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Title: Can visceral fat parameters on CT be used to predict occult peritoneal metastasis in patients with gastric cancer?

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Reviewer ID: 03475120

Dear Editor:

Thanks very much for your kind letters about the revisions of our paper titled "Can visceral fat parameters on CT be used to predict occult peritoneal metastasis in patients with gastric cancer?" (No. 81348).

We have finished the revisions carefully, and some corrections and the answers to the queries are provided below. We highlight all the amends on our manuscript. We have polished the revised manuscript by sending it to a professional English language editing company and updated the polished certificate.

Reviewer #1: Though sample size was small, this paper is well written.

Answer: Thank you for your approval and kind advice. One of the limitations of this paper is the small sample size. Firstly, there are fewer cases with occult peritoneal metastasis in clinical practice, especially those confirmed by exploratory surgery and pathology. Secondly, patients with occult peritoneal metastasis from nine years were enrolled and about twice the number of cases were collected as controls. We have supplemented relevant contents in the limitation section.

Reviewer #2: The utility of the study really needs to be adressed or validated. Does this study adds more or helps in change in the way we approach Management of Gastric cancer is what needs to be looked into.

Answer: Thank you for your professional questions. The study showed that the increased attenuation of visceral fat has potential to predict occult peritoneal metastasis of gastric cancer, which is very helpful for clinical diagnosis and treatment. First, preoperative indication of occult peritoneal metastasis may affect the operation choice. For example, laparoscopic exploration may become the prefer choice and intraperitoneal hyperthermic chemotherapy may be prepared before operation, and the open exploration may be the final choice for a patient with occult peritoneal metastasis. In addition, the changes of the attenuation of visceral fat may be helpful in evaluating treatment response to patients receiving neoadjuvant chemotherapy or chemotherapy. We have supplemented relevant contents in the introduction section.

Reviewer #3: This study developed an individualized model that combined mean attenuation of VF and clinical factors for predicting occult PM in patients with gastric carcinoma, and demonstrates the potential of VF parameters in predicting occult PM in GC.

Answer: Thank you for your approval. The study explored the potential of VF parameters in predicting occult PM in GC with two-tailed t-test and logistic regression. In addition, the Interobserver reliability of VF parameters and the relationship between VF parameters and

clinical characteristics were also assessed. The study has an integrate structure.

Reviewer #4: The authors determined usefulness of visceral fat (VF) parameters from computed tomography (CT) to predict occult peritoneal metastasis in the patients with gastric cancer. The workstation was used to measure of parameters of VF and subcutaneous fat from CT images. The mean attenuation was higher in the patient with peritoneal metastasis (PM). The AUC of the VF in the regions of interest to predict PM was 0.657. The authors concluded this study demonstrated the great potential of VF parameters to predict occult PM in gastric cancer patients. The Most important finding in this study is reproducible results in the measurement of VF parameters. There is a notable limitation in this study. The p value of mean attenuations of VF was statistical but not remarkable ($p = 0.048$) in the multiple regression logistic analysis. Conversely, mild ascites and cT stage were useful to predict PM ($p = 0.012, 0.024$) in Table 5. The AUC of VFROI2 was 0.657 in the manuscript, and 0.652 in the abstract. The value was not satisfactory enough in clinical use. Please show the sensitivity and specificity in the AUC curve. Small points Please check the OR in Table 5. The OR in cT stage ($\geq T4$ vs $\leq T3$) was 0.376, which is less than 1.0. Is it correct? The OR in intercept was 1085.396 in Table 5. Is it correct?

Answer: Thank you for your professional questions.

First, The AUC of VF_{ROI2} was 0.657. The regression reported that mean attenuation of VF ROI 2 was not an independent risk factor of PM, with a less predictive ability than ascites and cT stage. Investigate the reason, the changes of adipose microenvironment and the increase of mean attenuation of VF may mainly concentrated around the tumor, and the ROI of VF on the whole axial level may dilute this change and reduce the predictive sensitivity. However, the results confirmed that mean attenuation of VF was significantly different between PM-positive and PM-negative groups of both ROI 1 and ROI 2. The 30th, 50th, 70th, 25th and 75th percentiles of attenuation of VFROI 2 were also significantly different between two groups. Moreover, mean attenuation of VF were related to clinical features representing tumor invasiveness. Therefore, we have reason to believe that mean attenuation of VF is a potential auxiliary parameter to predict occult PM in patients with GC, especially for those only with non-enhanced CT image or upper abdominal CT image. We have supplemented relevant contents in the Discussion section.

Second, the OR in cT stage ($\geq T4$ vs $\leq T3$) was less than 1.0. This is because that T4 was used as the reference basis value for logistic regression. In the new manuscript, The OR in cT stage ($\geq T4$ vs $\leq T3$) was 2.631 after T3 was used as the reference basis value (T3 is defined as 1, T4 is defined as 2). This calculation method would not affect the results and makes it easy to understand.

Third, the OR in intercept was 1085.396 in Table 5. This is because that continuous variable (mean attenuations of VF_{ROI 2}) was directly included in the logistic regression. In the new manuscript, The OR in intercept was 0.009 after continuous variable was divided into two groups by the best cut-off value obtained from ROC curve. The ROC curve of the combined model was also changed accordingly.

Finally, Thanks again for your question. It is the ladder of our progress.