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Peer Review File

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Reviewer A:

Comment 1. Thank you for the opportunity to review this manuscript. The authors perform a literature review of colorectal NOSE with combined resection. This is an interesting topic. However, the data is too limited and heterogenous for a meaningful review of this topic. There is a large amount of selection bias in the cases performed. Moreover, there are no specific new insights to be gained in this manuscript.

Reply 1. First of all, we would like to thank the reviewer A for his/her positive comment. We agree with you about the data is too limited and heterogenous. And also bias may be in the cases. However, as a result, combined resections with NOSE are performed in many clinics and have taken their place in the literature with current case reports. We think that making a review within the existing literature, will definitely contribute to the surgeons (including us) performing the current technique to benefit from other experiences in the literature. And for the surgeons who consider performing the technique, this review may shed light on their path. In conclusion, we think that this study, which we have done upon the invitation from the journal (Annals of Laparoscopic and Endoscopic Surgery) for a special edition of 'Natural Orifice Specimen Extraction in Colorectal Surgery', will contribute as it is the first study of the literature.

Reviewer B:

Comment 1. I would like data from the table to be included in the body of the literature, to provide more information as to the nature of patients, BMI, etc.

Reply 1. First of all, thank you for your valuable comment and we agree with you. We thought about these details too, but we did not add them to the table due to the lack of data and clarity in the current case reports.

Comment 2. I would disagree with the essence of interpreting papers saying that they provide a better post-op outcome or there are no major complications. The papers cited are largely case reports and they state they were able to achieve NOSE in CRS combined surgery. And the conclusion can only be made that is technically feasible in experienced hands and select patients, however, no data is there regarding outcomes as that is primarily determined by the underlying surgery in these cases.

Reply 2. Thanks for your useful comment and we agree with you. The 'conclusion' part can only achieve this result and we have changed it in this direction. The data is there regarding outcomes as that is primarily determined by the underlying surgery in these

cases is sumerized in Table 1.

Changes in the text: NOSE in CRSs is a new and effective approach in current surgery. In cases requiring additional organ resection combined with colorectal diseases, NOSE is technically feasible in selected patients by experienced surgeons. It is certain that new studies on this subject are needed in order to obtain clearer results.

Reviewer C:

Comment 1. Mention extraction trough anus (rectum???) and ureter (????)

Reply 1. First of all, thanks for your useful comments. Anus and ureter are defined by these names in the literature as natural orifice specimen extraction surgery. That's why we mentioned these names in our article. You can examine the references numbered 3 and 4 in our article regarding these definitions. We have elaborated these definitions by adding references 3 and 4 after your comment.

Changes in the text: Natural Orifice Specimen Extraction (NOSE) is the technique in which the intra-abdominally resected specimen is extracted by opening a hollow organ that communicates with the outside of the body, including anus, vagina, mouth or ureter, and it aims to reduce postoperative pain, incisional hernia, wound infection and cosmetic concerns, due to abdominal incision (3,4).

Comment 2. Material and methods. Is it a systematic review?. It should follow the PRISMA model. how many papers?, which topics reviewed, nº of papers, rejected, why

Reply 2. The reviewer is right in his/her comment on the formatting, but we present the following article in accordance with the ‘clinical practice review’. In parallel with our manuscript, you can examine similar reviews which authors were invited and published like us for the 'Natural orifice specimen extraction surgery- special issue'.
Example:
-Benign and malignant colorectal pathologies for natural orifice specimen extraction surgery. Yusuf Murat Bag, Egemen Ozdemir Annals of Laparoscopic and Endoscopic Surgery 2022;7:26 (30 July 2022)

Comment 3. The paper is a merely description of cases, but do not enter in the main problem with these technique. 1.- Oncological protection for extraction, 2.- size limits, 3.- Short terme outcome, 4.- long term functional outcome, 5.- Long terme oncological outcome. another aspect is the experience of the surgical team....nº of cases, outcomes, evidence for seres not multiviceraal???
Personally consider that the paper, with a topic of interest, need a complete reshape, and try to get the level of evidence that could advise the use of these techniques.

Reply 3. Thanks for the reviewer's positive comment. Oncological protection for extraction and short term outcomes data is shown in the table (Table 1). Unfortunately, we could not include them in the table due to the lack of clear information about long-term functional and oncological outcomes. And we added a sentence about generally early and late period complications, and referred it. We shared the consensus suggestions and our own opinion in terms of 'size limits' in the article ('It has been suggested that the orifice selection should be based on the maximum circumferential diameter of the specimen in the consensus report (the transanal route for tumor <3 cm and the transvaginal route for tumor 3-5 cm). In conclusion, we think that using similar specimen extraction route principles for combined resections in colorectal cancer liver metastasis, if both of the specimens' circumferential diameters are suitable, would be better in terms of technical feasibility and postoperative results.').
Since the main subject of this article we invited and prepared for the special edition called 'Natural Orifice Specimen Extraction Surgery' is the evaluation of combined extractions in terms of the data in the literature, and this subject has never been examined in the literature except for case reports, we did not think to change the outline of the article. Our aim is to objectively evaluate the status of combined resections in NOSE in the literature and to state our opinion for the surgeons using or planning to use this technique. As a result, in conclusion part we indicated that 'It is certain that new studies on this subject are needed in order to obtain clearer results'.

Changes in the text: (Introduction-references) In addition to the benefits of the technique, rare complications such as perioperative organ injury, anastomotic leakage, fecal incontinence, intra-abdominal contamination, dyspareunia and recurrence in the specimen extraction area can be seen (9).
9. Complications and management of natural orifice specimen extraction in colorectal cancer: a narrative review. Zengin A, Okut G, Turgut E. Ann Laparosc Endosc Surg 2022;7:24.

Reviewer D:

This is an interesting manuscript dealing with a very interesting topic. But there are some required corrections and also a few remaining questions, that should be clarified and discussed, respectively

Comment 1. English needs further improvement
Reply 1. First of all, thanks to the reviewer for his/her useful comments. We have made the needs of further improvement about English. You can check the review again.

Comment 2. Authors should make a comment regarding the incidence of perioperative complications and relate them to those of NOSE in the literature

Reply 2. After the reviewer's comments, although it is not our title and main subject in this article we wrote on the invitation for special edition regarding 'Natural orifice specimen extraction with combined resections', we changed and detailed our sentences about complications, cited them and made comments.

Changes in the text: (Introduction) In addition to the benefits of the technique, rare complications such as perioperative organ injury, anastomotic leakage, fecal incontinence, intra-abdominal contamination, dyspareunia and recurrence in the specimen extraction area can be seen (10). In order to minimize these complications, recommendations such as preoperative rectal and vaginal cleaning, selection of a natural orifice compatible with the specimen diameter, or removal of the specimen in a protective sheath, were presented in the 'CRS combined with NOSE consensus report' in 2019 (3).
(Conclusion) To minimize the complications, we think consensus recommendations should be followed as similar to single organ resections.

Comment 3. The international consensus on natural orifice specimen extraction surgery (NOSES) for colorectal cancer in 2019 suggests "Despite significant decrease in surgical trauma of NOSES have been observed, the potential pitfalls of this technique have been demonstrated." The authors should make a comment.
Reply 3. Thanks for your useful comment. We think that, the changes we made due to your comment 2 also meet your comment 3. Our changes and comment is shown in 'reply 2'.

Comment 4. The authors should comment on NOSE in robotic surgery

Reply 4. We also agree with the reviewer. Minimally invasive surgery includes both laparoscopic and robotic surgery. For this reason, we have made a change in the Introduction section to enlighten the readers. And we transformed the word 'laparoscopic' to 'minimally invasive' in all the manuscript.

Comment 5. The problem with case reports is that there is patient selection. It is difficult to draw a conclusion

Reply 5. We agree with the reviewer's comment. So we stated that 'It is certain that new studies on this subject are needed in order to obtain clearer results' in the conclusion part.

Reviewer E:

Comment 1. This is an interesting analysis dealing with a very interesting topic.
In my opinion, there are some required corrections, additions and remaining questions:

Please give the paper a scientific structure (methods, results, discussion).

Reply 1. First of all, thanks for the reviewer for his/her useful and positive comments. We present the following article in accordance with the 'clinical practice review'. In parallel with our manuscript, you can examine similar reviews which authors were invited and written like us for the 'Natural orifice specimen extraction surgery- special issue'.
Example:
- Benign and malignant colorectal pathologies for natural orifice specimen extraction surgery. Yusuf Murat Bag, Egemen Ozdemir Annals of Laparoscopic and Endoscopic Surgery 2022;7:26 (30 July 2022)

Comment 2. Please define the aim of the analysis, more than "to review the literature including NOSE for combined resections with CRSs". You would like to review the literature with regard to what?

Reply 2. We agree with the reviewer. We added the aim of our analysis to the abstract part.

Changes in the text: (Abstract) We aimed to review the literature in terms of NOSE for combined resections with CRS, including preoperative details, technical feasibility, perioperative findings and postoperative results.

Comment 3. What do you mean with "protection" in table 1?

Reply 3. We mean 'protection sheath' usage. We changed in in the table. Thanks for your useful comment.

Comment 4. Please refer to the table 1 in the text.

Reply 4. We referred the Table in the text.

Comment 5. In addition, I would recommend adding two more important papers for this topic:
One paper analyzing the first 139 patients of the German NOTES Registry (GNR) with colon resections (1).
The second paper compared transvaginal sigmoid resection with traditional laparoscopic resection for diverticulitis. It showed a comparable safety but some advantages of the transvaginal technique regarding morphine requirement as well as postoperative length of hospital stay in this patient population (2). Furthermore, in this study, there are three cases with an additional organ resection and transvaginal removal, one resection of benign omentum nodes, one cholecystectomy, and one liver resection (see the second paragraph of the result section).

1. Bulian DR, Runkel N, Burghardt J, et al. Natural Orifice Transluminal Endoscopic

Surgery (NOTES) for colon resections--analysis of the first 139 patients of the German NOTES Registry (GNR). International journal of colorectal disease 2014;29(7):853-61. doi: 10.1007/s00384-014-1883-1
2. Derstadt M, Thomaidis P, Seefeldt CS, et al. Transvaginal hybrid-NOTES vs. traditional laparoscopic sigmoid resection for diverticulitis: a short-term comparative study. Sci Rep 2020;10(1):22321. doi: 10.1038/s41598-020-79461-1 [published Online First: 2020/12/20]

Reply 5. First of all, thanks for your useful and positive comment. Since NOTES is one of our article exclusion criteria, we did not consider these articles. However, at your valuable comment, we also benefited from the information in these articles. For the first article, there are five NOTES failed cases and laparoscopic resection with NOSE was used. Due to parameters like operation time and complications, heterogeneity was likely to occur and we thought it was not correct. For the second article, the hybrid NOTES technique used in the article is very similar to NOSE. And there are two cases parallel to our data. We included these cases to our review after your useful comment. We excluded one case because of only abdominal lymph nodes were extracted with sigmoid colon. And also we cited this article in the 'References'. Thanks again.

Reviewer F:

Comment 1. There are cases with unknown complications and cases of suture failure (p. 37). Please tell me if there is any difference in complication rates compared to CRS surgery, just as far as you have considered in this paper.

Reply 1. First of all, thanks to the reviewer for his/her useful comments. It was a limitation for our review and we agree with you. We added the answer of this question to the introduction part. As we know, there is no difference in terms of general complications and anastomosis leakage.

Changes in the text: (Introduction) The studies have shown that while general complication rates are similar, NOSE is superior to transabdominal specimen extraction, especially in terms of postoperative pain, length of hospital stay and cosmesis, and this result have been very effective in these increasing numbers (9).

Comment 2. What is the long-term prognosis for cases of malignant disease? Please tell me if there is any difference in the recurrence rate compared to CRS surgery.

Reply 2. The long-term prognosis of this technique in malignant patients is similar to conventional methods. The main reason for this is likely the same oncological principles. However, although rare, local recurrence can be seen in the natural orifice which the specimen was extracted. To prevent this, the use of a protective sheath is recommended,

as stated in the consensus report. We tried to highlight this in our article.

Changes in the text: (Introduction) In addition to the benefits of the technique, rare complications such as perioperative organ injury, anastomotic leakage, fecal incontinence, intra-abdominal contamination, dyspareunia and recurrence in the specimen extraction area can be seen (10). In order to minimize these complications, recommendations such as preoperative rectal and vaginal cleaning, selection of a natural orifice compatible with the specimen diameter, or removal of the specimen in a protective sheath, were presented in the 'CRS combined with NOSE consensus report' in 2019 (3).

Comment 3. Please tell me why NOSE (transanal) was chosen for right hemicolectomy (P13-16).
Also, if you know the gender of the case, please let me know.

Reply 3. In patients 13-14, the specimens were extracted via colonoscope (transcolonic access). In patients 15-16, specimens were extracted via transanal endoscopic microsurgery (TEM) scope. The reasons for the choice of natural specimen was not specified. We think, the choice reasons may be surgeon's or patient's choice, surgical experience, endoscopic experience, pelvic anomalies or perioperative other technical requirements. Unfortunately, detailed information about the ages of the patients was not provided.