Editorial

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

Andrew E. Giles[1], Biniam Kidane[1,2,3]

[1]Section of Thoracic Surgery, Department of Surgery, Max Rady College of Medicine, [2]Department of Community Health Sciences, University of Manitoba, Winnipeg, MB, Canada; [3]Research Institute in Oncology & Hematology, Cancer Care Manitoba, Winnipeg, MB, Canada

Correspondence to: Biniam Kidane. Health Sciences Centre, GE-611, 820 Sherbrook St., Winnipeg, Manitoba, Canada. Email: bkidane@hsc.mb.ca.

Comment on: Drake J, Tauer K, Portnoy D, *et al.* Adjuvant chemotherapy is associated with improved survival in patients with nodal metastases after neoadjuvant therapy and esophagectomy. J Thorac Dis 2019;11:2546-54.

Submitted Aug 14, 2019. Accepted for publication Aug 26, 2019.
doi: 10.21037/jtd.2019.08.112
View this article at: http://dx.doi.org/10.21037/jtd.2019.08.112

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.

Acknowledgments

None.

Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Rizk N, Venkatraman E, Park B, et al. The prognostic importance of the number of involved lymph nodes in esophageal cancer: Implications for revisions of the American Joint Committee on Cancer staging system. J Thorac Cardiovasc Surg 2006;132:1374-81.
2. Rice TW, Rusch VW, Ishwaran H, et al. Cancer of the Esophagus and Esophagogastric Junction: Data-Driven Staging for the Seventh Edition of the American Joint Committee on Cancer/ International Union Against Cancer Cancer Staging Manuals. Cancer 2010;116:3763-73.
3. Burt BM, Groth SS, Sada YH, et al. Utility of Adjuvant Chemotherapy After Neoadjuvant Chemoradiation and Esophagectomy for Esophageal Cancer. Ann Surg 2017;266:297-304.
4. Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J Clin Oncol 2012;30:2327-33.
5. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11-20.
6. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715-21.
7. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet 2019;393:1948-57.
8. NCCN Guidelines Version 2.2019 Esophageal and Esophagogastric Junction Cancers. www.nccn.org 2019. Available online: https://www.nccn.org/professionals/

physician_gls/pdf/esophageal.pdf.
9. Drake J, Tauer K, Portnoy D, et al. Adjuvant chemotherapy is associated with improved survival in patients with nodal metastases after neoadjuvant therapy and esophagectomy. J Thorac Dis 2019;11:2546-54.
10. Alghamedi A, Buduhan G, Tan L, et al. Quality of life assessment in esophagectomy patients. Ann Transl Med 2018;6:84.

Cite this article as: Giles AE, Kidane B. Bridging the gap: how do we improve long-term survival of locally-advanced esophageal cancer patients? J Thorac Dis 2019;11(Suppl 15):S1841-S1843. doi: 10.21037/jtd.2019.08.112

