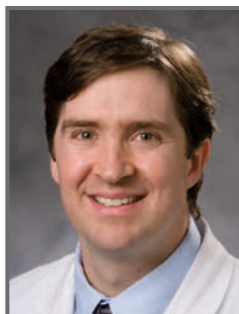
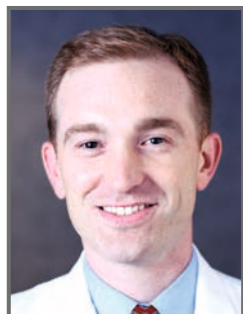


# The CROSS trial: end of the debate on neoadjuvant therapy for esophageal cancer?



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“This trial firmly establishes the role of neoadjuvant chemoradiotherapy followed by surgery as a standard of care in the treatment of resectable esophageal and gastroesophageal junction malignancies.”

The incidence of esophageal cancer has increased dramatically over the last few decades [1,2]. Despite substantial advances in surgery, chemotherapy and radiation therapy, mortality rates for this disease remain high [3]. The optimal treatment approach for patients with locally advanced disease remains controversial. Preoperative chemoradiotherapy is established as a standard of care in rectal cancer [4] and has shown promise in the treatment of other gastrointestinal malignancies. Preoperative chemoradiotherapy offers several potential biological and technical advantages when compared with either surgery alone, or with postoperative therapy delivery, including:

- An intact tumor vasculature which may improve tumor oxygenation and responsiveness to radiation therapy, as well as chemotherapy delivery;

- Potentially smaller and more accurate radiation-treatment field design, which in turn could improve treatment tolerance and disease-related outcomes;
- Potential tumor downstaging, facilitating curative (R0) resection rates and decreasing the risk of local tumor recurrence by eradicating subclinical disease not removed at resection;
- Potential identification of patients with biologically aggressive disease for whom surgery should be avoided.

Results of randomized trials evaluating this treatment approach for esophageal cancer have been conflicting. Previously, two randomized trials have shown an overall survival benefit of the use of neoadjuvant chemoradiotherapy followed by surgery, compared with surgery

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alone, for esophageal cancer [5,6]. One study from Ireland, which randomized 113 patients with resectable esophageal- or gastroesophageal (GE)-junction adenocarcinoma to either preoperative chemoradiotherapy or upfront surgery, demonstrated a superior 3-year overall survival benefit favoring the chemoradiotherapy arm (32 vs 6%;  $p = 0.01$ ) [5]. Another Phase III study from the Cancer and Leukemia Group B randomized 56 esophageal cancer patients to either preoperative chemoradiotherapy (50.4 Gy using concurrent cisplatin and 5-fluorouracil) followed by surgery or initial surgical resection. A statistically significant overall survival improvement was again detected at 5 years (39 vs 16%;  $p = 0.002$ ) favoring neoadjuvant therapy [6]. However, several legitimate criticisms have been levied at these studies, including low accrual, short median follow-up (10 months), lack of prerandomization CT scanning and worse-than-expected outcomes in the surgery-alone arm in the Irish trial [5]. While the Cancer and Leukemia Group B trial implemented more modern radiation techniques and conventional fractionation, it was handicapped by low patient accrual (it was planned for more than 500 patients).

Conversely, three other randomized trials have shown no survival benefit of preoperative chemoradiotherapy versus upfront surgery alone [7–9]. An EORTC trial randomized 282 patients with squamous cell carcinoma of the esophagus to neoadjuvant chemoradiotherapy followed by surgery, compared with surgery alone. There was no difference in median survival (18.6 months), although a disease-free survival benefit was noted favoring preoperative therapy. However, this study implemented split-course radiation therapy using unconventional fractionation (37 Gy in ten fractions in two separate, 1-week courses, separated by a 2-week treatment break, possibly contributing to postoperative morbidity and mortality) and cisplatin monotherapy, as opposed to a chemotherapy doublet [7]. Another study from the University of Michigan (USA), which randomized 100 patients with both squamous cell carcinoma and adenocarcinoma to a neoadjuvant approach versus surgery demonstrated improvements in local control favoring preoperative chemoradiotherapy [8]. Overall survival at 3 years was different (30 vs 16%), but did not reach statistical significance ( $p = 0.07$ ), although the trend favoring a neoadjuvant

approach may reflect a statistically underpowered study [8]. Another study from Australia similarly showed no difference in overall survival between treatment arms, but could also be criticized for suboptimal radiotherapy dose and fractionation (35 Gy in 2.33 Gy fractions), as well as single-course chemotherapy delivery [9].

The recently published CROSS trial is an important and well-designed Phase III study, which provides clarity to the role of preoperative chemoradiotherapy compared with surgery alone [10]. Compared with some of the previously described trials with equivocal or negative results, this study provides significant support to a neoadjuvant chemoradiotherapy treatment approach for esophageal cancer. In brief, Dutch investigators randomized 368 patients with resectable esophageal or GE junction cancer to either preoperative chemoradiotherapy followed by surgery, or to surgery alone. Most patients (75%) had adenocarcinoma. The primary end point was overall survival. Radiation therapy was conventionally fractionated (41.4 Gy in 1.8 Gy fractions) and a contemporary chemotherapy regimen (weekly carboplatin and paclitaxel for five cycles) was implemented. Surgery was performed 4–6 weeks following chemoradiotherapy completion. The majority of patients were clinical T3 by endoscopic ultrasound staging and clinically node positive. After a median follow-up of 49 months, 5-year overall survival (47 vs 34%;  $p < 0.001$ ) and median disease-free survival (24 months in the surgery-alone arm vs not reached in the chemoradiotherapy arm) were improved in the combined modality arm, compared with the surgery-alone group. This benefit was seen in both squamous cell and adenocarcinoma patients based on an unplanned subset analysis. R0 resection rates (92%) were also significantly superior in the chemoradiotherapy arm, with no difference in perioperative complications or surgical mortality between the treatment arms. Thus, the survival difference between the two arms can be attributed to the benefits of preoperative chemoradiotherapy.

Do these results end the debate on neoadjuvant chemoradiotherapy for esophageal cancer? Yes and no. The CROSS trial, the largest Phase III trial to date examining preoperative chemoradiotherapy followed by surgery for esophageal cancer, conclusively demonstrates that preoperative chemoradiotherapy improves

“Do these results end the debate on neoadjuvant chemoradiotherapy for esophageal cancer? Yes and no.”

R0 resection rates, as well as overall survival. This trial firmly establishes the role of neoadjuvant chemoradiotherapy followed by surgery as a standard of care in the treatment of resectable esophageal and GE junction malignancies.

However, the question of whether neoadjuvant chemoradiotherapy is superior to neoadjuvant chemotherapy followed by surgery remains unanswered. Four randomized controlled trials have been performed comparing neoadjuvant chemotherapy alone followed by surgery, compared with surgery alone [11–14], with the three European trials showing a statistically significant improvement in overall survival favoring the preoperative chemotherapy arm [12–14]. However, several of these also included a substantial percentage of gastric cancer patients. Only one Phase III trial has attempted to directly compare a neoadjuvant chemotherapy-alone approach to preoperative chemoradiotherapy in GE junction patients (the German POET trial) [15]. This study was hampered by poor accrual and showed no statistically significant difference between the two arms at 3 years (28 vs 48%), although a strong trend was seen favoring the chemoradiotherapy arm, including superior pathologic complete response and R0 resection

rates [15], suggesting that tumor response was improved with the addition of radiotherapy to chemotherapy prior to esophagectomy.

In conclusion, the CROSS trial solidifies the role of preoperative chemoradiotherapy followed by surgery for locally advanced but resectable esophageal cancer patients, which represents most presentations in the USA at present [2]. In this population, it is clear that surgery alone is inadequate therapy. A neoadjuvant chemoradiotherapy approach has become standard in the USA and many European countries. The debate will continue as to whether preoperative chemotherapy or chemoradiotherapy is the optimal treatment approach for resectable disease.

#### Financial & competing interests disclosure

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“The CROSS trial solidifies the role of preoperative chemoradiotherapy followed by surgery for locally advanced but resectable esophageal cancer patients...”

#### References

- Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 83(10), 2049–2053 (1998).
- Brown LM, Devesa SS, Chow WH. Incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, age. *J. Natl Cancer Inst.* 100(16), 1184–1187 (2008).
- Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J. Clin.* 62(1), 10–29 (2012).
- Sauer R, Becker H, Hohenberger W *et al.* Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N. Engl. J. Med.* 351(17), 1731–1740 (2004).
- Walsh TN, Noonan N, Hollywood D *et al.* A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N. Engl. J. Med.* 335(7), 462–467 (1996).
- Tepper J, Krasna MJ, Niedzwiecki D *et al.* Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *J. Clin. Oncol.* 26(7), 1086–1092 (2008).
- Bosset JF, Gignoux M, Triboulet JP *et al.* Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. *N. Engl. J. Med.* 337(3), 161–167 (1997).
- Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *J. Clin. Oncol.* 19(2), 305–313 (2001).
- Burmeister BH, Smithers BM, Gebski V *et al.* Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled Phase III trial. *Lancet Oncol.* 6(9), 659–668 (2005).
- van Hagen P, Hulshof MC, van Lanschot JJ *et al.* Preoperative chemoradiotherapy for esophageal or junctional cancer. *N. Engl. J. Med.* 366(22), 2074–2084 (2012).
- Kelsen DP, Ginsberg R, Pajak TF *et al.* Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. *N. Engl. J. Med.* 339(27), 1979–1984 (1998).
- Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. *Lancet* 359(9319), 1727–1733 (2002).
- Cunningham D, Allum WH, Stenning SP *et al.* Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N. Engl. J. Med.* 355(1), 11–20 (2006).
- Ychou M, Boige V, Pignon JP *et al.* Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter Phase III trial. *J. Clin. Oncol.* 29(13), 1715–1721 (2011).
- Stahl M, Walz MK, Stuschke M *et al.* Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J. Clin. Oncol.* 27(6), 851–856 (2009).