Reviewer’s report

Title: A Long-term follow-up of the imatinib mesylate treatment for the patients with recurrent gastrointestinal stromal tumor: the liver metastasis and the outcome

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Reviewer: Massimo Chiarugi

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Background
The manuscript refers to a large series of patients with recurrent GIST and may have a respectable relevance in this field.

Major Compulsory Revisions
1) The major concern of the reviewer is about the study population that eventually includes three different patterns of patients with recurrent GIST: those with no liver metastases, those with only liver metastases, and those with either liver and extra-hepatic metastases. Authors merged the two latter in a single group but this may result inappropriate. It is far to be proved that the behaviour of recurrent GISTs involving the liver and other abdominal viscera would be the same of GISTs recurred in the liver only. Thus, it is suggested that comparisons should be made only between the group of patients with no liver metastases and the group of patients with both hepatic and extra-hepatic metastases. By this way one can assure that the only, as expressed by the study title, would be the presence or not of liver metastases. Alternatively comparisons might be made including three groups: recurrent abdominal GISTs, recurrent abdominal and liver GISTs, recurrent liver GISTs.

2) The aggressive behavior of GISTs may be predicted by several items: site of origin (foregut, midgut, hindgut), type of histological pattern (spindle, epitheliod or mixed cells) and, outmost important, by applying the risk criteria assessment as proposed by Fletcher and al. (Human Pathology 2002; 33; 459-467). These include the size of the primitive tumor and the number of mitosis for HPF. In the study there is no data referring to these items. Thus, conclusions may be biased by a different distribution in the two groups of GISTs with low- or high-risk of aggressive behaviour.

3) Response to imatinib treatment achieves best results for GIST caused by mutations in the KIT or PDGFRalpha receptor tyrosine kinase genes. Conversely, response is very low for GIST that have a wild-type genes pattern. Again, to avoid bias, a mutational analysis should have been performed.

Based on this comment I would encourage Authors to review the manuscript by re-arranging the population groups and adding, at least, data according to the Fletcher’s criteria.
Mutational analysis of the specimens, if available, could add extra value to the study.

Minor Essential Revisions
1) The minimum interval from radical resection and recurrence was 2 months: can you surely state that resections were R0 in all patients, including those in which GIST recurred within few weeks?

2) Page 4 of the main text (Discussion), line 23: "Oral imatinib mesylate, instead of another surgery, was the reasonable choice for the patients who had recurrent GIST after a radical resection". This sentence may be misleading. One can agree with the message coming from the sentence, but only when re-resection appears not radical. In other terms, if recurrence seems to be amenable by radical resection, thus surgery should be warranted. If radicality seems to be out of reach, then patients should be posed on medical treatment. Sentence should be re-arrange accordingly.

3) Same page, line 29 and following. The sentences..."Obviously, the liver metastasis did not influence the patients' survival so seriously if…So the liver metastasis should not be regarded as an important…” may be re-arranged as follows. Survival was not significantly affected by liver metastases when imatinib mesylate treatment was warranted.

4) The following sentences: ..However it should be noted that adverse effects of the long-term imatinib mesylate treatment were frequently observed. The most common adverse effects were edema and anemia: Fortunately, the toxicities were mild and well tolerated. No grade 4 toxicity was observed. No treatment-related death was reported. Our data presented a good tolerance of long-term imatinib mesylate treatment.... May be re-arranged as follows: Edema and anemia, although mild and well tolerated, were the commonest adverse effects observed during long-term imatinib mesylate treatment.

5) The following period (discussion chapter) starting at line 38, page 4 (...An adjuvant use of imatinib mesylate was reported to be a promising......) and ending on page 5,line 8 (...after a radical resection of the primary tumor is still worth further considering.) deals with the object of whether to give imatinib to patients after primary resection of a GIST. This is beyond the main aim of the study and the period should be deleted.

6) The following sentence may be re-arranged as: Tumor’s resistance to imatinib mesylate is still a major problem.

Level of interest: An article of importance in its field

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

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I declare that I have no competing interest.