



Induction Chemoradiotherapy for Esophageal Cancer: Comparing Carboplatin/Paclitaxel with Cisplatin/5-FU

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**Induction Chemoradiotherapy for Esophageal Cancer:
Comparing Carboplatin/Paclitaxel with Cisplatin/5-FU**

by

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**Submitted in Partial Fulfillment of the Requirements for the M.D. Degree
with Honors in a Special Field at Harvard Medical School**

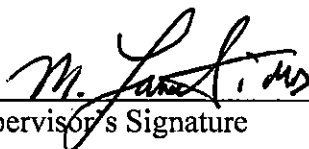
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I have reviewed this thesis. It represents work done by the author under my supervision and guidance.



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ABSTRACT

Purpose

Since publication of the CROSS trial in 2012, trimodality therapy using carboplatin/paclitaxel (“CP”) has become the standard of care in the treatment of locally advanced esophageal cancer. Yet few studies have directly compared CP to its predecessor, cisplatin/5-fluorouracil (“CF”), and little is known about the comparative efficacy of these two regimens. The purpose of this study is to directly compare the antineoplastic potency of these two regimens as components of trimodal therapy in the treatment of locally advanced esophageal cancer.

Patients and Methods

Patients completing trimodal therapy with CP or CF for locally advanced esophageal cancer at a single institution from 2002 to 2017 were included in this retrospective study. Clinical and treatment details were obtained from medical records. The primary outcome was pathologic complete response (pCR). Secondary outcomes were overall (OS) and disease-free survival (DFS). Primary outcomes were measured with logistic regression; survival was estimated with Kaplan-Meier and Cox proportional hazards models.

Results

325 patients were included. 186 patients (57%) received CP; 139 (43%) received CF. Median follow-up was 23.1 months. Tumor stages were similar between groups ($P=.89$). CF was associated with improved pCR compared to CP in both univariate (33% vs. 21% respectively, $P=.02$) and multivariate (OR 2.2, $P=.01$) analyses. pCR was associated with significantly improved 5-year OS (60% vs. 31%, $P<.001$). CF showed improved median OS compared to CP (42 vs. 29 months, $P=.04$). In multivariate analysis, CF was associated with improved OS (HR .668, $P=.02$) and DFS (HR .708, $P=.04$) compared to CP.

Conclusions

Trimodal therapy with CP has become the standard of care for curative treatment of LAEC, yet most studies compare it against surgery alone. Here we directly compare CP to the historical standard regimen (CF), finding that, amongst patients who complete trimodal therapy, CP is associated with worse tumor response and survival. These observations invoke caution that the anti-tumor efficacy of the CROSS regimen is reduced compared to CF and is more dependent on tumor histology. Alternative induction chemotherapy strategies should be evaluated in esophageal carcinoma.

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Glossary of Terms

BMI	Body mass index
CAD	Coronary artery disease
CF	Cisplatin/5-Fluorouracil
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CP	Carboplatin/paclitaxel
CRT	Chemoradiotherapy
CT	Computed tomography
CVD	Cerebrovascular disease
DFS	Disease-free survival
EAC	Esophageal adenocarcinoma
ECF	Epirubicin/cisplatin/5-Fluorouracil
ECOG	Eastern Cooperative Oncology Group
ESCC	Esophageal squamous cell carcinoma
FOLFOX	5-Fluorouracil/Leukovorin/Oxaliplatin
GEJ	Gastroesophageal junction
Gy	Gray
HR	Hazard ratio
IMRT	Intensity modulated radiation therapy
LAEC	Locally advanced esophageal cancer
MIE	Minimally-invasive esophagectomy
npCR	Near pathologic complete response
OR	Odds ratio
OS	Overall survival
pCR	Pathologic complete response
PET	Positron emission tomography
PFS	Progression-free survival
PVD	Peripheral vascular disease
SD	Standard deviation
U.S.	United States
2D	2-dimensional
3D	3-dimensional
5-FU	5-Fluorouracil

BACKGROUND

Overview

Despite tremendous progress in cancer treatment in the last few decades, esophageal cancer remains a significant source of morbidity and mortality in the United States. The last half century has seen an important evolution in the approach to treatment of patients with locally advanced esophageal malignancies, centering nowadays on trimodality therapy involving neoadjuvant chemoradiotherapy (CRT) followed by surgical resection. Yet questions about the optimal treatment – such as chemotherapy regimen, radiation dose, and surgical approach – are the subject of ongoing debate. Treatment decisions are fraught with trade-offs: tolerability versus oncologic efficacy, curative potential versus operative candidacy. For much of the evolution of esophageal cancer treatment, the standard of care was driven mostly by considerations of oncologic control and survival benefit. Recently, increasing attention has been paid to the toxicity and tolerability of various treatment regimens. The most recent and practice-changing example of this paradigm shift occurred in 2012 following the publication of the CROSS Trial.¹ This randomized controlled trial from the Netherlands showed that patients with esophageal malignancies could achieve acceptable outcomes following trimodality therapy using a lower dose of preoperative radiation and less toxic chemotherapy than had previously been the standard practice in the U.S. This “CROSS regimen” has since become the standard of care in the treatment of locally advanced esophageal cancer in the States. Yet the limitations of the CROSS Trial have led some to question its widespread adoption. Specifically, concerns that the improved tolerability of the CROSS regimen (compared to its predecessor) may be associated with inferior antineoplastic potency have led some to question its use in all patients, particularly in otherwise healthy patients who may well tolerate the potential toxicity of a more potent regimen. This study aims to investigate the antitumoral potency of the CROSS regimen and compare it to the historical standard of care neoadjuvant regimen to investigate whether the improved tolerability of the CROSS regimen has indeed come at the cost of oncologic efficacy.

Epidemiology

Worldwide, esophageal cancer represents the 8th most common solid organ malignancy.² It accounted for an estimated 17,290 new cancer diagnosis and 15,950 deaths in the U.S. in 2018, corresponding to an incidence of 4.2 cases per 100,000 patient-years.³ The average estimated

individual lifetime risk of developing esophageal cancer is 0.4%. The overall 5-year survival of all patients from the time of diagnosis is 19%, though survival varies considerably based on the extent of tumor dissemination at the time of diagnosis.³ In particular, 5-year survival may be as high as 45% amongst patients with only localized disease at initial presentation, yet only 19% of cancers are diagnosed at this early stage. Nearly 40% of patients have distant disease at initial presentation, and survival in this subgroup is a dismal 4.8% at 5 years (Figure 1). The diagnosis is most often made during the sixth to eighth decade of life, with a median age at diagnosis of 68 years, and is more common in men than in women (Figure 2).³ Encouragingly, recent trends suggest overall improvements in survival over the last half century; whereas the current overall 5-year survival is 19%, it was as low as 5% in the 1970s, prior to the widespread adoption of multimodality therapy.

Esophageal cancers generally fall into one of two major histologic subtypes: squamous cell carcinoma – the most common histology of esophageal malignancies worldwide – and adenocarcinoma, which predominates in the U.S., and whose incidence here is currently increasing more rapidly than any other solid tumor.⁴ Esophageal squamous cell carcinoma (ESCC) tends to occur in the middle or upper third of the esophagus, while esophageal adenocarcinoma (EAC) is most commonly found in the lower esophagus or gastroesophageal junction (GEJ). Once representing less than 10% of esophageal cancers in the U.S., lower esophageal and GEJ tumors (predominantly of the EAC histology) have become far more common in the last 30-40 years, now accounting for over 80% of cases.⁴ This alarming increase of EAC is thought to be related to the growing prevalence of obesity and its associated gastroesophageal reflux disease (GERD) in the U.S. over the last half century. Current thinking points to a mechanism of chronic chemical injury to the distal esophagus caused by longstanding reflux of gastric acid, eventually leading to intestinal metaplasia of the esophageal mucosa, a transformation known as “Barrett’s esophagus.” While the average person’s risk of esophageal cancer is 0.4% over a lifetime, patients with known Barrett’s esophagus have an estimated risk of malignant transformation of 0.5% *per year*.⁵ Tobacco smoke has also been shown to increase the risk of both EAC and ESCC. Other risk factors for ESCC have in common the tendency to act as mucosal irritants, including alcohol, caustic ingestions, and very hot liquids (Table 1).

Clinical presentation and workup

Patients presenting with yet-undiagnosed esophageal cancer frequently fit into one of two patterns. Asymptomatic patients are identified either incidentally after undergoing workup for some unrelated issue, or during routine screening esophagoscopy for patients with Barrett's. These tumors, not yet large enough to cause symptoms, tend to be smaller and better-localized. Alternatively, patients may present with symptoms such as dysphagia, odynophagia, chest pain, regurgitation, hematemesis, or weight loss from poor oral intake. Uncommonly, patients may complain of hoarseness from invasion of the recurrent laryngeal nerve, either by the primary tumor or a regional lymph node metastasis; or hiccups from involvement of the phrenic nerve. The association of these symptoms often suggests a more locally advanced tumor (i.e. a higher T stage); indeed, dysphagia has been shown to be almost 90% predictive of at least cT3 disease (indicating penetration of the muscularis propria and adventitia).⁶ Erosion into adjacent structures – leading to, for instance, a tracheo-esophageal fistula – occurs in only a small minority of cases, but can significantly complicate treatment, particularly surgical planning. Once a diagnosis of esophageal cancer is entertained, initial workup commonly involves a barium swallow. This study is inexpensive, non-invasive, and may provide a roadmap for esophagoscopy, which typically follows. Endoscopy should include adequate visualization from the proximal esophagus to the stomach to assess for intramural cranio-caudal spread, and should include biopsies for pathologic confirmation of the diagnosis. After a tissue diagnosis has been made, clinical staging involves PET-CT to rule out distant metastases and identify suspicious regional lymph nodes for more invasive staging, often in the form of endoscopic ultrasound (EUS) with fine needle aspiration (FNA). EUS is used to assess the depth of transmural invasion (T stage) and increase the diagnostic sensitivity of FNA for nodal staging (N stage).

Treatment – historical perspective

The current management algorithm for esophageal cancer treatment pivots on the extent of disease and degree of dissemination at the time of diagnosis. Like many solid tumors, intramucosal lesions are increasingly being treated with parenchymal-sparing resection or ablative techniques, owing to advances in minimally- and non-invasive technologies and made possible by improved characterization of the extent of local spread. Conversely, metastatic disease is generally considered incurable, and systemic therapy is the mainstay of treatment. The focus of this study, however, is on locally advanced esophageal cancer. That is, tumors with direct extension beyond

the submucosa or with locoregional nodal involvement, but without distant metastases – in essence, tumors whose extent lies entirely within the planned field of resection and are thus theoretically amenable to curative treatment through a combination of chemotherapy, radiation and surgery.

Our understanding of esophageal cancer and its treatment has evolved significantly in the last century since the earliest reports of transthoracic esophageal resection for cancer in 1913.⁷ Prior to this, radiotherapy was the mainstay of treatment for esophageal malignancies. In the early 20th century it was recognized that some esophageal tumors could be effectively treated (and occasionally cured) by complete surgical excision. Early implementation of esophageal resection was hobbled by poor operative outcomes, but gradual improvements in surgical technique and the near-universal lethality of otherwise untreated tumors eventually led to the widespread adoption of esophagectomy in the treatment of locally advanced disease. Yet long-term survival after esophagectomy remained poor in the majority of patients, and recurrent disease was an important cause of death in previously resected patients. Early attempts to solve this problem advocated for more extensive and aggressive resections and lymphadenectomy in the hopes that radical excision might eliminate residual tumor burden and increase the likelihood of cure. Yet failure to improve survival of patients who died of metastatic disease shed light on the propensity of esophageal cancers to become systemic at even “early” stages, and highlighted the imperative for systemic therapy. In theory, chemotherapy could treat micrometastatic disease at a more nascent – and potentially responsive – stage. Moreover, neoadjuvant therapy could help select patients with more favorable tumor biology to undergo surgical resection, since disease progression during systemic treatment may portend an unfavorable tumor phenotype for which resection is unlikely to be curative. The synergistic combination of radiosensitizing chemotherapy with concurrent radiation could help to shrink tumors, making them more amenable to resection and increasing the likelihood of clean margins. This intuition, which had been tested with some promising results in other solid organ malignancies, was eventually applied to esophageal cancer in the late 20th century.

One of the earlier studies of multimodality therapy for esophageal cancer was published in 1988 from a group at the MD Anderson Cancer Center. It randomized 39 treatment-naïve patients with tumors of the middle or lower esophagus to undergo esophagectomy either alone (n=20) or with perioperative cisplatin, vindesine, and bleomycin (n=19). Forty-seven percent of patients receiving chemotherapy showed evidence of treatment response upon pathologic examination of

resection specimens. At a median follow-up of 30 months, these treatment responders showed longer overall survival than non-responders or patients randomized to surgery alone.⁸ This early study shed light on the centrality of treatment responsiveness to long-term survival, and laid the groundwork for important future clinical trials. Several years later, a study from the United Kingdom reported on 113 patients with esophageal tumors randomized to surgery alone (n=55) or multimodality therapy (n=58) consisting of neoadjuvant cisplatin/5-fluorouracil (5-FU) with 40 gray (Gy) of concurrent radiotherapy followed by surgery. Pathologic complete response (pCR) was achieved in 25% of the multimodality group. More importantly, 3-year survival was 32% in the multimodality group compared to only 6% in the surgery alone group (P=.01).⁹ This 1996 study was among the first randomized trials to show convincingly that neoadjuvant concurrent chemoradiation could improve survival of patients undergoing surgical resection for esophageal cancer, and the cisplatin/5-FU regimen gained traction in the U.S.

The superiority of multimodality therapy over surgery alone was further corroborated in 2006 with the publication of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial. This multicenter trial included 503 patients with resectable adenocarcinomas of the stomach, GEJ, and lower esophagus. Patients were randomized to undergo surgery either alone (n=253) or with perioperative epirubicin, cisplatin, and 5-FU (n=250). At a median follow-up of 4 years, the authors reported a 5-year survival of 36% in the multimodality group versus 23% in the surgery alone group (P=.009). In multivariable analysis, perioperative chemotherapy was associated with a decreased risk of death (HR .74, P=.008) compared to surgery alone. The multimodality group also showed better progression-free survival, lower rates of local and distant recurrence, smaller tumor diameter, and higher rates of pathologic downstaging.¹⁰ The MAGIC Trial was among the largest and highest-quality studies to provide level-1 evidence for the benefit of multimodality therapy in the treatment of locally advanced esophageal cancer, and was generally considered to provide sufficient rationale for the continued use of cisplatin/5-FU (“CF”) neoadjuvantly, already common practice and similar to the regimen used in the trial. Yet only 26% of participants had esophageal or GEJ tumors; the great majority of participants had gastric cancers. Doubt lingered within the thoracic oncology community about the generalizability of these findings to esophageal malignancies, and whether the survival differences between treatment arms may have been driven primarily by the gastric cancers. Moreover, though neoadjuvant radiotherapy was already standard practice in the U.S. for locally advanced disease,

it's absence from either treatment arm in the MAGIC Trial left unanswered questions about its role in light of the trial's findings.

Further clarity was provided two years later with the Cancer and Leukemia Group B (CALGB) 9781 Trial. This study randomized patients to either upfront surgery or neoadjuvant chemotherapy (CF) with 50.4 Gy of concurrent radiation followed by surgery. At a median follow-up of 6 years, five-year survival was 39% in the trimodality group versus only 16% in the surgery alone group ($P=.002$). Of note, 40% of patients in the trimodality group exhibited pCR and 50% of patients with cN1 disease showed pathologic nodal downstaging.¹¹ Importantly, the CALGB 9781 Trial used higher doses of neoadjuvant radiotherapy than had previously been studied (which may have contributed to the higher rate of pCR than had been reported historically), and had done so without detrimental impact on perioperative outcomes, leading many institutions to adopt this as the standard dose for neoadjuvant concurrent chemoradiation. Yet it's small size ($n=56$) left many to question the trial's reproducibility, and thus a large, high-quality randomized trial focused specifically on esophageal malignancies was still needed.

Treatment – current perspective

By the start of the 21st century, trimodality therapy was commonly used in the treatment of locally advanced esophageal cancer. Yet evidence for its efficacy was gleaned mostly from studies that were older or that suffered from poor accrual and/or generalizability. Moreover, treatment toxicity constituted an ongoing concern, as many of the commonplace neoadjuvant regimens were not well-tolerated. In fact, treatment toxicities (grade ≥ 3) had been reported in 30-60% of patients receiving trimodality therapy, depending on the trial.^{10,11} It was in this context that the Chemoradiotherapy for Oesophageal Cancer followed by Surgery Study (CROSS) Trial, a multi-center trial from the Netherlands, was published in 2012. This randomized trial sought to address lingering doubts about the role of trimodality therapy for locally advanced esophageal cancer. Three hundred sixty-eight patients with esophageal cancer (EAC or ESCC) were randomized to upfront surgery ($n=188$) or trimodality therapy consisting of neoadjuvant chemoradiation followed by surgery ($n=178$). Deviating from previous trials, however, chemotherapy in the CROSS Trial consisted of a combination of carboplatin and paclitaxel (contrary to the historically favored CF), and radiation was administered at a total dose of only 41.4 Gy. Chemotherapy was administered at the start of each week for 5 weeks, consisting of carboplatin (titrated to an area under the curve

of 2 mg/mL/min) and paclitaxel (50 mg/m² BSA) and 41.4 Gy of concurrent radiotherapy was administered in 23 fractions five days per week. The authors reported five-year survival of 47% in the trimodality group versus 34% in the surgery alone group (P=.003). Additionally, pCR was achieved in 29% of the trimodality group; their R0 resection rate was 92%, compared to only 69% in the upfront surgery group (P<.001). Of note, the pCR rate was much higher in patients with ESCC histology (representing 25% of tumors in the study) than in patients with EAC histology (which accounted for 75% of tumors).¹ The importance of the CROSS trial was not only finding that trimodality therapy improved survival over surgery alone in patients with esophageal cancers; it demonstrated that good oncologic results could be achieved with a regimen that was perhaps better-tolerated than its predecessors. Grade 3+ hematologic toxic effects were observed in 7% of patients and non-hematologic toxic effects in less than 13% of patients. Following its publication, this “CROSS regimen” was quickly adopted as the new standard of care treatment for locally advanced esophageal cancer in the U.S.

Goals of this study

Since its publication in 2012, the CROSS regimen has become the standard of care for treatment of locally advanced esophageal cancer, its popularity owing to its ability to achieve acceptable oncologic outcomes with favorable tolerability compared to historical standards. Yet the CROSS regimen was adopted before it was directly compared to the pre-existing standard of care – its only comparison was indirect, using historical data. Moreover, the initial study from 2012 that popularized the CROSS regimen did not actually compare it against the existing standard of care (which would have been trimodality therapy with CF and 50.4 Gy of radiation), rather, it was compared against surgery alone, a treatment strategy that had long since been abandoned. Thus the perception that the CROSS regimen could offer improved tolerability without sacrificing therapeutic efficacy was in fact based mostly on cross-study comparisons and extrapolations from older trials using CF as part of a multimodal regimen. This has led to some concern that the CROSS regimen may not be truly equivalent to its predecessor (with respect to oncologic control). Very few trials have directly compared the CROSS regimen to the previous standard of care, and those that do suffer from small sample sizes and mixed results. An accurate understanding of the comparative efficacy of these two regimens is essential for informed clinical decision-making. This study aims to directly compare the CROSS regimen (trimodality therapy using

carboplatin/paclitaxel [“CP”]) to the historical accepted standard of care (trimodality therapy using CF), specifically to compare their respective potencies and anti-tumoral effects.

METHODS

Patient selection

This retrospective cohort study included patients who underwent trimodality therapy for esophageal cancer at a single institution between mid-2002 and mid-2017. Trimodality therapy was defined as neoadjuvant chemoradiotherapy followed by surgery. An initial list of patients was queried from a prospectively-collected institutional database of patients who had undergone esophagectomy. This database is sourced directly from patient medical records and curated by a dedicated research nurse, and undergoes periodic auditing for data quality. Whenever possible, information missing from the database was sourced directly from clinical records by the authors.

Data gathering

For each patient identified as having undergone esophagectomy during the study period, medical records were again reviewed to determine the neoadjuvant regimen that was used and to review the pathology report for response to treatment. Follow-up was taken from medical records, the Social Security Death Index, and other public records. Patients were included in the final analysis only if they had undergone chemotherapy consisting of either carboplatin/paclitaxel (CP) or cisplatin/5-Fluorouracil (CF), followed by surgery within ≤ 6 months, for treatment of primary esophageal adenocarcinoma (EAC) or squamous cell carcinoma (ESCC). This study was approved by the Partners Institutional Review Board (IRB #2006P002188, activated November 14, 2006), which waived the need for informed consent.

Trimodality therapy

Patients underwent pretreatment staging with esophagoscopy and CT of the chest, abdomen, and pelvis with PET. Endoscopic ultrasound with fine needle aspiration was implemented in most cases, but was omitted in the more contemporary cohort (since around 2016) in patients with at least moderate dysphagia. The authors increasingly accepted the reliability of dysphagia as a predictor of T3 disease.⁶ Patients then underwent neoadjuvant chemotherapy with

concurrent radiation. Chemotherapy consisted of either 2 cycles of CF or 5 cycles of CP. CF cycles typically involved 100 mg/m² of cisplatin over 96 hours with 4,000 mg/m² continuous infusion of 5-FU. As in the CROSS Trial, the CP group received chemotherapy once weekly, involving carboplatin titrated to an area under the curve of 2 mg/mL/minute and 50 mg/m² of paclitaxel. Selection of chemotherapy regimen was guided principally by existing standards of care and was fairly standardized for all patients, but was ultimately at the discretion of the medical oncologist; CF was favored in the early years but was largely replaced by CP following widespread adoption of the CROSS regimen in 2012. Concurrent radiotherapy was administered with a target dose of 50.4 Gy at 1.8 Gy/fraction, which was lowered to 41.4 Gy following adoption of the CROSS regimen in select patients. Intensity-modulated radiotherapy (IMRT) became the institutional standard, especially for cardiac sparing for distal esophageal and GEJ cancers, in 2004. 3D conformal radiotherapy (3DCRT) was typically employed in select cases to limit lung exposure or in cases of insurance denial. Regarding radiation fields, standard margins were used including 3-3.5 cm craniocaudal clinical target volume extensions and 0.5-1.0 cm planning target volume expansions. The celiac axis was included for distal esophageal and GEJ cancers. Daily image guidance using cone beam CT was implemented in 2008. Radiotherapy was typically initiated within 24 hours of day 1 chemotherapy. After induction CRT, patients were routinely restaged with CT chest/abdomen/pelvis, and infrequently with PET. Esophagectomy was routinely performed within 1-3 months of completing neoadjuvant therapy. Adjuvant therapy was offered to patients with advanced nodal disease (pN2-3) or in highly selected cases after multidisciplinary evaluation.

Primary outcomes

The primary outcome was pathologic complete response, determined by review of pathology reports from patients' medical records. Analyses involving the primary outcome were run twice: first strictly using pCR as the outcome of interest, then a second time using a more liberal outcome of pCR or near complete response (npCR). Near complete response was defined as having no more than a single focus of residual viable tumor no more than 1 mm in greatest diameter.

Secondary outcomes

Secondary outcomes included overall survival (OS) and disease-free survival (DFS). Survival was calculated from the date of surgery until the date of death from any cause (for OS and DFS) or date of first known recurrence – either locoregional or distant – as determined radiologically (DFS only).

Statistical analysis

Patient characteristics were compared using Student's T, Mann–Whitney U, chi square, and Fisher's exact tests, where appropriate. The association of chemotherapy regimen with pCR was first modeled using univariable logistic regression to determine the unadjusted odds ratio (OR) of pCR for the two chemotherapy groups. The correlation of other variables with pCR was then modeled using Student's T or Mann–Whitney U tests for continuous variables and chi square or Fisher's exact tests for categorical variables. The adjusted odds ratios for pCR and pCR/npCR were estimated using multivariable logistic regression, including as independent variables all factors that were either significantly different between the two groups or independently associated with pCR or pCR/npCR in the univariate models. All regression models use robust standard errors. Results are reported as odds ratios with 95% confidence intervals (95%CI). In the analysis of secondary outcomes, survival was analyzed by the Kaplan–Meier method (using the log rank test for significance of differences) and Cox proportional hazard modeling was used to analyze time-to-event outcomes, controlling for potential confounders. All tests of association were two-sided and P values below 0.05 were considered statistically significant. Data was analyzed using SPSS © v25.

RESULTS

Patients

Between mid–2002 to mid–2017, 961 esophagectomies were performed at our institution. Of the 527 patients who received trimodal therapy for primary esophageal adenocarcinoma or squamous cell carcinoma, records of specific regimens were unobtainable for 103 patients (most of whom were treated at outside hospitals whose records were inaccessible). Of the 424 patients who received trimodal therapy with known chemotherapy regimens, 325 were treated with either CP (n=186) or CF (n=139) and were included in the final analysis.

Patient characteristics

Patient characteristics are described in Table 2. Baseline characteristics were similar between treatment groups, yet several differences exist: the CP group was older (mean age 64 vs. 59 years, $P<.001$) and had a higher rate of hypertension (9% vs. 35%, $P=.016$). The CP group also trended toward higher rates of cigarette smoking (76% vs. 67%, $P=.06$) and COPD (8% vs. 3%, $P=.057$), while the CF group had worse overall performance status (ECOG score >0 in 99% of patients vs. 89% for CP, $P<.001$). Sex, race, and other comorbidities analyzed were all well-balanced between groups ($P>0.1$ for all). Adenocarcinomas predominated; only 16% of tumors were squamous cell carcinomas. The CP group contained 86.1% adenocarcinomas and 13.9% squamous cell carcinomas while the CF group contained 81.3% adenocarcinomas and 18.7% squamous cell carcinomas (P value for difference = .242).

Staging workup

PET-CT was used for clinical staging in 93% of CP patients and 94% of CF patients ($P=.865$). EUS was employed in 74% of all CP patients and 87% of all CF patients ($P=.004$). However, after excluding patients who routinely forewent EUS for presumed cT3 disease based on symptomatology or clear cN1-2 disease by PET-CT (i.e. patients for whom EUS would not have changed management), EUS was used in 83% of CP patients and 87% of CF patients ($P=.286$).

Treatment effects

Of note, final pre-treatment clinical stage was similar between groups ($P=.890$) yet final pathologic staging showed more early-stage tumors in the CF group compared to the CP group, corresponding to a higher rate of pathologic downstaging seen in the CF group compared to the CP group (68% vs. 55%, $P=.024$) (Table 2). Negative margins were achieved in 93% of patients in the CP group and 98% of patients in the CF group ($P=.048$). Importantly, no differences were identified between groups with respect to the total radiation dose ($P=.402$) or radiotherapy technique ($P=.751$) (Table 2). While no differences were identified between groups with respect to surgical approach ($P=.428$) or number of lymph nodes examined ($P=.243$), postoperative complications occurred less frequently in the CP group than in the CF group (46% vs. 61%, $P=.007$).

Primary Outcome

The primary outcome of this study was pathologic complete response (pCR). Separate parallel analyses first looked at pCR only and then at pCR combined with near-complete response (npCR). Results are reported separately in Table 3. In univariate analysis, factors associated with pCR were tumor histology ($P<.001$) and CF neoadjuvant chemotherapy ($P=.018$). Factors associated with pCR/npCR were tumor histology ($P<.001$), CF neoadjuvant chemotherapy ($P<.001$), coronary artery disease ($P=.042$), and diabetes ($P=.006$). Overall, 86 patients (26.4%) achieved pCR and an additional 21 (6.4%) achieved npCR (Table 3). 21.4% of patients in the CP group (40/186) achieved pCR compared to 33.1% (46/139) in the CF group ($P=.018$). Compared to the CP group, the CF group was more likely to achieve pCR (OR 1.82, $P=.018$) or pCR/npCR (OR 3.03, $P<.001$) (Table 4). Among adenocarcinomas only ($n=273$), the CF group ($n=112$) was still more likely than the CP group ($n=161$) to achieve pCR (OR 2.14, $P=.011$) or pCR/npCR (OR 3.26, $P<.001$). While patients with squamous histology ($n=52$) were twice as likely to have a pathologic complete response to neoadjuvant therapy, no difference was found between CP ($n=26$) and CF ($n=26$) in rates of pCR ($P=.781$) or pCR/npCR ($P=.154$).

In multivariable analysis, only chemotherapy regimen and tumor histology were significantly associated with pCR, while chemotherapy, tumor histology, and diabetes were associated with pCR/npCR (Table 4). Compared to patients with adenocarcinoma, those with squamous histology were more likely to achieve pCR (OR 4.18, 95%CI 2.19–7.97, $P<.001$) or pCR/npCR (OR 4.77, 95%CI 2.45–9.29, $P<.001$). After controlling for other factors, patients receiving CF were more likely than patients receiving CP to experience pCR (adjusted OR 2.21, $P=.006$) or pCR/npCR (adjusted OR 3.78, $P<.001$) (Table 4).

Secondary Outcomes

Secondary outcomes were OS and DFS. In univariate analysis (Figure 3), median OS was 29.0 months in the CP group (95%CI 19.4–38.5) and 41.9 months in the CF group (95%CI 23.7–60.0, $P=.042$). In Cox regression (Table 5), CF was associated with decreased risk of death compared to CP after controlling for age, sex, performance status, tumor histology, clinical stage, and comorbidities (HR .668, 95%CI .471–.947, $P=.023$). In univariate analysis (Figure 4), median DFS was 17.3 months in the CP group and 25.6 months in the CF group, but this difference did

not reach statistical significance ($P=.110$). In multivariate regression (Table 5), however, after controlling for age, sex, performance status, histology, clinical stage, and comorbidities, CF was associated with improved DFS compared to CP (HR .708, 95%CI .512-.981, $P=.038$). In univariate analysis, median OS was 27.5 months after surgery in patients who did not achieve pCR (95%CI 22.0–32.9 months), and was not reached in patients who did achieve pCR. Median DFS was 14.2 months among patients without (95%CI 10.1–18.3 months) versus 90.3 months among patients with complete pathologic response (95%CI 62.4–118.2 months, $P<.001$) (Figure 5).

DISCUSSION

Summary of findings

The current study is the largest to directly compare the antineoplastic potency of CF and CP as components of trimodality therapy in the curative treatment of locally advanced esophageal cancer. We found that CF, the historical standard of care, was associated with higher rates of pCR and npCR than CP, the current standard of care. CF was also associated with improved pathologic downstaging, higher rates of complete surgical resection, and longer overall and disease-free survival compared to the current standard, CP.

Treatment response

Pathologic response rate is a direct measure of tumor kill. Thus, it constitutes an intuitive endpoint for a study aimed at comparing the antineoplastic effect of two treatment regimens. Because the two groups underwent similar radiotherapy and surgical therapy, the treatments differed only in the chemotherapy arms; consequently, differences in observed oncologic outcomes are likely the result of differences in those chemotherapy regimens. In addition to complete pathologic response, systemic therapy can have marked anti-tumor effect that falls just short of complete response, leaving behind only a single millimeter focus of residual disease. Though the presence of any amount of residual disease likely represents a clinically meaningful departure from true complete response, this “near-complete response” likely demonstrates noteworthy antitumor effect. We therefore decided that a composite endpoint of complete or near-complete pathologic response would offer worthwhile insight into the efficacy of these two regimens in a way not fully captured by a strict endpoint of only complete response. The current

study demonstrates higher rates of pCR and npCR associated with use of CF compared to CP. Importantly, this finding was recapitulated both in univariate analysis in groups with similar characteristics, and in multivariate analysis controlling for minor baseline differences and other confounders. Interestingly, this difference was most notable in tumors of adenocarcinoma histology, whereas ESCC tumors tended to be highly treatment-responsive irrespective of the regimen used. This fact has implications for contextualizing the current study within the existing body of literature, and particularly in relation to the CROSS Trial, discussed further below.

That CF offers improved tumor kill and higher rates of pCR compared to CP is largely in agreement with prior studies comparing the efficacy of various neoadjuvant chemotherapies for esophageal cancer. Haisley et al. similarly found that patients treated with neoadjuvant CF were more likely than patients treated with CP to achieve pCR (OR 2.7, $P=.032$).¹² They also showed an apparent increase in OS and DFS in the CF group (6.8 years and 2.5 years, respectively) compared to the CP group (1.8 and 1.25 years, respectively), though neither of these differences was significant ($P>.05$ for both). This may be due to the greater proportion of higher-stage cancers in the CF group than the CP group, or to the very limited sample size ($n=142$ patients overall) rendering the study underpowered to detect survival differences at a follow-up of less than 2 years. After controlling for confounding factors, however, the authors did show a decreased risk of death associated with CF compared to CP (HR .460, $P<.05$), which they attribute to the superior survival associated with pCR status – a finding we corroborate in the current study. The phase II CALGB 80803 trial compared pCR rates between induction with modified FOLFOX 6 (oxaliplatin, leucovorin, 5-FU) (mFOLFOX6) and CP as part of trimodal therapy for EAC. Initial results suggest CP may be associated with a higher proportion of non-responders than mFOLFOX6 (49% vs. 39%) and a lower proportion achieving pCR (12.5% vs. 30%).¹³ These initial results suggest a lower potency of CP in the treatment of esophageal cancer, and specifically of EAC.

Pathologic downstaging

In addition to higher rates of pCR, the CF regimen was associated with higher rates of pathologic downstaging than the CP regimen. This is reflected in the trend toward earlier pathologic stages of tumors in the CF group compared to the CP group. An alternative explanation for this finding is that the CF group tended to have earlier-stage tumors to begin with, or that the CF group was more likely to be clinically over-staged (or the CP group under-staged), or that there

may have been some differences in the accuracy of the pathologic staging between groups. Yet none of these appear to be the case: the pre-treatment staging workup was similar between groups without significant differences in the staging modalities utilized. Thus, we expect the reliability of clinical staging to be similar for each group. The observed pre-treatment clinical stages were well-balanced between groups. Moreover, the number of lymph nodes examined was similar between groups, and thus the pathologic staging should be similarly accurate. Consequently, we believe the results suggest a genuine increase in pathologic downstaging in the CF group.

Complete resection

Though the rate of complete resection was high in both groups, it was slightly higher in the CF group than in the CP group – a difference of statistical significance. This likely also reflects differences in anti-tumor potency underlying these two treatments, as regimens with better tumor kill would theoretically sterilize resection margins more effectively. An alternative explanation might suggest that lower R0 resection rates in the more contemporary CP cohort reflect a less aggressive or radical resection than was done previously when the CF regimen was commonplace. Yet this does not appear to be the case, as surgical approaches were similar between groups and the extent of lymphadenectomy was no different either.

Survival

That pCR portends a favorable prognosis is well-established.¹⁴ The current study demonstrates a dramatic benefit to pCR in terms of long-term overall survival. Yet improved survival was also demonstrated in the CF group overall, and did not appear to be restricted to patients achieving pCR or npCR. This is likely a result of the higher rate of pathologic downstaging, which also confers a survival advantage, and was present in 68% of CF patients but only 55% of CP patients. Differences in overall survival were significant in both univariate and multivariate analyses. Differences in DFS, though observed in univariate analysis, only met statistical significance in multivariate analysis after controlling for baseline differences and other prognostically important variables. This may be due to the fact that DFS is often much more difficult to ascertain in a retrospective study. Long-term follow up was taken from medical records to the extent possible. But some patients who lacked recent follow up in our system (particularly

those who were found to have died during the follow-up period) represented a challenge to reliably identifying recurrences.

It should be noted that OS and DFS were secondary outcomes of this study, but the study was actually designed around its primary outcome (pCR). Quantifying rates of pCR requires evaluation of resection specimens, and thus nothing is gained by including patients who failed to undergo surgical resection following neoadjuvant therapy – the degree of treatment response cannot be quantified in these patients without a resection specimen. A study designed to compare survival differences between CF and CP, however, *would* include such patients. An intention-to-treat analysis would include all patients who began each treatment arm, regardless of whether or not they completed the entire treatment. In fact, this distinction is key, since a high percentage of patients failing to complete treatment may skew the results of a survival analysis by excluding patients unable to undergo surgery after neoadjuvant therapy – patients with a poor prognosis. The survival analyses presented in this study should be interpreted in light of this, recognizing that designing the study to evaluate pCR leads the survival analyses to resemble a per-protocol design rather than an intention-to-treat.

Treatment toxicity

Since its publication in 2012, the CROSS regimen has gained wide acceptance within the thoracic oncology community; the trial offered high-quality data showing good oncologic results with a well-tolerated regimen. Though never directly compared, CP is generally felt to be less toxic than other regimens, including CF. Indeed, the advanced age and higher prevalence of comorbidities seen in the CP group in this study may reflect the belief that CP could be tolerated by older, sicker patients previously deemed ineligible for neoadjuvant chemotherapy under the CF regimen. Because our current study selected patients from a surgical database, we are unable to quantify the proportion of patients excluded from resection due to treatment-related toxicity. Only three patients in each treatment group received dose-reduced regimens for toxicity-related reasons, though a suggestion of the increased toxicity of CF compared to CP may be surmised from the higher rate of postoperative complications seen in the CF group compared to the CP group (61% vs. 46%, $P=.007$). Other studies have reported the relative incidence of CRT-related toxicities with mixed results. Honing et al. reported an increased incidence of grade 3+ toxicities in patients treated with CF compared to CP (57% vs. 22%, respectively, $P=.001$).¹⁵ Sanford et al. found that

CF patients were more likely than CP patients to experience dehydration (29% vs. 13%), but CP patients were more likely to experience esophagitis (18% vs. 6%), and no significant differences were found between the two groups with respect to other toxicities recorded.¹⁶ Importantly, current management of treatment-related toxicities has greatly improved over the years, and thus data on the toxicities of older regimens may overstate their current relevance. Another valid metric of toxicity is the death rate associated with each neoadjuvant regimen. Because our study selected patients from a surgical database, we are unable to report on the number of patients who died before surgery as a result of treatment-related toxicity, though these figures have been reported elsewhere in the literature. The toxic death rate for CP is reported to be around 6%, while that of CF has been reported to be around 7%, a difference of questionable clinical significance.^{1,17}

Limitations

The results of the current study should be interpreted in light of certain limitations. Firstly, our study is retrospective in nature. Without true randomization, we found a few differences in the baseline characteristics of the two treatment groups. Differences in patient characteristics were addressed by including those characteristics as independent variables in our multivariate models. Additionally, 103 patients who were identified as having received trimodal therapy for esophageal cancer were excluded because records detailing their chemotherapy regimen could not be obtained. While EUS was employed more often in the CF group overall, this difference is skewed by a change of practice at our institution that disproportionately affected CP patients: in the later years of the study, patients presenting with dysphagia were presumed to have at least cT3 disease, necessitating neoadjuvant therapy and obviating additional T staging by EUS. After excluding this subset of patients, EUS utilization was well-balanced between groups ($P=.286$).

By sourcing patients from a surgical database, this study was further limited by the exclusion of patients not undergoing esophagectomy following chemoradiotherapy due to treatment-related toxicity, disease progression, or for other reasons. Historically, the CROSS regimen gained popularity owing to the perception of improved tolerability compared to its predecessor; if a significantly higher percentage of CP patients successfully proceed to esophagectomy than CF patients, then contrary to our current findings, an intention-to-treat analysis may suggest an overall benefit to CP. By contrast, our current study resembles a per-protocol design, including in the final analysis only those patients who successfully complete each

treatment “per protocol” (i.e. neoadjuvant CRT followed by surgery). Consequently, our study does not demonstrate that CF is the optimal regimen for all patients. If this study selects for patients who can tolerate a more potent regimen associated with higher toxicity, then we may conclude that in this subset of healthier patients, CF may offer improved oncologic control compared to CP, particularly for those with adenocarcinoma histology. This does not justify a wholesale shift toward CF or similar regimens for all patients. Rather, it speaks to the limitation of a one-size-fits-all approach to esophageal cancer treatment, wherein the imperative to treat even the sickest patients may leave healthier patients under-treated.

With respect to generalizability, all our patients were treated in whole or in part at an academic tertiary care center, where practices may differ from those of community hospitals. Importantly, the two treatment groups in this study are chronologically staggered. The majority of CF patients were treated before 2011–2012 while most of the CP patients were treated after publication of the CROSS trial in 2012. Consequently, follow up was longer for the CF group than for the CP group. However, there was no difference in duration of follow-up between early vs. late stage cancers or other prognostic factors.

The broader changes to care of the esophageal cancer patient during the period under study may have influenced survival, but are less likely to have had an impact on pathologic response. An early iteration of our study included year of treatment as a covariate in the Cox regressions of OS and DFS, finding that year of treatment (a surrogate for unmeasurable changes to medical care over the 15-year study period) was not associated with OS ($P=.631$) or DFS ($P=.419$).

IMRT became the standard of care at our institution in 2004; 3DCRT was used with or without IMRT only in a small subset of patients throughout the study period. Thus, no changes in radiotherapy technique are likely to have affected the impact of chemotherapy regimen on treatment outcomes. With respect to surgical techniques, we found that operative approach was well-balanced between treatment groups. Moreover, we believe it would be unlikely to influence completeness of response to neoadjuvant therapy (indeed, we found no association between surgical approach and pCR rate [$P=.737$]). Several studies have suggested equipoise between open and minimally-invasive esophagectomy with respect to oncologic outcomes.¹⁸⁻²⁰ Our group has previously reported similar lymph node yield during esophagectomy when comparing open to minimally invasive technique.²¹ No difference in lymph node yield was identified between treatment groups in the current study ($P=.254$).

Conclusion

We believe the current study sheds light on an important question about the antineoplastic efficacy of the CROSS regimen, the current standard of care in the treatment of locally advanced esophageal cancer, in comparison to its predecessor. This study gives substance to what seems to have been suspected intuitively by many within the thoracic oncology community: that the improved tolerability of the CROSS regimen may indeed come at the cost of oncologic control. Yet as compelling an endpoint as pathologic treatment response is, overall and disease-free survival are what truly matter in clinical decision-making surrounding potentially curable disease. While the current study presents some noteworthy survival analyses, it is not specifically designed to answer these questions per se. In light of its findings and limitations, we believe this work provides sufficient justification for a prospective randomized study.

Future directions

The aforementioned limitations stemming from the retrospective design of this work speak to the need for further study in a prospective fashion. The evidence presented is compelling that, when administered to completion, CF may have superior anti-tumor potency than CP in the treatment of esophageal cancer, at least for tumors of adenocarcinoma histology (which now represents as much as 80% of esophageal malignancies in the U.S.).⁴ Yet if this increased potency is associated with increased *treatment-limiting* toxicity, the survival benefit conferred by improved oncologic control may be offset by the risk of failing to progress to surgical resection, a necessary component of curative therapy. A prospective randomized study has the benefit of eliminating selection bias. This is significant, as the perceived differences in toxicity and tolerability of the two treatments under study could, in theory, lead to important selection bias. Though we do not believe this to be the case (since choice of treatment regimen was based mostly on the standard of care at the time of treatment), addressing this concern is best done through randomization. Additionally, a prospective study would allow for an intention-to-treat analysis of survival outcomes. The exclusion of patients failing to undergo surgical resection after neoadjuvant therapy constitutes an important limitation of the current study, particularly if overarching conclusions are to be drawn about optimal clinical management of patients with esophageal tumors. By following

participants prospectively after randomization, patients failing to undergo esophagectomy after induction therapy can be tracked and included in survival analyses.

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Table 1. Risk factors for esophageal squamous cell carcinoma and adenocarcinoma

Esophageal Squamous Cell Carcinoma	Esophageal Adenocarcinoma
Tobacco	Chronic GERD
Alcohol	Barrett's esophagus
Caustic injury (alkaline > acid)	Obesity
Prior ionizing radiation	Male sex
Prior head & neck cancer	Caucasian ethnicity
Achalasia	Tobacco smoke
Plummer-Vinson syndrome	
Nitrosamine-rich diet	
Chronic ingestion of hot liquids	

Table 2. Patient characteristics

Characteristic	Total (n=325)	Carboplatin/Paclitaxel (n=186)	Cisplatin/5-FU (n=139)	P value
Age, years (mean ± SD)	61.8 ± 10.0	64.1 ± 10.0	59.3 ± 9.8	<.001
Sex, % female	19.0	16.6	22.3	.193
Race, % White	96.3	96.3	96.4	.270
ECOG Score (%)				
0	6.7	11.2	0.7	<.001
1	92.9	88.8	98.6	
2	0.3	0	0.7	
BMI, kg/m ² (mean ± SD)	27.0 ± 5.4	27.2 ± 5.1	25.9 ± 5.0	.107
Smoking status (%)				
Never smoker	27.4	23.5	32.6	.060
Past smoker	61.5	62.6	60.1	
Current smoker	11.1	13.9	7.2	
Pack-years (mean ± SD)	37.8 ± 27.0	38.5 ± 26.6	39.0 ± 28.9	.830
Neoadjuvant radiotherapy (%)	97.9	98.4	97.1	.465
Dose, Gy [median (IQR)]	50.4 (50.4-50.4)	50.4 (50.4-50.4)	50.4 (50.4-50.4)	.402
IMRT technique (%)	82.6	81.4	84.6	.751
Tumor histology (%)				
Adenocarcinoma	84	86.1	81.3	.242
SCC	16	13.9	18.7	
Tumor location ^a (%)				
Proximal	1.6	0	3.2	.360
Middle	14.9	15.1	14.7	
Distal	83.5	84.9	82.1	
Staging PET-CT	93.3	93.0	93.5	.865
Staging EUS ^b	79.7	74.2	87.1	.004
Clinical Stage ^c (%)				
I	2.2	2.7	1.5	.890
II	19.8	20.5	18.8	
III	71.7	70.3	73.7	
IV	6.3	6.5	6.0	
Surgical approach ^d (%)				
Open Ivor Lewis	36.7	33.5	46.0	.428
Thoracoabdominal	18.1	20.0	12.7	
Open McKeown	4.0	4.3	3.2	
Open Transhiatal	0.4	0.5	0	
Minimally invasive	40.7	41.6	38.1	
Lymph nodes examined (mean ± SD)	19.1 ± 8.4	19.6 ± 7.9	18.4 ± 9.0	.243
Hypertension (%)	42.9	48.7	35.3	.016
Congestive heart failure (%)	0	0	0	1.00
Coronary artery disease (%)	12.9	15.0	10.1	.191
Peripheral vascular disease (%)	4.0	5.3	2.2	.146
Cerebrovascular disease (%)	2.1	2.7	1.4	.703
COPD (%)	5.8	8.0	2.9	.057
Diabetes (%)	12.9	12.8	12.9	.975
Other Comorbidities (%)	1.8	0.0	4.3	.006
Pre-operative steroid use (%)	0.9	0.5	1.4	.577
Pathologic Stage ^e (%)				
I	50.3	43.9	59.1	.003
II	11.4	12.3	10.2	
III	35.2	38.5	30.7	
IV	3.1	5.3	0	
Pathologic Downstaging (%)	60.4	55.1	67.9	.024
Pathologic Upstaging (%)	8.9	11.9	4.6	
Resection margins (%)				
R0 – uninvolved	95.1	93.0	97.8	.048
R1 – microscopically involved	4.9	7.0	2.2	
30-day mortality (%)	1.5	1.1	2.2	.659

30-day morbidity (%)	52.5	46.0	61.2	.007
90-day mortality (%)	2.8	1.6	4.3	.178

SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; IQR, interquartile range; IMRT, intensity-modulated radiotherapy; SCC, squamous cell carcinoma; COPD, chronic obstructive pulmonary disease

a Tumor location is reported for 93 CP patients and 95 CF patients for whom this data was obtainable.

b EUS usage is reported for all 326 patients. After excluding patients for whom EUS was routinely omitted for presumed cT3 disease based on symptomatology or clear cN1-2 disease by PET-CT, EUS was employed in 82.6% of CP patients and 87.1% of CF patients (P=.286)

c Clinical and pathologic staging are based on the 8th edition AJCC staging of cancer of the esophagus and esophagogastric junction.

Table 3. Incidence and unadjusted odds ratios for pathologic complete response (pCR) and near-complete response (npCR). The ORs express odds of achieving pCR or pCR/npCR in the CF group using the CP group as the reference group.

	CP (%)	CF (%)	OR (95%CI)	P value
Overall (n=325)				
pCR	40 (21.4)	46 (33.1)	1.82 (1.11–2.99)	.018
pCR/npCR	42 (22.5)	65 (46.8)	3.03 (1.88–4.89)	<.001
EAC only (n=273)				
pCR	26 (16.1)	33 (29.3)	2.14 (1.19–3.84)	.011
pCR/npCR	28 (17.4)	46 (40.7)	3.26 (1.87–5.68)	<.001
ESCC only (n=52)				
pCR	14 (53.8)	13 (50)	.857 (.289–2.55)	.781
pCR/npCR	14 (53.8)	19 (73.1)	2.33 (.729–7.42)	.154

CP, carboplatin/paclitaxel; CF, cisplatin/5-FU; OR, odds ratio; CI, confidence interval; pCR, pathologic complete response; npCR, pathologic near-complete response; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma

Table 4. Adjusted odds ratios for factors impacting pathologic complete response or near-complete response

FACTOR	Pathologic Complete Response			Pathologic Complete or Near-Complete Response		
	OR	95% CI	P value	OR	95% CI	P value
Age ≤ 55	1	-		1	-	
56–63	1.06	.484–2.34	.174	1.19	.572–2.48	.730
64–69	2.06	.972–4.36		1.50	.724–3.11	
≥ 70	1.74	.775–3.88		1.38	.626–3.02	
ECOG > 0	.459	.167–1.26	.132	.610	.218–1.71	.347
Hypertension	.866	.493–1.52	.617	1.02	.586–1.77	.949
COPD	1.77	.609–5.13	.295	2.04	.698–5.96	.193
CAD	-	-	-	.563	.230–1.38	.207
Diabetes	-	-	-	.318	.119–.852	.023
ESCC histology	4.18	2.19–7.97	<.001	4.77	2.45–9.29	<.001
Chemotherapy						
CP	1	-	Reference	1	-	Reference
CF	2.21	1.25–3.89	.006	3.78	2.17–6.60	<.001

OR, odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; ESCC = esophageal squamous cell carcinoma; CP, carboplatin/paclitaxel; CF, cisplatin/5-FU

Table 5. Adjusted hazard ratios for factors impacting overall and disease-free survival

	Overall Survival			Disease-Free Survival		
FACTOR	HR	95% CI	P value	HR	95% CI	P value
Age	.995	.979-1.01	.549	.990	.975-1.01	.208
Female sex	1.34	.903-1.98	.147	1.42	.977-2.07	.066
ECOG (vs. 0)						
1	.682	.261-1.78	.434	1.17	.495-2.78	.718
2	8.87	.949-82.9	.056	4.00	.452-35.4	.213
Histology						
EAC	1	-	Reference	1	-	Reference
ESCC	.643	.383-1.08	.093	.581	.353-.958	.003
Hypertension	.908	.641-1.29	.587	.914	.660-1.26	.588
COPD	.950	.453-1.99	.891	.799	.398-1.61	.529
CAD	1.33	.784-2.26	.290	1.48	.921-2.38	.105
PVD	.460	.161-1.31	.147	.632	.265-1.51	.302
Diabetes	1.01	.638-1.60	.967	1.12	.727-1.72	.611
Clinical stage						
I	1	-	Reference	1	-	Reference
II	.679	.260-1.77	.429	.763	.292-2.00	.582
III	.759	.305-1.89	.555	.894	.359-2.22	.810
IV	.864	.288-2.59	.794	1.04	.360-3.00	.943
Chemotherapy						
CP	1	-	Reference	1	-	Reference
CF	.668	.471-.947	.023	.708	.512-.981	.038

HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; PVD, peripheral vascular disease; CVD, cerebrovascular disease; CP, carboplatin/paclitaxel; CF, cisplatin/5-FU

Figure 1A. Percent of esophageal cancer cases by stage (adapted from Surveillance, Epidemiology and End Results Program [SEER] 18 2008-2014, All Races, Both Sexes by SEER Summary Stage 2000)³

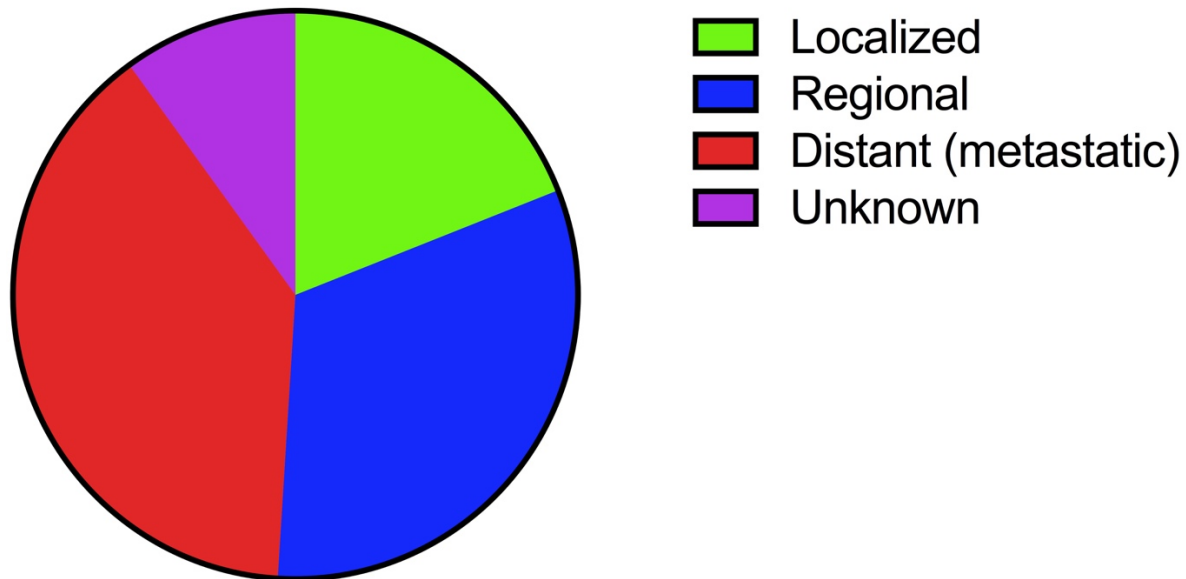


Figure 1B. Esophageal cancer survival by stage (adapted from SEER 18 2008-2014, All Races, Both Sexes by SEER Summary Stage 2000)³

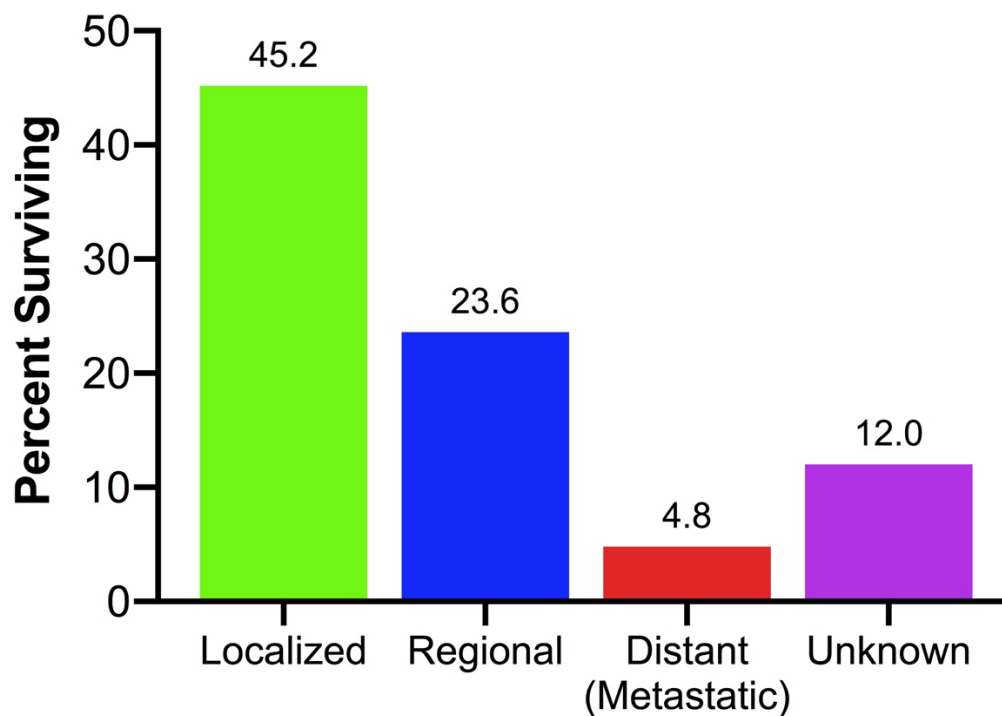


Figure 2. Incidence and mortality of esophageal cancer in the U.S. (adapted from SEER 18 2011-2015, All Races, Both Sexes by SEER Summary Stage 2000)³

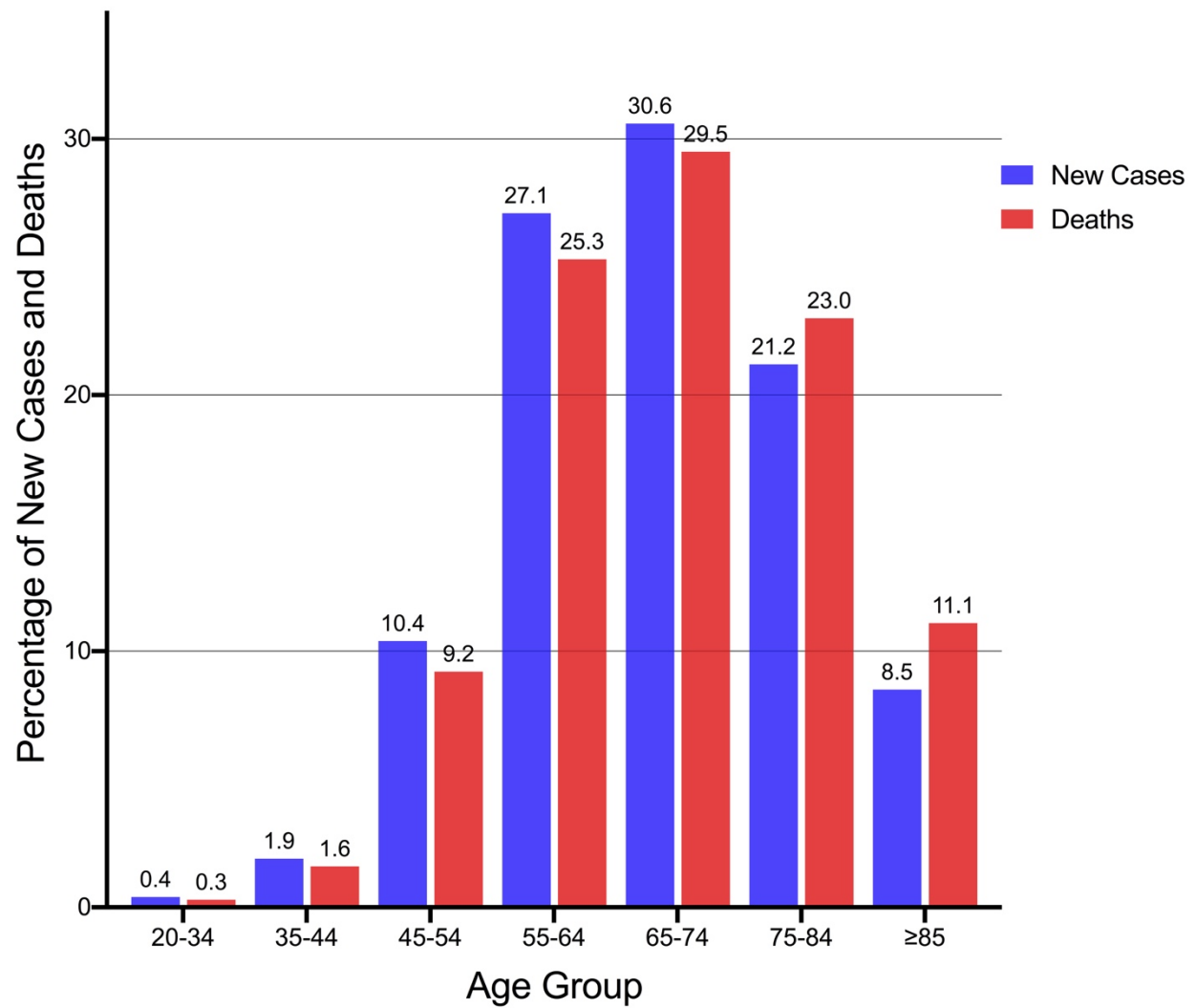


Figure 3. Overall survival stratified by treatment group

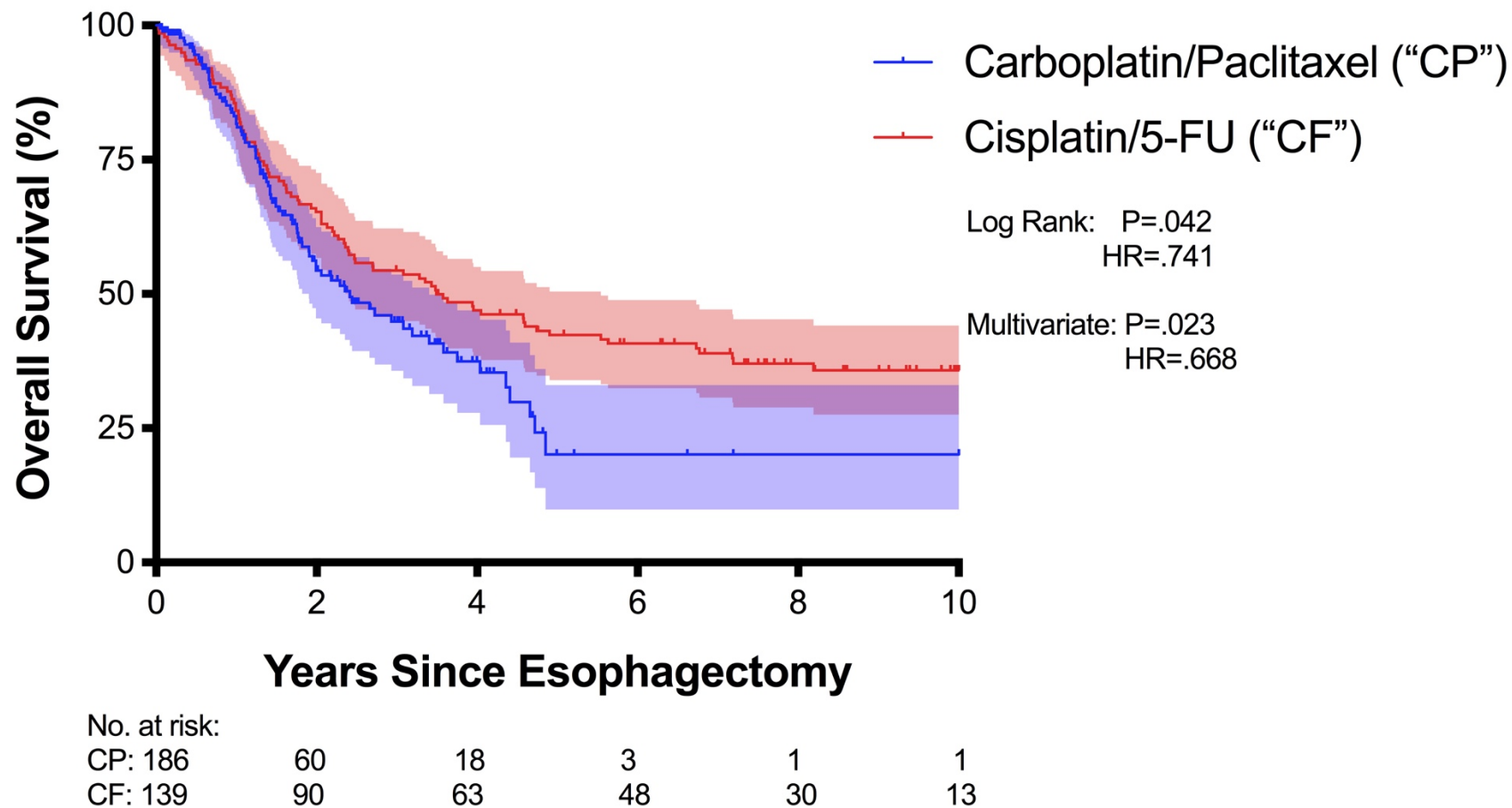


Figure 4. Disease-free survival stratified by treatment group

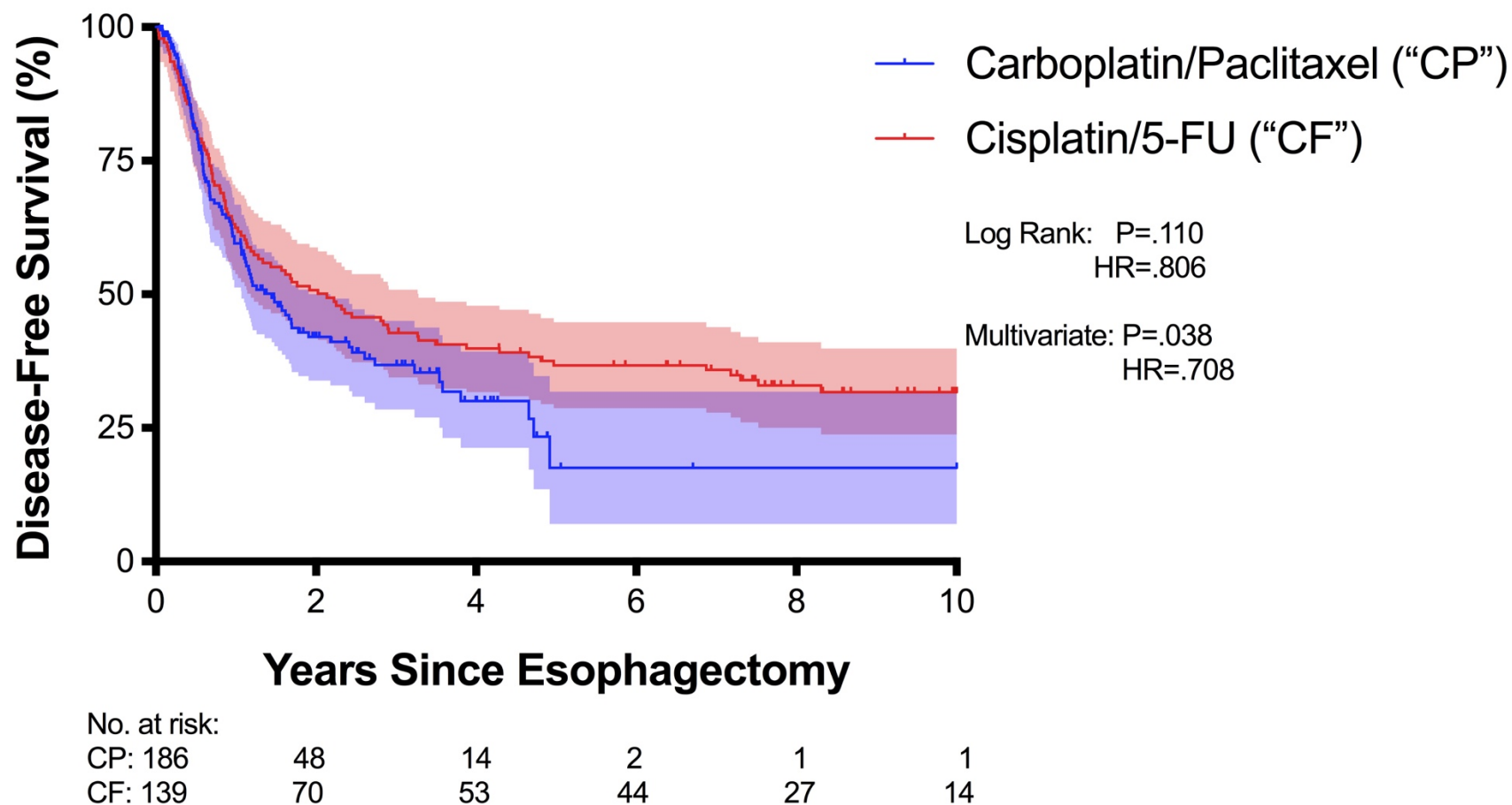
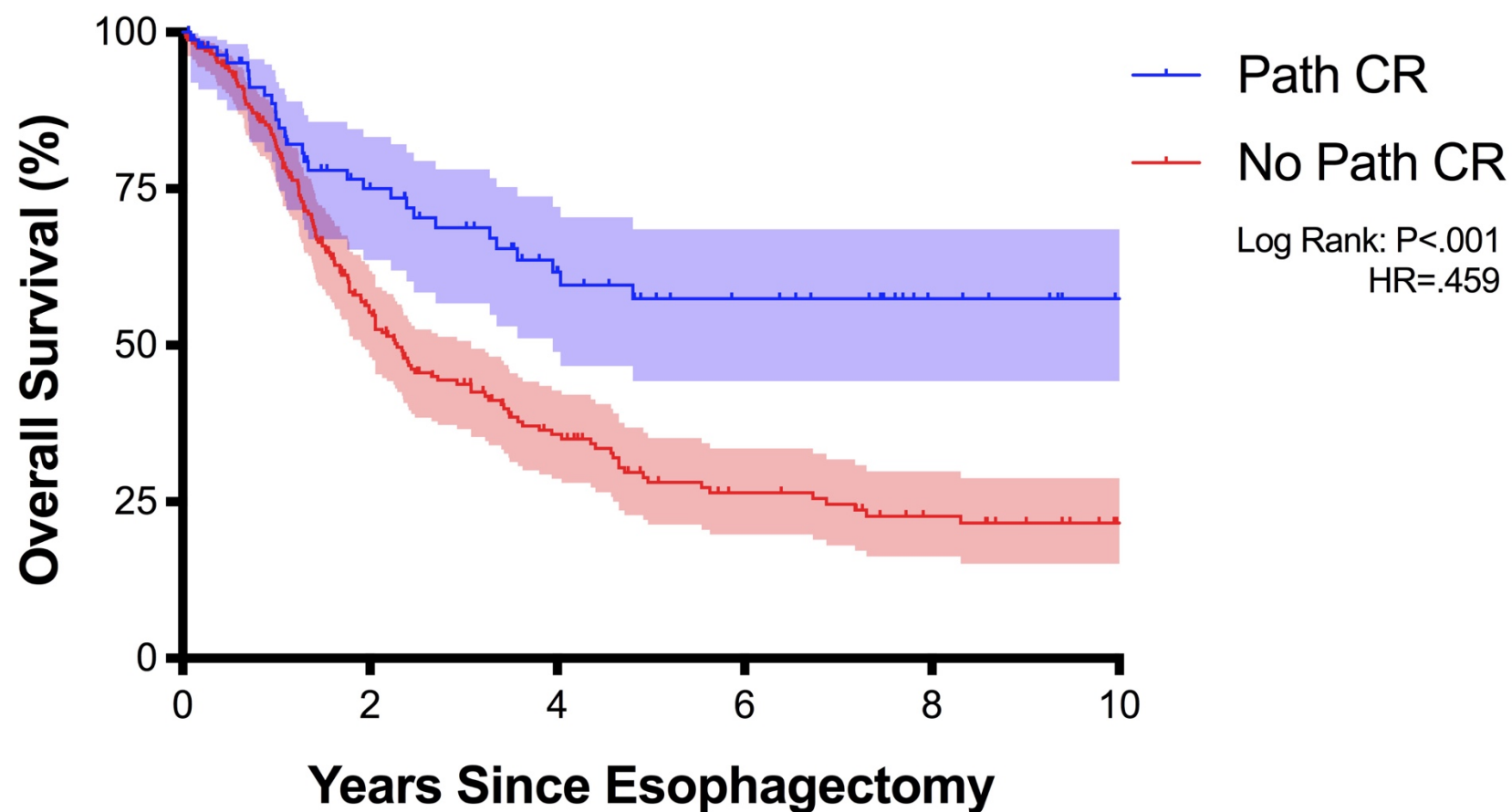


Figure 5. Overall survival of patients achieving pathologic complete response



No. at risk:

Path CR: 86	51	31	21	11	5
No Path CR: 239	101	51	30	20	10

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