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REPLY, LETTER TO THE EDITOR

Author's Reply: Significance of Intramural Metastasis in Patients with Esophageal Squamous Cell Carcinoma: An Indicator of Aggressive Cancer Behavior

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Dear Editor,

First of all, we appreciate the letter from Dr. Zhang and colleagues as well as their interest in our recent article. In this particular article, published in the *World Journal of Surgery*, we aimed to clarify the prognostic significance of intramural metastasis (IM) from esophageal squamous cell carcinoma (ESCC) in the era of multidisciplinary esophageal cancer treatment [1]. Although several studies reported the significance of IM from ESCC in patients who did not receive any preoperative treatment [2–4], few studies demonstrated the implication of IM in the multidisciplinary treatment era. In this study, we defined the isolated tumor nests that lacked apparent therapeutic changes as IM. Regarding the definition, Zhang et al. mentioned that the prognostic value of IM defined in this study might be overestimated.

In the pathologic specimens of ESCC cases after neoadjuvant treatment, residual tumor nests sometimes show a similar appearance to IM. Because we wanted to diagnose true IM to elucidate the prognostic significance, we used the strict definition in this study. As a result, we revealed that pathologically confirmed IM is a worse prognosticator even in the era of multidisciplinary treatment. However, in some cases after neoadjuvant treatment, IM may have shrunken in the resected specimens. Therefore, such cases might be excluded from the IM positive group in this study, and we thought that what Zhang et al. pointed out was quite right from this point of view. What we have to do next is to clarify whether there are benefits of neoadjuvant therapy for patients with clinical IM. The problem is that the clinical diagnostic accuracy of conventional diagnostic tools, including endoscopy and computed tomography, remains insufficient. The efficacy of novel modalities, such as endoscopic ultrasonography, magnetic resonance imaging and positron-emission tomography, in diagnosing IM should be evaluated.

Zhang et al. also mentioned the significance of tumor deposits (TDs) which are isolated tumor foci found in the peri-organic fat or peri-nodal fat away from the tumor and with no evidence of residual lymph node tissue [5]. Although IM is defined in the Japanese Classification of Esophageal Cancer, TDs have not yet been incorporated into the classification. Therefore, we don't have the data on the significance of TDs in our cases. Certainly, IM and TDs should have similar biologic meaning and may have a similar prognostic impact. In the cross-stage comparison, the survival of pStage I–II patients with IM was relatively similar to that of pStage III–IV patients without IM as we have already described the results in Supplementary Figs. Therefore, revision of the staging system adding IM/TDs might provide additional information to improve prognostic prediction.

Finally, we again thank Dr. Zhang and colleagues for their helpful comments on our article. TDs as well as IM are attractive as a useful indicator of poor prognosis. We are hoping for the establishment of more precise staging system which guides the decisions of optimal treatment strategy based on additional clinical findings.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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