Author's response to reviews

Title: Clinicopathological and prognostic significance of HER-2/neu and VEGF expression in colorectal carcinomas

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Author's response to reviews: see over
Dear Editor:

Thank you very much for your kind letter and advice. We have revised the manuscript in accordance with the details comments of Reviewer 1 (Prof. T Rajkumar).

**MAJOR COMPULSORY CORRECTIONS**

1. The sample size is only 86 and includes a heterogeneous mix of site (colon = 48; rectum = 38) and stage (T1, T2 = 23 versus T3, T4 = 63). The biology of colon cancer is different from the rectal cancer; requiring sub set analysis, which will reduce the number of cases. Additionally, it is not clear whether there were any metastatic disease (M1) patients included. It is also not clear whether the cases enrolled for the study were consecutively seen patients or were selected. Overall, the sample number will need to be enhanced substantially. The HER2 positivity is around 15 - 20% in colon cancer, which would mean that at least 300 samples minimum will be required to get around 50 HER2 positive colon cancers. Hence, ideally the sample size should be above 300 and preferably colon cancer only.
   - We have enhanced the sample number to 317 patients, and all patients were colon cancer only.
   - Patients who received elective surgery for colon cancer at our department between January 2000 and December 2005 were all included in the research.
   - Patient who have distant metastases was showed in TABLE.2.

2. IHC has been done for c-erbB2/HER2/neu and VEGF. There is no mention as to which form of VEGF was studied (A, B, C or D). The photomicrographs look to be wrongly labelled – the strong membrane staining is seen in ‘b’ but is labeled as VEGF. It would be better to have cancers which are negative also included in the panel.
   - In general, Vascular endothelial growth factor (VEGF) means VEGF-A, it have been mention in the second paragraph of background section.
   - The Figure.1.b have been changed with new photomicrographs, the negative control figure was added in the panel.

3. HER2/neu has been shown to regulate VEGF expression (Kumar and Yarmand-Bagheri, 2001). The current IHC study by Li et al., will not be able to assess this functionally and the concluding remark is unwarranted.
   - It has been shown that HER2/neu regulates VEGF expression in breast cancer, but not all kinds of cancer, for example, Do et al found no correlation between VEGF and c-erbB-2 in squamous cell carcinoma of the head and neck (Do NY, 2004), and there is conflicting data of HER2/neu expression with a wide range from 0% to 80% in present articles, so it deserves to know whether there is correlation between VEGF and HER2/neu expression in colon cancer. The review of Kumar and Yarmand-Bagheri mainly probe the signaling pathways linking HER2/neu and angiogenesis.

4. This study does not mention about the earlier study published by Ochs et al.,(2004), in which HER2 and VEGF levels were studied using IHC in 109 colon cancers, with pretty similar results.
   - Ochs et al study was about HER2 and VEGF expression in 109 stage II colon cancer, it was mentioned in discussion section in our paper.

**MINOR ESSENTIAL CORRECTIONS**

1. There are many spelling mistakes throughout the manuscript, which will need to be corrected.
   - Done
Such as “HER-2/neu and VEGF overexpression are correlated with disease behavior in various cancers” in background of abstract was corrected as “HER-2/neu and VEGF overexpression are correlated with disease behaviors in various cancers”