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LETTER TO THE EDITOR

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

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We read with great interest the excellent article by Okamura et al. in *World Journal of Surgery* [1]. The authors found that the presence of intramural metastasis (IM) was an independent poor prognostic indicator in patients with esophageal squamous cell carcinoma (ESCC) undergoing surgery. We congratulate Okamura et al. for this innovative and excellent study, but some points of the study warrant discussion.

The diagnosis of IM by Okamura et al. was based on postoperative histopathologic examination of the surgical specimen. This study included a subset of patients receiving neoadjuvant therapy. However, neoadjuvant therapy could influence the presence of IM and tiny IM might disappear after neoadjuvant therapy. In order to distinguish residual tumor after preoperative treatment from IM, Okamura and associates diagnosed the isolated tumor nests that lacked apparent therapeutic changes as IM, in our opinion, which obviously represent real-world outcomes for lesions without any response to neoadjuvant therapy. To our knowledge, patients with persistent disease after neoadjuvant therapy was associated with worse median survival than those achieving pathologically completely response [2]. Therefore, the prognostic value of IM defined in the study of Okamura et al. might be overestimated. Nevertheless, data of Okamura et al. are of great value, demonstrating IM might be a potential risk factor in patients with ESCC undergoing neoadjuvant therapy followed by surgery.

Our team has previously investigated the prognostic value of tumor deposits (TDs) in a cohort of ESCC patients treated with surgical resection alone [3]. Intriguingly, there exist similar association of TDs and IM with clinicopathologic features and their similar impacts on survival in patients with ESCC. Both of TDs and IM are discontinuous with either the primary lesion or locoregional lymph nodes, have the same histological type as the primary tumor, are seen in advanced and aggressive cancer and are associated with poor prognosis. Besides, TDs and IM share the same pattern of tumor spread (a metastasis spreading from the primary lesion through the vascular structures). Therefore, we speculate IM and TDs might be classified as the same type of metastatic lesion but two different locations.

To our knowledge, some patients without lymph node or distant metastases will die as a result of local or systemic recurrence even after curative surgery. We speculate the possible reason might be tumor upstage migration as patients with TDs presented in our study [3]. IM/TDs could be considered as an intermediate step between primary tumor and distant metastasis and was significantly associated with poor prognosis. However, what category of stage should IM/TDs be included in is still uncertain. We would like to know whether Okamura et al. performed the cross-stage comparison, such as comparing the survival of node-negative patients with IM to node-positive or N1 disease. Further study should also focus on the combination of IM/TDs with TNM system to improve prognostication and stratify ESCC patients into risk categories requiring adjuvant therapy to improve prognosis.

Compliance with ethical standards

Conflict of interest All the authors declare that there are no conflicts of interest in the manuscript.

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