Optimal management of locally advanced esophageal squamous cell carcinoma

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The NEOCRTEC5010 trial, the largest multi-institutional trial, proved the long-term overall survival benefit of trimodality treatment for resectable locally advanced esophageal squamous carcinoma cell (LA-ESCC) (1). In the invited comment by Ceppa et al. (2), the transthoracic approach with 3-field lymphadenectomy was considered the key. Actually, the standard procedure of the NEOCRTEC5010 trial is McKeown or Ivor Lewis esophagectomy with 2-field lymphadenectomy (3). We offer the following comments with respect to the quality, reproducibility, and utility of the technique.

Firstly, among all the potential reasons, while the advantage of the extent of lymphadenectomy earned mixed reviews, the standardization of circumferential marginal status and pathologic evaluation is on the same page. Unfortunately, the circumferential histologic margins were not assessed in the NEOCRTEC5010 trial, so the interpretation of the results of the R0 resection rate (98.4% *vs.* 91.2%; P=0.002) must be cautious. The complete pathological response (pCR, ypT0N0) rate of the NEOCRTEC5010 trial was 43.2%, comparing with 49% of ESCC in the CROSS trial (4). However, the pCR rates of external cohorts with CROSS regimen were only 24.6% in the real-world setting (5) and 27.7% in the latest phase 3 prospective randomized controlled trial (RCT) (6).

Secondly, the issue of variability by surgical procedure types and quality is emphasized by previous RCTs, which may reduce the generalizability of results from such clinical trials (7). In the CROSS trial, transthoracic and transhiatal esophagectomy were justified for tumors located in-between, taking into account patient and tumor characteristics and local preferences. It is hardly understood that the surgical approach did not affect survival in both study arms (8).

Finally, it's worth noting that vinorelbine used in the NEOCRTEC5010 trial has not been approved with an indication for treatment of esophageal cancer by the Chinese National Medical Products Administration (NMPA) or U.S. Food and Drug Administration (FDA). Currently, we are conducting three registered multicenter phase 3 RCTs to compare different perioperative treatments aiming to determine the optimal multimodality treatment for LA-ESCC, which are preoperative chemotherapy followed by surgery versus surgery alone (NCT02442440), perioperative anti-PD-1 plus chemotherapy versus neoadjuvant chemotherapy only followed by surgery (ChiCTR2000040034), and adjuvant anti-PD-1 plus chemotherapy versus anti-PD-1 alone for non-pCR LA-ESCC yielded after neoadjuvant therapy (ChiCTR2100045651).

In summary, ours is not the task of fixing the entire world all at once but stretching to mend the part within our reach. The search for optimal management of LA-ESCC is still on the way.

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