Editorial

Do we have enough evidence for adjuvant postoperative chemoradiation in esophageal cancer?

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There is little doubt that locally advanced esophageal cancer needs multimodality treatments. Multidisciplinary therapy comprising of surgery, chemotherapy, and radiotherapy have been widely introduced in an attempt to eliminate micrometastasis, reduce recurrence and improve prognosis in esophageal cancer. However, the optimal combination has been the subject of long standing debate. Following the success of the landmark Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial, neoadjuvant chemoradiation followed by surgery has become the standard and most popular protocol (1). However, the adjuvant postoperative management of patients who undergo definitive esophagectomy is less straightforward. For example, the current National Comprehensive Cancer Network guidelines for esophageal squamous cell carcinoma recommend adjuvant postoperative treatment only if there is residual disease at the surgical margin (2).

We therefore commend Wong and colleagues for their retrospective study including 4,893 patients diagnosed with stage pT3-4Nx-0M0 or pT1-4N1-3M0 esophageal carcinoma treated with definitive esophagectomy in the National Cancer Data Base (3). Wong *et al.* have tried to address the question of the impact of adjuvant postoperative radiotherapy and chemotherapy on survival after esophagectomy for esophageal carcinoma. They concluded that the addition of postoperative chemoradiation (either sequentially or concomitantly) after esophagectomy was associated with improved overall survival (OS) for patients with node-positive disease or positive margins.

On subgroup analysis, postoperative radiation was associated with improved OS for patients with regional (node-positive) disease (3-year OS 34.3% *vs.* 27.8%, P<0.001), but not for those with localized disease (3-year OS 39.4% *vs.* 42.6%, P=0.47). However, for localized disease with positive margins, there was a survival benefit associated with postoperative radiotherapy (3-year OS 36.4% *vs.* 18.0%, P<0.001). These findings were not surprising as the current National Comprehensive Cancer Network guidelines for esophageal adenocarcinoma, which constitutes the majority (76.7%) in their cohort, also recommends postoperative treatment for non-R0 resection and pN+ tumor in patients who have not received preoperative treatments (3).

Interestingly, whereas multivariate analysis showed no significant benefit after postoperative radiotherapy alone, there remained a significant OS improvement associated with postoperative radiotherapy plus chemotherapy in both unmatched and propensity matched groups. Indeed, the survival benefit of adjuvant postoperative chemoradiation has been reported by Bedard, whose study showed a significant survival advantage with adjuvant chemoradiation (median OS: 47.5 *vs.* 14.1 months, P=0.001) (4). In the propensity-matched analysis by Rice and colleagues (5), the benefit of adjuvant chemoradiation was demonstrated again

(median OS: 28.0 *vs.* 15.0 months, P<0.05). The phase II study by Cleveland Clinic group also demonstrated that adjuvant chemoradiation are with acceptable toxicity for patients after esophagectomy (6). Our recent Taiwan Cancer Registry based study again confirmed that esophagectomy with adjuvant chemoradiation is significantly more effective than surgery alone for increasing OS (3-year OS 44.9% *vs.* 28.1%, P=0.006) (7). The subgroup analysis in our study even suggested that patients with pT3/4 stage, pN+ stage tumors, larger tumor size, poorly differentiated tumors, and R1/2 resections were more likely to have survival benefit from adjuvant chemoradiation.

The remaining question is how good adjuvant chemoradiation is? Unfortunately, very limited trials ever compared adjuvant chemoradiation to neoadjuvant chemoradiation, which is the current standard of care in esophageal cancer. Lv *et al.* did the randomized trial comparing preoperative chemoradiation, postoperative chemoradiation and surgery alone in patients with clinical stage II and III esophageal squamous cell carcinoma (8). Although significant differences in the 5-year OS (43.5% *vs.* 42.3% *vs.* 33.8%, P=0.018) and progression-free survival (PFS; 37.5% *vs.* 37.2% *vs.* 25.9%, P=0.015) were detected among the three arms, there were no significant differences in OS and PFS between the preoperative and postoperative chemoradiation arms (P>0.05). These results were compatible with our recent report (9). Patients with esophageal squamous cell carcinoma who underwent neoadjuvant chemoradiation followed by surgery and those had adjuvant chemoradiation following upfront esophagectomy in the Taiwan Cancer Registry were included for propensity score matching which controlled for differences in tumor factors and patient characteristics, including comorbidities. The OS were not significantly different between two groups (3-year OS 44.0% versus 37.9%, P=0.315). In patients who had complete resection, the freedom from recurrence rate at 1 year after surgery was 74.8% and 67.6% in neoadjuvant and adjuvant groups, respectively (P=0.270). The multivariable analysis again demonstrated that treatment modality (neoadjuvant or adjuvant) was not a significant factor for OS (P=0.258) or disease-free survival (P=0.521). In contrast, Hong *et al.* used the Surveillance, Epidemiology, and End Results (SEER)-Medicare registry to assess neoadjuvant and adjuvant therapy in patients with non-metastatic T3+ or N+ esophageal cancers (10). The neoadjuvant chemoradiation group yielded median OS of 37 months, greater than surgery alone (17 months, P=0.002) and adjuvant chemoradiation (17 months, P=0.06) groups. The neoadjuvant chemoradiation had better OS versus any other treatment combinations in the multivariable analysis.

Interpreting the conflicting results from these studies, we must keep in mind that there is a significant confounding from unrecognized or unmeasurable factors ranging from disease biology to indication for treatment and treatment regimens in retrospective observational studies. Although the bias can be minimized by statistical methods, such as propensity score matching, it cannot be completely eliminated, and therefore may cause disparities. However, whereas randomized controlled trials have stringent inclusion criteria to minimize bias and confounding factors to achieve precise measures of treatment efficacy, the retrospective population-based data analysis is better in representing the usual care, and reflecting the real situation.

So, do we have enough evidence for adjuvant postoperative chemoradiation in esophageal cancer? Can definitive esophagectomy followed by adjuvant postoperative treatments be one of the standard treatment protocols? My current answer is "no". As the level one evidence provided by the CROSS trial, neoadjuvant chemoradiation followed by surgery is still the recommended approach. Although suggested by many retrospective studies, the role of adjuvant chemoradiation at present is for those have not received preoperative treatments. Before a direct comparison between preoperative chemoradiation followed by surgery and definitive esophagectomy followed by postoperative chemoradiation in a randomized controlled trial, neoadjuvant chemoradiation followed by resection remains the treatment of choice. But we believe that the evidence from retrospective studies can form the basis for prospective randomized trials. We continue awaiting compelling evidence that may make changes to current clinical practice.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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