Author's response to reviews

Title: Elevated IGFIR expression regulating VEGF and VEGF-C predicts lymph node metastasis in human colorectal cancer

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Response to Reviewer Markus Moehler

1. It is not answered whether the data are made retrospectively or prospectively. This should be addressed in Methods.

Response: The data in our manuscript are made retrospectively. We made some corrections to address this issue in Methods as follows:

We retrospectively reviewed all patients who underwent curative-intent surgery and were randomly selected at the Department of Surgery from 2002 to 2005.

2. The results discussion and conclusions are not yet well balanced and adequately supporting the data: Evidently the authors and elaborate on IGFR and VGFs, included in the revised version now important new data on survival of the patients, but still did not mention or discuss previous important publications for colorectal cancer.

Response: According to the reviewer’s suggestion, we addressed this issue in the Discussion section (Page 14, Line 13-18) as follows, and added the previously important publications for colorectal cancer in the references list.

“…Lymphangiogenic factors, such as VEGF-C and VEGF-D, have been show to stimulate tumor lymphangiogenesis and metastasis to regional lymph nodes by interacting with their receptor VEGF receptor 3 (VEGFR-3). High levels of VEGF-C and VEGF-D can promote tumor growth and lymph node metastasis in human colorectal cancer. Moreover, strong expression of VEGF-C and VEGF-D was significantly linked to a trend for decreased survival in colorectal cancer patients…”

3. Again as the reviewer suggested earlier: the implication for response prediction
have not yet been discussed or addressed.

Response: We addressed this issue to demonstrate the predictive and prognostic value in the Discussion section (Page 17, Line 14-22) as follows:

“…Predictive prognostic markers in colorectal cancer were studied, and a few statistically significant associations between the studied markers and longterm prognosis were found. In the current study, we found a clear and significant correlation between high IGFIR, VEGF and VEGF-C expression and lymph node metastasis in human colorectal cancer. In addition, high expression of these molecules in colorectal cancer patients showed significantly less favorable survival rates. The combination analysis of IGFIR/VEGF and IGFIR/VEGF-C co-expression demonstrated a negative impact on prognosis. Therefore, these findings may enable more an accurate assessment of the predictive prognosis of patients with colorectal cancer.”

Response to Reviewer Paolo Bruzzi

1. My suggestions are considered in the present version of the paper. I suggest to mention in the abstract the results of the survival analyses

Response: According to the reviewer’s suggestion, we mention the results of the survival analyses in the section of Abstract as follows:

“…Moreover, Patients who had strong staining for IGFIR, VEGF and VEGF-C showed significantly less favorable survival rates compared with patients who had low staining for these molecules (P < 0.001). The survival rates of patients who were both high expression of IGFIR/VEGF and IGFIR/VEGF-C also were significantly lower compared with patients who were negative or one of high expression of these molecules (P < 0.001).”