

Optimal multimodality treatment followed by surgical resection results in cure for less than half of patients with operable adenocarcinoma of the lower oesophagus or gastroesophageal junction. This is true whether the adjunctive therapy is neoadjuvant chemotherapy, perioperative chemotherapy or neoadjuvant chemoradiotherapy. Therefore it is reasonable to question whether additional treatment beyond current standards of care might increase the proportion of patients cured. In this issue of JAMA Oncology, Mokdad and colleagues, in a propensity score matched analysis based on a large National Cancer Database cohort, examine the effects of adjuvant chemotherapy following chemoradiotherapy and surgery for resectable gastroesophageal adenocarcinoma. They find that patients treated with adjuvant chemotherapy had improved overall survival compared to those who did not receive adjuvant treatment (median OS 40 vs. 34 months, HR hazard ratio, 0.79; 95% CI, 0.73 to 0.88, $p < 0.01$) and propose a randomised clinical trial of adjuvant chemotherapy vs. observation following neoadjuvant chemoradiotherapy and surgical resection in order to provide a definitive answer to this question.

The dataset explored by Mokdad et al is large, containing more than ten thousand patients, of whom 814 (8%) received adjuvant chemotherapy following neoadjuvant chemoradiotherapy. That such a small proportion of patients were treated with adjuvant chemotherapy is reassuring; neoadjuvant chemoradiotherapy and surgery followed by adjuvant chemotherapy is not a treatment approach endorsed by current national or international guidelines. In the unadjusted cohort, patients treated with adjuvant chemotherapy had more advanced disease measured using T and N stage, and had more frequent positive resection margins. They were also more likely to have medical insurance, an adequate number of lymph nodes resected and a shorter time to diagnosis than the group who did not receive adjuvant therapy. The authors note that all significant measured differences between the two groups were adjusted for in the propensity matched analysis. Even so, it is possible that the second set of variables above could reflect unmeasured confounders in the quality of care between the two groups which could impact on overall survival. Also unknown are the pre-operative chemotherapy regimens with which patients were treated, the dose intensity of these regimens, and the dosage and fractionation of radiotherapy received. Notwithstanding these potential weaknesses, the results of Mokdad et al demonstrate a small but clinically relevant absolute benefit in overall survival of 4% at 3 years for patients treated with adjuvant chemotherapy following chemoradiotherapy plus surgical resection. As most recurrent gastroesophageal cancers occur within three years of surgery, this possibly represents an increase in the proportion of patients cured. However, clearly, these findings can only be confirmed in a randomised trial.

Current national and international guidelines suggest that evidence based treatment for patients with operable oesophageal and gastroesophageal junctional adenocarcinoma may include neoadjuvant or perioperative chemotherapy, or neoadjuvant chemoradiotherapy, followed by surgical resection. Since publication of the CROSS trial in 2012, neoadjuvant chemoradiotherapy with weekly carboplatin and paclitaxel plus radiotherapy has been widely adopted as a standard of care. Concerns regarding the lack of systemic efficacy of the low intensity chemotherapy in CROSS have been alleviated, in part, by data from a long term follow-up of the trial which demonstrated a reduction in the occurrence of distant metastases for up to two years following surgery in patients treated on the experimental arm of the study. However, the results of Mokdad et al appear to indicate that even after contemporary neoadjuvant chemoradiotherapy, survival outcomes could be improved by the addition of further systemic chemotherapy. This is unsurprising, as for most patients, gastroesophageal adenocarcinoma is a systemic disease.

The recently presented results of the FLOT4-AIO study underline the importance of systemic therapy for patients with resectable gastroesophageal cancer. In this large, randomised, phase III trial, patients with resectable gastroesophageal junctional or gastric cancer were treated with one of two triplet chemotherapy regimens; two weekly FLOT (docetaxel, oxaliplatin and infused 5-fluorouracil) or three weekly ECX (epirubicin, cisplatin and capecitabine). Patients treated with perioperative FLOT demonstrated pathological complete response rates comparable to adenocarcinoma patients treated with neoadjuvant chemoradiotherapy in the CROSS trial (24%) and had an absolute survival benefit of 9% at 3 years compared to ECX treated patients (median OS 37 vs. 50 months 0.77 [0.63 - 0.94], $p=0.012$). In fact, overall survival for FLOT treated patients in FLOT4-AIO (49 months) was superior to that of patients with adenocarcinoma treated in the CROSS trial (43 months); although this observation must be caveated as a cross trial comparison. As optimal systemic chemotherapy is clearly an effective treatment for patients with resectable gastroesophageal adenocarcinoma, we think that randomisation to a control arm with no active treatment following neoadjuvant chemoradiotherapy and surgery might be difficult to accept. Furthermore, given the challenges associated with administration of adjuvant chemotherapy following oesophagogastrectomy, intensification of systemic treatment before surgery may be more appropriate; this approach is currently being examined in the international, randomised TOPGEAR trial.

In conclusion, the results presented by Mokdad et al appear to indicate that additional systemic chemotherapy could be advantageous for patients treated with chemoradiotherapy for resectable gastroesophageal cancer. However, these results clearly require validation in the form of a randomised trial. Based on the results of the FLOT4-AIO study, integration of

FLOT chemotherapy into neoadjuvant chemoradiotherapy treatment paradigms would appear to be the optimal choice for any future study.