

Gene-expression signature may be useful for the prediction of lymph node metastasis in esophageal cancer

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Esophageal cancer is the eighth most common cancer and the sixth most common cause of cancer mortality worldwide (1). Squamous cell carcinoma and adenocarcinoma are the dominant histological types of esophageal cancer (2). Squamous cell carcinoma, which mainly locates in the middle thoracic esophagus, predominates in the Eastern hemisphere (e.g., Japan), whereas adenocarcinoma of the distal esophagus predominates in the West (3). These two histological types present as different diseases in terms of their epidemiologic, histological, and molecular features, they require different therapeutic strategies.

The presence or absence of lymph node (LN) metastasis is crucially important for therapeutic decision-making, especially in patients with relatively early T stage tumor. Without LN metastasis, early-stage esophageal squamous cell carcinoma (ESCC) is potentially curable by local endoscopic treatment, such as endoscopic submucosal dissection (4-6). However, in cases in which the tumor is most likely to metastasize to LNs, esophagectomy with extended LN dissection is accepted as the current standard treatment. Chemoradiotherapy may become an alternative standard option for early ESCC because a Japanese phase II trial [a Japan Clinical Oncology Group study (JCOG) 9708] has shown that survival after definitive chemoradiotherapy is comparable to that following surgery (7). Another value of preoperative LN status

identification is to decide whether patients should undergo neoadjuvant therapy first. For the above reasons, the current standard treatment in Japan for patients with LN-positive esophageal cancer is preoperative chemotherapy followed by surgery. In addition, the relationship between the presence of LN metastasis and clinical outcome has been demonstrated in ESCC (8); patients with a large number of metastatic LNs experienced unfavorable clinical outcome compared with those with fewer metastatic LNs. Taken together, the prediction of LN metastasis from ESCC before treatment is crucially important in the clinical setting. Diagnostic imaging techniques, including computed tomography (CT) and endosonography, have the limitation of being unable to predict LN status sufficiently. To date many efforts have been devoted to the development of a diagnostic biomarker for LN metastasis and a prognostic biomarker in patients with ESCC (9-11). However, the majority of these markers are limited by their detection potential.

Recent developments in whole genome and transcriptome sequencing technology have resulted in molecular characterization in most types of human cancers (12). The transcriptomes can provide a critical relationship between cellular phenotypes and their molecular characteristics. As for human cancers, this relationship represents an opportunity to clarify tumor complexity and heterogeneity and to develop new biomarkers or therapeutic strategies (13).

Most previous RNA-based biomarkers include a number of genes, and specialized assays have been developed for each panel, depending mainly on quantitative reverse transcription polymerase chain reaction (PCR). But, with the fast-growing decrease in the prices of whole-transcriptome sequencing, a strategy of embedding a number of panels within a single assay has become viable.

In a study recently published in *Annals of Surgery* (14), Sonohara and colleagues demonstrated a promising gene-expression signature for the preoperative prediction of LN metastasis in ESCC. Sonohara *et al.* first defined a priority for 16-gene signature out of the total 20,531 mRNAs utilizing The Cancer Genome Atlas (TCGA) dataset. The established 16-gene panel was able to effectively predict LN metastatic status with an area under the curve of 0.77. Next, the authors selected 5 genes (*PLAC8*, *SLC12A8*, *CSPG4*, *TFPI*, and *TNFSF10*) by a recursive feature elimination approach and demonstrated its validity and robustness using two independent cohorts including 267 Japanese patients. Importantly, the diagnostic accuracy of their newly developed 5-gene panel was significantly superior to currently used clinical and pathological features, CT imaging and serum SCC tumor antigen levels in diagnosing LN metastasis. Furthermore, a combined signature encompassing a 5-gene panel together with lymphatic vessel and venous invasion was superior to the pre-treatment diagnostic modalities and clinicopathological features associated with LN status in ESCC patients. I respectfully emphasize that this is the first study for developing a multigene panel for determination of ESCC LN status.

There are some limitations in this study. First, not all of the surgically resected specimens underwent preoperative systemic chemotherapy. Recently, a Japanese randomized trial (JCOG9907) revealed that neoadjuvant chemotherapy with CDDP plus 5-FU improves the overall survival of ESCC patients (15). Since then, neoadjuvant chemotherapy followed by radical esophagectomy is the standard therapeutic strategy for resectable clinical stage II/III ESCC in Japan (16). However, in the present study, not all patients underwent chemotherapy before the surgery, and this may have influenced the effectiveness of the gene signature. Second, given that it is common practice to endoscopically collect biopsy samples before the surgery, it would have been ideal to validate this gene-signature in endoscopically resected specimens.

Overall, in contrast to the prior investigations, this study by Sonohara *et al.* could develop a promising gene-expression signature for the detection of ESCC LN

metastasis using more systematic and comprehensive analysis. This study may have clinical implications, although we acknowledge that these panels need to be confirmed by independent cohorts in the future. In addition, whether these findings are applicable to Western populations also requires investigation.

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Footnote

Conflict of Interest: The authors have no conflicts of interest to declare.

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