Reviewer's report

Title: High infiltration of mast cells predicts worse outcome following resection of colorectal liver metastases

Version: 3 Date: 30 June 2015

Reviewer: Girolamo Ranieri

Reviewer's report:

This is an interesting paper showing that the high infiltration of mast cells predicts worse outcome following resection of colorectal liver metastases. Although of interest the paper is not acceptable for publication in its present form and several issues need to be answered to make it suitable for publication.

Major Comments

1) As in background section explained tissue mast cells can be identified via several histochemical methods and immunohistochemical markers as a consequence to make the title manifest I would suggest to specify in it: “mast cells positive to tryptase”.

2) What mean cancer specific survival? Should it to mean Overall Survival? Please explain this. Anyway I would suggest to delete cancer specific survival in that it is not a common definition in international medical oncology community.

3) In background section, at pag. 5, line 19 the sentence: “Tryptase releases additional angiogenic factors (interleukin 6 and granulocyte-macrophage colony-stimulating factor) from MCs [21], and its degradation aids the invasion and metastasis of tumor cells by induction of angiogenesis [22]” is not clear. How can tryptase to release additional angiogenic factors (interleukin 6 and granulocyte-macrophage colony-stimulating factor) from MCs? In what way or manner? Please specify this. In my opinion reference 21 is not appropriate to explain this. On the other hand reference 21 explain that protease-activated receptor-2 regulates vascular endothelial growth factor expression in breast cancer cells via MAPK pathways.

4) In Patients and Methods sections the employed protocols/schedules of neoadjuvant chemotherapy should be better detailed for group of treated patients. In the cited section the authors reported the following sentence: “Preoperative staging, preoperative chemotherapy, hepatectomy procedures, adjuvant chemotherapy, and patient follow-up were previously described [37,38]”. From a translational medical oncology point of view the reported sentence is not complete and clear. In fact in references 37 and 38 a series of 334 and 24 patients has been evaluated respectively while in the present study 135 patients have been evaluated. For example it is important to know how many patients received oxaliplatin that is able to induce hepatic sinusoidal dilatation that in turn
could to interfere with mast cells positive to tryptase count. Furthermore I am surprised: are there patients that received bevacizumab or cetuximab? I read that the submitted retrospective study included 135 patients who underwent potentially curative resection for CRLM between 2001 and 2010.

- InPatients and Methods sections, at Immunohistochemical evaluation, line 4 I read: “Micro vessel density was defined as the number of blood vessels, which were identified as areas surrounded by DAB-positive basement membranes”. Is this a standardized method according to Weidner’s or Chalkley’s count? I think no. Please comment this important methodological point for the reproducibility of any experimental data. Please insert specific references.

5) In results section, at Patient characteristics, line 5 I read: “The clinicopathological features of patients enrolled in this study are summarized in Table 1”, and in Table 1 no indication regarding RAS status is reported. Why? RAS status should be included in the Univariate and multivariate analyses.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**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'