



Customizing Therapy for Esophageal Cancer: CROSS vs. FLOT

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Locally advanced esophageal cancer (cT2–4 and/or cN+) has been shown to have better outcomes with either neoadjuvant CROSS (41.4 Gy plus carboplatin/paclitaxel)¹ or perioperative FLOT (5-fluorouracil/leucovorin/oxaliplatin/docetaxel)² treatment compared with surgery alone. However, there are no clear guidelines for choosing one versus the other. Most decisions are made based on institutional or provider practice, patients' performance status, and resources available. Preliminary data from the Neo-Aegis trial comparing CROSS to Magic (ECF/ECX/EOF/EOX; pre-2018) and FLOT (2019–2020) showed no superiority of one over the other.³

In this month's issue of *Annals of Surgical Oncology*, the manuscript by Gebauer et al. retrospectively explores the 5 year outcomes of CROSS versus FLOT as a multimodal treatment for locally advanced esophageal or gastroesophageal junction (GEJ Siewert I–II) adenocarcinoma in a single center.⁴

All patients underwent either an open, hybrid, or minimally invasive Ivor Lewis esophagectomy with two-field lymphadenectomies. Gebauer et al. showed a 54 [44.4, NA] month overall survival for the CROSS group (416, 72%) compared with 37.2 [24, 67.2] month overall survival for the FLOT group (162, 18%) but 5-year survival was comparable in both groups (48% versus 43%). The authors report they did not perform a propensity matching due to the inaccuracy of preoperative staging and that all other preoperative characteristics were comparable. Instead, they performed a pathological stage to stage comparison and a histomorphological grade analysis, showing no significant difference between the two treatment regimens.

The retrospective nature of this study and the lack of propensity matching limits the generalization of these findings. The rationale of choosing CROSS or FLOT for the respective patients also remains unclear. The presence of signet ring cells or a pattern of more gastric involvement is unknown. The question remains whether all patients were originally suitable candidates for both regimens. If certain preoperative factors favored one treatment protocol over the other, the lack of matching would skew the data.

Multiple retrospective propensity-matched analyses of CROSS versus FLOT have been published before. One study showed similar short-term outcomes including overall survival, but higher grade 3 complications after FLOT, including a higher rate of pylorospasm.⁵ Another study showed similar short-term outcomes for both FLOT and CROSS but higher pathological response in CROSS.⁶ CROSS has also been associated with lower number of lymph node harvest and higher incidence of distant recurrences.⁷ The theme of CROSS producing more local regression but yielding the same overall survival echoes in all studies demonstrating the importance of systemic control in esophageal cancer.

In the new era of immunotherapy and circulating DNA testing, the treatment for esophageal cancer will continue to evolve. This study digs into an important issue about choosing a perioperative chemotherapy regimen versus neoadjuvant chemoradiation. Although the conclusions are limited, they set the stage for further randomized studies comparing the CROSS and FLOT regimen, which continues to be a source of debate in tumor boards across institutions.⁸

DISCLOSURES None.

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