SERVIZIO SANITARIO REGIONALE
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UNIMORE
UNIVERSITÀ DEGLI STUDI DI
MODENA E REGGIO EMILIA

Modena, October 10th, 2016

To the Kind Attention of the Editor-in-Chiefs

Of *World Journal of Gastrointestinal Oncology*

Prof. Hsin-Chen Lee, PhD

Institute of Pharmacology, School of Medicine,

National Yang-Ming University, Taipei 112, Taiwan

Prof. Dimitrios Roukos, MD, PhD

Department of Surgery,

University of Ioannina, Ioannina, TK 45110, Greece

Manuscript N°: 30025

Manuscript title: Heavily calcified gastrointestinal stromal tumors: pathophysiology and implications of a rare clinicopathologic entity

Authors: Salati M. et al.

Dear Prof. Lee and Prof. Roukos,

Thank you for your letter. We were pleased to know that our manuscript was rated as potentially acceptable for publication in Journal, subject to adequate revision and response to the comments raised by the reviewers.

Based on the instructions provided in your letter, we uploaded the file of the revised manuscript in type of word processor on the journal's website.

As you notice, we have revised the manuscript according to the comments made by the reviewers. Accordingly, we have uploaded a copy of the original manuscript marked with

all the changes made during the revision process. The new text is highlighted in yellow, while the crossed-out text refers to the deleted original text.

As requested, we addressed the comments raised by the reviewers with a point-by-point response, that you can find below:

1. "*At the end of the case description, "At time of this report, ..." should be changed in duration of the follow up in months. In the discussion, "The most acknowledged process is dystrophic calcification that tipically involve degenerated tissues ..." should be "The most acknowledged process is dystrophic calcification that typically involves degenerated tissues ..." and "Still, metastatic calcification occurring ..." should be "Still, metastatic calcifications occurring ...". The "unique case of osseous metaplasia with mature bone formation has also been described in a newly diagnosed gastric GIST" requires a reference.*": we specified the duration of follow-up in months, made the required grammatical corrections and inserted the reference.

2. *"If the authors have abdominal X-ray, the authors should shows the image of abdominal X-ray of this case."*: unfortunately the image of abdominal X-ray is not available.

3. *"How about mutations of c-kit and of PDGFRA in past reported cases?":* the mutational status of C-KIT and PDGFRA is not reported in any of the cases of massively calcified GIST we found in the literature.

4. *"The authors should show the prognosis of reported cases on Table 1.":* the risk class reported by the authors in the cases is often based on different risk classification systems. Therefore, in table 1 we reported the risk class defined on the basis of the modified NIH classification system, which was also used for our case.

5. *"What was the preoperative diagnosis of the author's reported case? Did authors perform EUS-FNAB?":* due to the location of the lesion, which was circumscribed, as well as the limited excision required, we decided to perform upfront surgery, omitting EUS-FNAB. According to ESMO/European Sarcoma Network Working Group guidelines, immediate laparotomic/laparoscopic excision can be considered an

alternative to biopsy on an individual basis. In addition, as reported in the Asian Consensus guidelines for GIST (*Koo DH et al., Cancer Res Treat. 2016*) preoperative histological diagnosis may sometimes be difficult to interpret and if the tumor is strongly suggestive of GIST and is considered resectable, preoperative biopsy can be omitted.

6. *"The tumor size of this case was 9.3 x 5.5 cm. Why did the authors perform laparoscopic surgery? Because laparoscopic surgery is not recommended for GIST with the size > 5cm on GIST guideline.":* laparoscopic surgery is an alternative approach for GIST resection, which has been associated with several advantages if compared to open surgery, such as less intraoperative blood-loss, less pain, early recovery and shorter hospitalization (*Ohtani H et al., Anticancer Res. 2013;33(11):5031-41*; *Koo DH et al., Cancer Res Treat. 2016*). Additionally, in a meta-analysis by Ohtani and colleagues (*Ohtani H et al., Anticancer Res. 2013;33(11):5031-41*) a significantly lower rate of long-term overall recurrence, metastatic recurrence and local was reported with GIST laparoscopic surgery in comparison to open surgery. We certainly know that these data refer most to smaller tumors, as well as that ESMO/European Sarcoma Network Working Group guidelines tend to discourage a laparoscopic approach patients who have large tumours, because of the higher risk of tumour rupture. However, NCCN guidelines *(Soft Tissue Sarcoma NCCN guidelines, Version 2.2016)* consider laparoscopic surgery an adequate alternative for select GISTs in favorable anatomic locations (greater curvature or anterior wall of the stomach, jejunum, ileum) by surgeons with appropriate laparoscopic experience, regardless the size of the lesion. To conclude, given the favorable anatomic location of the lesion and considering the high expertise in laparoscopy of the Hepato-Pancreato-Biliary Surgery and Liver Transplantation Unit of the University Hospital of Modena and Reggio Emilia, along with the known advantages of this technique versus open surgery, we consider laparoscopic surgery a suitable approach for the case we reported.

7. *"The authors should show the macroscopic picture of cut surface of the tumor.":* unfortunately the macroscopic picture of cut surface is not available.

We would like to take this opportunity to express our sincere thanks to the reviewers who identified areas of our manuscript that needed corrections or modification. We would like also to thank you for allowing us to resubmit a revised copy of the manuscript.

I hope that the revised manuscript is accepted for publication in Journal.

Sincerely Yours,

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