From standardization to personalized medicine: Moving beyond cookie-cutter treatment of esophageal cancer

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Central Message

Systemic recurrence of esophageal cancer after multimodality treatment remains high. Individualization of care and more aggressive postoperative intervention may improve outcomes over observation.

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Significant advances in diagnosis and therapy for esophageal cancer during the last 4 decades have resulted in improved 5-year overall survival (OS) from 4% to 22.4%.¹ In particular, multimodality treatment, including chemotherapy or radiation administered before or after esophagectomy, has been shown to improve survival for patients with locoregional disease relative to surgery alone.² Studies from the 1980s through the 2000s demonstrated the superiority of neoadjuvant chemotherapy (nCT) and chemoradiotherapy (nCRT) relative to surgical resection alone.³ As earlier studies were criticized for small sample sizes and poor design, it was the CROSS (ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study) trial published in 2012 that first definitively established the superiority of neoadjuvant therapy combined with surgery relative to surgery alone.⁴ The results of this randomized study of 366 patients with locally advanced esophageal cancer demonstrated a 47% 5-year OS with the use of nCRT, significantly surpassing previously reported data with the use of nCT.² Subsequently, nCRT became, and has remained, the standard approach for treatment of patients with clinically positive nodal disease and advanced tumor depth (>T2) in the United States. Current National Comprehensive Cancer Network guidelines recommend the use of nCRT for all patients with locally advanced esophageal cancer who are good surgical candidates,⁵ and we believe that the adoption of a more standardized approach to this disease has contributed to the observed improved outcome.

As the adoption of nCRT has increased, the use of adjuvant therapy has fallen out of favor for several reasons. Although the results of 2 randomized studies (Medical Research Council Adjuvant Gastric Infusional Chemotherapy [MAGIC], Federation Nationale des Centres de Lutte Contre le Cancer [FNCLCC] and Federation Francophonede Cancerologie Digestive Collaborative [FFCD]) demonstrated pathologic downstaging and up to 13% improvement in 5-year OS with perioperative

chemotherapy (nCT and adjuvant chemotherapy [aCT]) relative to surgery alone, the rates of complete resection and pathologic complete response (pCR) were far lower than those demonstrated after nCRT.^{6,7} Moreover, nearly half of the patients in both studies were unable to receive any postoperative chemotherapy, and many patients were unable to complete the entire recommended dose of aCT because of high reported toxicity. To date, no randomized trials comparing outcomes of neoadjuvant therapy and surgery alone versus addition of postoperative aCT have been completed; however, retrospective studies have suggested that there may be a benefit for patients with persistent nodal disease.^{8,9} This benefit is supported by the article in this issue of the *Journal* by Samson and colleagues.¹⁰

The authors of this study used the National Cancer Data Base (NCDB) to evaluate the role of aCT in patients with residual nodal disease after nCT or nCRT. In this retrospective study of 9307 patients between 2006 to 2012, a total of 475 of 3100 patients with persistent nodal disease (15.3%) received additional adjuvant therapy. Subanalysis demonstrated that patients who received nCRT were less likely to have positive margins than those who received nCT and also had a lower number of positive lymph nodes.

Patients with node-positive disease who received aCT had significantly longer median OS. In a subanalysis of patients with R0 node-positive disease, aCT significantly increased median OS, and similar trends were observed in comparisons across all levels of positive nodal disease (N1-N3). Improved OS in patients who received aCT

persisted after propensity matching. After controlling for patient and tumor characteristics, a 29% reduction in mortality was demonstrated in patients who received aCT. Samson and colleagues¹⁰ conclude that aCT after neoadjuvant therapy may be associated with a survival benefit for patients with positive nodal disease.

The results of this study are encouraging but also demonstrate ongoing difficulties with selection bias with the use of the NCDB. In fact, patients who received aCT were younger, better educated, had higher income, and had better insurance. They were also less likely to have received nCRT. Because the database lacks specificity with respect to chemotherapy regimen and number of cycles administered, it is difficult to determine whether observed residual nodal disease is the result of a more aggressive disease process or an effect of undertreatment. Furthermore, although the data suggest that aCT may be beneficial, difficulty in characterization of postoperative complications with the use of the NCDB challenges the ability to determine the safety of this approach.

Studies evaluating the role of aCT after neoadjuvant therapy for patients with residual nodal disease are limited. For this reason, the National Comprehensive Cancer Network guidelines for patients with persistent nodal disease after nCRT are highly unsatisfying, recommending observation until disease progression in patients with squamous cell carcinoma and consideration of aCT in patients with adenocarcinoma.

Samson and colleagues¹⁰ are to be commended for their important contribution to the available knowledge and their attempt to answer 2 important questions that remain partly unanswered: (1) Does aCT after neoadjuvant therapy offer any survival benefit, and if so does the benefit outweigh the risk of treatment? (2) Would all patients benefit from treatment or just a specific subset, and how do we identify that group of patients for which more chemotherapy will result in improved survival? These questions are important today, because although the survival benefits of multimodality treatment have clearly been demonstrated, median OS in patients with locoregional disease has only increased from 6 months in the 1970s to 13 months in the 2000s, despite increased use of neoadjuvant therapy with time.^{3,11,12} Are we offering sufficiently aggressive treatment for such an aggressive disease? There is no question that important prognostic risk factors for survival are directly related to tumor response to therapy and that current therapeutic options for locoregional esophageal cancer are limited in their ability to minimize disease recurrence. The achievement of pCR is one of the most important determinants of recurrence free and OS after neoadjuvant therapy; however, pCR is achieved in fewer than 30% of patients.^{4,13,14} Furthermore, recurrence rates remain high even in patients with pCR.¹⁵ Once the disease has recurred, prognosis is grim, with reported median

survival of 3 to 10 months after diagnosis.¹⁶ Therein lies a problem—recommendations for watchful waiting in the setting of high recurrence rate and limited treatment options for recurrence juxtaposed with limited options for prevention of recurrence. Most recurrences are systemic, even in patients with pCR.¹⁵ Although the benefits of preoperative radiation therapy include reduced dysphagia, increased R0 resection, and pCR, the primary impact of chemotherapy is systemic. This suggests room for improvement with use of additional chemotherapy. The Combination Chemotherapy in Treating Patients With Esophageal Cancer (OE05) trial in fact demonstrated that more aggressive preoperative chemotherapy may result in delayed disease recurrence, but this approach may not be well tolerated in all patient groups.¹⁷

Furthermore, it has been proposed that the presence of postoperative nodal disease may be more prognostic than residual primary tumor. If persistent positive nodes do represent a more aggressive disease form that has been refractory to neoadjuvant treatment, these patients may not respond to additional chemotherapy. The Metabolic response evaluation for Individualisation of neoadjuvant Chemotherapy in oesophageal and oesophagogastric adenocarcinoma (MUNICON) trial in fact demonstrated superior survival in patients that had a metabolic response to preoperative chemotherapy relative to those without a response.¹⁸ Should we completely change our approach and offer more chemotherapy to those with node-negative disease and pCR; that is, those with a response? This concept was explored in a recent NCDB study of aCT after nCRT by Burt and colleagues,¹⁹ who found no difference in OS in patients treated with aCT after nCRT with pCR. That study did demonstrate similar findings to those of Samson and colleagues,¹⁰ with a 30% overall reduced risk of death for patients with residual nodal disease who received aCT. It has been shown that higher numbers of positive nodes may predict distant recurrence.²⁰ Samson and colleagues¹⁰ demonstrate that although patients with residual N3 nodal disease had shorter median OS, aCT still improved their prognosis. These studies are likely biased by selection, however, with patients with more extensive disease and lower response to therapy most likely receiving aCT.

Other studies that have used different data sets have shown conflicting results with the use of aCT after neoadjuvant treatment. In one series of 96 patients, aCT after neoadjuvant therapy did not improve survival in patients with node-positive disease.²¹ It should be noted, however, that 89% of patients received only 1 cycle of chemotherapy. Subsequent studies both demonstrated improved survival and suggested that at least 2 cycles of chemotherapy are needed to achieve a benefit.^{8,22,23} Lack of uniformity in current studies of aCT complicate the ability to draw a meaningful conclusion regarding the associated benefits.

Esophageal cancer is a heterogeneous disease, and the time has come for individualized patient treatment. Appropriate patient selection for aCT after neoadjuvant treatment remains unknown; however, it is likely not appropriate to offer this treatment to all patients. Current ongoing randomized trials (NEOadjuvant trial in Adenocarcinoma of the oEsophagus and oesophagoGastric junction International Study [Neo-AEGIS], Perioperative Chemotherapy Compared To Neoadjuvant Chemoradiation in Patients With Adenocarcinoma of the Esophagus [ESOPEC], Trial of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma [TOPGEAR]) may help to clarify some of these questions, although the answer may lie in tumor genetic characteristics rather than patient and cancer types.²⁴⁻²⁷ In the current setting of poor prognosis for patients with persistent nodal disease and limited therapeutic options, the study by Samson and colleagues¹⁰ may provide enthusiasm and motivation for us to do more rather than just sit and wait for recurrence.

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