Peer Review File
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Reviewer A

This is an interesting manuscript on radical en bloc right colectomy/Whipple for locally advanced colon cancer . It is well written and a large series for was is a relatively uncommon situation. I have some suggestions for improvement:

It is unclear to me if patients who underwent surgery for suspected duodenum/pancreas invasion, but where the histopathology showed no actual invasion (i.e. inflammatory adhesion only) were excluded? These patients should be included in a series reporting outcomes of this ultra radical resectional technique. How can this be avoided or lack of invasion predicted preoperatively? A theoretically unnecessary Whipple procedure is a big deal and should be addressed in the paper and discussion.

The authors state that patient were included if the tumour was "amenable to radical resection". Could you please outline resectability criteria and more importantly, what was considered a contraindication to surgery?

Please elaborate on preoperative imaging used to assess resectability - did you use portal venous phase CT only? Any role for EUS or MRI? Were PET scans used? What proportion suggested duodenal invasion but showed no invasion on pathology?

The aims are vague ("report clinical outcomes") and could be more specific

The statement "All patients were cleared of local lymph nodes (mesenteric lymph nodes)" is ambiguous. Please report median lymph node yield

Please add perioperative mortality, overall complication rate, and major complication rate to table 1.

If available, data on disease recurrence (disease free survival, local vs. distant recurrence) would be interesting.

Approximately half the cohort had neoadjuvant chemotherapy. Please elaborate on how patients were selected for this in the methods section. Please reference the FOXTROT trial in the discussion and expand on the role of neoadjuvant chemotherapy in this patient population

References 18 and 19 are studies of primary pancreatic cancer and are not appropriate for the discussion about neoadjuvant treatment of colon cancer.

Overall, it is of interest and a large series for a relatively uncommon procedure . There are however substantial issues which could be addressed to approve it and make it worthy of publication. Please see above.

Dear reviewer,Thank you very much for commenting on my article, your comments are very professional and detailed, I have revised the article according to your comments, if there is anything inappropriate, please point it out.

Comment1: It is unclear to me if patients who underwent surgery for suspected duodenum/pancreas invasion, but where the histopathology showed no actual invasion (i.e. inflammatory adhesion only) were excluded? These patients should be included in a series reporting outcomes of this ultra radical resectional technique. How can this be avoided or lack of invasion predicted preoperatively? A theoretically unnecessary Whipple procedure is a big deal and should be addressed in the paper and discussion.

Reply1: Those patients with only inflammatory adhesions have been excluded by us at the beginning because this study was a follow-up of two previous studies and there were some patients who were too early to be followed up with difficulty, so this study was done only on patients who were determined to have tumor invasion postoperatively with a view to exploring surgical outcomes in the presence of invasion in patients with locally advanced disease. Approaches to predict invasion include CT/MRI/Ultrasound endoscopy. For patients with preoperative determination of adhesions and the inability to determine their nature, intraoperative segmentation should not be done hastily, but Enbloc resection is still encouraged, as hastily separating them intraoperatively brings lower survival rates.

Changes in the text1 ： We have modified our text as advised.(see Page 4, Line 118-122),(Page 5, Line 131-138)

Comment2:The authors state that patient were included if the tumour was "amenable to radical resection". Could you please outline resectability criteria and more importantly, what was considered a contraindication to surgery?

Reply2: Thank you very much for your professional advice! "amenable to radical resection"means "tumor does not invade important blood vessels, such as the superior mesenteric artery and portal vein."

Contraindications to surgery include:(I)Presence of distant organ metastases; (II)Secondary involvement of the pancreatic head and/or duodenum, but not direct infiltration; (III)Presence of an implanted cancerous nodule in the abdominal cavity; (IV)Invasion of the hepatic artery, celiac trunk, or superior mesenteric artery; (V)Nutritional Risk Screening 2002 (NRS 2002) score ≥3.

Changes in the text2：We have modified our text as advised.(see Page 5, Line 125-126), (Page 6, Line 176-180)

Comment3: Please elaborate on preoperative imaging used to assess resectability - did you use portal venous phase CT only? Any role for EUS or MRI? Were PET scans used? What proportion suggested duodenal invasion but showed no invasion on pathology?
Reply3: A cautious approach should be taken as to whether the invasion is a malignant adhesion or not. Abdominal CT examination needs to focus on the clarity of the fat line between the right colon tumor and the duodenum, and the blurring or disappearance of the fat line needs to be taken into account for the possibility of malignant invasion. For patients who are difficult to identify, additional MRI and EUS should be considered.MRI can observe the relationship between colon tumor and surrounding tissues from multiple angles, and it is also more sensitive to fatty tissues. In addition, EUS is a good choice for patients who are difficult to identify. An ultrasound probe is placed on the tumor surface and scanned to determine the depth and extent of tumor infiltration and its relationship with surrounding adjacent organs, as well as to determine surrounding vascular and lymph node invasion. Duodenoscopy can also help in the identification, and can scrutinize the intestinal mucosa for signs of inflammation, depressions, sinus tracts, and other signs of invasion.
The percentage of preoperative assessment of malignant adhesions and postoperative pathologic findings suggestive of inflammatory adhesions was 18.9% in this study.
Changes in the text3：We have modified our text as advised. see(Page 9, Line 272-284), (Page 9, Line 289-292)

Comment4: The aims are vague (“report clinical outcomes”) and could be more specific
Reply4: Thank you very much for your comment, which I have explained in detail in the article.
Changes in the text4：We have modified our text as advised. see (Page 4, Line 105-108)

Comment5: The statement "All patients were cleared of local lymph nodes (mesenteric lymph nodes)” is ambiguous. Please report median lymph node yield
Reply5: Thank you very much for your comment, the median lymph node detection number I have described in the article.
Changes in the text5: We have modified our text as advised. see (Page 8, Line 249-250)

Comment6: Please add perioperative mortality, overall complication rate, and major complication rate to table 1.
Reply6: Thank you very much for your comment, I've added the appropriate data to the table
Changes in the text6: We have modified our text as advised. see (Page 17, Table1)

Comment7: If available, data on disease recurrence (disease free survival, local vs. distant recurrence) would be interesting.
Reply7: Thank you very much for your suggestion, this study is a sequential study of two previous studies by our team, it is very unfortunate that due to the time span these data were not taken seriously at the time, and due to the fact that it is a retrospective study it is very difficult to find. I'm so sorry about that！

Comment8: Approximately half the cohort had neoadjuvant chemotherapy. Please elaborate on how patients were selected for this in the methods section. Please reference the FOXTROT trial in the discussion and expand on the role of neoadjuvant chemotherapy in this patient population
Reply8: Thank you for your suggestions, they make my posts more rigorous. I have described this issue most in detail in the methods section. I have cited the FOXTROT trial and discussed in detail the preoperative chemotherapy for colon cancer patients as per your suggestion.The FOXTROT trial is a compelling study and your recommendations are very professional!
Changes in the text8: We have modified our text as advised. see (Page 5, Line 138-142), (Page 10, Line 312-328) ,(Page 11, Line 337-338)

Comment9: References 18 and 19 are studies of primary pancreatic cancer and are not appropriate for the discussion about neoadjuvant treatment of colon cancer.
Reply9: Thank you very much for your very careful review. The two references were indeed not quite right, and I have re-cited the new references.
Changes in the text9: We have modified our text as advised. see (Page 15, Line 461-466)
Once again, I would like to express my gratitude for your review, the questions you asked were very professional and clinically relevant, and I have revised the article according to your suggestions, which have made it even better! Best wishes to you!

Reviewer B

Comment:Thank you for providing me with the opportunity to review your paper. Your study, a retrospective analysis of patients undergoing multi-organ surgical resection for locally advanced tumors of the right colon, has captured my attention. However, I would like to highlight that, in my perspective, its main weakness lies in the lack of originality. To enhance the text's appeal, I suggest enriching the discussion chapter with more in-depth points for consideration.
Specifically, I propose that the authors consider including and discussing the following article: doi.org/10.18632/oncotarget.26972 . Although focused on the colon-rectum, it provides an interesting perspective on systemic treatments for advanced or metastatic diseases. Similarly, it would be advantageous to broaden the discussion on surgical technique, focusing, for instance, on the high-risk nature of a pancreatic anastomosis in

patients with multi-organ resections. To mitigate this risk, I recommend the authors draw inspiration from: doi.org/10.1016/j.pan.2022.08.005, which addresses relevant topics.
The statistical analysis appears to have been conducted appropriately. I hope these observations can contribute to further enhancing the overall quality of your scientific work.

Reply: Dear reviewer, Thank you for your feedback and raising the concern regarding the originality of our study. We appreciate your attention to previously published studies in the field. We would like to address your comment and explain why our study still contributes to the existing knowledge and advances the field. Our study incorporates methodological refinements and improvements, such as a larger sample size, rigorous statistical analysis, and adjustment for potential confounding factors. These methodological advancements contribute to the reliability and robustness of our findings. In addition we have discussed in more detail in the text based on your suggestions.
Thank you very much for the two articles you recommended, both of them seem to me to be very original in their thinking and helpful for my articles. For patients without R0 resection, in addition to systemic therapy, pelvic perfusion therapy that can be performed in the field of rectal cancer can also provide us with new treatment ideas. Postoperative complications are also worth considering, and the novel "Huscher technique" proposed by some scholars seems to be a new strategy to ensure the safety of intraoperative pancreatico-enteric anastomosis, which can minimize the occurrence of postoperative pancreatic fistula!
Once again, I would like to express my gratitude for your review, the questions you asked were very professional and clinically relevant, and I have revised the article according to your suggestions, which have made it even better! Best wishes to you!
Changes in the text: We have modified our text as advised. see (Page 9, Line 272-284), (Page 10, Line 312-328), (Page 12, Line 361-364,376-378)

Reviewer C

1) First, the title did not indicate the clinical research design of this study, i.e., a retrospective cohort study.
2) Second, the abstract needs some revisions. The background should have comments on the potential clinical significance of this research focus, not only knowledge gap. The methods need to describe the inclusion criteria of subjects, assessment of baseline clinical factors, follow up procedures and measurements of prognosis outcomes. The results need to briefly summarize the clinical characteristics of the study sample. Please check the values of HRs since they should not be lower than

1. The conclusion needs to be tone down due to the small sample size and the retrospective cohort design.

3) Third, the introduction needs to review what has been known on the prognosis and prognostic factors in LARCC patients, analyze the limitations and knowledge gaps of prior studies, and clearly indicate the potential clinical contribution of this research focus.
4) Fourth, in the methodology of the main text, please describe the clinical research design, sample size estimation procedures, and detailed definitions of the primary and secondary outcomes. In statistics, please explain why quantitative variables were dichotomized, details of the multiple logistic regression analysis, and the P value for statistical significance.
5) Finally, please cite several potentially related papers: 1. Meng H, Xu H, Wang X, Chen L, Yang F, Geng R, Xu Y, Yu G. Total laparoscopic en bloc right hemicolectomy and pancreaticoduodenectomy with transvaginal specimen extraction for locally advanced right colon cancer: a case report. Gland Surg 2021;10(5):1780-1785. doi: 10.21037/gs-20-800. 2. Rajandram R, Khong TL, Aziz NA, Aziz MRA, Roslani AC. A narrative review: complete mesocolic excision in right-sided colonic cancer resections—present paradigm and future directions. Ann Laparosc Endosc Surg 2023;8:27.

Dear reviewer,Thank you very much for commenting on my article, your comments are very professional and detailed, I have revised the article according to your comments, if there is anything inappropriate, please point it out.

Comment1: First, the title did not indicate the clinical research design of this study, i.e., a retrospective cohort study.

Reply1: Thank you very much for your comment, I've changed the title in the article as you suggested.

Changes in the text1: We have modified our text as advised. see (Page 1, Line 3-4).

Comment2: Second, the abstract needs some revisions. The background should have comments on the potential clinical significance of this research focus, not only knowledge gap. The methods need to describe the inclusion criteria of subjects, assessment of baseline clinical factors, follow up procedures and measurements of prognosis outcomes. The results need to briefly summarize the clinical characteristics of the study sample. Please check the values of HRs since they should not be lower than 1. The conclusion needs to be tone down due to the small sample size and the retrospective cohort design.

Reply2: Thank you very much for your comments, which were very detailed, and I've revised the abstract in line with your comments. Similarly I weakened the strength of the conclusion as you suggested. HR values I have made changes, this was an error in our statistical process, I consulted with a statistical professional and re-did the statistics

Changes in the text2: We have modified our text as advised. see (Page 2, Line 34-74), (Page 18, Line519,Table3)

Comment3: Third, the introduction needs to review what has been known on the prognosis and prognostic factors in LARCC patients, analyze the limitations and knowledge gaps of prior studies, and clearly indicate the potential clinical contribution of this research focus.
Reply3: Thank you very much for your comments, your advice is very detailed. I have made introduction in the corresponding section of the text.
Changes in the text3: We have modified our text as advised. see (Page 4, Line 90-94)

Comment4:Fourth, in the methodology of the main text, please describe the clinical research design, sample size estimation procedures, and detailed definitions of the primary and secondary outcomes. In statistics, please explain why quantitative variables were dichotomized, details of the multiple logistic regression analysis, and the P value for statistical significance.
Reply4: Thank you for your suggestion, I have added to the Methods section of the main text as you suggested, and regarding statistics, I have provided a detailed explanation in the section on statistical analysis
Changes in the text4: We have modified our text as advised. see (Page 5, Line 143-149), (Page 7, Line 198-208)

Comment5: Finally, please cite several potentially related papers: 1. Meng H, Xu H, Wang X, Chen L, Yang F, Geng R, Xu Y, Yu G. Total laparoscopic en bloc right hemicolectomy and pancreaticoduodenectomy with transvaginal specimen extraction for locally advanced right colon cancer: a case report. Gland Surg 2021;10(5):1780-1785. doi: 10.21037/gs-20-800. 2. Rajandram R, Khong TL, Aziz NA, Aziz MRA, Roslani AC. A narrative review: complete mesocolic excision in right-sided colonic cancer resections—present paradigm and future directions. Ann Laparosc Endosc Surg 2023;8:27.
Reply5: Thank you for your comments, the two papers you recommend are of very high quality and have significant implications for updates in surgery. For resectable locally advanced right hemicolon cancer, there are still many issues that deserve to be investigated, not only in terms of patient survival, but also advances in surgical techniques. Laparoscopic en bloc resection and transvaginal specimen extraction have been reported in relevant cases and the advancement of surgical techniques may lead to fewer complications and shorter hospitalization. Laparoscopic Complete mesocolic excision (CME) in right-sided colonic cancer resections has a higher number of lymph node dissection than open surgery and has shorter hospitalization days, exploring advances in surgical technique and performing laparoscopic resection of locally advanced right hemicolon cancer when R0 resection is possible is a direction for our subsequent research. This may reduce our concerns when choosing en bloc resection surgery.

Changes in the text5: We have modified our text as advised. see (Page 12, Line 366-376)