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EDITORIAL – THORACIC ONCOLOGY

Clinical Stage II or III Esophageal Squamous Cell Carcinoma and Neoadjuvant Chemotherapy: Further Considerations

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Esophageal cancer remains a disease with most dismal survivals. Although it is resectable, surgical resection alone does not provide satisfying outcomes. Therefore, multidisciplinary treatments, including neoadjuvant chemotherapy, chemoradiotherapy, and adjuvant treatment, are essential, especially for locally advanced esophageal cancer.[1,2]

JCOG9907, a Japanese randomized control study, showed that neoadjuvant chemotherapy (two courses of 5-fluorouracil [5FU] and cisplatin) resulted in significantly longer survival in patients with clinical stage (cStage) II or III esophageal squamous cell carcinoma (ESCC) than adjuvant chemotherapy.[3] Recently, JCOG1109 revealed that a neoadjuvant triplet regimen (three courses of docetaxel, 5FU, and cisplatin) improved survival in patients with cStage II or III ESCC compared with the standard treatment (two courses of neoadjuvant 5FU and cisplatin) and neoadjuvant chemoradiotherapy.[4]

However, clinical trial results can only be applied to a limited number of patients. Therefore, it would be extremely meaningful to confirm whether neoadjuvant chemotherapy results in better survival than adjuvant chemotherapy for patients with cStage II or III ESCC in clinical settings. Dr. Sun and colleagues recently published their data showing that neoadjuvant chemotherapy followed by esophagectomy prolonged overall survival and disease-free survival compared with esophagectomy followed by adjuvant chemotherapy for patients with cStage II and III ESCC.[5] Their study should be noteworthy from the perspective of real-world data.

However, this study might have several problems. First, this is a retrospective study, and differences in patients' backgrounds between the groups may have resulted in selection bias. For example, there were differences in the Charlson comorbidity index, tumor site, and tumor length between the two groups before matching. Moreover, it is not clear how the patients were grouped into those who underwent esophagectomy after neoadjuvant chemotherapy or upfront esophagectomy with adjuvant chemotherapy. Second, this study defined some clinical factors (postoperative serious complications, positive pathological margins, and pathological supraclavicular lymph node metastasis) as exclusion criteria; however, this is inappropriate as these factors could be affected by neoadjuvant treatment. Third, although the authors used propensity score-matched analysis to decrease bias stemming from the differences in backgrounds between the two groups, the resulting p-values after matching seem improbable. The differences in Charlson comorbidity score, tumor site, and tumor differentiation were significant (p = 0.031, 0.037, and 0.028, respectively) before matching but not after when the p-values were all close to 1 (p = 0.902, 0.989, and 0.888, respectively). Generally, this result would be considered unlikely after propensity score-matching analysis.

This study showed that, compared with adjuvant chemotherapy, neoadjuvant chemotherapy could improve survival for patients with cStage II or III ESCC. Currently, neoadjuvant treatment strategies, including immune checkpoint inhibitors, are rapidly being examined worldwide even for patients with ESCC. We expect that it will take several years to validate the superiority of the new neoadjuvant treatments; therefore, the current use of neoadjuvant chemotherapy will

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be more important for patients with ESCC as the standard treatment at the beginning of this new era.

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