Reviewer’s report

Title: Response of the primary tumor in symptomatic and asymptomatic stage IV colorectal cancer to combined interventional endoscopy and palliative chemotherapy

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Reviewer: Marwan Fakih

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I recommend revision before consideration for acceptance.

This is a very interesting article on primary tumor response to systemic chemotherapy. Little has been published in this field. Although deferring the resection of primary colon or rectal cancer in the setting of stage IV disease has become the norm, there is still resistance among community surgeons to this practice and many stage IV colon cancer still undergo unnecessary primary tumor resections. This manuscript may increase the comfort level with managing patients with unresected primaries with chemotherapy only.

The major weakness of this manuscript is the definition of partial response which lacks objectivity. The authors define a PR as a decrease in primary tumor size or disappearance followed by recurrence. However, there are no objective measures of a decrease in size which decreased the scientific value of their findings. If no measures were taken, the authors should concede to the subjective nature of their assessment and its limitations.

The manuscript could be improved significantly by addressing the following points:

I would suggest that the authors revise keywords to: Colorectal cancer, metastatic, unresected primary, chemotherapy, and interventional endoscopy.

Page 4: "initial partial response is 50-70%" is an over-estimation. Depending of the regimen used, the RR is 20% to 70%. Most phase III trials using combination therapy have reported RR in the order of 40%. Please revise the range and included appropriate references.

Page 6: The statement "tumor staging was performed after the 1st cycle" is likely not accurate since a cycle is typically 2-4 weeks (indeed chemo regimens were FOLFOX or FOLFIRI which are 2 weeks for each cycle. Furthermore, repeat restaging of 3-4 months seems long.

Since these patients had different types of treatments, it would be preferable that the rate of scanning is given in terms of time range rather than cycles.
Page 6: Partial regression definition is confusing- What is "tumor relapse after treatment break" does this mean patients with complete response and than recurrence of tumor? This is very confusing. The typical definition of partial regression is a certain decrease in tumor size. If RECIST criteria are uses, this would be a 30% reduction in longest dimension. The definition here is very subjective and unclear. Were measurement taken endoscopically and if so, what kind of regression was considered partial?

Page 7: states patients were enrolled- Since this is a retrospective study, patient could not have enrolled. Please correct- Patients were identified through a retrospective review.. Patients could have only enrolled if there was a prospective clinical trial and would have had to consent--- which was not the case.

Page 8: please give some detail regarding the perforation- Was it in the setting of bevacizumab (Avastin) and did it occur within 1 week from an endoscopic procedure?

Page 9: it is unclear why some patients required further debulking for obstructive symptoms when they indeed had tumor regression- Please explain why this occurred- Was this done prophylactically? Did these patients have prior obstructive symptoms and if so did these symptoms worsen? It would be unusual to have discordance between the regression on endoscopy and the clinical symptoms. Again, one of the main issues I have with this study is the characterization of a clinical response-This seems very subjective, how did the investigators determine that someone had shrinkage vs. no change-This is an impossible task without the integration of some objective methods of measurement.

Consider the change of Time to Progression to Time to Primary Tumor progression

Did the authors look at TTP of metastatic disease and was it less or equal to primary disease TTP

I am not sure that the IIa group should be counted as partial responders- These patient fit the criteria of a complete response- a relapse after a complete response does not make that CR and PR.

In the discussion, the authors should give recommendations regarding the surveillance of the primary. I am not aware of any data that supports the practice of colonoscopies during systemic chemotherapy to assess primary response. The practice of endoscopy every 3-4 months in the setting of the study institute seems too aggressive and may be a risky approach. Bevacizumab therapy is associated with increased risk of bowel perforation and this may be exacerbated
by colonoscopy.

Please revise the manuscript to correct the numerous writing errors.