Modi *et al. J Cancer Metastasis Treat* 2024;10:30
DOI: 10.20517/2394-4722.2024.74

Journal of Cancer Metastasis and Treatment

Commentary

Open Access

Check for updates

ESOPEC trial: enhancing treatment approaches for esophageal adenocarcinoma

Shivani Modi[1], **Supriya Peshin**[2], **Gahyun Gim**[3]

[1]Internal Medicine, Jefferson Einstein Healthcare Network, Philadelphia, PA 19401, USA.
[2]Internal Medicine, Norton Community Hospital, Norton, VA 24273, USA.
[3]Hematology & Oncology, University of Rochester, Rochester, NY 14627, USA.

Correspondence to: Dr. Shivani Modi, Internal Medicine, Jefferson Einstein Healthcare Network, 559 W Germantown Pike, Philadelphia, PA 19401, USA. E-mail: shvnmd@gmail.com

How to cite this article: Modi S, Peshin S, Gim G. ESOPEC trial: enhancing treatment approaches for esophageal adenocarcinoma. *J Cancer Metastasis Treat* 2024;10:30. https://dx.doi.org/10.20517/2394-4722.2024.74

Received: 21 Jul 2024 **First Decision:** 10 Oct 2024 **Revised:** 24 Oct 2024 **Accepted:** 12 Nov 2024 **Published:** 30 Nov 2024

Academic Editor: Ciro Isidoro **Copy Editor:** Fangling Lan **Production Editor:** Fangling Lan

Abstract

Esophageal cancer is a highly lethal cancer with notable global variations in incidence and risk factors. In the U.S., it ranks as the fifth most common gastrointestinal cancer, with around 16,940 new cases annually, while globally, it is the sixth most common cancer. Significant regional disparities are highlighted by the "esophageal cancer belt" across northern Iran, southern Russia, central Asia, and northern China, where squamous cell carcinoma (SCC) dominates, comprising 90% of cases. In contrast, the U.S. has seen a rise in esophageal adenocarcinoma, primarily due to obesity and gastroesophageal reflux disease, with SCC rates declining as tobacco and alcohol use decrease. Key trials have shaped current treatment approaches. The CROSS trial (2012) showed a survival advantage with neoadjuvant chemoradiotherapy (carboplatin/paclitaxel with radiotherapy) plus surgery over surgery alone, extending median overall survival (OS) from 24 to 49.4 months. The FLOT4 trial (2017) established perioperative FLOT chemotherapy as superior to ECF/ECX, with median OS increasing from 35 to 50 months. The Neo-AEGIS trial (2020) found comparable OS between the CROSS and perioperative chemotherapy regimens, supporting treatment flexibility. Recently, the ESOPEC trial (ASCO 2024) demonstrated a median OS benefit with perioperative FLOT (66 months) over CROSS (37 months) in resectable esophageal adenocarcinoma, positioning FLOT as the preferred strategy. These findings highlight the value of tailored, multimodal therapies in enhancing survival and quality of life for esophageal adenocarcinoma patients. Future research will explore immunotherapy's role and the potential to omit surgery in patients achieving a complete pathological response.

Keywords: Esophageal cancer, esophageal adenocarcinoma, neoadjuvant chemoradiation, perioperative chemotherapy, FLOT regimen, CROSS protocol, survival benefit

DISCUSSION

Esophageal adenocarcinoma (EAC), originating in the esophagus's glandular cells, is commonly linked to gastroesophageal reflux disease (GERD), Barrett's esophagus, obesity, and smoking. EAC incidence has notably risen in Western countries, where it is often diagnosed at advanced stages. While multimodal therapy (surgery, chemotherapy, and radiation) is standard, survival rates remain low, especially for advanced or metastatic cases.

The pivotal 2012 CROSS trial compared neoadjuvant chemoradiotherapy (carboplatin, paclitaxel, and radiation) followed by surgery to surgery alone in esophageal cancer patients, showing improved survival (median OS of 49.4 *vs.* 24.0 months) and higher complete tumor resection rates (92% *vs.* 69%) in the chemoradiotherapy group[1]. While effective, the trial highlighted a high distant relapse rate (24%) over long-term follow-up, signaling a need for enhanced systemic therapy strategies. The 2017 FLOT4 trial established FLOT chemotherapy (docetaxel, oxaliplatin, leucovorin, and 5-FU) as superior to the prior ECF/ECX regimen in resectable gastric and gastroesophageal junction (GEJ) adenocarcinoma, with improved median OS (50 *vs.* 35 months) and progression-free survival (PFS)[2]. Subsequently, the Neo-AEGIS trial (2016-2020) compared the CROSS regimen with perioperative chemotherapy (primarily MAGIC, and some FLOT) in locally advanced adenocarcinoma of the esophagus and GEJ. No significant OS difference was found, suggesting perioperative chemotherapy is non-inferior to CROSS, thus supporting clinical flexibility[3].

The ESOPEC trial now aims to address whether FLOT directly surpasses CROSS, given FLOT's demonstrated superiority over MAGIC in FLOT4. These trials, as shown in Table 1, collectively underscore the evolving treatment landscape for EAC, emphasizing the importance of multimodal and potentially more aggressive systemic approaches.

The emergence of immunotherapy and enhanced chemotherapy regimens is transforming gastric cancer treatment, providing new opportunities to improve patient outcomes and quality of life. The CheckMate 577 trial, a global phase 3 study, evaluated nivolumab as adjuvant therapy in patients with resected (R0) stage II or III esophageal or gastroesophageal junction (GEJ) cancer who had residual pathological disease after neoadjuvant chemoradiotherapy and surgery. Participants were randomized 2:1 to receive either nivolumab or placebo, with nivolumab administered at 240 mg every two weeks for 16 weeks, followed by 480 mg every 4 weeks for up to one year. The primary endpoint was disease-free survival (DFS). After a median follow-up of 24.4 months, patients receiving nivolumab had a median DFS of 22.4 months (95% Confidence Interval [CI], 16.6 to 34.0), significantly longer than the 11.0 months (95%CI: 8.3 to 14.3) for the placebo group (hazard ratio for recurrence or death, 0.69; 96.4%CI: 0.56 to 0.86; $P < 0.001$). This benefit was consistent across subgroups[4]. However, grade 3 or 4 adverse events related to treatment were more frequent with nivolumab (13%) compared to placebo (6%), resulting in higher discontinuation rates of the trial regimen (9% *vs.* 3% in the placebo group). In conclusion, adjuvant nivolumab therapy significantly improves DFS in patients with esophageal or GEJ cancer post-neoadjuvant chemoradiotherapy, positioning it as a promising treatment option in this setting.

ESOPEC center of attention?

The ESOPEC trial presented at the ASCO annual meeting 2024 marks a significant milestone in the management of resectable esophageal adenocarcinoma, comparing two established treatment protocols: perioperative chemotherapy with FLOT versus neoadjuvant chemoradiation with CROSS. Conducted across 25 sites in Germany, this prospective, randomized phase III trial enrolled 438 patients, aiming to elucidate the optimal approach to improve OS in this challenging cancer subtype. The primary endpoint of

Table 1. Summarizes the key trial designs and results of the CROSS, FLOT4, Neo-AEGIS, and ESOPEC trials, highlighting the study population, inclusion/exclusion criteria, treatment regimens, primary endpoints, and key findings to enhance clarity and facilitate reader comprehension

Trial	Study population	Inclusion/exclusion criteria	Treatment regimen	Primary endpoints	Key results
CROSS	368 patients with resectable esophageal or esophagogastric-junction cancer	Inclusion: resectable esophageal or GEJ cancer; Exclusion: incomplete records	Neoadjuvant chemoradiotherapy (carboplatin and paclitaxel with radiotherapy) followed by surgery *vs.* surgery alone	Overall survival (OS)	Median OS: 49.4 months (chemoradiotherapy) *vs.* 24.0 months (surgery alone); HR: 0.657; $P = 0.003$
FLOT4	716 patients with resectable gastric or GEJ adenocarcinoma	Inclusion: resectable gastric/GEJ adenocarcinoma; Exclusion: incomplete records	Perioperative FLOT (docetaxel, oxaliplatin, leucovorin, and 5-FU) *vs.* ECF/ECX (epirubicin, cisplatin, 5-FU/capecitabine)	OS	Median OS: 50 months (FLOT) *vs.* 35 months (ECF/ECX); HR: 0.77; $P = 0.012$
Neo-AEGIS	377 patients with locally advanced adenocarcinoma of esophagus and GEJ	Inclusion: locally advanced adenocarcinoma; Exclusion: incomplete records	CROSS regimen (carboplatin/paclitaxel with radiotherapy) *vs.* perioperative chemotherapy (ECF/FLOT)	OS	No significant difference in OS; 3-year survival: 57% (CROSS) *vs.* 55% (perioperative chemotherapy)
ESOPEC	438 patients with resectable esophageal adenocarcinoma	Inclusion: resectable esophageal adenocarcinoma; Exclusion: incomplete records	Perioperative FLOT *vs.* neoadjuvant CROSS chemoradiation	OS, PFS, pathological complete response	Median OS: 66 months (FLOT) *vs.* 37 months (CROSS); HR: 0.70; $P = 0.012$; Pathological CR: 19.3% (FLOT) *vs.* 13.5% (CROSS)

the study was OS, and secondary endpoints included progression-free survival (PFS) and pathological complete response[5]. Other secondary endpoints were event-free survival (EFS) and quality of life (QoL) assessments.

The ESOPEC trial results indicating that FLOT may be superior to CROSS in terms of survival outcomes raise important questions about the mechanisms underlying this advantage. One potential reason is the deeper pathological response observed with FLOT, as perioperative chemotherapy is known to target micrometastatic disease more effectively, potentially leading to a more thorough eradication of cancer cells before and after surgery. In contrast, CROSS primarily focuses on localized tumor shrinkage through chemoradiation, which may not address micrometastatic disease comprehensively. FLOT's systemic control, particularly its ability to reduce distant metastases by targeting circulating tumor cells, may play a crucial role in improving overall survival. Moreover, FLOT may be more effective in downstaging tumors and achieving complete resection (R0), which is critical for long-term outcomes. Additional analyses, such as evaluating tumor regression grade, depth of response, and long-term recurrence patterns, would help clarify whether these factors contribute to FLOT's superiority. Furthermore, the molecular effects of FLOT on tumor biology, including its impact on immune activation and genetic pathways, could also be explored to better understand why it may offer better systemic control and long-term survival compared to CROSS.

The ESOPEC trial is a pivotal multicenter, randomized phase III study comparing perioperative FLOT chemotherapy with neoadjuvant CROSS chemoradiation for resectable adenocarcinoma of the esophagus or gastroesophageal junction (GEJ). Its primary objective is to evaluate OS among adults eligible for surgical resection without distant metastases, while secondary endpoints include DFS, recurrence patterns, postoperative morbidity and mortality, and quality of life.

Despite its robust design, the ESOPEC trial faces potential biases that may limit generalizability. The strict inclusion criteria exclude older, frailer patients or those with comorbidities, skewing results toward healthier populations. Additionally, the underrepresentation of racial and ethnic minorities, particularly Black, Hispanic, and Asian patients, raises concerns about the applicability of findings to diverse populations, given differences in tumor biology and healthcare access. Geographic and socioeconomic disparities also affect patient outcomes, as those in low- and middle-income countries may lack access to comprehensive cancer care.

Key findings demonstrate the superiority of FLOT, with a median OS of 66 months compared to 37 months for CROSS (hazard ratio [HR] 0.70, $P = 0.012$). FLOT also achieved higher rates of pathological complete response (19.3% *vs.* 13.5% for CROSS). The survival benefit of FLOT was consistent across subgroups, particularly in patients under 65 and those with lower-stage disease at diagnosis. Neoadjuvant treatment completion rates were higher for FLOT (87%) than for CROSS (80%), reflecting historical rates from the CROSS (88%) and FLOT4 (86%) trials. Treatment-related deaths were similar (1.4% for FLOT and 1.8% for CROSS)[6]. While FLOT had increased rates of neutropenia and gastrointestinal side effects, CROSS led to more esophagitis and pulmonary complications; both regimens exhibited manageable adverse effects. Thus, clinicians should consider these biases and limitations when applying ESOPEC trial findings in real-world settings, particularly for diverse patient groups.

The trial's robust design, including its multicenter, randomized nature and well-balanced patient demographics, enhances the reliability and generalizability of its results. The significant survival benefit observed with FLOT chemotherapy has profound implications for clinical practice, potentially reshaping treatment guidelines and improving outcomes for patients with esophageal adenocarcinoma[2].

The ESOPEC trial's presentation at the ASCO annual meeting 2024 attracted attention not only for its clinical impact but also for its methodological rigor and comprehensive data analysis. The study's findings provide a compelling rationale for adopting perioperative FLOT chemotherapy as a preferred treatment strategy in resectable esophageal adenocarcinoma, offering clinicians a potent tool to optimize patient outcomes in this challenging disease context. In conclusion, the ESOPEC trial represents a pivotal advancement in the field of gastrointestinal oncology, setting a new standard in the management of esophageal adenocarcinoma and underscoring the transformative potential of tailored, multimodal treatment approaches in improving survival and quality of life for patients.

Immunotherapy integration with FLOT or CROSS regimens

Immunotherapy, particularly immune checkpoint inhibitors (ICIs) like nivolumab and pembrolizumab, has shown promising results in various cancers, including esophageal adenocarcinoma. Combining ICIs with FLOT or CROSS regimens could potentially enhance antitumor efficacy by improving the immune response. Chemotherapy and radiation can induce immunogenic cell death, increasing tumor antigen presentation and making the tumor more susceptible to ICIs. Additionally, ICIs can potentially eliminate micrometastatic disease that remains post-chemotherapy/radiotherapy.

To optimize the integration of immunotherapy with FLOT or CROSS, several strategies can be explored. Trials should investigate whether administering ICIs concurrently with neoadjuvant chemotherapy/radiotherapy or sequentially after completion yields better outcomes. Finding the optimal dose and scheduling to minimize toxicity while maximizing efficacy is crucial. Biomarker-guided therapy, using PD-L1 expression, tumor mutational burden (TMB), and other biomarkers, can help select patients most likely to respond to ICIs[7]. Exploring combinations of ICIs with other novel agents such as anti-angiogenic drugs,

PARP inhibitors, or other targeted therapies is another promising approach.

Robust clinical trials are needed to validate these strategies. Phase I/II trials should evaluate the safety, tolerability, and preliminary efficacy of combining ICIs with FLOT or CROSS regimens. Larger phase III trials can confirm the efficacy and survival benefits of these combinations, with endpoints including OS, DFS, and QoL. Translational research will help understand the mechanisms of response and resistance, identify predictive biomarkers, and optimize patient selection. Additionally, collecting real-world evidence will assess the feasibility and effectiveness of these combinations in diverse patient populations.

Surgery omission in esophageal adenocarcinoma

To explore omitting surgery in esophageal adenocarcinoma patients achieving pathological complete response (pCR) after neoadjuvant therapy, several criteria are key. Molecular and genetic markers, like circulating tumor DNA (ctDNA) and specific mutations, could help identify patients likely to reach pCR. Advanced imaging, such as PET-CT and MRI, along with post-neoadjuvant endoscopic biopsies, would aid in confirming pCR and assessing for residual disease. Clinical factors, including tumor size, location, and initial staging, further stratify patients at low recurrence risk. Validating this approach requires randomized controlled trials (RCTs) comparing surgery with active surveillance in pCR patients. Surveillance should involve regular endoscopic checks, imaging, and biomarker monitoring. Primary endpoints include OS and DFS, with QoL and treatment morbidity as secondary endpoints[8]. Using adaptive trial designs with strict inclusion criteria ensures patient safety and focuses resources on the most effective strategies.

Unmet needs

EAC faces several critical unmet needs that, if addressed, could enhance patient outcomes considerably. Early detection remains a major challenge, as effective screening for high-risk groups is lacking, often resulting in late-stage diagnoses and poorer prognoses. Treatment strategies also need optimization; there is no established consensus on the ideal preoperative approach, with ongoing debates about the benefits of perioperative chemotherapy versus neoadjuvant chemoradiation. Furthermore, targeted and immunotherapy options are limited, highlighting the need for new agents designed to address the unique molecular characteristics of EAC. Recurrent disease is another pressing issue, as effective strategies to prevent and manage recurrence after curative treatment are scarce. Advancements in early detection and more personalized, biologically informed therapies are essential to improve survival rates and quality of life for EAC patients.

Ongoing trials combining FLOT or CROSS with ICIs

Combining perioperative FLOT chemotherapy with PD-1/PD-L1 inhibitors, such as pembrolizumab (KEYNOTE-585) and atezolizumab (DANTE trial), is an innovative approach for treating resectable gastric and GEJ adenocarcinomas. The strategy leverages chemotherapy-induced neoantigen exposure, potentially enhancing immune response. Both trials focus on OS, EFS, and DFS, with attention to PD-L1 expression and TMB to identify patients most likely to benefit from immunotherapy[6].

Similarly, ongoing research with ICIs in the CROSS protocol (neoadjuvant chemoradiation) for esophageal and GEJ cancers examines whether ICIs enhance outcomes by targeting residual disease post-chemoradiation. Trials using nivolumab evaluate disease-free survival, recurrence-free survival, and OS, while CheckMate 577 supports the benefits of adjuvant nivolumab post-surgery, particularly in non-complete responders.

Biomarkers like PD-L1 expression and TMB are increasingly essential in refining treatment. High PD-L1 expression and TMB suggest a more immunogenic tumor environment, possibly improving ICI efficacy. Current trials stratify patients by PD-L1 (using CPS) and explore TMB, neoantigen load, and immune infiltration to tailor immunotherapy approaches, aiming to optimize outcomes in these aggressive cancers[9].

The integration of ICIs into perioperative and neoadjuvant settings, guided by biomarkers like PD-L1 and TMB, holds promise for more personalized esophageal and GEJ cancer treatments. Emerging data suggest that combining ICIs with standard FLOT or CROSS regimens may enhance pathological responses, lower recurrence rates, and improve survival, especially in biomarker-selected patients. Ensuring that these combinations remain safe and well-tolerated, with vigilant monitoring for immune-related adverse events, is crucial for expanding their use in clinical practice.

CONCLUSION

Future research in esophageal adenocarcinoma is poised to explore the potential of omitting surgery in patients who achieve a complete pathological response to FLOT or CROSS regimens, with active surveillance for disease progression. This shift reflects a growing interest in minimizing invasive treatments when systemic control is achieved. However, the generalizability of the ESOPEC trial, conducted predominantly in Germany, may be limited due to demographic, geographic, and healthcare system differences in broader populations. Although the trial provides valuable data as a prospective randomized phase III study, concerns remain regarding patient selection biases, treatment allocation, and endpoint interpretations, which may influence the applicability of its findings in real-world settings. The evolving role of immunotherapy, especially checkpoint inhibitors such as PD-1 and PD-L1 inhibitors, presents new opportunities for treatment advancement. Emerging evidence suggests these agents may enhance outcomes either as monotherapy or in combination with FLOT or CROSS, particularly for patients with higher tumor mutational burden or positive PD-L1 expression. Future research should prioritize integrating immunotherapy into multimodal treatment strategies and determining optimal patient selection. To fully refine treatment approaches, ongoing clinical trials and translational research are essential to enhance survival outcomes and quality of life for esophageal adenocarcinoma patients. The continued evolution of these therapies highlights the need for a more nuanced and patient-specific understanding of the disease. In this perspective, the future of managing EAC lies in personalized medicine and the integration of biomarkers to tailor treatments based on individual patient profiles. Advances in genomics and molecular profiling are enabling the identification of actionable mutations and pathways that drive tumor growth, offering the potential for targeted therapies. Biomarkers such as HER2 overexpression, PD-L1 status, and microsatellite instability are already showing promise in guiding the use of immunotherapies and targeted agents, such as trastuzumab and checkpoint inhibitors, for specific subgroups of EAC patients. Beyond targeted therapies, biomarkers could also play a crucial role in predicting treatment response to chemotherapy or radiation, enabling clinicians to stratify patients based on the likelihood of benefit from conventional therapies. The clinical utility of these biomarkers is also seen in their potential to improve early detection, monitor minimal residual disease post-treatment, and provide a prognostic outlook based on tumor biology. As research in this field evolves, the integration of biomarker-driven approaches will likely enhance treatment precision, improve survival outcomes, and minimize the toxicity associated with non-specific therapies, ultimately transforming the standard of care for EAC.

DECLARATIONS

Authors' contributions

Substantial contributions in writing, editing, and gathering data for the study and interpretation: Modi S, Peshin S, Gim G

Availability of data and materials
Not applicable.

Financial support and sponsorship
None.

Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

REFERENCES
1. Tramontano AC, Nipp R, Mercaldo ND, Kong CY, Schrag D, Hur C. Survival disparities by race and ethnicity in early esophageal cancer. *Dig Dis Sci* 2018;63:2880-8. DOI PubMed PMC
2. van Hagen P, Hulshof MCCM, van Lanschot JJB, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84. DOI
3. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006;24:2137-50. DOI
4. Hoeppner J, Brunner T, Lordick F, et al. Prospective randomized multicenter phase III trial comparing perioperative chemotherapy (FLOT protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus (ESOPEC trial). *J Clin Oncol* 2024;42:LBA1. DOI
5. Morgan E, Soerjomataram I, Rumgay H, et al. The global landscape of esophageal squamous cell carcinoma and esophageal adenocarcinoma incidence and mortality in 2020 and projections to 2040: new estimates from GLOBOCAN 2020. *Gastroenterology* 2022;163:649-58.E2. DOI PubMed
6. Short NJ, Kantarjian HM, Konopleva M, et al. Combination of ponatinib and blinatumomab in Philadelphia chromosome-positive acute lymphoblastic leukemia: early results from a phase II study. *J Clin Oncol* 2021;39:7001. DOI
7. Frick MA, Vachani CC, Bach C, et al. Survivorship and the chronic cancer patient: patterns in treatment-related effects, follow-up care, and use of survivorship care plans. *Cancer* 2017;123:4268-76. DOI
8. Fuchs CS, Doi T, Jang RWJ, et al. KEYNOTE-059 cohort 1: efficacy and safety of pembrolizumab (pembro) monotherapy in patients with previously treated advanced gastric cancer. *J Clin Oncol* 2017;35:4003. DOI
9. Janjigian YY, Kawazoe A, Yanez PE, et al. Pembrolizumab plus trastuzumab and chemotherapy for HER2+ metastatic gastric or gastroesophageal junction (G/GEJ) cancer: initial findings of the global phase 3 KEYNOTE-811 study. *J Clin Oncol* 2021;39:4013. DOI