Pre-operative carboplatin and paclitaxel-based chemoradiotherapy for esophageal/gastroesophageal carcinoma: Results of a modified CROSS regimen within a multidisciplinary upper foregut malignancy program at a NCI-designated cancer center

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Purpose

Trimodality therapy for potentially resectable esophageal and gastroesophageal junction (GEJ) cancers utilizing pre-operative radiotherapy with concurrent carboplatin and paclitaxel-based chemotherapy is being increasingly utilized secondary to the favorable results of the multi-institutional phase III CROSS trial. However, there is a paucity of domestic reports of this chemotherapy regimen as a component of chemoradiotherapy (CRT) in North America.

The specific aim of this present analysis was to report on our clinical experience using a modified CROSS regimen with dose-escalated radiotherapy.

Methods

Patients with locoregionally advanced (cT2 - cT4 or node positive) esophageal/GEJ adenocarcinoma or squamous cell carcinoma receiving trimodality therapy with pre-operative carboplatin and paclitaxel-based CRT and subsequent esophagectomy were identified from an institutional database. All patients had pre- and post-CRT PET/CT scans. Patient, imaging, treatment and tumor response characteristics were analyzed.

Results

Twenty-seven patients were analyzed. Median follow-up interval was 9.8 months (23 days - 2 years). Median age was 64 years (44 - 76 years) and 85% were male. All but one tumor had adenocarcinoma histology. A mean of 6 weeks of pre-operative carboplatin/paclitaxel was administered. The median radiation dose was 50.4 Gy (19 patients received 50.4 Gy, 3 received 41.4 Gy, 2 received 50 Gy, 2 received 54 Gy, and 1 received 45 Gy). Pathologic complete response (pCR) was achieved in 26% of patients, with all of these patients receiving 50.4 Gy. Median post-op hospital stay was 10 days (8 - 28 days). Three patients died prior to hospital discharge, due in part to acute respiratory distress syndrome (ARDS) and all three patients received 50 - 50.4 Gy. When excluding and including early post-operative deaths, median survival was 24.0 and 17.7 months, respectively.

Results

Table 1. Demographics and Tumor Characteristics

	N=27
Gender	23 (85%) male
Median Age	64 (44-76) yo
Pre-treatment median weight	194 (117-266) lb
ECOG Performance Status	
0	2 (7%)
1	25 (93%)
Clinical Stage	
IB	2 (8%)
IIA/B	10 (37%)
IIIA/B/C	15 (55%)
cT Stage	
T2	5 (19%)
T3	20 (74%)
T4	2 (7%)
cN Stage	
N0	11 (41%)
N1	15 (55%)
N2	1 (4%)
Tumor histology	
Adenocarcinoma	26 (96%)
Squamous Cell Carcinoma	1 (4%)
Tumor Grade	
Well Differentiated	0 (0%)
Moderate-Poorly Differentiated	27 (100%)
Histology Subtypes	
Signet-ring	7 (26%)
Mucin	0 (0%)
Tumor Location	
Distal Esophagus	7 (26%)
Gastro-Esophageal Junction	20 (74%)
Average Proximal Extent	35.9cm
Average Distal Extent	40.3cm
Average Length	4.26cm

ECOG, Eastern Cooperative Oncology Group; COPD, Chronic Obstructive Pulmonary Disease; OSA, Obstructive Sleep Apnea.

Table 2. Treatment and Clinical Parameters

Carboplatin/Paclitaxel	27 (100%)
Median Number of Weeks	6
Radiation Dose	
5040 cGy	20 (74%)
4140 cGy	3 (11%)
5400 cGy	1 (4%)
4500 cGy	1 (4%)
Unknown	2 (7%)
Radiation Dose per Fraction	
180 cGy	25 (93%)
200 cGy	2 (7%) †
Radiation Modality	
IMRT	17 (63%)
3D conformal	10 (37%)
Esophagectomy Procedure	
Open Ivor Lewis	1 (4%) *
Minimally-invasive Inversion transhiatal	1 (4%)
Minimally-invasive Three Field	25 (92%)
Elapsed Time (median days)	
Diagnosis** to end CRT	62.5 (46-91)
Diagnosis to Surgery	121 (100-272)
CRT to Surgery	59.5 (47-211)

† Received a total of 50 Gy.
* Synchronous colon cancer resected same day per open laparotomy.
** Diagnosis was defined by the date of endoscopic ultrasound.
IMRT, Intensity-Modulated Radiotherapy; CRT, Chemoradiotherapy.

Results

Table 3. Operative Parameters and Post-operative Pathological Response

pCR	7 (26%)
MRD	9 (33%)
GRD	11 (41%)
pN0	12 (45%)
pN1	8 (30%)
pN2	5 (19%)
pN3	2 (7%)
Mean LNs harvested	21.4
R0	24 (89%)
R1	3 (11%)
LVI	
No	23 (85%)
Indeterminate	1 (4%)
Yes	3 (11%)
maxSUV	
Avg maxSUV pre-tx	11.2 (3.42-35)
Avg maxSUV post-tx	4.84 (2.7-7.9)
Avg change	-7.04
Avg % change	-42.6%

pCR, Pathologic Complete Response; MRD, Minimal Residual Disease (defined as <2mm of residual disease); GRD, Gross Residual Disease (>2mm of residual disease); LN, Lymph Node; LVI, Lymphovascular Invasion; Avg, Average, maxSUV, Maximum Serial Uptake Value.

Table 4. Total Lung Radiation Doses for Early Post-operative Deaths

	Mean (Gy)	V20 (%)	V10 (%)	V5 (%)	VS5 (cc)
Patient 1	6.6	4.5	23	49	1906
Patient 2	16.6	30	57	80	472
Patient 3	13.9	18	60	73	637

Volume of the total lungs receiving 20 Gy (V20), 10 Gy (V10) and 5 Gy (V5). VS5, volume of total lungs spared from doses of greater than 5 Gy.

Conclusion / Discussion

Trimodality therapy utilizing concurrent weekly carboplatin/paclitaxel with dose-escalated radiation therapy resulted in pCR rates similar to the published CROSS trial results, but with a higher post-operative death rate. Although the sample size is small and further follow-up is necessary, dose-escalation may not be warranted secondary to a potentially increased risk of severe radiation-induced acute lung injury.