Author's response to reviews

Title: Survival after laparoscopic and open surgery for colon cancer: a comparative, single-institution study

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Author's response to reviews: see over
Dear Dr. Rowles,

Please find a copy of revised manuscript n. 1780021721147743 entitled, “Survival after laparoscopic and open surgery for colon cancer: a comparative, single-institution study”. It has been amended according to some of the reviewers’ suggestions. Please also find our point-by-point reply to the criticisms raised by the reviewers.

My co-authors and I are very grateful for the constructive criticism that was offered regarding our work. We feel that it has assisted us in significantly improving the quality of our paper.

We hope that the present manuscript will be acceptable for publication in BMC Surgery.

Sincerely yours,

Fabio Cianchi, M.D.
1. The limitations of the study (i.e., retrospective and presence of biases in the selection of patients) have been stated in the Discussion (page 8, lines 19-21) and in the Conclusions. Although one surgeon performed only open procedures, the surgical technique and in particular lymphadenectomy was identical in the laparoscopic and open operations since all three surgeons were part of the same colorectal surgical team.

2. As stated in the Discussion (page 9-10), we do not have a clear explanation for the higher number of harvested lymph nodes after laparoscopic resection when compared with open surgery. However, we do not believe that this is due to technical superiority of the laparoscopic procedure: in fact, the same types of lymphadenectomy performed during open surgery were exactly reproduced in the laparoscopic operations. Therefore, we hypothesized that this difference was simply a consequence of a progressively greater effort by both the surgeons and pathologists to remove and examine the maximum number of lymph nodes in more recent years and thus, during our more recent laparoscopic experience. Moreover, we hypothesized that the survival advantage for stage II patients within the laparoscopic group might be correlated not only to a better prognostic classification of these patients but also to a potentially more efficient postoperative immune response. Altogether, these data clearly showed that laparoscopic resection is at least as effective as open surgery in the treatment of colon cancer. The potential oncological benefit has yet to be definitively demonstrated.

3. The finding of a higher number of harvested lymph nodes in the laparoscopic group and the lack of a significant difference in survival between open and laparoscopic patients with stage III tumors are not in contrast with our findings in stage II patients: in fact, this result indicates that the survival advantage in stage II patients is most likely due to a better prognostic stratification and not to a therapeutic effect of lymphadenectomy.

4. The revised manuscript has been reviewed by a native English professional medical editor.
Reviewer: Marco Allaix

1. The median length of follow-up after laparoscopic resection was 42.0 months (range, 3-120) while it was 50.0 (range, 4-120) after open resection. These data have been added to the Results (page 6, lines 19-21). The shorter follow-up time in the laparoscopic group was due to our more recent experience with this type of procedure. However, our follow-up periods are among the longest reported in the literature: Lacy et al. (ref. n.5) reported a median length of 43 months, Law et al. (ref. n.12) analyzed the 3-year survivals (median follow-up: 22.1 months) of their patients, whereas the median follow-up time was 26.7 and 33.8 months following laparoscopic and open resection, respectively, in the study published by Day et al. (ref. n. 13). Since it is well known that most tumor recurrences occur < 2 years after resection, we believe that this difference in the follow-up length between the two study groups did not significantly influence survival analysis. However, this point has been stated as a limitation of the study in the Discussion (page 8, lines 12-14).

2. As stated in the Methods, surgery was performed with curative intent for all study patients. We excluded from the study those patients who had undergone conversion to open surgery because the main reason for conversion was the presence of a huge, locally advanced tumors, which could not be removed radically even after open surgery. On this basis, we selected 227 laparoscopic patients available for survival analysis. This point has now been clearly stated in the Methods (page 4, lines 19-21). The sentence on page 6, lines 4-6, has been changed.

3. As stated in the Discussion, we made a stage-to-stage survival comparison between the two groups of patients just to avoid any bias due to heterogeneity in tumor stage distribution. The two study groups did not significantly differ in other potential prognostic parameters, with the exception of the numbers of harvested lymph nodes. However, it is impossible to establish a definite threshold of examined lymph nodes which can distinguish patient prognosis after colorectal cancer resections. As consequence, this parameter cannot be included in a multivariate analysis.

4. The revised manuscript has been reviewed by a native English professional medical editor.
5. Parametric data have been reported as mean ± SEM whereas non-parametric data as median and range.

6. All P values have been reported in the Tables.

7. The first sentence in the Abstract has been modified. The sentence, “However, data from randomized trials and meta-analyses have definitively established that laparoscopic colonic surgery is at least equivalent to open surgery” just stated the concept underlined by the reviewer, i.e., laparoscopic surgery can provide similar oncological results in the treatment of colon cancer when compared with open surgery.

8. The sentence on page 3, lines 14-17, has been modified according to the reviewer’s suggestions.

9. Another recent meta-analysis comparing survival after laparoscopic and open surgery has been added (see ref. n. 9).

10. The study was defined as single-institution since all operations were performed by only three surgeons who were part of the same colorectal surgical unit. However, at least eight gastroenterologists/endoscopists from different hospitals in Florence and Tuscany were involved in the recruitment of patients and significantly contributed to acquisition of the data during the entire length of the study period (12 years). This has been stated in the Authors’ Contribution section.
1. As stated in the Discussion, the heterogeneity in tumor stage distribution between the two study groups is certainly a confounding factor that might affect survival analysis. For this reason, we performed a stage-to-stage comparison between the two groups of patients and found a significantly better prognosis only for laparoscopic stage II patients. Comments in the Discussion almost exclusively focus on this result and its possible correlation/explanation with the number of examined lymph nodes.

2. There was no significant difference in the tumor site (proximal or distal) and thus in the type of resection (right hemicolecotomy extended to mid-transverse colon or left hemicolecotomy plus high anterior rectal resection) between the two study groups. This point has been added to the Results (page 7, lines 1-3) and Table 1.

3. Parametric data have been reported as mean ± SEM whereas non-parametric data as median and range.

4. The length of follow-up is now expressed as median value and range. The detailed follow-up protocol has been added into the Methods (page 4, lines 11-14). Only 5 patients were lost to follow-up, 3 in the open and 2 in the laparoscopic group, 2 years after surgery. As stated in the Statistical Analysis section, they were censored in the survival analysis at the date last known to be alive. The rate of patients lost to follow-up was added to the Results (page 6, lines 18-19).

5. Postoperative complications have been defined according to the Clavien-Dindo classification (ref. n. 18). These data were added to Table 1.

6. Statistical tests used to obtain each P values are shown in the Tables footnotes.