



Reply to B. Li et al

We thank our colleagues Li and Chen¹ for their comments in response to our article.² Indeed, there is still no full consensus about the best treatment strategy for locally advanced esophageal cancer and more specifically about the optimal neoadjuvant regimen. Li and Chen¹ argue that extended lymphadenectomy is a crucial part of treatment in these patients and that the neoadjuvant chemoradiotherapy as applied in the CROSS trial simply compensated for inadequate surgery. We feel that their viewpoint is not supported by the available evidence.

The overall survival benefit of patients who received neoadjuvant chemoradiotherapy persists for at least 10 years. Surgical approach (transthoracic v transhiatal) did not affect this survival advantage.² Li and Chen¹ argue that these results are not in line with our earlier randomized HIVEX trial in which limited transhiatal resection was compared with extended transthoracic resection (exclusively in patients with adenocarcinoma).^{3,4} However, the HIVEX trial did not show an overall benefit for the extended resection, but the post hoc analyses showed a benefit only in patients with a type-1 esophageal tumor and a limited number of positive lymph nodes. We realize that this specific subgroup is most relevant for our Asian colleagues who are mainly confronted with type-1 esophageal patients (with squamous cell carcinoma).

Also, Li and Chen¹ argue that the results of CROSS are conflicting with their Fudan University Shanghai Cancer Center trial, in which a right-sided transthoracic resection (with extended lymphadenectomy) is compared with left-sided transthoracic resection (with limited lymphadenectomy).⁵ In the surgery-alone arm of the CROSS trial, however, the median number of resected nodes ($n = 18$, interquartile range [IQR] 13-27) was only marginally lower than that in the extended lymphadenectomy arm of the Fudan trial ($n = 22$, IQR 17-33), whereas the R0 radicality rate was comparable (69% v 68%, respectively).^{5,6} This is even more striking, considering the fact that the patients in the surgery-alone arm of the CROSS trial had substantially more advanced tumor stages than the patients in the Fudan trial (pT3-4: 80% v 49%, pN+: 75% v 44%, respectively). Hence, we conclude that in the CROSS trial, the surgical part of the multimodality treatment was up to standards.

What is the evidence that extended lymphadenectomy can add any survival benefit in patients who undergo multimodality treatment according to CROSS? In the original CROSS trial, the number of resected lymph nodes was not associated with survival if patients

received chemoradiotherapy before surgery.⁷ This finding was confirmed in a larger cohort study, showing no prognostic effect of transthoracic over transhiatal resection in patients who were treated with the CROSS regimen.⁸ Moreover, in a nationwide Dutch propensity score-matched study including 1984 patients, survival was comparable between those with ≥ 15 versus < 15 lymph nodes resected after neoadjuvant chemoradiotherapy.⁹

Finally, Li and Chen¹ state that a difference in death from other cause was observed in the CROSS trial and that the proportion of deaths from other cause was higher than that in the Fudan trial. In the neoadjuvant chemoradiotherapy plus surgery arm, however, 18% of patients died from other cause (not 28%, as wrongly cited by Li and Chen¹) compared with 12% of patients in the surgery-alone arm (cause-specific hazard ratio 1.17; 95% CI, 0.68 to 1.99). Also, comparison of the proportion of deaths in the CROSS trial with those in the Fudan trial should be done with caution since the median follow-up of the Fudan trial was only 68 months (IQR 62-82 months), whereas the median follow-up of the CROSS trial was 147 months (IQR 134-157 months). Thus, patients in the CROSS trial ran a substantially longer risk of dying.

In conclusion, surgery in the CROSS trial can be considered as adequate. Addition of neoadjuvant chemoradiotherapy to such adequate surgery results in substantially improved survival even after 10 years of follow-up and, in these patients, more extended lymph node dissection is probably not beneficial.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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