May27, 2020

Company Editor-in-Chief, Lian-Sheng Ma, Professor

World Journal of Clinical Cases

MS.Ref.No.:55782

Title: Isolated metachronous splenic multiple metastases after colon cancer surgery: A case report and literature review

Authors: Li Hu, et al

Dear Professor Lian-Sheng Ma,

Thank you very much for your decision letter and advice, regarding our manuscript (Manuscript NO.: 55782). We are pleased you will consider a revised version of our manuscript for publication in *World Journal of Clinical Cases*. We also thank the reviewers for their constructive and positive comments and suggestions. Accordingly, we have revised the manuscript and submitted the revised manuscript. All the major amendments are highlighted in red in the revised manuscript. In addition, our point-by-point responses to the editors'and reviewers' comments and explanation of the changes in our paper are listed in the following pages.

We hope that our responses and revisions meet the editors' and reviewers' expectation and that the revised manuscript is acceptable for publication in your journal. I look forward to hearing from you soon.

Yours sincerely,

Zhi-Long Yan, Professor

Responses to Comments from the Editors and Reviewers

First and foremost, we would like to express our sincere gratitude to the editors and reviewers for their constructive and positive comments that help improve our manuscript tremendously.

Responses to the Comments from Reviewer

1. Core tip should be shorter and focused on the impact this manuscript can have on clinical practice.

Response:We appreciate very much your suggestion. We have now revised the Core tip as follows:“Isolated splenic metastasis is a rare clinical entity. We report a case of 48-year-old woman with isolated splenic metastasis 21 months after radical colon adenocarcinoma resection. Close monitoring of serum CEA levels is crucial after colon adenocarcinoma surgery.Splenectomy seems to be the preferred treatment and multiple disciplinary team plays an important role in the entire process of disease management”.

2. Introduction needs to be completely rewritten as it summarizes the entire article.

Response:We appreciate very much your suggestion. We have now revised the introduction as follows: “Splenic metastases in patients with malignant tumors generally indicate multiple metastases.Isolated splenic metastasis after radical colon adenocarcinoma resection is a rare clinical entity.The mechanism of their rarity is unknown and many theories have focused on anatomical and histological aspects.We report a case of isolated splenic metastasis 21 months after radical colon adenocarcinoma resection which was successfully treated by totally laparoscopic splenectomy. We discuss the clinical and pathological aspects of this case,and

consider the diagnostic and therapeutic options based on our observation of the case. We also reviewed the literature and identified 34 relevant papers, including 28 cases of metachronous metastasis and 6 cases of simultaneous metastasis.

3. does not provide a background on the pathology being described in the manuscript?.

Response:We are so sorry for the missing information in the original submission. In fact, The first postoperative pathology indicated a poorly-differentiated adenocarcinoma, 4 out of 15 perirectal lymph nodes harvested were positive,and circumferential,proximal and distal margins were negative.The second postoperative pathology showed the same results.Following your suggestion, we therefore have now added the pathology information into the revised manuscript.

4. It is very repetitive and the information regarding the case itself is described at least 3 times and it should only be detailed on the abstract and on the "Case Presentation" section.

Response:Thank you very much for the suggestion.We have now revised the manuscript, and only described the information regarding the case itself on the abstract and on the "Case Presentation" section.

5. The patient was submitted to a radical laparoscopic sigmoidectomy of a pT4aN2 colon cancer.Was it an adenocarcinoma? The histologic type is NOT referred through the manuscript. Was it an oncologically correct resection? Please state circumferential, proximal and distal margins as this can relate to early local recurrence.

Response: We are so sorry for the missing information in the original submission. In fact, it was absolutely an adenocarcinoma. The pathological type has been mentioned in the pathological background. Surgical resection fully complies with tumor principles. Circumferential,proximal and distal margins showed free of tumor.Following your suggestion, we therefore have now added the information into the revised manuscript.

6. What was the second surgery performed? Local resection is vague and does not described the extent of resection. Again, what were the margins of the specimen? It is

referred that it had "extra-serosal and muscularis invasion"; does it mean it was staged as pT4b? Do you think that splenic metastasis could be due to direct peritoneal dissemination?

Response:We are very sorry for the unclear report in the second surgery performed. The extent of local resection based on a laparoscopic exploration and no other recurrences were found. Local resection of the recurrence in the intestinal tract and one-stage anastomosis were carried out during surgery. The tumor edge is 5cm away from the proximal and distal margin.Circumferential,proximal and distal margins were negative. "extra-serosal and muscularis invasion" does not mean that it was staged as pT4b, because it was discovered 14 months after the primary tumor was removed, it means a local recurrences.I do not think that splenic metastasis could be due to direct peritoneal dissemination. The spleen is far away from the original lesion and is not direct; peritoneal dissemination is usually manifested in multiple organs, not just the spleen.Following your suggestion, we therefore have now added the information into the revised manuscript.

7. Of course CEA levels monitoring is mandatory in colon adenocarcinoma but you also state that AFP, Ca125 and Ca 15.3 were performed. Can you explain why?

Response:We are so sorry for the confusion in the understanding of this section in the original submission. In fact it is a routine examination before surgery, it is used to screen for the possibility of combining with other tumors.

8. First endoscopy revealed sigmoid colon mass but the second and third were normal - local recurrence was diagnosed solely based on PET-CT?

Response:We apologize for the missing information in the original submission. In fact, local recurrence was diagnosed based on elevated serum carcinoembryonic antigen (CEA) and PET-CT, final diagnosis depends on pathology. We therefore have now added the information into the revised manuscript.

9. If no mucosal changes were present it is concurrent with the hypothesis of local recurrence due to non-oncological primary resection.

Response:Once again, you have raised an important point related to thelocal recurrence. The primary surgery was oncological resection. I think the local

recurrence may be caused by the shedding of tumor cells in the case of T4a.

10. Was CT repeated after diagnosis and initial staging? If so, were splenic metastasis described?

Response:We apologize for the missing information in the original submission. In fact, the original CT has been supplemented. CT repeated revealed no local tumor recurrence and splenic metastasis until PET-CT and PET-MRI were found.We therefore have now added the information into the revised manuscript.

11. The references could be updated as the most recent is from 2016.

Response:Thank you very much for the suggestion. We have now updated references from 2016 as the most recent.