

Peer Review File

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Review comments

Reviewer A

Comment 1: When operating on complex (fistulizing) Crohn's disease you have alluded to some determinants of higher conversion rate to laparotomy including pus/ abscess in the abdomen and that preoperative optimisation with drainage and antibiotics may decrease this conversion. Clearly this is very surgeon dependant. What other determinants/risk factors have been identified to increase the success rate of MIS in complex CD and decrease the laparotomy conversion rate? for example: >20 MIS with complex CD a year, duration of surgical experience, lower CRP, absence of biologic therapy etc.

Reply 1: We thank the reviewer for the question.

We mentioned other risk factors associated with conversion to open surgery.

We added the following sentence: Other risk factors associated with higher odds of conversion to open surgery are recurrent medical episodes of Crohn's disease, previous ileocolic open resection and longer operation time, and so less surgical experience, stressing the need for greater surgical skills to face such complex and severe cases.

Comment 2: Despite stating that it is possible for complex penetrating CD to be operated on laparoscopically Table 2 doesn't sound terribly convincing with high conversion rates and postoperative morbidity. Can the authors please give a range of estimates on what proportion of patients end up with conversion to laparotomy? I would phrase the paragraph with "Studies of MIS in complex penetrating CD have shown the advantage of however conversion rates to laparotomy have been as low asand as high as....., Factors that determine higher rates of conversion to laparotomy include....."

Reply 2: We thank the reviewer for the comment.

We provided a range of conversion rate and added a conclusion to the paragraph as suggested:

In conclusion, fistulizing CD is surely a complex situation to deal with, and laparoscopic approach may be difficult and with conversion rates as low as 9% and as high as 40%, mainly depending on the presence of intra-abdominal abscesses, recurrent medical episodes or poor surgical experience; nevertheless, when feasible and with adequate surgical skills, MIS in complex penetrating CD has shown better postoperative outcomes, lower stoma rate and fewer additional small bowel procedures than conventional approach. Nutritional, pharmacological and radiological preoperative patient optimization is then pivotal, and must be consider for all intents as the initial part of a minimally invasive approach which culminates with laparoscopic elective surgery, when feasible.

Comment 3: A similar approach described above should be applied to the other sections e.g for post operative recurrence surgery.

The question of higher or lower postoperative recurrence rate in those undergoing laparoscopic surgery compared to laparotomy has not been answered. Do the authors have any data on this?

Reply 3: We thank the reviewer for the comments. We tried to answer by adding the following sentence:

Going back to minimally invasive laparoscopic surgery, the encouraging results of early retrospective studies were confirmed by prospective not randomized studies(31–33) and randomized controlled trials(34–37) on the same topic, as well as by meta-analyses and systematic reviews(21,38–40), with additional hints on possible favorable fertility outcomes in female patients undergoing laparoscopic surgery and more solid evidence even for long-term outcomes. Among

these, postoperative recurrence rate has been studied, with several meta-analyses and RCT comparing the two surgical approaches in terms, reporting a recurrence rate of laparoscopy as low as 0% and as high as 30%.

In 2005, Rosman (39) et al published a meta-analysis on 16 studies reporting a lower recurrence rate in laparoscopically treated patients; however, a statistically significant difference was observed in only one study. The possible reason behind these data may reside in the fact that the lower complication rate associated with laparoscopic surgery would translate also into a lower recurrence rate, being disease recurrence closely associated with postoperative septic complications.(41) More recent meta-analyses(1) and RCT(35,36), however, failed to demonstrate a statistically significant advantage of laparoscopic surgery in terms of surgical recurrence with respect to open surgery, making this topic still open to debate.

Comment 4: What is an acceptable conversion rate and operative times for laparoscopic surgery compared to laparotomy? We need a reported benchmark to compare what is acceptable or advantageous.

Reply 4: We thank the reviewer for the comment. We provided conversion rate and operative times from laparoscopic procedures performed for colorectal cancer, which have been more extensively studied, considering them a valid reference value to compare our data on CD.

Conversion rate ranged between 4.8 and 29.2%, with bleedings, adhesions, masses, fistulas, inability to deliver specimen and suspected carcinoma, being the main reasons for conversion.(21) These data are in line with conversion rates from colorectal resections performed for oncological disease, having a mean conversion rate of 14,3%, with right colectomy having the lowest (12.9%) and proctectomy the highest conversion rate (31.2%).(22)

As regards the duration of surgery, data from tertiary referral centers with high surgical volumes reported no difference in operative time between laparoscopic and open procedures (136.0+44.4 min vs 119.5+35.6 min, respectively), compared to centers with fewer than eight cases per year in which duration of surgery was significantly longer in the laparoscopic group, thus implying a relevant learning curve associated with the laparoscopic approach for the surgical treatment of this complex disease.(19,21) In fact, when considering high volume centers, data on laparoscopic operative time are comparable to those reported for laparoscopic right hemicolectomy for oncological disease (133.0+4.7 min).(23)

Reviewer B

Comment 1: Biologic therapy is immunomodulatory and not just anti-inflammatory.

Reply 1: We thank the reviewer for the comment and modified the sentence as requested.

Comment 2: 90% of patients requiring a second surgery is from an old reference and it is too high. The authors should update it.

Reply 2: We thank the reviewer for the comment. We updated the data with more recent reference. We modified the sentence as following:

up to 50% of patients who underwent surgery require a second intervention within 10 years, and multiple procedures are necessary in up to 30% of patients, with a considerable risk of developing short bowel syndrome and intestinal failure because of multiple bowel resections.

Comment 3: The authors should point out that MIS for CD in experienced hands seems to be associated with lower complications that potentially could translate into lower recurrence rates, as postoperative recurrence is closely associated with postoperative septic complications.

Reply 3: We thank the reviewer for the comment. We added the following sentence:

Going back to minimally invasive laparoscopic surgery, the encouraging results of early retrospective studies were confirmed by prospective not randomized studies(31–33) and randomized controlled trials(34–37) on the same topic, as well as by meta-analyses and systematic

reviews(21,38–40), with additional hints on possible favorable fertility outcomes in female patients undergoing laparoscopic surgery and more solid evidence even for long-term outcomes. Among these, postoperative recurrence rate has been studied, with several meta-analyses and RCT comparing the two surgical approaches in terms, reporting a recurrence rate of laparoscopy as low as 0% and as high as 30%.

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Further Review Comment

Reviewer A

Comment 1: The authors have made reasonable effort to address the queries, however I would suggest the authors to do a thorough language revision as the paper reads very poorly.

Reply 1: We thank the reviewer for the comment. The revised manuscript together with a certificate of official translation are now available.