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13/10/2017

Dear Prof Y Qi and Prof K Chen,

Re: ID number of editorial board member, UK – Dr Yeng S Ang – 0027412 and author number 00006607 - Gastric endoscopic submucosal dissection as a treatment for early neoplasia and for accurate staging of early cancers in a UK Caucasian population (**Manuscript NO.:** 36162).

Rebuttal letter:

Reviewer #1: This is a descriptive retrospective study about the value of ESD on neoplastic gastric lesion, performed on a western tertiary hospital . It is very interesting because it shows the results of this procedure in real clinical practice , but unfortunately the follow up is very short in order to compare with other surgical approaches But there are some question the author should answer There are some acronyms that should be explained at the material and methods or at the introduction for all the best understanding of all kind of readers : mapping OGD?, KATO? , MDT? Material and methods it should be clearly specified THE inclusion and exclusion criteria there should be explained where the ESD procedure was made ; at the operating room?, with the patient intubated? , with Co2?? , there should be explained the treatment after the procedure PPI ?, and for how long, and the schedule for the endoscopic surveillance, the time interval and for how long ? “ 10 were indefinite group, only 2 patients were considered potential candidates for surgery. The rest were only offered endoscopic follow-up as complete resection had been achieved ... “ Could you comment why not Chemo/radiotherapy as an adjuvant therapy , please

add some comments based on the literature knowledge Could you point out and explain all the ESD complications (early and late) of the procedure appeared during AND after the procedure(early and late) such as perforation, fever pain, delay bleeding Results It should be notified the duration of the ESD procedure in minutes Endoscopic follow up “....A positive secondary outcome was observed in 40% and 80% at 12-month and at the latest follow-up respectively. “ What does it mean ? could you give us a better explanation “Survival Rate ..Survival rate in ESD patients was 94.7% (18 out of 19 patients)”. You should add: at what time of follow up , 1year?

Answers:

Acronyms that should be explained at the material and methods for all the best understanding of all kind of readers;

- (1) mapping OGD is mapping oesophagogastrroduodenoscopy – basically a pre-ESD check to see if the case is suitable for ESD (inserted in page 7)*
- (2) KATO – a grading system to see if the polyp is suitable for ESD - On assessing the polyp itself, the first consideration should be a judgement of the neoplastic potential. Pit pattern assessment by chromoendoscopy or vascular pattern by Olympus Narrow Band Imaging (NBI) together with morphological features; fixity, indrawing of folds, depression or non-lifting sign (Kato sign, inserted in method section page 7 and reference number 24, inserted as reference no 24 by Kato H et al).*
- (3) MDT means multi-disciplinary team meeting (inserted in method section page 7)*

The inclusion and exclusion criteria are now inserted in page 7:

Inclusion criteria:

Data was obtained for a period of 2 years from May 2015 to June 2017. The initial selection of patients for the assessment of their suitability for ESD with mapping oesophagogastrroduodenoscopy (OGD) was made on the basis of computed tomography (CT) scans (or Positron Emission Tomography/Computed Tomography (PET-CT) in a few cases) and Endoscopic Ultrasound (EUS). Only Caucasian patients with gastric cancers staged at or below T1aN0M0 using these imaging techniques were included in this study

Exclusion criteria:

Patients with gastric cancers staged at T1bN0M0 or above have been excluded from the study on the basis of computed tomography (CT) scans (or Positron Emission

Tomography/Computed Tomography (PET-CT) in a few cases) and Endoscopic Ultrasound (EUS)

The ESD procedure was carried out in theatre (operating room) with the patient under general anaesthesia. The patient was intubated with the assistance of an anaesthetist and endoscopy performed using carbon dioxide gas only (inserted in page 8).

The treatment after the procedure is with oral Omeprazole 40 mg twice daily for at least 3 months (or another equivalent proton pump inhibitor) and the schedule for the endoscopic surveillance for site check in 3 months and then 6 monthly for first year and then yearly thereafter, for 5 years (inserted in page 8).

Adjuvant chemotherapy/radiotherapy is only given in cases of proven lymph node or distant metastases (based on CT and PETCT staging or laparoscopy if more than T1aN0M0 disease – see exclusion criteria). In all our cases, after careful staging with CT, PETCT, none were positive for lymph node or distant metastases at the very outset. Hence chemotherapy would not be appropriate as an adjuvant treatment (inserted in page 10).

Complications are defined as acute (during the procedure), early (<48 hours) or late (>48 hours). The most common acute complication reported was oozing small blood vessels (6). In 4 of these cases, bleeding was mild and treated with argon, coagulation forceps or endo-clips. In the other 2, the procedure had to be aborted due to profuse bleeding. Both cases were in the same patient. The patient was on anti-coagulation for atrial fibrillation and had a normal INR after stopping warfarin for 5 days prior to ESD. The marked mucosal friability resulted in bleeding even on mild trauma from the water jet used during endoscopy (Figure 4). A further 2 cases also had to be aborted, one due to the location of the lesion, which would have led to gastric outlet obstruction in due course and the other due to extensive scarring secondary to a previous ESD attempt. There was only one case of early complication of vomiting within 24 hours of the procedure and no cases of late complications (inserted in page 8).

The mean duration of the ESD procedures was 160 minutes and the median 140 minutes (depending on size of lesion, location and tissue factors) (median duration inserted in page 8)

The secondary end-point was complete reversal of dysplasia at endoscopic follow-up after ESD. In the cohort considered to have achieved curative resection with ESD, 80% were found to be free of dysplasia at their latest endoscopic follow-up at a mean follow-up period of 6.8 months (Figure 8). Hence, with both cohorts (CR and 'indefinite') combined, 7 of the 11 patients (81.8%) who had had at least one endoscopic follow-up were found to be free of dysplasia on endoscopy at their latest follow-up at a mean follow-up period of 7.7 months (inserted in page 11).

Survival rate in ESD patients was 94.7% (18 out of 19 patients) at a mean follow-up period of 15 months (inserted in page 12).

Reviewer #2: General comments Sooltangos et coworkers present a retrospective study derived from their clinical audit data on the technical and clinical outcome of endoscopic submucosal dissection of early gastric neoplasia in a Caucasian population. There are already several publications of ESD in the caucasian population although the uptake in the UK is still slow -whether this justifies a publication is disputable (Endoscopy. 2017 Sep;49(9):855-865, Endoscopy. 2010 Dec;42(12):1037-4, Gastrointest Endosc. 2015 Nov;82(5):804-11, Endoscopy. 2014 Nov;46(11):933-40, Gastric Cancer. 2010 Nov;13(4):258-63, Gastrointest Endosc. 2012 Jun;75(6):1166-74, GE Port J Gastroenterol. 2015 Mar 20;22(2):52-60). The numbers included is small, only 19 patients underwent ESD in this study. 4 ESD attempts were aborted. En bloc resection was achieved only in 71%, histological complete resection only in 38%. Where did the endoscopist train and learn the techniques of ESD? In the West or in the East? This would be important to state for the message of this study. Poor tissue handling, the event that ESD specimen reached the laboratory without formalin, inconsistencies in pathology reporting indicate that the infrastructure has to be improved and team education is required. Specific comments Please explain the KATO classification and give a reference.

Answers:

Endoscopy. 2017 Sep;49(9):855-865 - Germany

Endoscopy. 2010 Dec;42(12):1037-4 - Germany

Gastrointest Endosc. 2015 Nov;82(5):804-11 - Colombia

Endoscopy. 2014 Nov;46(11):933-40 - Portugal

Gastric Cancer. 2010 Nov;13(4):258-63 - Italy

Gastrointest Endosc. 2012 Jun;75(6):1166-74 - Germany

GE Port J Gastroenterol. 2015 Mar 20;22(2):52-60 - Portugal

The studies listed above have indeed been carried out in Western countries, possibly on Caucasian populations, but no similar studies can be found in the UK. The importance of a UK study specifically is justified by the urgent need for local guidelines on the procedure, which are set by the National Institute of Health and Care Excellence (NICE). Due to the lack of local evidence for the efficacy of gastric ESD up to this date, NICE still considers ESD an experimental technique to be applied on a case-by-case basis. There are many reasons to account for this: firstly, ESD is a technically demanding procedure exclusively offered in a few tertiary

centres in the UK. Secondly, the lack of screening programmes for gastric cancer in the UK leads to these cancers being detected at more advanced stages when they are no longer amenable to ESD, thus resulting in a smaller study sample. Furthermore, differences in the histology (diffuse vs. intestinal) and in aetiology, notably genetic, of gastric cancer cases between populations of the West and the East make translation of studies between these two populations inappropriate and lend further support to the need for country-specific studies. Moreover, as mentioned in the paper (Page 4), the outcome of ESD is heavily dependent on the skills of the endoscopist and thus evaluation of ESD more locally in the UK is relevant to the literature (inserted in page 6).

The ESD procedures were jointly carried out by two interventional endoscopists. One of the interventional gastroenterologists trained in the West (Germany) and the other in the East and West (Japan and Germany) (inserted in page 8).

The one single case pertaining to a delay in preserving the ESD specimen in formalin was due to practical reasons. There was a delay in getting formalin to the operating theatre as the assistants to the endoscopists were not aware of the low stock in the operating theatre. Formalin was later obtained from another theatre.

The Kato classification - The degree of lift of each lesion was graded according to the Kato classification where Kato 1 denotes lifting without any resistance, Kato 2 lifting with some resistance and Kato 3 no lifting (inserted in page 7, reference number 24)

Reviewer #3: To the Authors, Congratulations for your interesting work. I hope that ESD will gain popularity in European countries. Please, pay attention that all abbreviation in the text should be explained. Also, may corrections to some spelling (oesophageal, esophageal?, OGD or EGD).

Answers:

All abbreviations have now been spelled out in full (Refer to Reviewer #1)

The paper has been written in British English, thus the differences in spellings to American English.

Reviewer #4: I read the manuscript named “Gastric endoscopic submucosal dissection as a treatment for early neoplasia and for accurate staging of early cancers in a UK Caucasian population” (Manuscript NO: 36162). and my recommendations are as follows. Title: It accurately reflects the major topic and contents of the study. Abstract: Adequate, summarizing the topic. Discussion: Topics has been discussed with all aspects. References are appropriate, relevant, and updated. Figures and tables are reflects the major findings of the study, and they are appropriately presented. Recently, endoscopic techniques have been used increasingly in the treatment of early gastric cancer. Generally speaking, it is a good study and has significant clinical value.

This manuscript is well written and documented. Also, this manuscript gives additional new knowledge to the literature. I think that this manuscript is suitable and worth to be published in World Journal of Gastroenterology.

We thank reviewer #4 for his positive comments that “this manuscript is suitable and worth to be published in World Journal of Gastroenterology”.

Editors' comments:

(1) Authors' department:

Please rearrange all the authors' affiliations with Department, University or Institute, City, Postcode, Country, etc. Please see the format in the attachment (without any symbol or figure like * or 1).

Gunda Millonig, Michaela Kern, Othmar Ludwiczek, Karin Nachbaur, Wolfgang Vogel

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(3) Institutional review board statement:

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(4) Informed consent statement:

This file must be provided in a PDF format, and the statement must also be mentioned as a footnote in the manuscript text.

Sample wording: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

(5) Correspondence to:

for example: Correspondence to: Koji Takeuchi, PhD, Department of Pharmacology and Experimental Therapeutics, Division of Pathological Sciences, Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607-8414, Japan. takeuchi@mb.kyoto-phu.ac.jp

Please provide your detail address. definite to the street number. Thank you!

(6) Core tip:

Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers. Audio Core Tip

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(7) Article Highlights

Please write the section at here. See the format in the Format.

(8) Figure 2 Please add a title.

Thank you for suggesting these changes. The manuscript has been updated to reflect the above recommendations.

Sincerely,



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