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Commentary: Crossing off CROSS for treatment of esophageal adenocarcinoma

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CENTRAL MESSAGE

Although CROSS retains a role for esophageal squamous cell carcinoma, better systemic options exist for adenocarcinoma, for which high-quality surgical resection remains a mainstay of treatment.

The invited opinion from De Silva Sewastjanow and colleagues¹ stimulates reflection on the treatment of esophageal cancer and highlights how little progress has been made during the past decade.¹ The authors applauded the Chemoradiotherapy for Esophageal Cancer followed by Surgery Study (CROSS) regimen,² then critiqued it, and then finally suggested we stick with it until we find something better—at last we can now give adjuvant immunotherapy!

I agree that novel therapeutic strategies and more-targeted approaches to treat patients with esophageal cancer are needed. However, the first step in moving away from what the authors call “empiricism” is looking beneath the surface of recent trials because the devil is in the details.

One key discovery of the past decade is that esophageal adenocarcinoma (EAC) and squamous cell carcinoma are completely different entities at the molecular level.³ It is no surprise that the CROSS regimen (ie, carboplatin and paclitaxel with concurrent radiotherapy) has been disappointing for EAC because most of the benefit is derived from the radiation, to which most squamous-type cancers are fairly sensitive. EAC, instead, is prone to systemic spread, which is supported by nodal disease being the most important prognostic factor for survival.⁴ In the

Neoadjuvant Trial in Adenocarcinoma of the Esophagus and Esophago-Gastric Junction International Study, in fact, which enrolled only patients with EAC, 3-year survival was similar between patients treated with chemoradiation and patients treated with perioperative chemotherapy, despite the higher rate of pathological complete response with chemoradiation.⁵ Most patients in this trial received epirubicin, cisplatin, and capecitabine (ECX) therapy, to which 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) therapy has already proved superior.⁶ Moreover, the patients enrolled in the FLOT trial had more-aggressive disease than those in CROSS or the Neoadjuvant Trial in Adenocarcinoma of the Esophagus and Esophago-Gastric Junction International Study (ie, higher rates of nodal disease, T4, and signet cell cancers). Therefore, if the CROSS regimen and ECX have similar outcomes but FLOT is better than ECX (even with worse disease), it seems reasonable to assume that FLOT may be better than the CROSS regimen. Data from CALGB 80803 and my institution further confirm that carboplatin-paclitaxel is a suboptimal regimen to achieve micrometastatic control in EAC.^{7,8} Radiation may improve local control in cases of lower-quality surgical resections (almost half of patients in the CROSS trial underwent transhiatal esophagectomy!), but the prospect of preserving the esophagus through the use of chemoradiation—which the authors argue is possible—appears to be a mirage as elusive as the meaning

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of clinical complete response. Let us not forget that the heavy lifting in the treatment of esophageal cancer is done by surgical resection and that the addition of either perioperative chemotherapy or chemoradiation adds a mere 10% to 15% benefit to surgery alone. Finally, adjuvant immunotherapy may not be as miraculous for all comers as first advertised because a real benefit is seen only in patients with a programmed death-ligand 1 combined positive score >5 .⁹

I remain optimistic that we will soon be able to offer every patient a personalized treatment plan based on cancer type, tumor genetics, circulating DNA, and patient preference. But for the time being, let us stop using CROSS to treat EAC because we have better systemic options with or without radiotherapy.

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