

To  
Jin-Xin Kong,  
Science Editor, Editorial Office  
Baishideng Publishing Group Inc

**Re: Manuscript NO.: 34044**

Title: Emergency surgery for symptomatic colorectal cancer: prognostic factors for patterns of recurrent disease and survival

Detailed below is the point-by-point response to reviewer's comments regarding the aforementioned manuscript. Format of the manuscript has been adapted as per author guidance. Figures have been amended and copies in excel format are submitted separately to facilitate editing. Changes in the manuscript text are notable as highlighted or deleted.

**Reviewer 1: 2017-04-01 23:45**

Comments to Authors: The authors found that the emergency surgery is associated with adverse disease free and long-term survival. T4 disease, LVI and LNR provide strong independent predictive value of long-term outcome and can inform surveillance strategies to improve outcomes. It have some clinical implication value and the results were interesting, however, there are still some revision needed to be solved.

1. In the Abstract section, the Clinical and histological features were analysed retrospectively over a six-year period, however, the results were analysed over sever year, please check it.

**Response:** The reviewer is correct in highlighting the different value of period of study in the abstract. This has been corrected reflecting the period between Jan 2001 to Dec 2008 as 8 years.

2. The two hundred and sixty six should be expressed as 266.

**Response:** We felt the sentence read better starting with the numbers given in words. However, in order to give a visible figure of 266, the sentence has been re-written.

3. In the Introduction section, the previous study on the prognostic factors for patterns of recurrent disease and survival should be cited.

**Response:** These references have been added in the introduction with a greater detail in the discussion section. The second paragraph in the introduction now includes: *"Compared to elective resection, emergency surgery is associated with adverse postoperative outcomes (post-operative mortality 4.6% vs. 16%), disease-free and overall long-term survival [18, 19, 20]. This may represent a multifactorial basis due to altered physiology, immunosuppression, advanced disease and aggressive tumour biology [21, 22]."*

4. The 266 patients were enrolled consecutively or enrolled based on inclusion and exclusion criteria, please describe the detail in the paper.

**Response:** These patients represent a consecutive cohort of patients undergoing curative cancer resection. Patients with metastatic disease on presentation or at the time of resection were excluded to assess pattern of metastatic disease in different patient

groups. The sentence has been modified with the added term 'consecutive'.

5. The Variables with  $P > 0.100$  on univariate analysis were excluded from multiple regression predictive model analyses, in general cases, the  $P > 0.05$  was selected as the criteria, the authors should add the related references in the paper or discuss the limitation in the Discussion section.

**Response:** The inclusion of variables with  $p < 0.1$  in the multiple regression model was undertaken to explore the potential influence of the independent predictive significance of other variables. This proves useful when a potential effect could have been underestimated due to the sample size. The threshold of 0.05 is in keeping with the standard cut-off for significance.

6. The number of the patients in the whole manuscript should be expressed as one style, such as, 10 or ten, just only one style.

**Response:** This correction has been undertaken in the text.

7. The paragraph of "The value of early detection of metastatic disease in offering an absolute reduction in mortality is clear" should be described briefly.

**Response:** This paragraph has been reduced and the section on surveillance has been described in a different paragraph.

8. The clinical implication and the limitation of the study should be added as a separate paragraph in the Discussion section.

**Response:** Limitations and clinical implication of predictive features is incorporated in the penultimate paragraph.

Classification: Grade C (Good)

Language Evaluation: Grade B: minor language polishing

Conclusion: Major revision

#### **Reviewer 2: 2017-04-05 10:42**

Comments to Authors: Thank you for giving me the opportunity to review the manuscript: "Emergency surgery for symptomatic colorectal cancer: prognostic factors for patterns of recurrent disease and survival". I enjoyed this paper. I think this conclusion seemed self-evident and no new knowledge. However, I feel there was interesting detail in this results. I have following comments,

1. I was wondering how many patients have had peritoneal recurrence during the study period. I think that perforation due to colorectal tumor growth means micro peritoneal dissemination, therefore, if there was no patient with peritoneal recurrence, that brings me a feeling of strangeness.

**Response:** Total number of patients developing local recurrent disease during the study period for the cohort 260 patients was 10. In the emergency group, only a single local recurrence was noted which presented with peritoneal, liver and lung metastasis. Rest of local recurrence (9 patients) was encountered in the elective group.

2. I am interested in the reason why there were more dominant metachronous liver metastasis in patients with emergency surgery than in those with elective surgery. Does it depend on T4 stage or other factors? Emergent resection was an independent predictors of poor survival, in addition to T4 stage. Please discuss the reason.

**Response:** A greater proportion of patients undergoing emergency resection received adjuvant therapies compared to the elective population (45.7% vs. 28.9%). This is hardly surprising as the proportion of advanced disease was smaller in the elective group along with some receiving neo-adjuvant therapies. (T4 disease 51.4% vs. 20.4%, N positive disease 49.9% vs. 34.7%).

Within the emergency resection group, a positive correlation ( $p=0.004$ ) was noted with adjuvant therapies and T4 disease (Table 1). Although a trend was visible towards presentation of liver metastases in patients undergoing adjuvant therapies, this did not reach significance ( $p=0.089$ ) and possibly presents some beneficial effects of chemotherapy in reducing risk of recurrent disease. The details are provided in Table 2.

A detailed analysis of impact of adjuvant therapies had not been included in the discussion for two reasons. Although patients receiving adjuvant therapies were recorded, data on individual regimes and doses received were not collected. Furthermore, more heterogeneity would be introduced into already a small subset of patients in each group (emergency resection 45.7% - 16/35, elective resection 28.9% - 65/225).

An addition has been made in the 2<sup>nd</sup> paragraph of the 'Emergency surgery for colorectal cancer' section of the discussion and reads: *"A subset analysis demonstrated a greater proportion of patients undergoing emergency resection received adjuvant therapies compared to elective resection (45.7% vs. 28.9%). In the emergency surgery group, patients with T4 disease were likely to received adjuvant therapies ( $p=0.004$ ). These patients receiving adjuvant therapies demonstrated an increased trend towards risk of liver metastasis but it failed to reach significance ( $p=0.089$ )."*

Table 1

Emergency resection and adjuvant therapies (34*)	Liver mets	No liver mets	Total
Adjuvant therapies	10	6	16
No adjuvant therapies	6	12	18
Total	16	18	34

$P=0.089$ . \* 1 missing

Table 2

Emergency resection and T4 disease (32*)	Adj therapy	No Adj therapy	Total
T4 disease	12	5	17
<T4 disease	3	12	15
Total	15	17	32

$P=0.004$ . \* 3 missing

3. I am interested in the detail of adjuvant chemotherapy regimen including molecular targeting agents. Because those agents dramatically improve the prognosis of patients with colorectal cancer. In particular, new agents has been available since 2001. I was wondering if there were difference of the prognosis in patients using new agents or with wild type RAS.

**Response:** In addition to response to question 3, small number of patients comprising

emergency resection and even smaller receiving adjuvant therapies preclude meaningful analysis of impact of individual regimes or targeted therapies as that would require detailed data of regime, dose and timing in a much larger study group to yield meaningful results. For this purpose it was never included in the scope of this study.

4. I was interested in if there was difference of the recurrent rates in patients with emergent surgery between with or without adjuvant chemotherapy.

**Response:** Further to the response to question 2, patients receiving adjuvant therapies in the emergency group tended more often to have T4 disease. Although not statistically significant, there was a trend towards increased risk of recurrent metastatic disease in this group with T4 disease and adjuvant therapy (tables 1 and 2). This lack of significance may be related to the beneficial effects of adjuvant therapy or small sample size. Details of neo-adjuvant and adjuvant therapies are provided in tables 3 and 4 for the reviewer.

Table 3

Neo-adjuvant therapies	None	Chemo	Chemo+Rad	Radio	Missing
Elective resection (n=225)	166 (73.8%)	5 (2.2%)	10 (4.4%)	38 (16.9%)	6 (2.7%)
Emergency resection (n=35)	34 (97.1%)	0	0	1 (2.9%)	0
Total (n=260)	200 (76.9%)	5 (1.9%)	10 (3.8%)	39 (15%)	6 (2.3%)

Table 4

Adjuvant therapies	None	Chemo	Chemo+Rad	Radio	Missing
Elective resection (n=225)	156 (69.3%)	53 (23.6%)	5 (2.2%)	7 (3.1%)	4 (1.8%)
Dukes A (n=50)	45	0	0	3	2
Dukes B (n=86)	72	10	1	3	0
Dukes C (n=83)	34	42	4	1	2
Emergency resection (n=35)	18 (51.4%)	12 (34.3%)	2 (5.7%)	2 (5.7%)	1 (2.8%)
Dukes A (n=0)	0	0	0	0	0
Dukes B (n=20)	11	6	1	1	1
Dukes C (n=15)	7	6	1	1	0
Total (260)	174 (66.9%)	67 (25.8%)	7 (2.7%)	9 (3.5%)	6 (2.3%)

Classification: Grade C (Good)

Language Evaluation: Grade A: priority publishing

Conclusion: Major revision

**Reviewer 3: 2017-03-26 14:12**

Comments to Authors: This an interesting retrospective study about the impact of emergency surgery on disease recurrence and survival of patients with colorectal cancer. It would be appropriate to give readers more information about the specific adjuvant treatment used for patients in both groups.

**Response:** The reviewer raises an important point about the adjuvant therapy regime changes that have occurred during the study period. Subsequent to the publication of the MOSAIC trial<sup>[1]</sup> in 2004, Oxaliplatin based therapies have been the slandered of care in the adjuvant setting following curative resection. The role of Irinotecan, Bevacizumab or

Cetuximab has not been proven in this setting. This is expected to have affected the two populations (emergency and elective group) equally. Data on adjuvant therapy regime, dose and timing was not collected. Furthermore, subgroup analysis before and after 2004 in a small number of cases undergoing emergency resection would introduce further heterogeneity.

Reference:

1. André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, Topham C, Zaninelli M, Clingan P, Bridgewater J, Tabah-Fisch I, de Gramont A. Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer. Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. N Engl J Med 2004; 350:2343-2351 [DOI: 10.1056/NEJMoa032709]

Classification: Grade C (Good)

Language Evaluation:

Grade A: priority publishing

Conclusion: Minor revision