Bridging the gap: how do we improve long-term survival of locally-advanced esophageal cancer patients?

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Gastrointestinal and thoracic oncologists have long struggled with an ugly truth about esophageal cancers: as a whole, these cancers have an unfortunate tendency to progress and recur in the short- and medium-term. The most important predictor of this propensity is the presence of nodal metastases (1,2). It would follow that systemic intervention should be targeted to those patients who have residual nodal metastases identified on pathology after neoadjuvant treatment and resection. However, this has not been instituted on a wide scale due to a paucity of high-level evidence supporting such directed interventions (3).

A confluence of unfortunate factors has produced this indeterminate status quo; perhaps the greatest interrelated culprits are the low incidence of operable esophageal cancer and the lack of clarity that has resulted from conflation of esophageal and gastric cancers in randomized trials.

Trials have long interchanged esophageal and gastric malignancy. While often necessary to achieve adequate enrolment of esophageal cancers this has had the unpropitious consequence of sacrificing clarity at the altar of trial completion. To make matters worse, esophageal cancers comprise a minority of the cases accrued—20% in Intergroup Study 0116 (4) and 25% in the MAGIC trial (5). Even in the esophagus-specific trial by Ychou et al. (6), gastric cancer was added to their inclusion criteria during the accrual period, accounting for 25% of the study population. Despite the encouraging results of perioperative chemotherapy trials (6,7), with little data to rely on for resected node-positive patients who have received neoadjuvant chemoradiation, NCCN guidelines currently only recommend ongoing surveillance (8). In light of the scarcity of high-quality data specific to these patients, Drake et al. (9) aim to fill this gap; their study investigates whether adjuvant chemotherapy confers a survival benefit in node-positive esophageal cancer patients following complete resection after preoperative chemoradiation.

The findings of the accompanying study (9) highlight that adjuvant chemotherapy in the matched cohort was associated with an increase in median survival from 24.0 to 31.2 months and an increase in 5-year overall survival from 20.2% to 27.9%. While these appear to be meaningful differences, there are several issues that should be contemplated and considered prior to adopting this approach.

First, the incidence of toxicity and adverse events is not reported. This represents a major limitation, as interpretation of the reported survival benefit is incomplete without knowing the morbidity and quality of life reductions associated with the addition of postoperative chemotherapy. Given the substantial attrition rates of those receiving postoperative chemotherapy [50.5% in MAGIC (5), 50% in Ychou et al. (6)], it must be asked whether the added 7 months survival is worth the difficulties of chemotherapy. This must be considered in the context of evidence suggesting that it takes 3 to 6 months for the worsened patient quality of life to return to pre-treatment levels after multimodal esophageal cancer therapy (10). Furthermore, in the present study this benefit is only seen in patients who complete their intended course of therapy, as patients with...
complications precluding completion of chemotherapy were excluded from analysis. In the context of an RCT, this could be addressed using functional measures and quality of life; until such time this will remain a crucial discussion with the patient in the oncologist’s office.

Second, the available data prevents analysis of specific chemotherapeutic regimens. While this may in fact bolster the findings of this study, in that benefit was seen regardless of the specific treatment protocol, it does not inform management on a patient-specific level. Presumably, however, decisions can be guided by the chemotherapeutic regimens that have proven effectiveness in the perioperative setting [e.g., FLOT, ECF (7,8)].

Finally, this is an observational study and utilizes propensity matching to address biases that are inherent in non-randomized studies. Although propensity matching can be a valuable tool to attempt to reduce selection bias, it remains inferior to the gold-standard randomized trial. Although the analyses appeared to achieve balance of measured prognostic factors, they cannot account for unmeasurable factors. Given the burden of chemotherapy following major surgery, selection bias is likely and, by definition, favours patients with a baseline improved probability of surviving. That said, patients selected for adjuvant treatment were also the ones most likely to have higher stage disease and, therefore, worse survival; thus, the finding that adjuvant chemotherapy was associated with increased survival in the setting of such systematic bias lends further support to the inference that it is truly beneficial.

All this considered, this study adds valuable information to a crucial gap in the esophageal cancer literature. Clinically, it provides support for the idea that, in properly selected patients who are expected to tolerate adjuvant therapy, a survival benefit is likely to be seen. More broadly, while it may be premature to change standard treatment recommendations on this basis, studies like these provide increasing justification to proceed with properly-designed randomized trials that can truly answer the question of how to improve survival in patients with locally-advanced esophageal cancer.

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**Footnote**

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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**References**


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