Author’s response to reviews

Title: Laparoscopy-Assisted Colectomy as an Oncologically Safe Alternative for Patients with Stage T4 Colon Cancer: A Propensity-Matched Cohort Study

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Dear Dr. Alexandros Houssein,

We thank you and all reviewers for the critical feedback on our manuscript entitled “Laparoscopy-Assisted Colectomy as an Oncologically Safe Alternative for Patients with Stage T4 Colon Cancer: A Propensity-Matched Cohort Study” (BCAN-D-17-01823). Those review comments were useful for the improvement of our manuscript. We thank you for this chance of revision. The revised manuscript with tracked changes has been submitted. We hope our revision is satisfactory to you and reviewers.

Our point-by-point response to the comments from the reviewers is provided below.

Comments from Dr. Mario Schootman (Reviewer 1):
Comment 1: “First, a recent meta analysis (Dis Colon Rectum. 2017 Jan;60(1):116-125) published 5 studies on this same topic. It would be important to describe how this study goes beyond the meta analysis, which was not mentioned in the manuscript.”

Response: We sincerely thank this reviewer for this important comment. In this revised manuscript, as suggested by the reviewer, we discussed this recent meta-analysis by Adina E et al. [reference 22] in the first paragraph of “Discussion” section (page 10, line 14-21), by adding words “Recently, a meta-analysis published 5 studies on comparing the oncologic outcomes following laparoscopic versus open resection of pT4 colon cancer [22]. It concluded that LAC appears to be safe for selective patients with pT4 tumor, which is similar to ours. This analysis tried to adjust for confounders by using matching method. In its one concluded study in which matching was performed, it seems that several covariates, i.e. age, sex, tumor stage, body mass index and ASA score were controlled, however, some more critically factors, such as tumor size, which is an important factor causing intraoperative conversion for T4 tumor, were failed to controlled at baseline.”

Comment 2: “Second, the propensity score was not described in enough detail to assure that this was done correctly. For example, there was no mention of if/how balance in the covariates was assessed, why these covariates were included, and what the caliper was for matching.”

Response: We appreciated the reviewer’s comment. We provided the details of propensity score matching in the revised manuscript (“Method” section, “Measured outcomes” subsection, line 21 on page 6 to line 3 on page 7). Covariates included in the model for estimating propensity score and the ratio and caliper for matching were detailed. To show the balance after matching, we add a new figure (Fig. 2 in revised version, referenced in line 1 on page 8, “Results” section) to illustrate the distribution of propensity score before and after matching for laparoscopic and open groups. And before and after matching, all clinicopathologic characteristics at baseline, included the matched covariates, were compared in the Table 1, showing the efficacy of the match process.

Comment 3: “Third, page 8 describes the outcomes of the converted groups. There are simply too few patients to make this meaningful.”

Response: We really agree with the reviewer’s point. Sample size of the converted group was too small to make a meaningful comparison. In the revised manuscript, we removed Table 3 which containing the comparison results of converted group with others, and deleted the subsection “Surgical findings and short term outcomes of patients occurring procedure conversion” (line 10-21, page 9), and described the number and corresponding causes of converted patients in the section “Surgical findings and short-term outcomes comparison between LAC and OC groups” (line 5-10, page 8). We have also discussed the outcomes from others studies in “Discussion” section (line 22 on page 11, to line 15 on page 12).

Comment 4: “Fourth, there were 242 patients in the 2 groups, which is likely too few to be meaningful to examine disease-free survival. The 5 year DFS rates were 56.2% and 41.4% but this was not statistically different although this seems to be clinically important.”
Response: The reviewer’s concern about the sample size is reasonable. Based on the method proposed by Lakatos et al. [Biometrics, 1988, Volume 44, March, pages 229-241], we performed a log-rank test power analysis for current sample size, by using the parameter as follow: N1=121, N2=121, proportional survival (control)=41.4%, proportional (treat)=56.2%, alpha=0.05 (two-tailed). The final power is 81.98% (Beta=0.1802), at a moderate level. To further comparing the oncologic outcomes, as suggested by another reviewer, we analysed the long-term survival separately for the pT4a and pT4b group in this revised version. OS and DFS curves for pT4a and pT4b stages are shown in Fig 3 (survival plot for the whole cohort, i.e., previous figure 2 in original manuscript was deleted). The 5-year DFS rate was 64.2% for pT4a stage and 35.5% for pT4b stage in LAC group, and 62.9% and 33.7% in OC group for pT4a (p = 0.374) and pT4b (p = 0.385) stage respectively. For 5-year OS rates, two groups were also similar in pT4a stage (LAC 69.2% vs. OC 66.0%, p = 0.151) and pT4b stage (LAC 37.5% vs. OC 38.1%, p = 0.510). These results showed close survival rates, either DFS or OS between two groups, in both pT4a and pT4b groups. Thus, final conclusion that LAC appears to be safe for pT4 tumor was drawn in our study.

Comments from Dr. Pieter Tanis (Reviewer 2):

Comment 1: “The conclusion should be weakened, because it is not possible to definitively conclude that laparoscopic resection of a locally advanced cancer is oncologically safe based on the present data, given the single institution setting (restricted external validity), and the non-randomized design. So, it should be modified with words such as "appears to be safe for selected patients in centres with expertise in minimally invasive surgery".”

Response: We agree with the suggestions by the reviewer and have modified the conclusion appropriately throughout the manuscript, included Abstract (line 4-7, page 3), Discussion (line 3-5, page 11) and Conclusions (line 9-12, page 14) sections.

Comment 2: “The authors has used "pathologic" T4 colon cancer as an inclusion criterion. However, the decision to use a laparoscopic or open approach is made preoperatively. Therefore, inclusion should actually be based on clinical T4 stage. Please comment.”

Response: We really appreciated the reviewer’s comments. In clinical practice, the decision to perform a laparoscopic or open surgery is surely made preoperatively. However, our study is a retrospective cohort study, which is a specific post-hoc analysis. Since the limited precision of clinical stage, pathologic T4 but not clinical T4 was used as an inclusion criterion in our study, as well as other similar studies [reference 22]. Current clinical T stage was evaluated by imageological examination and/or endoscopic ultrasonography, which may cause more overstaging or understaging. Moreover, the precision of clinical staging varies from difference hospitals or medical centres. In this study, we aimed at evaluating the safety and oncologic efficacy of laparoscopic surgery for T4 colon tumor, and attempted to provide evidence, to some extent, for the application of laparoscopic surgery for patients with T4 colon tumor. Thus, precision of staging and homogeneity of included patients are important to draw a universal conclusion, which can be compared with other reports. And in clinical practice, one of another challenges to make our analyses with more clinical importance is to improve the precision of
staging. And the reviewer’s suggestion that inclusion should be based on clinical T4 stage will be a new insight in this topic in the future, with the improvement of the clinical staging system. Thus, based on current clinical staging technic, we think the pathologic T4 stage is more reasonable to be considered as an inclusion criterion.

Comment 3: “The authors mention that there is "confounding bias", but probably it is rather "allocation bias", because it several factors determine the decision for a specific surgical approach and it is likely that the more easy cases are selected for laparoscopy. Please comment.”

Response: We thank the reviewer for this comment on our manuscript. Besides the confounding bias, we must admit that there also existed allocation bias in the pre-matched cohort. We have modified the words “confounding bias” to “bias” throughout the manuscript. As mentioned by the reviewer, factors, such as previous abdominal surgery history, may affect the decision for a specific surgical procedure, which may contribute to allocation bias. In this study, we added all unbalanced covariates into a logistic regression model to estimate the propensity score, aimed at controlling bias from these factors, including those which may affect surgical technic difficulties. A new figure (Fig.2 in revised version) was added to address the distribution of propensity score before and after matching. Propensity score distributions were more similar between two groups after matching than that before matching and all clinicopathologic characteristics after matching did not differ in two groups (Table 1). Thus, we think the inherent bias within a retrospective study could be reduced, to some extent, by such matching method (reference [18]).

Comment 4: “The introduction can be shortened.”

Response: As suggested by the reviewer, introduction has been revised and shortened in a total number of 330 words.

Comment 5: “Why were "early" conversions (<30 min) ignored? Preemptive conversion is especially important to include in a study on locally advanced colon cancer. This should be included in an "intention to treat" analysis and these cases should not be included in the open group. Additionally, most other studies on conversion have included these preemptive conversions in the laparoscopic group.”

Response: We agree with the reviewer’s suggestion. Patients occurring preemptive conversion should be included in the laparoscopic group. In our study, there were 3 patients occurring conversion within postoperative 30 min, due to bulky tumor, and we have moved these patients from open group to laparoscopic group. We updated the propensity score matching results after such “patients moving”, finding that these 3 patients were not selected by a 1:1 matching process with the same parameter setting as before. Thus the after-matched cohort was the same as before. Table 1 was revised accordingly.

Comment 6: “There is an essential difference between pT4a and pT4b regarding the implications for a laparoscopic approach. Just serosal ingrowth (pT4a) is not more difficult than operating on a pT3 case. The problems for a laparoscopic approach are the large bulky tumours with ingrowth in other organs. Table 1 demonstrates that more than 60% of the cohort consisted of pT4a. The authors should analyse the outcome parameters separately for the pT4a and pT4b group.”
Response: As suggested by the reviewer, all outcome parameters, including surgical findings, short-term outcomes and long-term survival outcomes were analyzed separately for the pT4a and pT4b groups in this revised version. Table 2, containing the surgical findings and short-term outcomes has been revised and marked in red. In subgroup analysis of pT4a and pT4b stage, mean operating time and rate of intraoperative blood transfusion were similar between LAC and OC group. In LAC group, shorter time to first flatus and first liquid intake were observed in patients with pT4b stage disease, but not for patients with pT4a stage disease. Less blood loss and shorter length of postoperative hospital stay were examined in LAC group, including pT4a and pT4b stages. Related contents in Abstract (line 10-18, page 2) and Results (line 11 on page 8, to line 8 on page 9) sections were revised. Survival curves (Fig. 3 in revised version) were also plotted in subgroups. In general, long-term outcomes, including 5-year DFS and 5-year OS rate were similar between OC and LAC group, whether for pT4a or pT4b stage disease. Related contents in Abstract (line 18 on page 2, to line 3 on page 3), Results (line 3-11, page 8) and Discussion (line 17-21, page 13) sections were revised.

Comment 7: “Furthermore, the baseline table should include the number of multivisceral resections and mean tumour size, which are both important baseline variables determining the surgical approach.”

Response: We agree with this suggestion. After double-check, we found that tumor size has been included in the baseline table (Table 1), which was names as “Primary tumor size”, one of our matched covariates. In this revised version, as suggested by the reviewer, we added the multivisceral resections (named as “Multivisceral resection (+)” in Table 1) as one of baseline variables. Comparison results showed no significant difference of multivisceral resection rate between two groups.

We hope our revision are satisfactory and that the revised is acceptable for publication in BMC Cancer.

Thank you very much for your valuable comments, which helped us improve the quality of this work.

Yours sincerely,

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