Peer Review File

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Reviewer A

Comment 1: Very similar to our work of CEA/Vol in CRC lung mets. Good data.
Reply1: Thank you very much for your positive comments.
Changes in the text: None

Reviewer B

1. In stage II colorectal cancer, there are some high risk factors for recurrence, such as lymphatic/vascular invasion. The authors should consider these risk factors on analysis.
Reply1: Thank you very much for your comment. As your point of view, lymphovascular invasion is one of the high risk factors for recurrence and metastasis of stage II colorectal cancer, so we had focused on lymphovascular invasion on analysis. In addition, we also considered T stage, numbers of lymph nodes examined, and differentiation on analysis, which have been indicated in the National Comprehensive Cancer Network (NCCN) guidelines as prognostic risk factors for stage II colorectal cancer. (see Table 1-3; Page 9, line 181-191; Page 10, line 199-209)
Changes in the text: None

2. In hollow viscous organ like colon, depth of invasion of tumor is more important than tumor size. Moreover, you collected data of tumor size from pathologic report. How do you confirm the mximum size? There may be variation according the pathologist or measurement tool/method.
Reply2: Thank you very much for your comment. As your point of view, the depth of invasion of tumor is evaluated by T stage, which has been proved to be a prognostic risk factor in stage II colorectal cancer. How to determine the maximum tumor diameter was described in the method section of manuscript (see Page 7, line 129-130). The measured value may be variation according the pathologist, so the DMAX of each tumor specimen is confirmed by at least two pathologists.
Changes in the text: we have modified our text as advised (see Page 7, line 129).

3. In the Method, some patients took sigmoidectomy or transverse colectomy. Is it adequate surgery for complete resection?
Reply3: In this article, transverse colectomy is suitable for tumors in the middle of the transverse colon. The resection scope includes the greater omentum, transverse colon and corresponding mesentery, part of the ascending colon, descending colon, and lymphatic tissue in the drainage area of the tumor. Sigmoidectomy is suitable for sigmoid colon cancer. The resection scope includes both ends of enough sigmoid colon and corresponding mesentery, and the resection edge was at least 10 cm from the tumor

margin. Therefore, we think that transverse colectomy and sigmoidectomy are both adequate surgery for complete resection.
Changes in the text: we have modified our text as advised (see Page 9, line 176).

4. In Table 1. higher portion of T4 was included in high CEA/DMAX. What do you think it can affect the survival outcome more than CEA/DMAX ?
Reply4: T4 stage has been proved to be a prognostic risk factor in stage II colorectal cancer in many studies, so we also analyzed it in univariable and multivariable Cox regression analyses (see Table 2 and 3). The hazard ratio value of T stage compared with CEA/DMAX is 3.04 vs. 2.58 for OS and 2.53 vs. 1.97 for DFS (see Table 3), so we thought T stage can affect the survival outcome more than CEA/DMAX in stage II CRC. Although we included T stage in the multivariate analysis, CEA/DMAX still can independently affect OS (hazard ratio: 2.58, 95% confidence interval: 1.51–4.38, P <0.001) and DFS (hazard ratio: 1.97, 95% confidence interval: 1.38-2.83, P <0.001), which indicated that CEA/DMAX was a prognostic risk factor for stage II colorectal cancer independent of T stage (see Table 3).
Changes in the text: None

5. In the discussion, you suggested CEA/DMAX should be consideres as prognostic marker. To determine the concept, you should suggest the data or background data why or how CEA/DMAX can be independent prognostic marker. Moreover, you would better the possible explanation for this hypothesis.
Reply5: Thank you very much for your comments. We have shown in the revised manuscript that the data from multivariate Cox regression analysis have supported CEA/DMAX as an independent prognostic risk factor for OS and DFS, and patents with high CEA/DMAX had poor OS and DFS (see Page 12, line 252-253). In addition, we have explained the possible reasons: a higher CEA/DMAX value would reflect relatively greater CEA secretion per unit of tumor size, which would indicate a more aggressive and malignant phenotype that could explain the poor outcomes among patients with high CEA/DMAX values (see Page 13, line 273-277).
Changes in the text: we have modified our text as advised (see Page 12, line 252-253).