

World Journal of Gastroenterology

Science Editor, Editorial Office

Dear Editors:

We are grateful for your letter and suggestions from the reviewers and feel that the quality of this manuscript will be greatly improved with your assistance. Every point, major or minor, has been discussed and carefully examined. We have modified this manuscript and added detailed descriptions as the reviewer suggested. Our response to each point is as follows:

From Reviewer I

Point I- “As first impression, the abbreviation of Metastasis V doesn’t sound good. I strongly suggest to change this abbreviation is something more similar and/or more understandable (e.g.: ICS or ICSM). Moreover, change “isolated cancer cells in the mesentery of colorectal (named as Metastasis V)” in “isolated cancer cells in the mesentery of colorectum” or “large bowel” in many parts of the paper you are using the adjective of colorectal as noun, but the noun is colorectum or colon-rectum or large bowel. You have already use this type of acronym also for gastric cancer, so this is not mandatory but a suggestion, above all for the reader.”

-- Thank you for the suggestions. Metastasis V represents a type of oncological metastasis phenomena that has not been fully recognized by pathologists and oncologists. In fact, our group holds the view that meaningful discoveries could be achieved in this type of metastasis, and that partially explains why we name it after Metastasis V to make temporary consensus and facilitate the afterwards research processes (1-5). This point has been under discussion and we still intend to keep this abbreviation in this manuscript. However, your suggestion, e.g. ICS or ICSM, inspires us a lot in further nomenclature discussion concerning the Metastasis V. We are grateful for your contributions and suggestions.

Point II- “Notably, I have read with great interest the part “Little is known about the exact route or mechanism of Metastasis V. It was hypothesized that primary tumor lesions penetrates the intestinal wall, and then the cancer cells could probably scatter into the fatty

tissues enveloped by proper fascia. In this way, Metastasis V occurs not only in CRC and gastric cancers, but also in oral and head-neck tumors [12-14]”. I strongly suggest to read and cite these references, that are more appropriate:

1. Extranodal extension of lymph node metastasis is a marker of poor prognosis in oesophageal cancer: a systematic review with meta-analysis. Luchini C, Wood LD, Cheng L, Nottegar A, Stubbs B, Solmi M, Capelli P, Pea A, Sergi G, Manzato E, Fassan M, Bagante F, Bollschweiler E, Giacomuzzi S, Kaneko T, de Manzoni G, Barbareschi M, Scarpa A, Veronese N. J Clin Pathol. 2016 Jul 7. pii: jclinpath-2016-203830.
2. Extranodal Extension of Nodal Metastases Is a Poor Prognostic Indicator in Gastric Cancer: a Systematic Review and Meta-analysis. Veronese N, Fassan M, Wood LD, Stubbs B, Solmi M, Capelli P, Pea A, Nottegar A, Sergi G, Manzato E, Carraro S, Maruzzo M, Cataldo I, Bagante F, Barbareschi M, Cheng L, Bencivenga M, de Manzoni G, Luchini C. J Gastrointest Surg. 2016 Oct;20(10):1692-8.
3. Prognostic impact and implications of extracapsular lymph node involvement in colorectal cancer: a systematic review with meta-analysis. Veronese N, Nottegar A, Pea A, Solmi M, Stubbs B, Capelli P, Sergi G, Manzato E, Fassan M, Wood LD, Scarpa A, Luchini C. Ann Oncol. 2016 Jan;27(1):42-8.
4. Extranodal extension is an important prognostic parameter for both colonic and rectal cancer. Luchini C, Nottegar A, Pea A, Solmi M, Stubbs B, Capelli P, Sergi G, Manzato E, Fassan M, Wood LD, Scarpa A, Veronese N. Ann Oncol. 2016 May;27(5):955-6.
5. Prognostic impact of extra-nodal extension in thyroid cancer: A meta-analysis. Veronese N, Luchini C, Nottegar A, Kaneko T, Sergi G, Manzato E, Solmi M, Scarpa A. J Surg Oncol. 2015 Dec;112(8):828-33.
6. Extranodal extension in N1-adenocarcinoma of the pancreas and papilla of Vater: a systematic review and meta-analysis of its prognostic significance. Luchini C, Veronese N, Pea A, Sergi G, Manzato E, Nottegar A, Solmi M, Capelli P, Scarpa A. Eur J Gastroenterol Hepatol. 2016 Feb;28(2):205-9.”

-- Thank you for valuable suggestion. We have added these articles in the references. Corresponding replacement will be updated in the latest version of the manuscript.

Point III- “do the Authors suggest to perform immunohistochemical analysis on every case of colorectal cancer? ”

-- Yes we suggest that immunohistochemical analysis to be performed on every patient of colorectal cancer if affordable. However, due to the medical costs, immunohistochemical screening seems impractical. According to our results, Metastasis V is highly correlated to poorly differentiated tumor, advanced T and N stage. Therefore, immunohistochemical analysis in those patients is strongly recommended.

From Reviewer II

Point I- “It should be important to see the location of colorectal cancer in all cases and the TNM stage of the cancer. In the 14 patients showing metastasis V 12 of them had rectal location. Can you explain this fact ?”

-- Thanks again for your valuable suggestion. This could be explained by the limited number of recruiting patients in this study. We endeavored to analyze the results by expanding the number of patients. However, at present, we collect sixty-three cases of patients with traceable data and qualified samples. We will be honored to present you more convincing results with larger samples in the future. In our study, the rate of Metastasis V is 18.2% (2/11) in colon cancer and 23.1% (12/52) with no statistical significance. Therefore, there was no significant difference of patients with Metastasis V in tumor location.

Thanks again for your kindly help with our manuscript, and we hope to receive your positive feedback soon!

Best regards

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Reference

1. Xie, D., Osaiweran, H., Liu, L., Wang, X., Yu, C., Tong, Y., ... & Gong, J. (2013). Mesogastrium: a fifth route of metastasis in gastric cancer?. *Medical hypotheses*, 80(4), 498-500.
2. Xie, D., Liu, L., Osaiweran, H., Yu, C., Sheng, F., Gao, C., ... & Gong, J. (2015). Detection and characterization of metastatic cancer cells in the mesogastrium of gastric cancer patients. *PloS one*, 10(11), e0142970.
3. Xie, D., Gao, C., Lu, A., Liu, L., Yu, C., Hu, J., & Gong, J. (2015). Proximal segmentation of the dorsal mesogastrium reveals new anatomical implications for laparoscopic surgery. *Scientific reports*, 5.
4. Xie, D., Yu, C., Liu, L., Osaiweran, H., Gao, C., Hu, J., & Gong, J. (2016). Short-term outcomes of laparoscopic D2 lymphadenectomy with complete mesogastrium excision for advanced gastric cancer. *Surgical endoscopy*, 30(11), 5138-5139.
5. Xie, D., Yu, C., Gao, C., Osaiweran, H., Hu, J., & Gong, J. (2016). An Optimal Approach for Laparoscopic D3 Lymphadenectomy Plus Complete Mesocolic Excision (D3+ CME) for Right-Sided Colon Cancer. *Annals of Surgical Oncology*, 1-2.