Pre-operative Carboplatin/Paclitaxel Versus 5-Fluorouracil (5-FU)-based Chemoradiotherapy for Older Adults With Esophageal Cancer

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Abstract. *Background/Aim:* This study aimed to compare the efficacy and tolerability of pre-operative platinum/5-fluorouracil (P5F) and carboplatin/paclitaxel (CP), in combination with radiation therapy in older adults with locally advanced, stage I-III esophageal cancer. *Patients and Methods:* We retrospectively reviewed 51 patients aged ≥ 70 years who underwent chemoradiotherapy followed by esophagectomy for stage I-III esophageal cancer between 2008 and 2018. Pathological complete response (pCR) and survival rates were compared across the two chemotherapy regimen arms. *Results:* Treatment completion ($p=0.28$), pCR ($p=0.89$), and partial response rates were similar across both chemotherapy groups. Overall survival (OS) and disease-free survival (DFS) were similar across both groups with $HR=0.80$ ($p=0.62$) and $HR=0.72$ ($p=0.72$) respectively. *Conclusion:* The lesser toxic CP regimen may be used in older patients with locally advanced esophageal cancer,

with tumor response and survival rates similar to P5F chemotherapy.

Esophageal cancer (EC) is the 7th most common cancer worldwide and the 6th most common cause of death from cancer (1). Even after curative surgical treatment, the prognosis of EC remains poor with a 5-year survival rate of nearly 40% (2).

Although there is currently no global consensus (3), pre-operative treatment with chemoradiotherapy (CRT) followed by esophagectomy is an accepted standard of care for managing locally advanced esophageal cancer in the United States (US) and Europe (4, 5). Multiple trials and meta-analyses have established the superiority of a trimodality approach involving CRT followed by esophagectomy, to surgery alone or radiation therapy, in terms of achieving complete pathologic response (pCR) and significant increase in survival (6-10).

EC incidence is particularly rising in the geriatric population with a median age of diagnosis of 65 years (1). This is of particular concern in Western countries where the overall life expectancy has improved. In the US alone, 17,650 new EC cases were diagnosed in 2019 (11), and more than 50% of all EC cases were diagnosed in patients 70 years of age and older (12). Yet, and despite the higher prevalence of EC in the geriatric population, patients 65 years of age or older have historically been substantially underrepresented in cancer clinical trials (13). In older adult patients (>65 years) with EC specifically, the trimodality approach has been distinctively underutilized despite proven significant

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survival benefit and potential for cure with treatment compared to supportive care (14), and the lack of association between age and treatment outcome and complications (15). There is thus a need to better characterize outcomes and toxicities of the trimodality approach in the geriatric population of patients with locally advanced resectable EC.

The optimal neo-adjuvant chemotherapy regimen used as part of the CRT approach has not been well studied, with no randomized studies comparing the two most standard chemotherapy regimens for esophageal cancer: carboplatin/paclitaxel (CP) and platinum/5-fluorouracil (P5F). Historically, neo-adjuvant P5F has since long been the standard of care despite significant grade 3/4 toxicity rates up to 57% (5, 16-18). The CROSS trial demonstrated that neo-adjuvant CP with concurrent radiation therapy resulted in better toxicity profiles (grade ≥ 3 toxicity rates up to 23%) (10, 19).

These reports of a less severe toxicity profile and similar efficacy with neo-adjuvant CP are of particular interest in the geriatric population of patients with resectable, locally advanced EC. In this study, we present the first retrospective comparison of these two chemotherapy regimens in older adult patients with EC, in terms of treatment response and survival outcomes.

Patients and Methods

Study design and participants. In this Institutional Review Board (IRB) approved retrospective analysis of a prospectively maintained database, we have reviewed the records of patients with histologically confirmed stage I-III EC who received trimodality pre-operative CRT, followed by esophagectomy at the Kansas University Cancer Center between 2008 and 2018. Eligibility criteria for patients included age ≥ 70 years, histologically confirmed EC (squamous cell or adenocarcinoma) at presentation, good functional status (Eastern Cooperative Oncology Group score/ECOG: 0-1 and Charlson comorbidity score < 1), receipt of pre-operative CRT with chemotherapy consisting of either carboplatin/paclitaxel or 5-FU/platinum (cisplatin or oxaliplatin), and subsequent esophagectomy (transhiatal/transthoracic). Patients who received any other chemotherapy regimen, had recurrent disease, presented with distant metastasis, were not fit for surgery or had missing/incomplete treatment data, were excluded. Clinicopathological and follow-up data (including patients' characteristics and treatment outcome) were collected and analyzed, and patients were divided into two groups based on their administered chemotherapy: either carboplatin/paclitaxel (CP) or Platinum/5-FU (P5F).

Pre-treatment staging. All patients underwent initial pre-treatment staging. This included multi-disciplinary evaluation at the weekly esophageal care conference (medical oncology, radiation oncology, and surgical oncology), blood count and liver function testing, an upper gastrointestinal endoscopy with histologic biopsy and endoscopic ultrasonography (EUS), and computed tomography (CT). Radio-labeled fluorodeoxyglucose (FDG) whole body positron emission tomography (PET) was also performed as part of the pre-treatment staging in all patients.

Treatment groups. Treatment groups consisted of either carboplatin/paclitaxel (CP) or platinum/5-FU (P5F). Decisions regarding the choice of chemotherapy regimen were left to the discretion of the treating medical oncologist and were based on the patient's general condition and available evidence at the time of treatment. The CP regimen consisted of carboplatin with target area under the curve (AUC) of 2 mg/ml/min and paclitaxel at dose of 50 mg/m², administered at day 1, 8, 15 and 29 during radiation therapy (RT). In the P5F group, regimen consisted of either oxaliplatin (85 mg/m² on days 1, 15 and 29) or cisplatin (75 mg/m² on day 1), and 5-FU (day 1-4) at week 1 and 5 during RT, with two additional courses on week 8 and 11.

Radiation scheme. Pre-operative RT planning was carried out after direct simulation, based on diagnostic images or 3 D based on treatment planning CT images. A total radiation dose of 41.4 Gy was given in 23 fractions of 1.8 Gy each, with 4 fractions administered per week.

Surgical resection. All patients included in the study underwent esophagectomy four to eight weeks after CRT by either transhiatal or transthoracic technique, at the discretion of the treating surgeon and according to the location of the primary tumor. Post-operative residual tumor (R) classification and pathologic examination of all surgical resection specimens was performed. Histopathologic examination included descriptions of tumor type (squamous vs. adenocarcinoma) and extension, lymph node status (N) and resection margin (R). Complete resection (R0) refers to microscopically tumor-free margin, pathologic complete response (pCR) refers to absence of residual tumor from surgical specimen, and partial response refers to downstaging of pre-treatment TNM stage.

Outcomes. The primary outcome was pCR rate, defined as absence of residual tumor from surgical specimen. Secondary endpoints included overall survival (OS) and disease-free survival (DFS). OS is defined as the time from start of treatment to death from any cause and DFS refers to the time from start of treatment to the date of confirmed clinical/radiological progression or death from any cause.

Statistical analysis. For comparisons by chemotherapy group, Chi-squared tests were performed for categorical variables. Multivariable logistic regression was used to analyze pCR rates. OS and DFS were estimated for the two chemotherapy groups in the bivariate setting using the Kaplan-Meier method, while Cox proportional hazards models were utilized to estimate the adjusted hazard ratios. Analytical models were adjusted for age, stage, radiation dose, histology sub type, and time interval from completion of neo-adjuvant therapy to surgery. A *p*-Value < 0.05 [95% confidence interval (CI)] was considered significant.

Ethics approval and consent to participate. The study was performed in accordance with the ethical standards at the Kansas University Medical Center

Results

Patients and baseline characteristics. Between 2008 and 2018, a total of 647 patients were diagnosed with stage I-III EC, of whom 204 were above 70 years of age or older. Of those, 51 patients were identified for having undergone

Figure 1. Study schema. A retrospective review of the Kansas University Cancer Center database identified 647 treatment-naïve patients with esophageal cancer (EC), of who 204 were 70 years or older. Of those, 51 met inclusion criteria for receipt of trimodality chemoradiotherapy (CRT), and 32 received carboplatin/placlitaxel (CP) chemotherapy while 19 were treated with platinum/5-FU (P5F) chemotherapy.

trimodality pre-operative CRT with the chemotherapy regimen of interest (32 received CP and 19 received P5F), followed by esophagectomy, and were included in our analysis (Figure 1). Characteristics of these 51 patients are summarized in Table I.

The median age at diagnosis was 75 years (70-85 years). Patients were predominantly males (80.4%), Caucasian (76.5%), and with adenocarcinoma histology (66.7%). Tumors were mainly located in the mid (35.3%) and distal esophagus (43.1%) regions and the majority of patients (90.2%) had stage II/III disease at diagnosis. Age ($p=0.08$), sex ($p=0.097$), tumor location ($p=0.41$) and histology ($p=0.84$) did not differ significantly among treatment groups. While clinical T stages T2 and T3 were more common in the overall cohort (96.1% vs. 3.9% T1), the distribution among both treatment groups was not different ($p=0.70$). Similarly, N Stage ($p=0.64$) was comparable between both groups. Overall, the majority of patients were stage II-III (90.2% vs. 9.8% were stage I) but the difference in distribution of stages across treatment groups was not significant ($p=0.89$). All patients completed radiation therapy (50.4Gy; 28 fractions) with

variable individualized booster doses at the treating radiation oncologist's discretion.

Treatment response and tolerability. Based on the available follow-up information including pathologic/surgical specimen examination, 50 patients (98.0%) successfully underwent resection with microscopically-negative tumor margins (R0 resection). Overall, a pCR was seen in 27.4% of patients and partial response was seen in up to 43.1% of the entire cohort (Table II). Stratified by chemotherapy regimen, the pCR with CP vs. P5F was 28.1% vs. 26.3% ($p=0.51$). Tumor down-staging was achieved for 41.2% of the study population, 50% in the CP cohort and 31.6% in the P5F cohort ($p=0.20$). Similarly, nodal down-staging was achieved in 46.6% of patients who received CP compared to 36.8% of those treated with P5F ($p=0.48$).

In patients treated with pre-operative CP, 31 (96.9%) completed trimodality therapy including CRT and esophagectomy, compared to 17 (89.5%) in the P5F group ($p=0.28$). Two patients in the P5F group died within 30 days of surgery due to respiratory complications and sepsis, compared to none in the CP group ($p=0.06$).

Table I. Patient and treatment characteristics stratified by chemotherapy regimen.

Patient characteristics	Overall (n=51)	CP (n=32)	P5F (n=19)	p-Value
Age (median; range)	75 (70-85)	75.3	70.6	0.08
Gender				
Male (%)	41 (80.4)	28	13	0.097
Female (%)	10 (19.6)	3	7	
Race				
Caucasian (%)	39 (76.5)	25	14	0.88
African-American (%)	9 (17.6)	5	4	
Other (%)	3 (5.9)	2	1	
Tumor location				
Middle (%)	18 (35.3)	12	6	0.41
Distal (%)	22 (43.1)	15	7	
GEJ (%)	11 (21.6)	5	6	
Tumor histology				
SCC (%)	17 (13.3)	11	6	0.84
Adeno (%)	34 (66.7)	21	13	
Stage (AJCC 8 th ed.)				
I	5 (9.8)	3	2	0.89
II-III	46 (90.2)	29	17	
T stage (AJCC 8 th ed.)				
T1b	2 (3.9)	1	1	0.70
T2, T3	49 (96.1)	31	18	
N stage (AJCC 8 th ed.)				
N0	22 (43.1)	13	9	0.64
N1, N2	29 (56.9)	19	10	
Chemotherapy receipt	51 (100)	32 (100)	19 (100)	1.00
Completion of RTx (50.4 Gy;28 fx)	46 (90.2)	32	19	1.0
Trimodality CRT completion	48 (94.2)	31 (96.9)	17 (89.5)	0.28
Post-operative death (Within 30 days; %)	2 (3.9%)	0	2 (10.6)	0.06

CP: Carboplatin/paclitaxel; P5F: platinum/5-FU; 5-FU: 5-fluorouracil; GEJ: gastroesophageal junction; SCC: squamous cell carcinoma; Adeno: adenocarcinoma; AJCC: American Joint Committee on Cancer; T: tumor; N: nodal; RTx: radiation therapy; Trimodality CRT: chemoradiotherapy followed by surgery; Gy: Gray; fx: fraction.

Table II. Pathologic response for patients by chemotherapy regimen.

Pathologic response	Overall (n=51)	CP (n=32)	P5F (n=19)	p-Value
R0 resection (%)	50 (98.0)	32 (100)	18 (94.7)	0.19
Complete (pCR)	14 (27.4)	9 (28.1)	5 (26.3)	0.89
Partial				
Tumor down-staging	21 (41.2)	16 (50.0)	6 (31.6)	0.20
Nodal down-staging	22 (43.1)	15 (46.6)	7 (36.8)	0.48

CP: Carboplatin/paclitaxel; P5F: platinum/5-FU; 5-FU: 5-fluorouracil; R0: microscopically-negative margin; pCR: pathological complete response.

Multivariate logistic regression analysis. The choice of chemotherapy regimen (P5F vs. CP) was not associated with achieving pCR (OR=1.17; 95% CI: 0.59-2.3; $p=0.51$). Similarly, the number of days from CRT completion to surgery, the total dose of radiation received, the disease stage (1-2 vs. 3), histology (adenocarcinoma vs. squamous cell carcinoma) and receipt of adjuvant chemotherapy, did not associate with

pCR ($p>0.05$), although lower tumor stages (1-2) revealed a tendency towards a statistically significant difference in pCR rate in favor of lower stages (OR=0.54; 95% CI: 0.26-1.08; $p=0.08$). Table III summarizes these findings.

Survival outcomes. OS was comparable between the P5F group and the CP group ($p=0.62$; HR 0.80) with a median

Table III. Multivariate logistic regression analysis for achieving pCR.

Multivariate analysis	OR (95% CI)	p-Value
pCR (n=51)		
Chemotherapy regimen (P5F vs. CP)	1.17 (0.59-2.3)	0.51
Days from CRT to Sx	0.99 (0.97-1.01)	0.66
Total RTx dose	0.70 (0.99-1.0)	0.96
Stage (1-2 vs. 3)	0.54 (0.26-1.08)	0.08
Histology (Adeno vs. SCC)	1.13 (0.44-2.91)	0.80
Receipt of adjuvant Chx	1.50 (0.38-2.16)	0.62

OR: Odds ratio; CI: confidence interval; pCR: pathologic complete response; CP: carboplatin/paclitaxel; P5F: platinum/5-FU; 5-FU: 5-fluorouracil; CRT: chemoradiotherapy; RTx: radiation therapy; Sx: surgery; Chx: chemotherapy; SCC: squamous cell carcinoma; Adeno: adenocarcinoma.

survival of 20 and 32 months respectively (Figure 2A). DFS was also not significantly different between both groups ($p=0.72$; HR 0.72). Median DFS was 18 months in the P5F group and 20 in the CP group (Figure 2B).

Discussion

In this study, we described comparable outcomes in terms of pCR, OS and DFS between CP and P5F used as part of pre-operative CRT in a geriatric population of patients with EC. Our reported pCR rates as well as median OS and DFS are comparable to recently published results assessing pre-operative CRT in EC (20, 21). While prior observational studies have reported similar observations in terms of efficacy, this is to the best of our knowledge, the first study to compare efficacy of different types of pre-operative chemotherapy regimens in a geriatric population of patients 70 years or above.

Unlike younger patients, older patients with EC have unique issues pertaining to life expectancy, functional status, vulnerability to treatment-related morbidity, higher likelihood of competing comorbidities, and subsequent concern regarding patient's ability to tolerate chemotherapy, radiation therapy or surgery (22). Yet, while more than 50% of newly diagnosed EC are older than 65 years of age, the available evidence to guide therapy of EC patients were generated from trials that excluded geriatric patients (10, 13, 14, 19). For example, in the CROSS trial which established the use of pre-operative CRT as a standard approach for patients with locally advanced EC, the median age of patients was 60 years and no subset analysis for age was provided (10, 19). Our study is unique in that it focuses on patients who are ≥ 70 years of age and reveals no statistically significant difference in pCR rates or survival rates (OS and DFS) between CP and P5F.

Figure 2. Kaplan-Meier survival estimation of the overall survival (A) and disease-free survival (B) in months, for CRT with P5F (n=19) or CP (n=32). OS: Overall survival, DFS: disease-free survival, CP: carboplatin/paclitaxel (in green), P5F: platinum/5-FU (in blue), 5-FU: 5-fluorouracil, CRT: chemoradiotherapy, HR: hazard ratio.

Compared to the traditionally used 5FU-based regimens, pre-operative chemotherapy with CP has been shown to be a more tolerable and less toxic alternative treatment with similar survival outcomes (18-21, 23-27). While our study did not include toxicity data, our findings are consistent with published reports of CP being more tolerable and less toxic than 5FU-based regimen: more patients were able to complete trimodality therapy in the CP group compared to P5F, and 2 patients in the P5F group experienced post-operative death due to treatment-related sepsis and respiratory complications (Table I). The small numbers in the study pose a challenge to

drawing solid toxicity conclusions but remains in line with the reported literature. In light of the available literature evidence for toxicity differences that favor CP over 5FU-based therapies, our work constitutes a proof-of-concept retrospective study that can help guide decision making regarding the choice of a pre-operative chemotherapy regimen that achieves similar efficacy with a better tolerability.

Currently, there is no standardized EC-specific comprehensive geriatric assessment tool that can be used prior to treatment initiation (22). One tool developed by Hurria *et al.*, has been evaluated by the Cancer and Aging Research Group (CARG) in a multicenter prospective study to develop a predictive model for chemotherapy toxicity (28, 29). The model identified the following risk factors for chemotherapy associated toxicity: age ≥ 72 years, gastrointestinal and genitourinary cancers, poly-chemotherapy, anemia, creatinine clearance, as well as geriatric variables such as hearing, number of falls, and functional status. A similar tool called the Pre-operative Assessment of Cancer in the Elderly (PACE) was studied by Audisio *et al.*, and includes a combination of traditional surgical risk assessment along with the comprehensive geriatric assessment (30). The American Society of Clinical Oncology Guideline for Geriatric Oncology currently recommends the use of geriatric assessment in patients >65 years to identify vulnerabilities not routinely captured in oncology assessments and obtain estimates of chemotherapy toxicity risk, with either the CARG (Cancer and Aging Research Group) or CRASH (Chemotherapy Risk Assessment Scale for High-Age Patients) (31). Until geriatric EC-specific tools are validated, our study provides evidence that, along with routine geriatric assessment, it could help guide oncologists and patients in a shared decision-making process that takes into account the peculiar vulnerability of the geriatric population, without compromising efficacy and chance of cure.

While we provide a proof of concept for selection of pre-operative CRT in the treatment of older adult patients with locally advanced EC, our results should be interpreted with caution given the retrospective nature of the study. Patients were not randomized which could lead to differences in patient characteristics and treatment per treating oncologist between both treatment groups. Another limitation pertains to the single center setting of the study. Lastly, given the retrospective nature of the study, toxicity assessments based on the Common Terminology Criteria for Adverse Events (CTCAE) were not systematically reported, thus hindering inclusion of toxicity data in the study. Similarly, the study did not include a comprehensive geriatric assessment of patients using predictive toxicity tools. While the study was not powerful enough to conduct secondary multivariate analyses for OS and DFS (secondary outcomes), prior studies have shown that for patients with resectable gastric and EC who achieve pCR after neo-adjuvant chemotherapy,

pCR could be a surrogate marker of prolonged survival (OS and DFS) (32).

Our study findings justify a need for future, randomized prospective trials that focus on older adult patients with locally advanced EC, with implementation of a validated Comprehensive Geriatric Assessment (CGA). Such studies are warranted to validate our findings, and to further expand investigation into the development and use of an EC-specific predictive toxicity model, as well as characterizing differences in long term, post-therapy quality of life in this patient population. From a therapeutic strategy perspective, future studies ought to further focus on combinational approaches that can achieve similar efficacy with better tolerability: Immune checkpoint inhibitors are known to be more tolerable than chemotherapy, and their combination with traditional CRT needs to be explored as a strategy that achieves chemotherapy treatment de-intensification in this older adult population. This becomes more relevant in light of the many ongoing studies, and the recent approval of Nivolumab in adjuvant treatment of EC (33).

In conclusion, the present study suggests that pCR rates, OS and DFS are similar in both treatment regimens. CP could be used as an equally effective, less toxic alternative to P5F in older adult patients undergoing pre-operative CRT for locally advanced EC. We report on the first study to compare efficacy of different types of pre-operative chemotherapy regimens in a geriatric population of patients with EC, 70 years or above.

Conflicts of Interest

AS reports research grant (to institution) from Merck and consulting fees from Merck. WS reports research grant (to institution) from Merck. The remaining Authors declare no competing interests.

Authors' Contributions

MA and AS developed the study design. MA collected, and interpreted data, and performed statistical analysis. KC performed statistical analysis, made substantial contributions to data interpretation, discussion and drafted the manuscript. AA contributed to drafting of the initial manuscript. AB, RP, JB, and WS contributed to the discussion of the results and review of the manuscript. AS made substantial contributions to conception and design of the study, analyzed, and interpreted data and revised the manuscript. All Authors read and approved the final manuscript.

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