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EDITORIAL – THORACIC ONCOLOGY

Staying a Step Ahead: Tailoring Chemotherapy for Esophageal Cancer

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"It lives desperately, inventively, fiercely, territorially, cannily, and defensively—at times, as if teaching us how to survive. To confront cancer is to encounter a parallel species, one perhaps more adapted to survival than even we are." We cannot think of a better way to describe esophageal cancer than these words by Dr. Siddhartha Mukerjee. The very biology of esophageal cancer needs to be treated to improve outcomes. Although the CROSS trial was a major advancement in esophageal cancer treatment, we need to move forward, focusing on precision medicine, tailoring treatment to the cancer, and improving systemic control.[1]

In this month's issue of *Annals of Surgical Oncology*, the manuscript by Tankel et al. explores the long-term outcomes of perioperative docetaxel-based chemotherapy [docetaxel, cisplatin and 5-fluorouracil (DCF) and fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT)] for locally advanced esophageal cancer or gastroesophageal junction (GEJ) at a high-volume esophageal cancer center.[2] Their retrospective cohort study with 236 patients over 15 years was divided into a DCF group [docetaxel/cisplatin/5-fluorouracil (5FU)] and a FLOT group (5FU/leucovorin/oxaliplatin/docetaxel). Patients underwent en bloc esophagectomy with D2 dissection with a 95% R0 resection. Almost 10% had a complete pathologic complete response (PCR) with 23% having microscopic residual disease. Postoperative complications were comparable between both groups. The 5-year overall survival was 59.7% for the DCF cohort and 50% for the FLOT cohort. Median overall survival was 97.3 months for FLOT and 93 months for DCF.

The group reports remarkable results for patients with locally advanced esophageal and GEJ cancer. The FLOT-4 trial demonstrated a 50-month median overall survival for locally advanced gastric and GEJ cancers.[3] Some retrospective studies demonstrate an overall survival of 58 months for esophageal and GEJ cancers.[4] Signet cell cancers have been found to have a poorer response to docetaxel. In this study, 9% of patients had signet cell cancer; however, subgroup analysis was not performed. One of the main issues with FLOT remains the toxicity, with less than 50% of patients being able to complete the postoperative course.[3] In the current study, nearly 80% completed the preoperative course for FLOT (compared with 93% for DCF) with no significant difference. The authors were not able to comment on how many completed the postoperative course, although nearly 80% of patients started it. We wonder whether the high completion rate of preoperative DCF or FLOT in this group is generalizable to other institutions, as that would be key in conferring a survival advantage.

This study contributes to the ongoing debate on the role of CROSS in esophageal adenocarcinoma treatment. Many argue that esophageal adenocarcinoma shares similar biology to GEJ and gastric tumors and must be treated as such. The role of radiation has demonstrated a higher PCR, but a clear survival advantage has not been proven. The NeoRes I trial[5,6] and the Neo-AEGIS[7] trial demonstrated no significant survival difference between neoadjuvant chemotherapy and chemoradiotherapy. However, there was higher postoperative mortality in the chemoradiotherapy group compared with the chemotherapy group (9% versus 1%).[6] The results of the ESOPEC trial, which compares the CROSS and the FLOT

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protocol for locally advanced esophageal and GEJ adenocarcinoma, are much awaited.[8]

The ultimate survival limitation of esophageal cancer treatment is distal recurrence. Improving systemic therapy will prolong survival. A generic approach to esophageal cancer is outdated and we need to treat each case considering tumor type, biology molecular markers, and other areas of investigation, such as liquid biopsies. As cancer continues to become adept at survival, we cannot risk being static in our approach.

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