE Guidelines - Basic study. Did the author prepare the manuscript according to the appropriate research methods and reporting? YES 14 Ethics statements. For all manuscripts involving human studies and/or animal experiments, author(s) must submit the related formal ethics documents that were reviewed and approved by their local ethical review committee. Did the manuscript meet the requirements of ethics? YES Name of journal: World Journal of Gastroenterology Manuscript Type: FRONTIER Observational study Health-related quality of life after curative resection for gastric adenocarcinoma Grosek J et al. Health-related quality of life after gastrectomy Jan Grosek, Hana Zavrtanik, Aleš Tomažič Jan Grosek, Hana Zavrtanik, Aleš Tomažič, Department of Abdominal Surgery, University Medical Centre Ljubljana, Ljubljana, Slovenia; Medical Faculty, University of Ljubljana, Vrazov trg 4, 1000 Ljubljana Author contributions: Grosek J and Tomažič A made substantial contributions to the conception and design of the study; Zavrtanik H contributed to the acquisition, analysis and interpretation of the data; all authors participated in drafting the manuscript; Grosek J and Tomažič A revised it critically; all authors read and approved the final version of the manuscript. Corresponding author: Aleš Tomažič, MD, PhD, Professor, Department of Abdominal Surgery, University Medical Centre Ljubljana, Zaloška cesta 7, 1000 Ljubljana, Slovenia;



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(<https://orcid.org/0000-0002-1063-8636>) Abstract With improved survival in gastric cancer patients, health-related quality of life has become an important clinical endpoint next to primary oncological outcomes. In our cross-sectional survey we aimed to investigate health-related quality of life after different surgical procedures for gastric cancer treatment. Validated Slovenian version of the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30) and its gastric-cancer specific module (QLQ STO-22) were sent to the patients who underwent curative resection for gastric adenocarcinoma between January 2014 and December 2018 at our centre for self-completion. In total, 116 patients responded. Scores were compared between patients after gastrectomy and healthy Slovenian population, as well as patients after subtotal distal vs. total gastrectomy and patients after subtotal distal gastrectomy with Billroth II vs. Roux-en-Y reconstruction. Patients after gastrectomy reported several functional and physical symptoms when compared to the general population. The extent of resection did not influence daily functioning; however, higher symptom burden was reported in patients after total gastrectomy. Moreover, patients with Billroth II reconstruction after subtotal distal resection experienced poorer health-related quality of life compared to Roux-en-Y reconstruction. Based on our results, Roux-en-Y reconstruction after subtotal distal gastrectomy should be preferred over Billroth II reconstruction. Most importantly, patients should be informed preoperatively about functional treatment outcomes and should be regularly monitored postoperatively to ensure proper supportive care. Key words: Gastric cancer; Quality of life; Roux-en-Y; Billroth II; Gastrectomy Core tip: Quality of life assessment is an important tool to



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guide and evaluate treatment interventions, especially after a major surgery like gastrectomy. We conducted a cross-sectional survey among patients with gastric adenocarcinoma treated at our centre to provide insight into the overall well-being after curative resection. The information provided will guide the surgeon in selecting an optimal treatment approach, and inform the patients about expected treatment outcomes.

BIOGRAPHY Jan Grosek Curriculum vitae 1978 - Born in Slovenj Gradec, Slovenia 2003 - MD, Medical Faculty, University in Ljubljana 2005-2007 - Residency in General Surgery 2007-2011 - Residency in Abdominal Surgery 2011 - Board Examination 2011- - Surgeon, Dept. of Abdominal Surgery, UMC Ljubljana 2016 - PhD: Medical Faculty, University in Ljubljana 2017 - Visiting Doctor, Dept. for Surgery, UMC Amsterdam, Netherlands 2020 - Assist. Prof. of Surgery, Medical Faculty, University of Ljubljana 2020 - Program director: Robotic abdominal surgery Bibliography: 116 bibliographic units Membership in Professional and Scientific International Associations: Slovenian Society of Gastroenterology and Hepatology Slovenian Society for Endoscopic Surgery - general secretary Slovenian Medical Association EAES ECCO ESCP Main fields of interest: Robotic surgery, advanced laparoscopic surgery, colorectal and upper GI cancer, IBD surgery. International studies/registries: Intact (Intra-operative fluorescence angiography to anastomotic leak in rectal cancer surgery), ESCP-MASC (Management of acute severe ulcerative colitis audit), CORSICA- EYSAC.1 (Complete pathologic response rectal cancers), Tentacle rectum (Treatment of anastomotic leakage after rectal resection), 2017 ESCP snapshot audit (Left colon, sigmoid and rectal resections), GlobalSurg 3 (Quality and outcomes after global cancer surgery: a prospective international cohort study), GlobalSurg CovidSurg week, EURO-FIGS (European fluorescence imaging-guided surgery registry), DAMASCUS study (Diverticulitis management: A snapshot collaborative audit study), TRG snapshot study



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(European distribution of TRG-tumor regression grade distribution in locally advanced rectal cancer), MIRCAST (Minimally invasive right colectomy anastomosis study-application pending). INTRODUCTION Gastrectomy is a major operation which alters physiologic functions of the digestive tract. Consequently, patients who undergo this treatment commonly experience a broad range of metabolic disorders including malnutrition, weight loss, and several post gastrectomy symptoms which negatively impact patient's well-being[1]. With modern gastrectomy techniques and other treatment modalities, survival in gastric cancer patients has improved and health-related quality of life (HRQoL) has become an important aspect when evaluating treatment outcomes[2]. Different surgical procedures have been described for achieving oncological radicality in gastric cancer. In previous comparative studies, subtotal distal gastrectomy was associated with shorter operative duration, reduced postoperative complications and better recovery when compared to total gastrectomy[3-6]. On the other hand, total gastrectomy could still be performed safely with low morbidity while reducing the risk of inadequate safety margins or remnant carcinoma[7,8]. Following subtotal distal gastrectomy, there is no consensus regarding the best type of reconstruction[9,10]. Billroth II reconstruction is often performed due to its simplicity but associated reflux gastritis and esophagitis have been the limiting concerns. Roux-en-Y reconstruction is a recommended alternative, but can result in delayed gastric emptying, nausea, vomiting and abdominal pain[11]. Selection of the procedure is usually made based on tumour location, preoperative staging, patient's general physical status and surgeon's preference. In addition, quality of life assessment has become an increasingly important index for evaluating and selecting treatment interventions. Patient-reported measures regarding their physical and emotional state after treatment as opposed to objectively defined short-term perioperative outcomes should be taken into consideration to achieve optimal care. We conducted a cross-sectional survey



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among patients with gastric adenocarcinoma treated at a tertiary referral centre to provide insight into the overall well-being after curative resection. European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire (QLQ-C30) and its gastric cancer-specific module (QLQ STO-22) were used to assess HRQoL[12]. Its various aspects were compared in relation to the general population and among different surgical procedures. **MATERIALS AND METHODS**

Patients Patients with gastric cancer who underwent curative resection at the University Medical Centre Ljubljana between January 2014 and December 2018 were intended to be included in the study. Patients were eligible for inclusion if they were older than 18 years of age, underwent curative subtotal distal or total gastrectomy for histologically confirmed adenocarcinoma, and did not undergo previous gastric surgery. We excluded patients who were deemed unable to answer the questionnaires, who provided questionnaires with missing items that disabled final scoring, who suffered from other gastrointestinal (e.g. chronic inflammatory bowel disease, exocrine pancreatic insufficiency, cholestasis) or other malignant diseases, who underwent emergency or palliative surgery, or who experienced disease recurrence. The study was approved by the National Medical Ethics Committee of Republic of Slovenia (no. 0120-315/2019/3; July 9, 2019). Patients who met the inclusion criteria and provided a written informed consent were included for further analysis. **Data collection** Data of included patients regarding demographics, comorbidities, American Society of Anesthesiologists (ASA) score, tumour stage, type of resection, type of reconstruction, postoperative complications, hospital stay, histopathological characteristics of the tumour, cancer recurrence, and possible (neo)adjuvant therapy were collected retrospectively from electronic patient records. **Surgery** All patients underwent open gastrectomy, either subtotal distal or total, depending on the tumour location and preoperatively determined TNM stage. Gastric adenocarcinoma was confirmed upon histopathological



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examination of specimen. After total gastrectomy, reconstruction was performed with Roux-en-Y esophagojejunostomy in all cases. After subtotal distal gastrectomy, either a Billroth II or Roux-en-Y anastomosis was constructed. Braun enteroenterostomy was routinely performed in all cases of Billroth II gastrojejunostomy. Health-related quality of life assessment To assess postoperative HRQoL of our patient cohort, the validated Slovenian version of the EORTC QLQ-C30 (version 0.3) and QLQ STO-22 were used[12]. The EORTC QLQ-C30 questionnaire consists of 30 questions divided into five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), global health status/quality of life scale, and six single items to report other complaints (dyspnoea, loss of appetite, insomnia, constipation, diarrhoea, financial difficulties). The EORTC QLQ-STO22 is a gastric cancer-specific module to assess HRQoL of patients with adenocarcinoma of the stomach. It comprises 22 questions divided into five multi-item scales (dysphagia, chest and abdominal pain, reflux, eating restrictions, anxieties) and four single items (dry mouth, taste problems, body image, hair loss). Study description with informed consent form, EORTC QLQ-C30 and EORCT QLQ-STO-22 questionnaires were sent to the patients for self-completion. All completed questionnaires were scored and linearly transformed to a 0-100 scale according to the EORTC QLQ-C30 Scoring Manual[13]. On the functional scale, higher scores represent better functioning, while on the symptom scale, higher scores indicate higher symptom burden. Missing values were processed as follows: if at least half of the items from the scale were answered, the missing items were assumed to have values equal to the average of the completed items in the scale. HRQoL was compared between patients after gastrectomy vs. general Slovenian population; patients after subtotal distal vs. total gastrectomy; and patients after subtotal distal gastrectomy with Billroth II vs. Roux-en-Y reconstruction. To assess the differences in HRQoL among patients after gastrectomy and general population, reference data of the EORTC



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QLQ-C30 questionnaire for the general Slovenian population were used[14]. Statistical analysis Means with standard deviations (SD) as well as medians with interquartile ranges (IQR) of EORTC QLQ-C30 and EORTC QLQ-STO-22 scores were obtained. Shapiro-Wilk test was used to test the normal distribution of the data. Reference EORTC QLQ-C30 scores from general Slovenian population were assessed from the literature where they were presented by means and SD[14]. A one-sample t test was used for comparison with EORTC QLQ-C30 scores from our patient cohort. Scores of EORTC QLQ-C30 and EORTC QLQ-STO-22 of patients after subtotal distal vs. total gastrectomy and Billroth II vs. Roux-en-Y reconstruction were compared with Mann-Whitney U test. To assess the correlation between the type of operation and general health status adjusted for some demographic and clinical characteristics of patients, multiple linear regression was used. The assumptions of absence of multicollinearity (assessed by variance inflation factor), normal distribution of the residuals and homoscedasticity were met. A double-sided p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 27.0 (IBM Corporation, Armonk, NY, USA). RESULTS Patients Invitations for study participation were sent to 234 patients. A total of 116 (49,6%) patients who provided informed consent with completed questionnaires were further analysed. There were 63 men and 53 women aged 44-88 years. Ten questionnaires had missing items. In six questionnaires, only one item was missing. In four questionnaires, there were two missing items which were not part of the same scale. Patients who decided to participate in the study and ones who decided against participation did not differ significantly according to gender, type of gastric resection, type of reconstructive procedure, and postoperative complications. Participating patients were younger ($p=0.016$) and had significantly less advanced disease stage ($p=0.001$). Baseline characteristics of patients eligible for inclusion are presented in Table 1. EORTC



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QLQ-C30 questionnaire evaluation Patients after gastrectomy vs. general Slovenian population HRQoL of patients after gastrectomy was significantly lower on the physical functioning ($p<0.001$), role functioning ($p<0.001$), cognitive functioning ($p<0.001$) and social functioning ($p<0.001$) scales when compared to the general Slovenian population. Patients after gastrectomy also reported more problems with dyspnoea ($p=0.01$), insomnia ($p=0.002$), appetite loss ($p=0.003$), nausea/vomiting ($p<0.001$), diarrhoea ($p<0.001$), fatigue ($p<0.001$) and financial problems ($p<0.001$). Besides, they had significantly lower global health status/quality of life scores ($p=0.039$). The details of HRQoL assessed by EORTC QLQ C30 questionnaire for the two groups are summarized in Table 2. Patients after total vs. subtotal distal gastrectomy No statistically significant differences were observed in HRQoL of patients after total gastrectomy when compared to the patients after subtotal distal gastrectomy. The details are shown in Table 3. Patients after subtotal distal gastrectomy with Billroth II vs. Roux-en-Y reconstruction HRQoL of patients after subtotal distal gastrectomy with Billroth II reconstruction was significantly lower on the physical ($p=0.038$), and role functioning ($p=0.034$) scale when compared to the patients with Roux-en-Y reconstruction. Patients with Billroth II reconstruction also reported more pain ($p=0.01$) and fatigue ($p=0.028$). No differences were observed among the two groups in global health status/quality of life scores ($p=0.635$). The details are summarised in Table 4. Reported scores on different functional scales and global health status/quality of life scale among different surgical procedures are depicted in Figure 1. Patients after subtotal distal gastrectomy with Roux-en-Y reconstruction scored highest on cognitive, role functioning and physical scales when compared to the patients after total gastrectomy or subtotal distal gastrectomy with Billroth II reconstruction. Quality of life and type of surgery The type of surgery was significantly associated with stage of the disease ($p=0.002$) (Table 5). Patients with stage III gastric adenocarcinoma underwent either total gastrectomy



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(43.9%) or subtotal distal gastrectomy with Billroth II reconstruction (41.3%) rather than Roux-en-Y reconstruction (22.2%). When adjusted for demographic data, disease stage and postoperative complications in a multiple linear regression model, no statistically significant differences in global health status/quality of life scale were observed among different surgical procedures. Global health status/quality of life scores were significantly negatively associated with disease stage ($\beta=-0.21$, $p=0.029$) (Table 6). Patients with Roux-en-Y reconstruction had significantly higher scores on emotional ($\beta=0.24$, $p=0.041$), role functioning ($\beta=0.24$, $p=0.034$) and physical scale ($\beta=0.23$, $p=0.048$) when compared to the patients after Billroth II reconstruction even when adjusted for other variables in a regression model (Table 7). EORTC QLQ STO-22 questionnaire evaluation Patients after total vs. subtotal distal gastrectomy Patients after total gastrectomy reported more dysphagia ($p=0.020$) and eating restrictions ($p=0.017$) when compared to patients after subtotal distal gastrectomy. No differences were found in other scales of the EORTC QLQ STO-22 questionnaire (Table 8). Patients after subtotal distal gastrectomy with Billroth II vs. Roux-en-Y reconstruction Patients after subtotal distal gastrectomy with Billroth II reconstruction reported more problems with reflux when compared to patients with Roux-en-Y reconstruction. No differences were found in other scales of the EORTC QLQ STO-22 questionnaire (Table 9). **DISCUSSION** The results of this cross-sectional survey show that patients after curative resection for gastric adenocarcinoma have significantly lower HRQoL on functional, symptom as well as global health scale when compared to the general Slovenian population. Furthermore, the type of resection influences different aspects of HRQoL. Patients after total vs. subtotal gastrectomy had similar functional scores, but the former experienced more dysphagia and eating restrictions. At the same time, patients after subtotal gastrectomy with Billroth II (compared to Roux-en-Y reconstruction) reported worse physical and role functioning scores and complained of symptoms, such as pain, fatigue and reflux.



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However, these differences appear to be clinically less relevant as similar global health scores were reported among different surgical procedures. The information provided should advise the surgeon on the optimal treatment approach after considering oncological feasibility of the technique. Moreover, it should be used to inform the patients about expected functional sequelae. At first glance, decreased HRQoL in patients after gastrectomy as compared to the general population seems somehow predictable. Previous studies evaluated longitudinal changes of HRQoL after gastrectomy for gastric cancer and used preoperative scores as a reference[15-22]. However, these scores are highly influenced by circumstances surrounding the diagnosis as well as symptoms associated with the disease itself, such as nausea and vomiting, dysphagia, postprandial fullness, loss of appetite, fatigue due to anaemia, etc. resulting in worse HRQoL[17,18]. Hence, we opted to compare HRQoL after gastrectomy to the HRQoL of a healthy population to evaluate the actual life quality deviation that is caused by surgical treatment. We found that patients after gastrectomy scored worse on all but emotional scale and experienced several disturbing symptoms. Not surprisingly, this also influenced their perceived global health status, achieving lower scores than reported for general population. Our results are in contrast with the study conducted by Brenkman et al.[23] who concluded global HRQoL to be more or less comparable between patients after gastrectomy and general healthy Dutch population despite patients' worse scores on several functional and symptom scales. Similarly, Lee et al.[24,25] found no significant difference in global HRQoL between patients more than five years after surgery for gastric cancer and healthy volunteers awaiting routine screening exam. On comparison of different surgical procedures, the type of reconstruction appeared to have a greater effect on HRQoL than the extent of gastric resection which is somehow unexpected. Our data show that proximal gastric preservation has marginal advantages to improve patients' quality of life by reducing



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dysphagia and eating restrictions postoperatively while no differences in daily functioning were found. In line with our finding, subtotal distal gastrectomy was generally better tolerated in several previous studies, especially due to higher symptom burden reported with total gastrectomy such as nausea and vomiting, dysphagia, eating restrictions, and reflux[17,22]. In subtotal gastrectomy, gastric physiology is at least partly preserved, possibly leading to superior HRQoL. However, several studies found no difference in global HRQoL between the two groups[5,16,19,26]. Possible explanation for this finding is the time interval from the surgical procedure. HRQoL changes over time are well documented. In longitudinal analyses, significantly worse scores on almost all HRQoL scales were observed one to six months postoperatively compared to the preoperative scores[15–18,21]. Several functional scales recovered to the baseline in one year after surgery, however, symptoms such as nausea and vomiting, reflux and eating restrictions persisted even five years after surgery[20,24,25]. In long-term analysis by Lee et al.[26], HRQoL inferiority of patients after total when compared to subtotal distal gastrectomy generally disappeared beyond five years postoperatively, remaining inferior only in eating restrictions. In our study, the time interval from the surgery to the completion of the questionnaires ranged from one to five years, possibly diminishing some differences between the two groups. Regarding the type of digestive tract reconstruction after subtotal distal gastrectomy, the choice of the technique is often driven by surgeon's preferences and no clear recommendations exist in the current literature[9–11]. Several studies suggested Roux-en-Y reconstruction being superior to Billroth II reconstruction in terms of preventing bile reflux and remnant gastritis, thus, enabling better quality of life [10,27–29]. However, in a proportion of patients, Roux-en-Y may be associated with a Roux stasis syndrome causing delayed gastric emptying with postprandial pain, nausea and vomiting[30,31]. Our results are partly in line with previous studies reporting reduced HRQoL following Billroth II vs. Roux-en-Y



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reconstruction. Patients after Billroth II reconstruction achieved lower scores on some of the functional scales and reported more pain, fatigue and reflux symptoms. This occurred despite routine construction of Braun anastomosis which supposedly diverts bile from the remnant stomach, relieving reflux symptoms, dumping syndrome or other disturbances in food intake[32]. Although patients after Billroth II reconstruction were more likely to have a higher disease stage than those after Roux-en-Y reconstruction, statistically significant superiority of Roux-en-Y procedure in emotional, role and physical functioning scale remained after adjustment for demographic data, disease stage and postoperative complications. Study limitations This study has some limitations. First, the cross-sectional nature does not allow longitudinal assessment of HRQoL. Still, we believe this kind of design allows us to gain important insight into the overall HRQoL of patients following gastrectomy, which represent the basis for clinical decision making. Second, the number of participating patients is relatively low (116), representing 49.6% of patients who were eligible for study inclusion. Third, mail surveys lack data related to the actual health status of the patient. We have not seen the patients to obtain their health status objectively; therefore, their subjective measures could not be compared to their actual physical findings. Nonetheless, HRQoL is a multimodal construct of physical, psychological and social well-being in relation to disease treatment. Therefore, objective and subjective measures are not necessarily related. Even if a patient is objectively well, he or she may at the same time be subjectively unwell which should be addressed separately from objective measures. CONCLUSION Our study shows that patients after gastrectomy for gastric cancer experience several functional and symptom complaints affecting quality of life. Based on our results, with regard to HRQoL, subtotal distal gastrectomy with Roux-en-Y reconstruction should be preferred over subtotal distal gastrectomy with Billroth II reconstruction. Patients should be informed preoperatively about expected functional sequelae after surgery and should be



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regularly monitored postoperatively to ensure proper symptomatic and supportive care.

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stomach during long-term follow-up after distal gastrectomy for gastric cancer: Analysis of cumulative incidence and associated risk factors. *World J Surg* 2018; 42: 782–7 [PMID: 28924721 DOI: 10.1007/s00268-017-4227-9] 9. Tran TB, Worhunsky DJ, Squires MH, Jin LX, Spolverato G, Votanopoulos KI, Cho CS, Weber SM, Schmidt C, Levine EA, Bloomston M, Fields RC, Pawlik TM, Maithel SK, Norton JA, Poultides GA. To Roux or not to Roux: a comparison between Roux-en-Y and Billroth II reconstruction following partial gastrectomy for gastric cancer. *Gastric Cancer* 2016; 19: 994–1001 [PMID: 26400843 DOI: 10.1007/s10120-015-0547-3] 10. He L, Zhao Y. Is Roux-en-Y or Billroth-II reconstruction the preferred choice for gastric cancer patients undergoing distal gastrectomy when Billroth I reconstruction is not applicable? A meta-analysis. *Medicine (Baltimore)* 2019; 98: e17093 [PMID: 31770192 DOI: 10.1097/MD.00000000000017093] 11. So JBY, Rao J, Wong ASY, Chan YH, Pang NQ, Tay AYL, Yung MY, Su Z, Phua JNS, Shabbir A, Ng EKW. Roux-en-Y or Billroth II reconstruction after radical distal gastrectomy for gastric cancer: A multicenter randomized controlled trial. *Ann Surg* 2018; 267: 236–242 [PMID 28383294 DOI: 10.1097/SLA.0000000000002229] 12. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, Haes JCJMD, Kaasa S, Klee M, Osoba D, Razavi D, Rofe PB, Schraub S, Sneeuw K, Sullivan M, Takeda F. The European organization for research and treatment of cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; 85: 365–76 [PMID: 8433390 DOI: 10.1093/jnci/85.5.365] 13. Fayers P, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A. EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels: European Organisation for Research and Treatment of Cancer, 2001. 14. Velenik V, Secerov-Ermenc A, But-Hadzic J, Zadnik V. Health-related quality of life assessed by the EORTC QLQ-C30 questionnaire in the general slovenian population. *Radiol Oncol* 2017; 51: 342–50 [PMID: 28959171 DOI: 10.1515/raon-2017-0021] 15. Avery K, Hughes R, McNair A, Alderson D, Barham P,



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controlled trial. J Hepatobiliary Pancreat Sci 2016; 23: 364-72 [PMID: 27038406 DOI: 10.1002/jhbp.349] Figure Legends Figure 1 Median scores with IQR of functional scales and global health status/quality of life scale based on the type of surgery.

Table 1 Baseline characteristics of patients eligible for inclusion (n = 234) Study participants (n = 116) Declined participation (n = 118) p value Gender (n, %) 0.192 Male 63 (54.3) 74 (62.7) Female 53 (45.7) 44 (37.3) Age at surgery (years, median, IQR) 66 (58-74) 72 (63-78) 0.016 Performed procedure (n, %) 0.299 Total gastrectomy 43 (37.1) 55 (46.6) Distal-Billroth II 26 (22.4) 20 (16.9) Distal-Roux-Y 47 (40.5) 43 (36.4) Postoperative complications (n, %) Yes 28 (24.1) 38 (32.2) 0.170 TNM stage (n, %) 0.001 0 3 (2.6) 4 (3.4) I 52 (44.8) 25 (21.2) II 32 (27.6) 36 (30.5) III 29 (25.0) 53 (44.9)

Table 2 EORTC QLQ-C30 questionnaire scores for patients after gastrectomy and general population (one-sample t test) Patients after gastrectomy General population p value Min Max Mean (SD) Median (IQR) Mean (SD) Functional scales Physical functioning 13 100 80.1 (20.6) 87 (67-100) 91.8 (14) <0.001 Role functioning 0 100 79.3 (26.4) 91.5 (67-100) 88.7 (20.1) <0.001 Cognitive functioning 0 100 82.3 (20.9) 83 (67-100) 90.2 (16) <0.001 Emotional functioning 0 100 80 (21) 83 (67-100) 82 (18.5) 0.145 Social functioning 0 100 78.6 (24) 83 (67-100) 90.9 (17.3) <0.001 Symptoms Dyspnoea 0 100 10.6 (21.8) 0 (0-0) 5.3 (15.3) 0.010 Insomnia 0 100 28.4 (28.6) 33 (0-33) 19.8 (25.1) 0.002 Appetite loss 0 100 10.9 (20) 0 (0-33) 5.3 (15.5) 0.003 Nausea/ vomiting 0 67 8.5 (15.3) 0 (0-17) 3.3 (10.6) <0.001 Constipation 0 100 9.1 (19.4) 0 (0-0) 6.9 (16.9) 0.216 Diarrhoea 0 100 15.7 (23.4) 0 (0-33) 4.2 (13.6) <0.001 Fatigue 0 100 31.8 (23.3) 33 (22-44) 19.8 (19.8) <0.001 Pain 0 100 18.1 (22) 17 (0-33) 14.5 (20.2) 0.078 Financial problems 0 100 20.4 (29.4) 0 (0-33) 6.6 (17.5) <0.001 Global health status 25 100 66.9 (21.7) 67 (50-83) 71.1 (21.4) 0.039

Table 3 EORTC QLQ-C30 questionnaire scores by the type of resection (Mann-Whitney U test) Subtotal gastrectomy (n = 73) Total gastrectomy (n = 43) p value Mean (SD) Median (IQR) Mean (SD) Median (IQR) Functional scales Physical functioning



79.9 (21.4) 87 (67-100) 80.3 (19.5) 87 (73-100) 0.954 Role functioning 80.2 (26.7) 100 (67-100) 77.9 (26.1) 83 (67-100) 0.509 Cognitive functioning 81.9 (21.6) 83 (67-100) 82.9 (19.7) 83 (67-100) 0.842 Emotional functioning 82.1 (20.5) 92 (75-100) 76.1 (21.5) 79 (58-96) 0.116 Social functioning 81.5 (22.5) 83 (67-100) 73.7 (26) 83 (50-100) 0.115 Symptoms
Dyspnoea 10.5 (22.1) 0 (0-0) 10.8 (21.5) 0 (0-0) 0.869 Insomnia 28.7 (29.1) 33 (0-33) 27.8 (28.1) 33 (0-33) 0.917 Appetite loss 10 (19.7) 0 (0-0) 12.3 (20.6) 0 (0-33) 0.489 Nausea/vomiting 10.7 (17.4) 0 (0-17) 4.7 (9.8) 0 (0-0) 0.079 Constipation 10.5 (22.1) 0 (0-0) 6.9 (13.6) 0 (0-0) 0.665 Diarrhoea 13.6 (22.7) 0 (0-33) 19.3 (24.4) 0 (0-33) 0.141 Fatigue 30.5 (23.3) 22 (17-33) 34.2 (23.4) 33 (22-50) 0.263 Pain 18.3 (22.4) 17 (0-33) 17.9 (21.6) 17 (0-33) 0.906 Financial problems 16.4 (26.7) 0 (0-33) 27.1 (32.8) 0 (0-67) 0.069 Global health status 66.6 (22.9) 67 (50-83) 67.4 (19.9) 67 (58-83) 0.846

Table 4 EORTC QLQ-C30 questionnaire scores by the type of reconstruction (Mann-Whitney U test)

	Billroth II (n = 26)	Roux-Y (n = 47)	p value	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Functional scales																																																																																		
Physical functioning	73.1 (23)	73.5 (53-93)	83.7 (19.6)	92 (73-100)	0.038	Role functioning	70.5 (31.4)	67 (50-100)	85.5 (22.4)	100 (67-100)	0.034	Cognitive functioning	76.9 (26.3)	83 (67-100)	84.7 (18.3)	83 (83-100)	0.301	Emotional functioning	74.9 (27.7)	83 (58-100)	86 (14)	92 (75-100)	0.220	Social functioning	79.5 (25.9)	83 (67-100)	82.6 (20.5)	83 (67-100)	0.792	Symptoms	Dyspnoea	16.7 (30.3)	0 (0-33)	7 (15.4)	0 (0-0)	0.285	Insomnia	37.1 (33.2)	33 (0-67)	24 (25.8)	33 (0-33)	0.102	Appetite loss	12.8 (25.1)	0 (0-33)	8.4 (16.2)	0 (0-0)	0.651	Nausea/vomiting	15.4 (22.1)	0 (0-33)	8.1 (13.8)	0 (0-17)	0.194	Constipation	19.2 (31.5)	0 (0-33)	5.6 (12.5)	0 (0-0)	0.054	Diarrhoea	14.1 (31.6)	0 (0-0)	13.3 (16.4)	0 (0-33)	0.200	Fatigue	41 (28.6)	33 (22-67)	24.6 (17.5)	22 (17-33)	0.028	Pain	28.9 (28.1)	17 (0-50)	12.4 (16.1)	0 (0-17)	0.010	Financial problems	19.2 (28.6)	0 (0-33)	14.8 (25.8)	0 (0-33)	0.510	Global health status	68.2 (24.7)	67 (50-83)	65.7 (22)	67 (50-83)	0.635

Table 5 Surgery type among different stages of the disease

Total gastrectomy (n, %)	Subtotal-Billroth II (n, %)	Subtotal-Roux-Y (n, %)	p value	Stage
0	4 (4.1)	3 (6.5)	0.002	0



0 (0) I 25 (25.5) 14 (30.4) 38 (42.2) II 26 (26.5) 10 (21.7) 32 (35.6) III 43 (43.9) 19 (41.3)
20 (22.2) Table 6 Association between surgery type and global health status scores
adjusted for demographic and clinical characteristics β (p value) Male -0.11 (0.229)
Age (years) -0.05 (0.625) Total vs. Billroth II -0.001 (0.990) Roux-Y vs. Billroth II -0.08
(0.492) Postoperative complications-yes -0.15 (0.116) Stage II/III vs. 0/I -0.21 (0.029) β :
standardized regression coefficient Table 7 Association between surgery type and
scores on functional scales adjusted for demographic and clinical characteristics
Emotional Social Role Physical Cognitive β p value β p value β p value β p value β p
value Male 0.01 0.901 0.10 0.254 0.09 0.334 0.16 0.089 0.04 0.666 Age (years) 0.09 0.343 0.05
0.557 0.08 0.379 -0.09 0.343 0.18 0.054 Total vs. Billroth II 0.04 0.729 -0.11 0.343 0.15 0.199
0.15 0.201 0.16 0.194 Roux-Y vs. Billroth II 0.24 0.041 0.04 0.763 0.24 0.034 0.23 0.048 0.17
0.154 Postoperative complications yes -0.03 0.730 -0.13 0.150 -0.15 0.101 -0.10 0.292 0.01
0.915 Saage II/III vs. 0/I -0.17 0.062 -0.20 0.031 -0.27 0.003 -0.16 0.079 -0.09 0.324 Table 8
EORTC QLQ STO-22 questionnaire scores by the type of resection (Mann-Whitney U test)
Subtotal gastrectomy (n = 60) Total gastrectomy (n = 51) P value Mean (SD) Median
(IQR) Mean (SD) Median (IQR) Dysphagia 11.1 (15.8) 11 (0-11) 17.2 (17.1) 11 (0-33)
0.020 Pain 19.7 (17.9) 17 (8-33) 23.3 (20.9) 17 (8-33) 0.477 Reflux 16 (20.9) 11 (0-22) 22.7
(23.6) 11 (0-44) 0.089 Eating restrictions 14.7 (17.4) 8 (0-17) 21.6 (18.2) 17 (8-33) 0.017
Anxiety 33.1 (23.4) 33 (17-44) 31.4 (25.8) 22 (11-44) 0.591 Dry mouth 24.1 (28.5) 33 (0-33)
24.7 (28.3) 33 (0-33) 0.871 Taste 6.4 (18.1) 0 (0-0) 11.6 (21.7) 0 (0-33) 0.109 Body image
18.7 (29.9) 0 (0-33) 20.1 (27.4) 0 (0-33) 0.567 Hair loss 16.4 (27.9) 0 (0-33) 8.7 (20.9) 0 (0-0)
0.124 Table 9 EORTC QLQ STO-22 questionnaire scores by the type of reconstruction
(Mann-Whitney U test) Billroth II (n = 18) Roux-Y (n = 42) P value Mean (SD) Median
(IQR) Mean (SD) Median (IQR) Dysphagia 15.8 (22.3) 5.5 (0-22) 8.5 (10.2) 11 (0-11)
0.526 Pain 24.3 (23.9) 17 (8-33) 17.2 (13.3) 17 (8-25) 0.471 Reflux 28.5 (26.3) 22 (0-44) 9.1
(13) 0 (0-11) 0.001 Eating restrictions 22.3 (22.8) 17 (0-42) 10.4 (11.7) 8 (0-17) 0.069



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Anxiety 36.6 (26.9) 33 (22-55) 31.2 (21.3) 33 (11-44) 0.541 Dry mouth 23 (26.3) 33 (0-33)
24.7 (29.9) 0 (0-33) 0.965 Taste 11.5 (26.6) 0 (0-0) 3.5 (10.3) 0 (0-0) 0.247 Body image 26.8
(36.5) 0 (0-33) 14.1 (24.8) 0 (0-33) 0.127 Hair loss 14.1 (27) 0 (0-33) 17.7 (28.6) 0 (0-33)
0.541



RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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SPECIFIC COMMENTS TO AUTHORS

The manuscript has improved a lot. Congrats



RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Dear Authors, Thanks for making the changes at the relevant places. The article now



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appears a better shape. Thanks and regards



RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 63371

Title: Health-related quality of life after curative resection for gastric adenocarcinoma

Reviewer's code: 03478004

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: Japan

Author's Country/Territory: Slovenia

Manuscript submission date: 2021-01-31

Reviewer chosen by: Chen-Chen Gao

Reviewer accepted review: 2021-03-08 13:21

Reviewer performed review: 2021-03-09 08:47

Review time: 19 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The authors have sincerely responded to our comments.