Reviewer's report

**Title:** Role of the VEGF ligand to receptor ratio in the progression of mismatch repair-proficient colorectal cancer

**Version:** 1  **Date:** 26 May 2009

**Reviewer:** Samer Al-Quran

**Reviewer's report:**

This paper is interesting and nicely written except for few grammatical errors/punctuation. I have the following comments:

**Major Compulsory Revisions**

1. Page 5, tissue microarray samples. The major problem I do see in this study is the tissue sample size, which the authors do address as a weakness. The authors should explain more the size of the tissue on microarray, where the tumor sections were taken from (i.e. center, border, etc.) especially since they are taking about the pushing border vs infiltration, which I would think is hard to evaluate on tissue microarray. So is that data gathered from the original pathology case/report? And Please specify how much for these were biopsy samples or tumor resections. In the table1 on page 18, it was stated that 88 patients received chemotherapy, and all the microarray samples were before therapy

2. Page 9, was vascular invasion assessed within the tumor or at the tumor periphery? It may be difficult with tissue microarray specimens. Was that correlated to the actual resection and lymph node status (in table 2, 61% had lymph nodes metastases while vascular invasion was demonstrated in only 3% of cases)

3. Estimation of immunoreactivity (page 5 under evaluation), authors describe that scoring was performed using a “reproducible semi-quantitative method)? What is this method and its discrimination power (visual estimation or using image analysis), since they scored from 0% with 5% intervals, how did they adjust for non-specific staining or edge artifact. For the positive cases that should be easy, what about borderline cases that are close to the cut off points (if the cut off point is 50%, can this method reliable discriminate between 45% and 50%?)

4. Page 6, first paragraph. Why is the variation in % values used in the graphs for the VEGF/VEGFR (some use 50%, 70%, 90% or 95%) somewhat confusing! The authors are probably using the cutoff that gave them the most statistical significance, but it then makes it less reproducible to have to use it. Can you please address this issue?

5. Figure 1. Very poor quality images. Please provide higher resolution images with magnification. It may be easier to label images rather than in the legend
Minor Essential Revisions

1. Page 6, how many cases was the receptor 0%, and thus excluded.

2. Page 18, table 1,
   a. the % of right sided tumors should be 34.4% (127/369) not 64.4%. Under
tumor grade, please replace G1-G3 , in a foot note please explain if which is
well-, moderately- or poorly- differentiated.
   b. Explain the staging system
   c. Survival time, not easily understandable. Please specify if the 5 year survival is
58.9% and if 52-65 is months?
   d. Sites of distant metastasis (where they all to the liver?)
   e. Patients with local recurrences, what were the intervals between the surgery
and recurrence (was any case due to incomplete total tumor resection).

3. Page 8 under results, 4th paragraph, 5 year survival for the low vs grade
tumors. The numbers after CI represent what? The second is reported as % and
the fist not.

4. Page 8 under results, Third paragraph. VGFR2 was reportedly related to tumor
progression. Is there any difference in survival for patients that had infiltrative vs
bushing tumor borders in this study group?

5. Page 10, first line, 2 paragraph of discussion please add “to the” between
linked and absence “linked [to the] absence”.

6. Page 11 of discussion, please explain what is epithelial mesenchymal
transition

7. Survival data (including figure 3). What were the actual follow up periods for
these patients and how many were alive or dead 5 year and at 10 year after
diagnosis. What is the relationship to the 5 and 10 year survival data to the
ratios?

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being
published

Statistical review: Yes, but I do not feel adequately qualified to assess the
statistics.

Declaration of competing interests:

I declare that I have no competing interests