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Taxane-based or platinum-based combination chemotherapy given concurrently with radiation followed by surgery resulting in high cure rates in esophageal cancer patients

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Abstract

Background: Preoperative chemoradiotherapy (CRT) is one standard option for localized esophageal or gastroesophageal junction (GEJ) cancer patients but an optimal concurrent chemotherapy combination is not established.

Methods: 412 patients with resectable (cT1N1M0 or cT2-4N0-3M0) esophageal or GEJ cancer treated at the MDACC between October 2002 and June 2016 were analyzed. Exposures: CRT with DF or FOX followed by surgery (trimodality; TMT). Main outcomes and measures: Primary endpoints were overall survival (OS) and disease-free survival (DFS). Univariate and multivariate Cox analyses were performed.

Results: Of the 412 patients analyzed, 264 (64%) received DF and 148 (36%) FOX. The median age was 60 years, and 95% had adenocarcinoma. The clinical complete response, positron-emission tomography response, and pathologic complete response rates were 73%, 73%, and 30%, respectively. Median follow-up was 60.4 months. Median OS for the entire cohort was 81.6 months (95% confidence interval [CI], 56.3–122.0); 81.6 months (95% CI, 55.9–not estimable) for the DF group and 67.7 months (95% CI, 41.6–not estimable) for the FOX group ($P = .24$). The median DFS was 45.6 months (95% CI, 33.1–61.7) for the entire cohort; 49.5 months (95% CI, 38.6–70.3) for DF and 33.0 months (95% CI, 18.1–70.4; $P = .38$) for FOX. Higher tumor location (unfavorable) and clinical complete response (favorable) were prognostic for both OS and DFS in the multivariate analysis.

Conclusion: At our high-volume center, the outcome of 412 TMT esophageal cancer patients was excellent. Taxane-based chemotherapy produces nonsignificant favorable trend.

Abbreviations: BMI = body mass index, CRT = chemoradiotherapy, DF = docetaxel + fluoropyrimidine, DFS = disease-free survival, EAC = esophageal adenocarcinoma, EC = esophageal cancer, ESCC = esophageal squamous cell carcinoma, FOX = oxaliplatin + fluoropyrimidine, GEJ = gastroesophageal junction, OS = overall survival, PS = performance status, TMT = trimodality.

Keywords: esophageal cancer, neoadjuvant chemoradiotherapy, docetaxel, oxaliplatin, 5-fluorouracil, pathologic complete response, survival, recurrence

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1. Introduction

Seventeen thousands new cases of esophageal cancer (EC) were diagnosed in the United States in 2017.[1] Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) are the 2 major histologic types for EC. One out of 2 patients has localized EC at diagnosis but the 5-year survival rate remains poor. To overcome relapses after surgery, preoperative treatments have been developed.[2]

Patients with localized ECs can be treated with preoperative chemoradiation followed by surgery (trimodality; TMT).[3] Preoperative chemoradiotherapy (CRT) offers advantages over perioperative chemotherapy: synergism between chemotherapy and radiation and compliance and tolerance is better when adjunctive therapy is given before surgery. The CROSS trial showed favorable results for patients who received preoperative chemoradiation over surgery alone.[4] Thus, TMT is the preferred approach for patients with localized ECs.[3]

Optimization of chemotherapy combination during preoperative radiation is under evaluation. Carboplatin/paclitaxel was used in the CROSS trial and thus considered safe and effective, but there is currently no comparative data for preferring 1 regimen over another.[5] In the literature, various protocols have been described, such as 5-fluorouracil (5-FU) plus platinum-based drug,[6–11] 5-FU plus docetaxel,[12] cisplatin/irinotecan,[13] cisplatin/paclitaxel,[14] or cisplatin/vinorelbine.[15] Therefore, the NCCN guidelines provide several options to accommodate practices in all participating institutions. We have traditionally used 2 drug combination (5-FU plus taxane based or platinum based), but there is no study comparing this 2 regimens.

The objective of the current analysis was to compare the efficacy of docetaxel/5-FU (DF) and oxaliplatin/5-FU (FOX) in a large cohort of patients with localized EC treated with TMT.

2. Methods

2.1. Study design and participants

This study included 412 patients with localized EC treated at the University of Texas MD Anderson Cancer Center (MDACC) between October 2002 and June 2016. Patients were identified through a prospectively maintained database in the Department of Gastrointestinal Medical Oncology, approved by the Institutional Review Board of UT MD Anderson Cancer Center.

We included all patients who fulfilled the following key eligibility criteria: age ≥18 years; histologically confirmed SCC or EAC Siewert type I, II or involving the esophagus by the 7th edition (2010) of the American Joint Committee on Cancer TNM staging system[16]; cT1N1M0 or cT2-4N0-3M0 tumors; patient treated with preoperative CRT with a chemotherapy based on DF or FOX followed by surgery; and patients receiving induction chemotherapy were included. No other selection criteria were implemented.

Several clinical variables were collected: age, gender, past medical history (including risk factors for EC, past and synchronous malignancies, history of systemic or radiation therapy), Eastern Cooperative Oncology Group performance status (PS) score at diagnosis, baseline body mass index, 3-month post-CRT weight loss, 3-month postsurgery weight loss.

2.2. Staging, treatment, and follow-up

Endoscopic findings included tumor length, presence of Barrett esophagus, and macroscopic aspect of the lesion. Histologic subtype (EAC/SCC/adenosquamous), differentiation grade (G1/G2/G3), and the presence of signet ring cells (yes/no) were also recorded. Baseline TNM was assessed on imaging (computed tomography [CT] and/or positron emission tomography [PET]-CT scan) and eusTN on endoscopic ultrasonography when available. All patients were discussed in our multidisciplinary conference and were assigned to preoperative CRT and surgery.

All patients underwent a curative intent surgery. Prior to surgery, after recovery from CRT, all patients had preoperative staging with CT or PET/CT. PET responders were defined as those who had a ≥35% SUVmax reduction, as previously reported.[17,18] Clinical complete response meant the absence of suspicious lesion at endoscopy. Histologic response meant negative biopsies. A decision to proceed with surgery was made in the multidisciplinary conference. After surgical resection, variables such as surgical ypT and ypN stage, amount of residual tumor cells (%), pathologic stage (P0, 0% residual; P1, 1–50% residual; P2, >50% residual),[19] margin status (R0/R1), and lymphovascular invasion were assessed. Pathologic complete response (pCR) meant no cancer cells in the resected specimen (ypT0N0).

After surgery, patients were followed with imaging studies +/− endoscopic evaluations every 3 months for 1 year, then every 6 months for 2 additional years, and finally once per year for up to 5 years or until death. Electronic health records, tumor registry, or the Social Security Database were the sources to derive the survival status.

2.3. Outcome measures

The primary endpoints were overall survival (OS) and disease-free survival (DFS). Recurrence was primarily determined radiographically and was classified as locoregional (including the site of primary disease, locoregional lymph nodes), distant (nonregional lymph nodes, systemic metastases) or both.

2.4. Statistical analysis

Patient characteristics were summarized using descriptive statistics. OS was defined as the time interval between CRT start date and death date, and was censored at the last follow-up date for patients who were alive. DFS was defined as the time interval between CRT start date and relapse date or death date, whichever comes first, and was censored at the last follow-up date for patients who were alive without disease relapse. OS or DFS was estimated using the Kaplan–Meier method[20] and we used the 2-sided log-rank test for comparison.[21] Univariate and multivariate Cox proportional hazards regression models[22] were used with various variables. Patient characteristics that were significant in the univariate models at ≤0.10 level were included in the multivariate model. Backward elimination was implemented until all remaining predictors had a *P*-value <.05. The CRT regimen type was forced to remain in the final model. Statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC) and Stata 13.1 (Stata Corp, College Station, TX).

3. Results

3.1. Patient and tumor characteristics

A total of 412 patients were included in the final analysis with a median follow-up time among survivors of 60.4 months (range,

3.9–150.8 months). Only 4 individuals (1%) did not have baseline endoscopic ultrasound. Radiotherapy techniques encompassed intensity-modulated radiation therapy (58.0%), proton therapy (27.4%), 3-dimensional conformal radiotherapy (14.1%), and volumetric-modulated arc therapy (0.5%). The radiation dose ranged from 34.2 to 63.0 Gy (median, 50.4 Gy). Chemotherapy regimen associated to radiotherapy was either docetaxel/5-FU (or capecitabine) or oxaliplatin/5-FU (or capecitabine). In patients who received induction chemotherapy (n = 134), the 2 main regimens were FOX (or FOLFOX [5-FU/oxaliplatin/leucovorin] or CAPOX [capecitabine/oxaliplatin]) and DFOX (docetaxel/5-FU or capecitabine/oxaliplatin), prescribed in 53.7% and 34.3% of the cases, respectively. All other protocols were given in <3% of the cases. Esophagectomy with transthoracic or minimally invasive procedure was done in 96.4%; in this case, 3-field esophagectomy was done in 5.8%. Other types of surgery were uncommon (transhiatal esophagectomy [2.2%], total gastrectomy [1.2%], and unknown for 0.2% of the patients).

Table 1 summarizes patient and tumor characteristics overall and stratified by concurrent chemotherapy regimen. The median age was 60 years (range, 21–83). Patients were primarily men (88%), overweight or obese (78%), with baseline T3/T4 (88%) and N+ (64%) tumors. Concerning tumor location, Siewert type I lesions were predominant (51.5%) followed by Siewert type II (40.3%) and proximal esophagus (8.3%). Almost all tumors were EACs (94.7%). Poorly and well/moderately differentiated histologic grades were well-balanced 51.1% and 48.9%, respectively. Among the 412 patients, 264 (64%) patients had DF and 148 (36%) patients had FOX. Baseline prognostic factors were well balanced between the two groups except three-month post-CRT weight loss ($P < .01$), ECOG PS ($P = .003$), baseline T-stage ($P = .04$) and induction chemotherapy ($P < .01$). Patients treated with FOX were thus more likely to have ECOG PS of 0 (60% vs 44%), early baseline T1/T2 stage (17% vs 10%) and induction chemotherapy (55% vs 20%) when compared with DF patients. After preoperative CRT, clinical complete response and PET response were both observed in 73% of the cases. pCR rate was 30.3% in the entire cohort.

3.2. Overall survival

At the time of this analysis, 180 of 412 patients (44%) had died. There was no 30- or 90-day mortality in this cohort. The median OS for the entire cohort was 81.6 months (95% confidence interval [CI], 56.3–122.0) (Fig. 1A), 81.6 months (95% CI, 55.9–not estimable) in the DF group and 67.7 months (95% CI, 41.6–not estimable) in the FOX group, without significant difference ($P = .24$) (Fig. 1B). However, survival curves cross at 72 months, and after censoring all patients at 48 months, a significant OS improvement was noted for DF (log-rank $P = .04$). The 3-year OS rate was 66% (95% CI, 61–70%) overall, 69% (95% CI, 63–75%) in the DF group and 60% (95% CI, 52–68%) in the FOX group.

The OS curves according to histologic subtype are shown in Figure 1C, without significant difference between EAC and ESCC ($P = .08$). Survival was improved in patients with well to moderately differentiated tumor ($P < .001$), those with pCR ($P = .04$) and those with Siewert type II tumor ($P = .01$), whereas PET response and the presence of signet ring cells did not influence prognosis ($P = .55$ and $P = .17$, respectively) (Fig. 2).

Table 1

Patient and tumor characteristics.

Characteristic	Total (n = 412)	Docetaxel/ 5-FU (n = 264)	Oxaliplatin/ 5-FU (n = 148)	*P*-value
Age (n = 412), yr				
Median (range)	60 (21–83)	60 (21–83)	60.5 (29–77)	.70
Gender (n = 412), n (%)				
Female	51 (12.4)	38 (14.4)	13 (8.8)	.10
Male	361 (87.6)	226 (85.6)	135 (91.2)	
Baseline BMI (n = 412), n (%)				
Overweight/obese	323 (78.4)	201 (76.1)	122 (82.4)	.14
Normal/underweight	89 (21.6)	63 (23.9)	26 (17.6)	
Baseline ECOG (n = 412), n (%)				
PS 0	204 (49.5)	116 (43.9)	88 (59.5)	**<.01**
PS 1–2	208 (50.5)	148 (56.1)	60 (40.5)	
Weight loss (n = 402), n (%)*				
<10%	310 (77.1)	181 (70.7)	129 (88.4)	**<.01**
≥10%	92 (22.9)	75 (29.3)	17 (11.6)	
Histologic subtype (n = 412), n (%)				
Adenocarcinoma	390 (94.7)	249 (94.3)	141 (95.3)	.68
Squamous cell/adenosquamous carcinoma	22 (5.3)	15 (5.7)	7 (4.7)	
Tumor length (n = 409), cm				
Median (range)	5 (1–15)	5 (1–13)	5 (1.4–15)	.77
Tumor location (n = 412), n (%)				
Esophagus	34 (8.3)	27 (10.2)	7 (4.7)	.07
Siewert type I	212 (51.5)	127 (48.1)	85 (57.4)	
Siewert type II	166 (40.3)	110 (41.7)	56 (37.8)	
Histologic grade (n = 411), n (%)				
Well/Moderately differentiated	201 (48.9)	131 (49.8)	70 (47.3)	.62
Poorly differentiated	210 (51.1)	132 (50.2)	78 (52.7)	
Signet ring cells (n = 412), n (%)				
Yes	57 (13.8)	36 (13.6)	21 (14.2)	.88
No	355 (86.2)	228 (86.4)	127 (85.8)	
Baseline clinical T stage (n = 407), n (%)				
T1/T2	51 (12.5)	26 (10.0)	25 (17.0)	**.04**
T3/T4	356 (87.5)	234 (90.0)	122 (83.0)	
Baseline clinical N stage (n = 406), n (%)				
N0	147 (36.2)	97 (37.3)	50 (34.2)	.54
N+	259 (63.8)	163 (62.7)	96 (65.8)	
Baseline stage (n = 405), n (%)				
IB/II	163 (40.2)	102 (39.4)	61 (41.8)	.64
III	242 (59.8)	157 (60.6)	85 (58.2)	
Induction chemotherapy (n = 412), n (%)				
Yes	134 (32.5)	53 (20.1)	81 (54.7)	**<.01**
No	278 (67.5)	211 (79.9)	67 (45.3)	
PET response (n = 356), n (%)				
Yes	259 (72.8)	158 (70.9)	101 (75.9)	.30
No	97 (27.2)	65 (29.1)	32 (24.1)	
Clinical complete response (n = 406), n (%)				
Yes	295 (72.7)	182 (70.5)	113 (76.4)	.21
No	111 (27.3)	76 (29.5)	35 (23.6)	
Pathologic complete response (n = 412), n (%)				
Yes	125 (30.3)	84 (31.8)	41 (27.7)	.38
No	287 (69.7)	180 (68.2)	107 (72.3)	
Histologic margin (n = 406), n (%)				
R0	377 (92.9)	243 (93.8)	134 (91.2)	.32
R1	29 (7.1)	16 (6.2)	13 (8.8)	

Bold was used in case of significant results ($P < .05$).

BMI = body mass index, ECOG = Eastern Cooperative Oncology Group, 5-FU = 5-fluorouracil, PET = positron-emission tomography, PS = performance status, R0 = no cancerous cells seen microscopically, R1 = cancerous cells can be seen microscopically.

* Three-month postchemoradiotherapy weight loss.

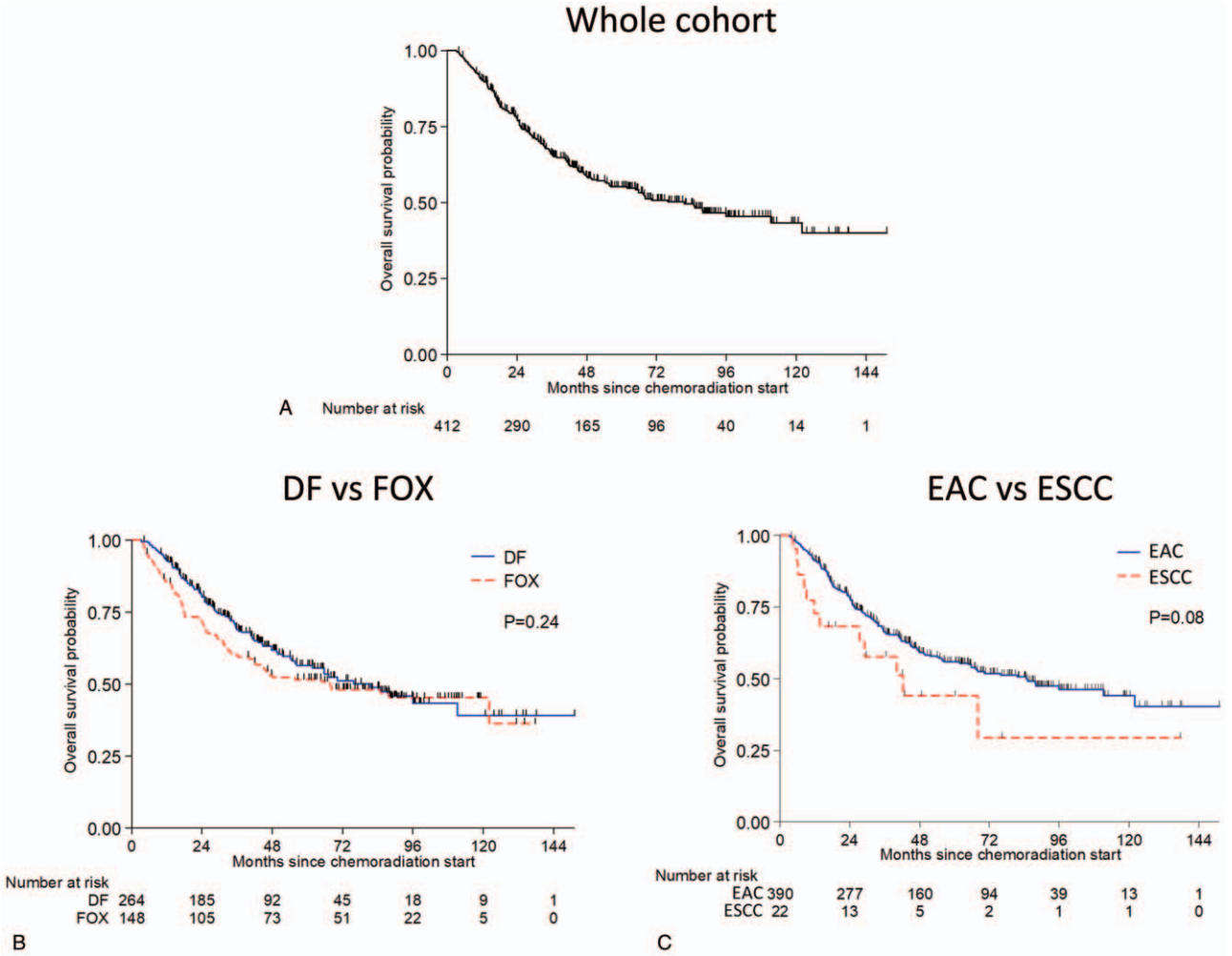

Figure 1. Kaplan–Meier estimate for overall survival of the whole cohort (A), according to treatment group (B), according to histologic subtype (C). DF = docetaxel/5-fluorouracil, EAC = esophageal adenocarcinoma, ESCC = esophageal squamous cell carcinoma, FOX = oxaliplatin/5-fluorouracil.

Table 2 shows the results of uni- and multivariate Cox regression models for OS. In the univariate analysis, age, tumor location, histologic grade, baseline stage, clinical complete response, pCR, and histologic margin were significantly associated with OS. However, there was no difference between FOX and DF in terms of OS (hazard ratio [HR], 1.2, 95% CI, 0.89–1.61; $P = .24$). After backward elimination, age, tumor location, histologic grade, baseline stage, and clinical complete response remained significantly associated with OS in the final model, while a CRT regimen was not significant (HR, 1.34, 95% CI, 0.98–1.83; $P = .06$). The prognosis decreased as the primary tumor was noted at a higher location, with HR for death of 2.91 (95% CI, 1.48–5.71; $P < .01$) for esophagus compared with Siewert type II cancers. Complete clinical response was strongly correlated with better survival (HR, 0.49, 95% CI, 0.35–0.69; $P < .01$) but not pCR (HR, 0.97, 95% CI, 0.67–1.41; $P = .88$).

4. Discussion

In the present study that analyzed 412 consecutive EC patients who had TMT. We observed a median OS of 81.6 (95% CI, 56.3–122) months. Although, this type of survival outcome for a large cohort is rare, it is a single experienced institution's effort. Since our group relies heavily on group decisions through multidisciplinary conference (dedicated only to EC), it may be that patient selection process is reflected in these results. These results are better than mutlicenter efforts like the CROSS trial, which also selected patients; however, the CROSS results are more generalizable than ours.[5] However, we also showed excellent survival results in patients with localized gastric adenocarcinoma who had surgery with or without adjunctive therapy treated at the MDACC, with a median OS of 9.2 years.[23]

One of the purposes of this report was to examine whether a specific chemotherapy combination provided an advantage. Various chemotherapy combinations have been studied and reported[24]; however, prospectively combinations have been compared only rarely.[6,14] In EC, the use of combination of drugs has been a tradition from early days.[4] We present one of the largest cohorts compared to previous reports,[6–9,13–15] to compare the 2 combinations we have traditionally used either on protocol or off protocol.[25] EACs being more chemoradiation resistant, represented 95% of our cohort compared to 75% in the CROSS trial. Acknowledging no overall difference in the 2 regimens we have used, the DF cohort had more unfavorable prognostic features (more PS 1 or 2 score, more weight loss, more T3 or T4 stage) than the FOX cohort and yet DF patients fared

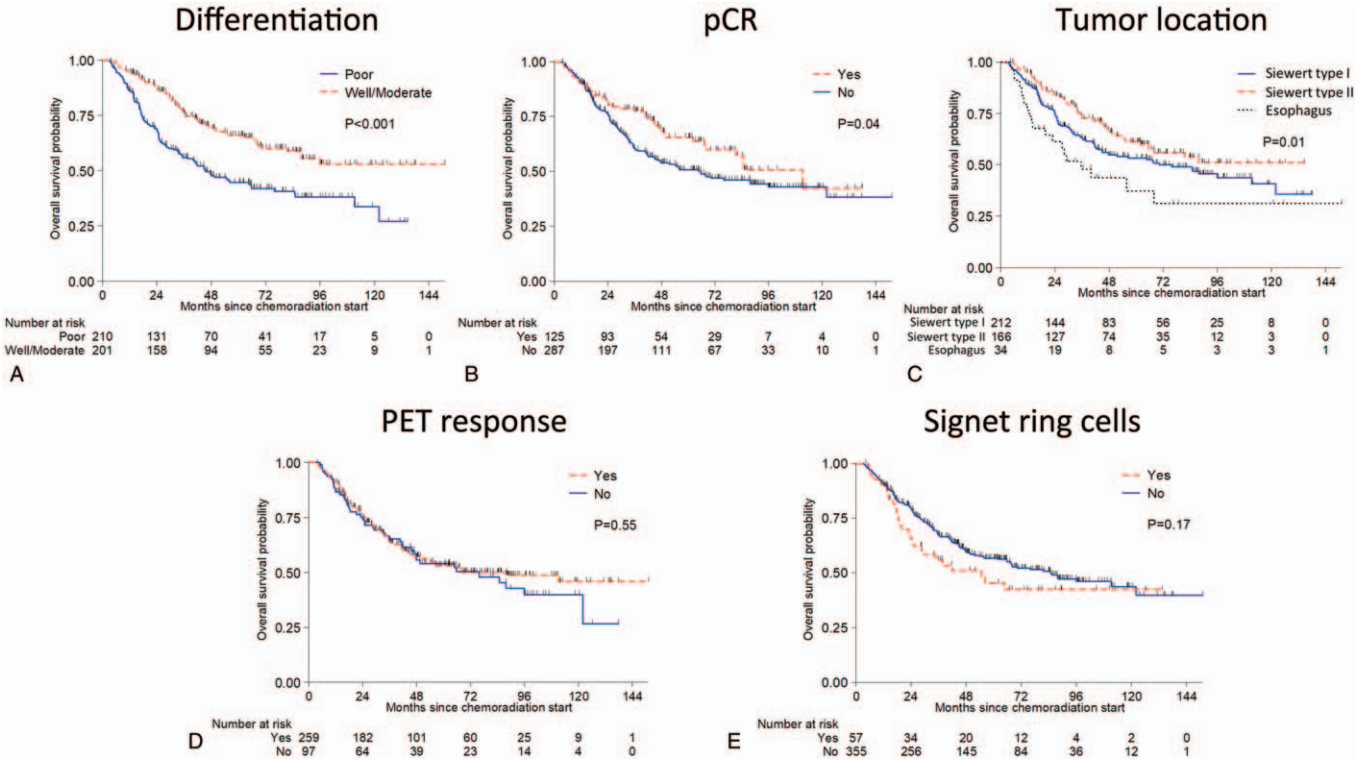

Figure 2. Kaplan–Meier estimate for overall survival of according to differentiation (A), according to pCR (B), according to tumor location (C), according to PET response (D), according to presence of signet ring cells (E). pCR = pathologic complete response, PET = positron-emission tomography.

better but not significantly. We observed better effects after censoring all patients at 48 months but we recognize this type of exploratory approach has little value. We also observed a superior DFS with DF in the multivariate model but this finding also has its limitations. We noted 2 randomized controlled trials worthy of mention. A phase II ECOG-ACRIN trial compared in 81 patients cisplatin/irinotecan with cisplatin/paclitaxel and found no significant differences in OS and DFS.[14] In the NEOSCOPE trial (n = 77), carboplatin/paclitaxel was compared with capecitabine/oxaliplatin[6] but OS and DFS were not reported. Moreover, a comparison between FOLFOX and carboplatin/paclitaxel during preoperative CRT is currently ongoing (NCT02359968).[26]

We identified prognostic factors for both OS and PFS in multivariate analysis, especially tumor location and clinical complete response. Patients with EC had 2 to 3 times higher risk of death and recurrence than those with "real" gastroesophageal junction (GEJ) cancer (Siewert type II). This finding was not reported in previous papers but it could be explained by different genomic profiles. The Cancer Genome Atlas Research Network recently performed a comprehensive molecular analysis of 164 carcinomas of the esophagus.[27] They demonstrated that there was a gradation of molecular subclasses from stomach to upper esophagus. For example, almost all cancers of the lower 3rd esophagus were chromosomally unstable, with especially ERBB2 and VEGFA amplification or TP53 mutation, whereas a small proportion of GEJ tumors had microsatellite instability, considered as a good prognostic factor. Another interesting result in our study is the strong correlation between complete clinical complete response after CRT and prognosis. The prognostic role of complete clinical response is not well established, contrary to pCR,[15,28,29] even if the latter was not associated to patient outcomes in our work.

Our study is comforting in many aspects. We reported similar pCR rate than in the CROSS trial (30% vs 29%) while using different chemotherapy regimens. Preoperative CRT seems thus effective irrespective of the type of prescribed drugs (as long as it is a combination of 2 classes of agents). Second, the CROSS trial only included patients with T1N1 or T2-3N0-1 tumors, and a recent suspicion of worsened outcomes emerged when original eligibility criteria were extended to patients with more advanced diseases.[30] However, we reported here excellent survival data among patients with T2-4N0-3 tumors. Positive results of the CROSS study were often associated to the low radiation dose incurred (41.4 Gy). In a small retrospective study, higher radiation dose (50.4 Gy) was correlated with higher morbidity and a poor median OS of 24 months.[31] Once again, our data are promising, with a median OS of 81.6 months in a large cohort of 412 patients who received a median radiation dose of 50.4 Gy. However, we did not evaluate treatment-related morbidity.

However, we can underline some limits in our work. First, this study was retrospective, but our database was built prospectively in a single institution with standardized protocols for staging, treatment, and specimen analysis. Second, as a referral tertiary center, our cohort may not reflect overall patients with locally advanced esophageal or GEJ cancer. Finally, 85% of our patients were treated with modern radiation techniques (intensity-modulated radiation therapy or proton therapy) whereas only 3-dimensional conformal radiotherapy was used in the CROSS trial. Significant improvements in radiation techniques over time could partially explain our positive results.

Table 2

Uni- and multivariate Cox regression models for overall survival (180 deaths in 412 patients).

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Chemotherapy regimen during neoadjuvant CRT				
FOX vs DF	1.2 (0.89–1.61)	.24	1.34 (0.98–1.83)*	.06
Age, yrs				
≥70 vs <70	1.55 (1.05–2.30)	**.03**	1.56 (1.04–2.32)	**.03**
Gender				
Male vs female	1.04 (0.66–1.63)	.88		
Baseline BMI				
Overweight/obese vs Normal/underweight	0.88 (0.62–1.25)	.47		
Baseline ECOG				
PS 1–2 vs PS 0	0.94 (0.70–1.26)	.69		
Weight loss†				
≥10% vs <10%	1.37 (0.99–1.91)	.06		
Histologic subtype				
SCC/adenosquamous vs ADK	1.67 (0.93–3.0)	.09	0.97 (0.44–2.14)	.94
Tumor length, cm				
≥6 vs <6	1.07 (0.79–1.44)	.66		
Tumor location				
Siewert type I vs Siewert type II	1.38 (1.00–1.90)	**.05**	1.17 (0.84–1.63)	.35
Esophagus vs Siewert type II	2.17 (1.31–3.61)	**.003**	2.91 (1.48–5.71)	<**.01**
Histologic grade				
Well/moderately vs poorly differentiated	0.51 (0.38–0.69)	<**.001**	0.48 (0.35–0.66)	<**.01**
Signet ring cells				
Yes vs No	1.32 (0.88–1.98)	.17		
Baseline clinical T stage				
T3/T4 vs T1/T2	1.77 (1.07–2.91)	**.03**		
Baseline clinical N stage				
N+ vs N0	1.47 (1.07–2.01)	**.02**		
Baseline stage				
III vs IB/II	1.52 (1.11–2.07)	**.01**	1.43 (1.04–1.97)‡	**.03**
Induction chemotherapy				
Yes vs no	0.80 (0.58–1.11)	.19		
PET response				
Yes vs no	0.90 (0.64–1.27)	.55		
Clinical complete response				
Yes vs no	0.48 (0.35-.65)	<**.001**	0.49 (0.35–0.69)	<.01
Pathologic complete response				
Yes vs no	0.70 (0.50–0.98)	**.04**	0.97 (0.67–1.41)	.88
Histologic margin				
R1 vs R0	2.2 (1.40–3.48)	**.001**	1.42 (0.85–2.37)	.18

Bold was used in case of significant results ($P < .05$).

ADK = adenocarcinoma, BMI = body mass index, CI = confidence interval, CRT = chemoradiotherapy, DF = docetaxel/5-fluorouracil, ECOG = Eastern Cooperative Oncology Group, FOX = oxaliplatin/5-fluorouracil, HR = hazard ratio, PET = positron-emission tomography, PS = performance status, R0 = no cancerous cells seen microscopically, R1 = cancerous cells can be seen microscopically, SCC = squamous cell carcinoma.

* This variable was forced to remain in the final model.

† Three-month postchemoradiotherapy weight loss.

‡ Only overall stage was introduced in the multivariate model for taking into account collinearity because overall stage is based on T stage and N, so these variables are highly correlated and introducing all of them in the multivariate would be inappropriate.

In conclusion, this large retrospective study confirms the excellent survival outcomes in a nonselected cohort of patients treated with preoperative CRT for esophageal or GEJ cancer, even beyond the original eligibility criteria for the CROSS trial, and regardless of the chemotherapy regimen or the histologic subtype.

Author contributions

Data collection and patient accrual: Anthony Lopez, Meina Zhao, Kazuto Harada, Wayne L. Hofstetter, Brian Weston, Jeffrey H. Lee, Fatemeh G. Amlashi, Mariela A. Blum-Murphy, David C. Rice.

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Manuscript writing: all authors.

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