Clinical Outcome in Definitive Concurrent Chemoradiation With Weekly Paclitaxel and Carboplatin for Locally Advanced Esophageal and Junctional Cancer

Vanita Noronha,* Kumar Prabhash,* Amit Joshi,* Vijay Maruti Patil,* Sanjay Talole,† Dipti Nakti,*
Arvind Sahu,* Srushti Shah,‡ Sarbani Ghosh-Laskar,§ Prachi S. Patil,¶ Shaesta A. Mehta,¶
Nirmala Jambhekar,# Abhishek Mahajan,** and Nilendu Purandare††

*Department of Medical Oncology, Tata Memorial Hospital, Mumbai, India
†Department of Epidemiology and Biostatistics, Tata Memorial Hospital, Mumbai, India
‡Clinical Research Secretariat, Tata Memorial Hospital, Mumbai, India
§Department of Radiation Oncology, Tata Memorial Hospital, Mumbai, India
¶Department of Digestive Diseases and Clinical Nutrition, Tata Memorial Hospital, Mumbai, India
#Department of Pathology, Tata Memorial Hospital, Mumbai, India
**Department of Radiodiagnosis, Tata Memorial Hospital, Mumbai, India
††Department of Nuclear Medicine, Tata Memorial Hospital, Mumbai, India

There are little data on the efficacy and safety of taxane/platinum with definitive radiotherapy (RT) for esophageal/GEJ cancer. This article is a retrospective analysis of patients who received weekly paclitaxel 50 mg/m² and carboplatin AUC 2 with radical definitive RT for locally advanced esophageal/GEJ cancer. Between February 2011 and July 2014, 179 patients were included. The median age was 54 years. Ninety-two percent of patients had squamous histology. Mean RT dose was 58.7 Gy in 32 fractions over 53 days, with mean of six chemotherapy cycles. Fifty-six percent of patients developed ≥grade 3 acute toxicities, commonly febrile neutropenia (12%) and infection (11%); ≥grade 3 laboratory abnormalities included hyponatremia (38%), leukopenia (49%), neutropenia (27%), and anemia (16%). Twelve percent of patients developed ≥grade 3 chronic toxicity. Fatal toxicities included six during CRT, eight within 30 days of completing CRT, and three chronic. Radiologic response was 49% (CR 5.6%, PR 43%). Follow-up endoscopy showed remission in 53% and residual disease in 14%. At a median follow-up of 28 months, median PFS was 11 months (95% CI: 8–13.9), median OS was 19 months (95% CI: 15.4–22.6), and estimated 1-year, 2-year, and 3-year survivals were 70%, 47%, and 39%, respectively. Weekly paclitaxel–carboplatin concurrently with definitive RT is efficacious with manageable toxicity. [The trial was registered with the Clinical Trials Registry-India (CTRI), registration number: CTRI/2014/07/004776.]

Key words: Chemoradiation; Definitive chemoradiotherapy; Esophageal; Esophagogastric cancer; Paclitaxel; Radical

INTRODUCTION

A diagnosis of esophageal cancer usually presages a dismal prognosis, with a 5-year survival between 5% (1) and 17% (2) and a disappointingly low median survival following radical esophagectomy ranging from 11 months (3) to 2 years (4–7). Potentially curative surgery is possible for approximately 25% of patients (8). In the rest of the patients with nonmetastatic disease, radical concurrent chemoradiotherapy (CRT) is considered standard treatment. Definitive CRT for esophageal cancer has not changed much in the past 23 years since the landmark RTOG 8501 trial (9). Herskovic et al. reported in 1992 that cisplatin and 5-fluorouracil (5FU) added concurrently to radiation (RT) improved local control, decreased metastases, and prolonged survival. The updated outcome publication from this trial reported a median survival of 14.1 months for the CRT-treated patients (10). This regimen has become the standard of care, but because of toxicity and logistic difficulties, acceptance has been limited in our country. The recent CROSS trial used a novel regimen of weekly paclitaxel and carboplatin (pacli-carbo) concurrently with RT as presurgery induction therapy. This

multimodality approach led to an unprecedented median overall survival of over 4 years (7). Several oncologists have explored the use of this regimen in the definitive setting as well, without surgery (11–16). However, data for pacli-carbo-based definitive CRT are limited.

We report our experience with weekly pacli-carbo concurrently with RT in the radical curative setting in patients with locally advanced esophageal and gastro-esophageal junction (GEJ) carcinoma as definitive CRT.

MATERIALS AND METHODS

Since January 2011, we have maintained a prospective database in Microsoft Excel format in the medical oncology department for patients treated with curative intent concurrent CRT for esophageal and GEJ carcinoma. We present the retrospective analysis of patients in this database who have received chemotherapy (at least one cycle) at Tata Memorial Hospital, Mumbai (TMH). The project was approved by the institutional ethics committee (IEC) of TMH, and the need for obtaining informed consent was waived by the IEC. All patient records/information were anonymized and deidentified prior to analysis. The trial was registered with the Clinical Trials Registry-India (CTRI), registration No.: CTRI/2014/07/004776.

After initial evaluation and baseline blood investigations, upper endoscopy, histopathology, and staging, the patients were discussed in the multidisciplinary thoracic oncology disease management group tumor board. Patients in whom the disease was locally advanced and unresectable or who were medically unfit for major surgery were advised definitive concurrent CRT. Patients with borderline resectable disease or patients in whom the disease was clearly unresectable, but with additional features like airway infiltration, were planned for induction chemotherapy followed by reassessment. After completion of induction chemotherapy, if R0 resection was not thought possible, then definitive concurrent CRT was planned. Patients who underwent surgery, but were found to have unresectable disease intraoperatively (R2 resection), were also planned for definitive intent CRT.

Chemotherapy consisted of intravenous carboplatin, area under the curve 2 calculated by Calvert's formula and paclitaxel 50 mg/m^2 administered weekly, started as soon as possible after the start of RT and continued as long as RT continued. RT planning and dose were at the discretion of the treating radiation oncologist. For the purpose of analysis, patients who received ≥50 Gy and ≥5 chemotherapy cycles were considered to have received an adequate dose of CRT. Toxicity was graded as per the common terminology criteria for adverse events (CTCAE), v 4.0. Acute toxicity was defined as toxicity that occurred from day 1 to day 90 after the start of RT. Toxicity that occurred beyond 90 days of start of RT was classified as chronic. During CRT,

patients were evaluated, and blood investigations were obtained weekly. Patients were evaluated approximately 6–9 weeks after the completion of definitive CRT with a contrast-enhanced CT scan (CECT) of the thorax and upper endoscopy. Response to CRT was calculated based on the new response evaluation criteria in solid tumors (revised RECIST guidelines), v 1.1, specifically measuring the maximal transverse diameter of the esophageal lesion and considering it measurable if ≥1 cm. For the patients who received induction chemotherapy, the response to CRT was calculated using the preinduction chemotherapy scan as the baseline, as long as the sum of measurable disease had become progressively smaller or remained stable on serial scans, that is, from baseline to postinduction chemotherapy to post-CRT scan. Patients in whom the sum of measurable disease on the post-CRT scan increased and fulfilled the criteria for progressive disease (PD), compared to either the postinduction scan or to the baseline preinduction chemotherapy scan, were considered to have PD. Patients were followed with physical examination, blood tests, and chest X-ray every 2–4 months for the first 2 years and then approximately every 6 months following that. If late toxicity or recurrence was suspected, patients were discussed in the multidisciplinary thoracic oncology tumor board, and further management was decided. An attempt was made to contact all the patients to update the survival information. Survival information was updated as of June 30, 2015.

Statistical package for the social sciences (SPSS v17) was used for analysis. Demographics, chemotherapy details, and toxicity are presented as absolute numbers and percentages. Survival was calculated using the Kaplan–Meier method. Progression-free survival (PFS) was calculated as the time between the date of diagnosis to the date of disease progression (persistent disease on endoscopy or radiologic or clinical progression) or death from any cause. Overall survival (OS) was calculated as the time between the date of diagnosis to the date of death from any cause. Patients who had not visited the hospital for >6 months and who could not be contacted telephonically were considered lost to follow-up. The patients who were lost to follow-up were coded as progressed and dead on the date of their last follow-up for the purpose of survival analysis. We performed univariate analysis with log rank test to assess whether overall survival was affected by performance status (ECOG 0,1 vs. ≥2), gender, tumor length (<5 cm vs. ≥5 cm), site of origin in the esophagus (cervical/upper third thoracic vs. mid-third esophagus vs. lower third thoracic/GEJ), histopathology, baseline hemoglobin (<10 mg/dl vs. ≥10 mg/dl), whether induction chemotherapy was administered or not, and whether or not the patient received an adequate dose of CRT. Multivariate analysis was then performed using Cox regression analysis.

Table 1. Demographic Details and Patient-Related Details

Characteristic	Result ($n = 179$)
Age (years)	
Median	54
Range	23–87
Gender	
Male	107
Female	72
Duration of presenting symptoms (months)	
Median	2
Range	0–60
Presenting symptoms	
Dysphagia	172 (96%)
Weight loss	94 (52.5%)
Chest/back pain	39 (21.8%)
Cough	29 (16.2%)
Vomiting	18 (10%)
Hoarseness	17 (9.5%)
Throat pain	16 (8.9%)
Weakness/fatigue	8 (4.5%)
Neck swelling	7 (3.9%)
Location of tumor in the esophagus	
Cervical	36 (20.1%)
Upper third thoracic	62 (34.6%)
Mid-third thoracic	55 (30.7%)
Lower third thoracic/GEJ	26 (14.5%)
Tumor length (cm)	
Median	6.5 cm
Range	0.1–17.5 cm
T stage	
T0	4 (2.2%)
T1	1 (0.6%)
T2	3 (1.7%)
T3	76 (42.5%)
T4	95 (53.1%)
N stage	
N0	46 (25.7%)
N1	52 (29.1%)
N2	61 (34.1%)
N3	20 (11.2%)
TNM stage	
Stage I	1 (0.6%)
Stage II	27 (15.1%)
Stage III	148 (82.7%)
Stage IV	3 (1.7%)
Comorbidities	
Hypertension	29 (16.2%)
Diabetes	19 (10.6%)
Chronic obstructive pulmonary disease	16 (8.9%)
Tuberculosis	10 (5.6%)
Cardiac disease	9 (5%)
Thyroid disorder	5 (2.8%)
Hepatic disorder (five chronic hepatitis C, two cirrhosis)	7 (3.9%)
Renal dysfunction	3 (1.7%)
Neurologic disorder	2 (1.1%)

(continued)

Table 1. (Continued)

Characteristic	Result ($n = 179$)
History of cancer in the past	
Past history of esophageal cancer	7 (3.9%)
Head and neck cancer	5 (2.8%)
Breast cancer	2 (1.1%)
Lung cancer	1 (0.6%)
History of substance abuse	
No tobacco use	60 (33.5%)
Only smoking	35 (19.6%)
Only smokeless tobacco	70 (39.1%)
Both smoking and smokeless tobacco	24 (13.4%)
Alcohol	41 (22.9%)
Histopathology	
Squamous cell carcinoma	165 (92.2%)
Adenocarcinoma	14 (7.8%)
Baseline weight (kg)	
Median	47 kg
Range	26–107 kg
Baseline laboratory parameters (median)	
Hemoglobin	12.5 g/dl
White blood cell count	$8.13 \times 10e9/L$
Platelet count	$282 \times 10e9/L$
Albumin	4 g/dl
Creatinine	0.9 mg/dl
Lactate dehydrogenase	166 U/L

RESULTS

Between February 2011 and July 2014, 179 patients received weekly pacli-carbo chemotherapy at TMH Mumbai, India, concurrently with definitive RT for locally advanced esophageal or GEJ cancer. Baseline details are provided in Table 1. Prior to mid-2012, staging consisted of CECT and upper endoscopy (esophagogastroduodenoscopy); fiber-optic bronchoscopy was done for patients with disease in the supracarinal esophagus. After approximately June 2012, PET/CECT was adopted at our center as a standard baseline staging modality for esophageal cancer. Thus, prior to June 2012, 19 out of 86 (22%) patients underwent PET/CECT as staging, and from June 2012 onward, 83 out of 93 (89.3%) patients had baseline staging PET/CECT scans. Endoscopic ultrasound (EUS) was not widely performed and was done in only eight patients. All patients were evaluated by the thoracic oncology multidisciplinary disease management group, which included experienced thoracic oncologic surgeons, radiation oncologists, and medical oncologists, in addition to radiologists and other team members like pulmonologists. The decision regarding resectability was made by the entire group, and only patients who were not considered resectable were planned for concurrent CRT. One patient with clinical T2N0 lower third esophageal squamous carcinoma was initially planned for surgery, but due to comorbidities (alcoholic liver disease, portal hypertension, esophageal variceal bleed, acute pancreatitis, and pancreatic pseudo cyst), which rendered him high risk for surgery, he received definitive CRT. The details of treatment and CRT are provided in Table 2.

Over one third of patients (75 patients, 41.9%) received induction chemotherapy. Sixty-nine patients received the same agents (pacli-carbo) as an induction chemotherapy regimen. Only the patients who had nonprogressive disease after induction pacli-carbo were planned for concurrent CRT with the same agents. Of the total of 69 patients who received pacli-carbo neoadjuvantly, 50 (72.5%) had a partial remission, and 18 (26.1%) had stable disease at response assessment after induction chemotherapy; one patient (1.5%) did not undergo repeat radiologic assessment but clinically had a good response and proceeded directly to CRT.

Compared to pre-CRT level of dysphagia (graded using CTCAE), the dysphagia while on CRT was reported as resolved in 22 patients (12%), improved in 77 (43%), unchanged in 46 (26%), and worsened in 25 (14%). Five patients had no baseline dysphagia, and in four patients, the change in dysphagia while on CRT was not documented.

The details of toxicity of CRT (both acute and chronic) are given in Table 3. One hundred fifty-nine patients (89%) had at least one ≥grade 3 acute toxicity from CRT (excluding lymphocytopenia). This consisted of ≥grade 3 laboratory abnormalities like asymptomatic leukoneutropenia or hyponatremia in 58 patients, while 101 patients

Table 2. Therapy Administered and CRT Details

Therapy	Number (Percentage)
Treatment delivered	
CRT alone	103 (57.5%)
Induction chemotherapy→definitive CRT	66 (36.9%)
Induction chemotherapy→surgery (R2 resection)→definitive CRT	9 (5%)
Surgery (R2 resection)→definitive CRT	1 (0.6%)
Induction chemotherapy details	
Given	
No	104 (58.1%)
Yes	75 (41.9%)
Regimen ($n=75$)	
Epirubicin+platinum+5-fluorouracil (ECF)	4 (adenocarcinoma histology)
Paclitaxel/cisplatin 3 weekly	27
Paclitaxel/carboplatin 3 weekly	39
Paclitaxel/carboplatin weekly	3
Others	2
Objective response to induction chemotherapy ($n=75$)	
Complete remission (CR)	0
Partial remission (PR)	56 (74.6%)
Stable disease (SD)	18 (24%)
Progressive disease (PD)	0
Not assessed	1 (1.3%)
Surgery done?	
Yes, but unresectable intraoperatively (R2)	10 (5.6%)
No surgery done	169 (94.4%)
Indication for definitive CRT	
Unresectable, or unlikely to be R0 resection (T4 primary/supracarinal disease/unresectable nodes, etc.)	136 (75.9%)
Extensive lymphadenopathy	6 (3.4%)
Medically unfit for surgery	17 (9.5%)
Surgery attempted, R2 resection	10 (5.6%)
Patient refused surgery	3 (1.7%)
Recurrent disease following surgery	6 (3.4%)
Recurrent disease following CRT	1 (0.6%)
Reasons for being medically unfit for surgery ($n=17$)	
Poor general condition	11 (6.1%)
Cachexia	2 (1.1%)
Morbid obesity	1 (0.6%)
COPD	1 (0.6%)
Heart disease	1 (0.6%)
Cirrhosis, portal hypertension, and chronic pancreatitis	1 (0.6%)
Reasons for being unresectable ($n=153$)	
T4b primary	84 (46.9%)
Bulky T4a primary	4 (2.2%)
Supracranial primary	45 (25.1%)
Supraclavicular lymph node involvement	5 (2.8%)
Recurrence following surgery	6 (3.4%)
Unresectable nodal disease	8 (4.5%)
Recurrent disease following RT	1 (0.6%)
Radiotherapy dose	
Median	58.74 Gy
Range	14.4–66 Gy
Radiotherapy fractions	
Mean	32
Range	8–35

(continued)

Table 2. (Continued)

Therapy	Number (Percentage)
Duration of CRT (days)	
Mean	53
Range	8–82
Number of chemotherapy cycles	
Mean	6
Range	1–8
Chemotherapy dose reduction	14 (7.8%)
Secondary growth factors	97 (54.2%)
Number of patients who received adequate dose?	
Chemotherapy	139 (77.7%)
Radiation	157 (87.7%)
CRT	131 (73.2%)

(56%) had a clinically significant ≥grade 3 toxicity. One hundred sixty-five patients were alive beyond 90 days of the start of CRT. One hundred eight (60.3%) patients had some form of chronic toxicity (any grade), 22 patients (12.3%) had ≥grade 3 chronic toxicities.

The level of dysphagia at the time of response assessment, that is, 6–9 weeks after completion of CRT, was complete resolution in 59 patients (33%), improvement in 42 (24%) compared to baseline and during CRT, stable in 19 (11%), and worsening in 9 (5%); dysphagia was not assessed in 47 patients (26%) after the completion of CRT. One hundred twenty-nine patients underwent restaging scans to assess the response to CRT; 9 patients did not have measurable disease by RECIST; the objective response rate (ORR), that is, CR+PR was 49%. Response evaluation and outcome data are presented in Table 4.

Progression following CRT occurred early. There were 128 events for PFS (either relapses, deaths, or loss to follow-up) of which 93 had occurred by 12 months, 116 had occurred by 24 months, and 125 occurred by 36 months. At a median follow-up of 28 months in surviving patients, the estimated median PFS was 11 months (95% CI: 8–13.9), and the estimated median OS was 19 months (95% CI: 15.4–22.6) (Fig. 1). The estimated 1-year, 2-year, and 3-year survivals were 70%, 47%, and 39%, respectively. On univariate analysis (Table 5), the factors that significantly correlated with overall survival were adequacy of dose of CRT (Fig. 2), histopathology, and site of origin in the esophagus. On multivariate analysis, the only factor that significantly correlated with overall survival was adequacy of the dose of CRT (Table 6).

DISCUSSION

To the best of our knowledge, our manuscript provides details on the largest group of patients with esophageal and GEJ cancer with predominantly squamous cell histology treated with weekly pacli-carbo concurrently with RT as definitive therapy. Thus far, most of the data for definitive CRT in esophagogastric cancer have been for cisplatin/5FU with RT. This combination has been studied in just under 500 patients distributed over three randomized trials: RTOG 8501 (9), INT 0123 (17), and FFCD 9102 (18). Based on these data, cisplatin/5FU-based CRT became the international standard of care for esophageal cancer. The National Comprehensive Cancer Network (NCCN) guidelines list 5FU-based regimens with a category 1 recommendation followed by pacli-carbo (category 2A) as the recommended concurrent chemotherapy regimens for definitive CRT, recognizing the role of taxane-based regimens in this setting (19).

Cisplatin and 5FU concurrently with RT are toxic and difficult to administer, especially in resource-constrained setups. Taxanes are radiosensitizers (20) and are efficacious against esophageal carcinoma (21); hence, the combination with RT likely produces a potent antineoplastic effect in esophageal cancer. In spite of the lack of level 1 evidence supporting the use of pacli-carbo with definitive CRT for esophagogastric cancer, several centers have adopted this regimen as standard, based on the preliminary reports of efficacy in the induction setting (11–16). We too report that pacli-carbo in combination with radical RT is an efficacious regimen with an objective response rate of 48.6% (CR 5.6%, PR 43%), estimated median PFS of 11 months (95% CI: 8–13.9), estimated median OS of 19 months (95% CI: 15.4–22.6), and estimated 1-year, 2-year, and 3-year survivals of 70%, 47%, and 39%, respectively. This regimen has so far been published by five groups of authors, some only in the abstract form. Meerten et al. have reported their phase II trial in abstract form on 52 patients with unresectable esophageal cancer. They had very similar outcomes to ours, with a median disease-free survival of 9 months, median overall survival of 17 months, and 1-, 2-, and 3-year overall survivals of 64%, 32%, and 16%, respectively (11). Two small studies

Table 3. Toxicity of CRT

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acute toxicity (n=179)					
Skin	31 (17.3%)	60 (33.5%)	14 (7.8%)	2 (1.1%)	0
Dysphagia	29 (16.2%)	57 (31.8%)	18 (10.1%)	2 (1.1%)	0
Throat pain	40 (22.3%)	65 (36.3%)	18 (10.1%)	2 (1.1%)	0
Fatigue	39 (21.8%)	63 (35.2%)	10 (5.6%)	0	0
Vomiting	36 (20.1%)	28 (15.6%)	11 (6.1%)	4 (2.2%)	0
Mucositis	38 (21.2%)	63 (35.2%)	5 (2.8%)	1 (0.6%)	0
Diarrhea	15 (8.4%)	16 (8.9%)	6 (3.4%)	2 (1.1%)	0
Weight loss	39 (21.8%)	48 (26.8%)	2 (1.1%)	0	0
Neuropathy	38 (21.2%)	13 (7.3%)	0	0	0
Leukopenia	9 (5%)	48 (26.8%)	74 (41.3%)	14 (7.8%)	0
Anemia	46 (25.7%)	82 (45.8%)	29 (16.2%)	0	0
Thrombocytopenia	80 (44.7%)	12 (6.7%)	1 (0.6%)	2 (1.1%)	0
Lymphocytopenia	0	6 (3.4%)	55 (30.7%)	118 (65.9%)	0
Neutropenia	27 (15.1%)	51 (28.5%)	38 (21.2%)	10 (5.6%)	0
Fever	28 (15.6%)	3 (1.7%)	0	0	0
Infection	0	32 (17.9%)	17 (9.5%)	2 (1.1%)	2 (1.1%)
Febrile neutropenia (FN)	0	0	15 (8.4%)	6 (3.4%)	2 (1.1%)
Increased liver function tests	48 (26.8%)	6 (3.4%)	2 (1.1%)	0	0
Increased creatinine	12 (6.7%)	1 (0.6%)	0	0	0
Hypokalemia	45 (25.1%)	2 (1.1%)	10 (5.6%)	0	0
Hyperkalemia	20 (11.2%)	4 (2.2%)	1 (1.1%)	0	0
Hyponatremia	67 (37.4%)	0	64 (35.8%)	4 (2.2%)	0
Stridor	0	0	1 (0.6%)	0	0
Acute coronary syndrome	0	0	0	1 (0.6%)	0
Upper GI hemorrhage	0	3 (1.7%)	1 (0.6%)	0	1 (0.6%)
Allergic reaction	1 (0.6%)	2 (1.1%)	0	0	0
Thromboembolic event	0	1 (0.6%)	0	0	0
Acute trachea–esophageal fistula (TEF)	0	0	2 (1.1%)	0	1 (0.6%)
Reasons for hospitalization [n=47 (26.3%)]					
Febrile neutropenia (FN): 10; pneumonia: 15; diarrhea: 5; stridor: 2; mucositis: 4; weakness: 1; sepsis: 2; vomiting: 3; acute myocardial infarction: 1; hematemesis: 1; TEF: 2; chicken pox: 1					
Acute fatal toxicities [n=14 (7.8%)]					
FN: 2; pneumonia: 1; sepsis: 1; tracheo-esophageal fistula (TEF): 1; hematemesis: 1; death at home of unknown cause within 30 days of completion of CRT: 8					
Chronic toxicity					
Patients with no chronic toxicity: 32 (17.9%)					
Patients not assessed for chronic toxicity: 25 (13.9%)					
Patients with any chronic toxicity: 108 (60.3)					
Patients with grade 3/4 chronic toxicity: 22 (12.3)					
Esophageal stenosis	3 (1.7%)	42 (23.5%)	1 (0.6%)	0	0
Pulmonary fibrosis	40 (22.3%)	30 (16.8%)	1 (0.6%)	0	0
Pleural effusion	8 (4.5%)	3 (1.7%)	2 (1.1%)	0	2 (1.1%)
Pericardial effusion	0	11 (6.1%)	1 (0.6%)	0	0
TEF	0	1 (0.6%)	1 (0.6%)	1 (0.6%)	1 (0.6%)
Esophagopulmonary fistula	0	0	3 (1.7%)	1 (0.6%)	0
Chest pain	1 (0.6%)	1 (0.6%)	1 (0.6%)	0	0
Pulmonary tuberculosis	0	3 (1.7%)	0	0	1 (0.6%)
Chronic stridor	0	1 (0.6%)	3 (1.7%)	1 (0.6%)	0
Fungal infection	0	4 (2.2%)	0	0	1 (0.6%)
Pneumonia	0	1 (0.6%)	2 (1.1%)	1 (0.6%)	1 (0.6%)
Xerostomia	3 (1.7%)	0	0	0	0
Coronary artery disease	0	1 (0.6%)	0	0	0

Table 3. (Continued)

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypothyroidism	1 (0.6%)	4 (2.2%)	0	0	0
Peripheral neuropathy	1 (0.6%)	1 (0.6%)	0	0	0
Chronic fatal toxicities [$n=6$ (3.4%)]					
Pleural effusion: 2; TEF: 1; pulmonary tuberculosis: 1; fungal infection: 1; pneumonia: 1					

by Ruppert et al. (13) and Honing et al. (14) retrospectively compared pacli-carbo to cisplatin/irinotecan and to cisplatin/5FU, respectively, both in combination with definitive RT, and found that pacli-carbo was comparable to cisplatin/5FU and significantly better than cisplatin/irinotecan in terms of cancer-specific and overall survival. Most recently, Haj Mohammad et al. reported on the acute toxicity experienced by 127 patients with inoperable or unresectable carcinoma esophagus treated with this regimen. They reported a median OS of approximately 17 months (12). Our efficacy results are very similar to those reported in the above studies and compare favorably to the efficacy of the cisplatin/5FU-based regimens (1- and 2-year survivals were 50% and 38%, and the median survival was 14.1 months in the RTOG 8501 trial).

At our center and elsewhere, surgery is considered an important tool in the multimodality therapy for non-metastatic esophageal and GEJ cancer, and every effort is made to perform surgery (22). Thus, many of our patients treated with radical definitive CRT were relatively poor prognosis patients—either due to extensive disease, poor general condition, or comorbidities compared to those who underwent surgery. Ninety-six percent of our patients had ≥T3 primaries (T3: 43%, T4: 53%) compared to the RTOG trial in which only 8% had T3 primaries and none had T4 primaries; 82% of the RTOG trial patients had T2 disease, and 10% had T1 (9). None of the patients included in the CROSS trial had T4 disease either (7). Similarly, only 26% of our patients had N0 disease, while 74% had node-positive disease. Compare this to the patients in the RTOG trial: 78% had N0 disease, while 13% had N1 disease. In spite of the fact that we included patients with far more advanced disease compared to the patients included in the previously published CRT trials, we found that pacli-carbo with RT seemed to lead to promising outcomes.

CRT for esophageal cancer is toxic. In the RTOG trial, 66% of the patients treated with RT concurrently with cisplatin/5FU experienced severe, life-threatening, or fatal toxicity compared to 28% of the patients who received RT alone (9). We found that pacli-carbo with RT was also toxic. Fifty-six percent of our patients experienced a clinically significant ≥grade 3 toxicity. Twenty-six percent of patients required hospitalization for management

of complications, most commonly pneumonia and febrile neutropenia (FN). The common ≥grade 3 acute clinically significant toxicities were infectious, including FN in 12% and non-neutropenic infection in 11% patients. The common asymptomatic ≥grade 3 laboratory abnormalities included hyponatremia (38%), leukopenia (49%), neutropenia (27%), and anemia (16%). Since infectious complications were common, liberal use of growth factors, prophylactic antibiotics, and a low threshold for dose reduction may be considered while evaluating this regimen in the future in an attempt to reduce the rate of complications. The most common chronic toxicities (any grade) included pulmonary fibrosis (40%) and esophageal stenosis (26%). In spite of significant toxicity, compliance to therapy was good: over 73% of the patients received an adequate dose of CRT.

The regimen of weekly pacli-carbo with RT may be less toxic than cisplatin/5FU with RT, although a prospective head-to-head comparison has not been made. In a retrospective comparison between 55 patients who received pacli-carbo with RT and 47 patients who received cisplatin/5FU with RT, Honing et al. reported that the pacli-carbo-treated patients experienced significantly lower toxicities, both hematological and nonhematological and had better compliance to therapy (14). None of the patients included in our study were eligible for curative resection. In patients with less advanced disease or who are medically fit to undergo curative resection and who receive pacli-carbo with RT as induction therapy, toxicity is less. Of the patients in the CROSS trial, 7.6% developed ≥grade 3 hematologic toxicities, and 13% had ≥grade 3 nonhematologic toxicities with no increase in postoperative complications (7). This emphasizes the fact that the regimen of pacli-carbo with RT is relatively safe and that patient selection is important. Better tolerability in the induction setting was likely due to a combination of factors, including better general condition of the patients, less extensive disease, and lower RT dose.

Relapses occurred early following CRT: 73% of relapses occurred within the first year. The most common site of recurrence was locoregional. On post-CRT endoscopy, 15.6% of patients had persistent disease; 16% of patients recurred locoregionally, 7% failed distantly, and 7% had combined locoregional and distant failure. This pattern of failure was also seen in the RTOG trial, where the majority

Table 4. Outcome

| Variable	Result [Number (Percentage)]
Radiologic response	
CR	10 (5.6%)
PR	77 (43%)
SD	13 (7.3%)
PD	20 (11.2%)
No assessable by RECIST	9 (5%)
Did no undergo radiologic imaging post-CRT	50 (27.9%)
Endoscopic evaluation post-CRT	
No evidence of disease	95 (53%)
Radiation changes	56 (31.3%)
Benign stricture	39 (21.8%)
Residual disease	25 (13.9%)
Not done	59 (32.9%)
Relapses/deaths	
Relapses	74 (41.3%)
Deaths without obvious relapse	47 (26.3%)
Deaths	99 (55.3%)
Site of relapse ($n=74$)	
Persistence of disease on endoscopy	15
Local	15
Regional	6
Locoregional	8
Distant	13
Persistence of disease/locoregional+distant	13
Second primary (head and neck)	2
Unknown	2
Sites of distant metastases ($n=26$)	
Lung/pleura	12
Liver	2
Retroperitoneal nodes	2
Brain	2
Omentum/ascites	1
Pericardial effusion	1
Parotid	1
Multiple sites (retroperitoneal lymph nodes, liver, bones, plura, omentum)	3
Unknown	2
Therapy at relapse ($n=74$)	
Palliative chemotherapy	29
Re-irradiation	1
Re-CRT	2
Surgery	1
Palliative RT	1
Stenting	4
Best supportive care	35
Unknown	1
Response to therapy at relapse (repeat CRT and palliative chemo) ($n=32$)	
CR	0
PR	5
SD	8
PD	1
No assessed	18
Current status	
Alive with no evidence of disease	50 (27.9%)
Alive with disease relapse	18 (10%)
Dead	99 (55.3%)
Lost to follow-up	12 (6.7%)
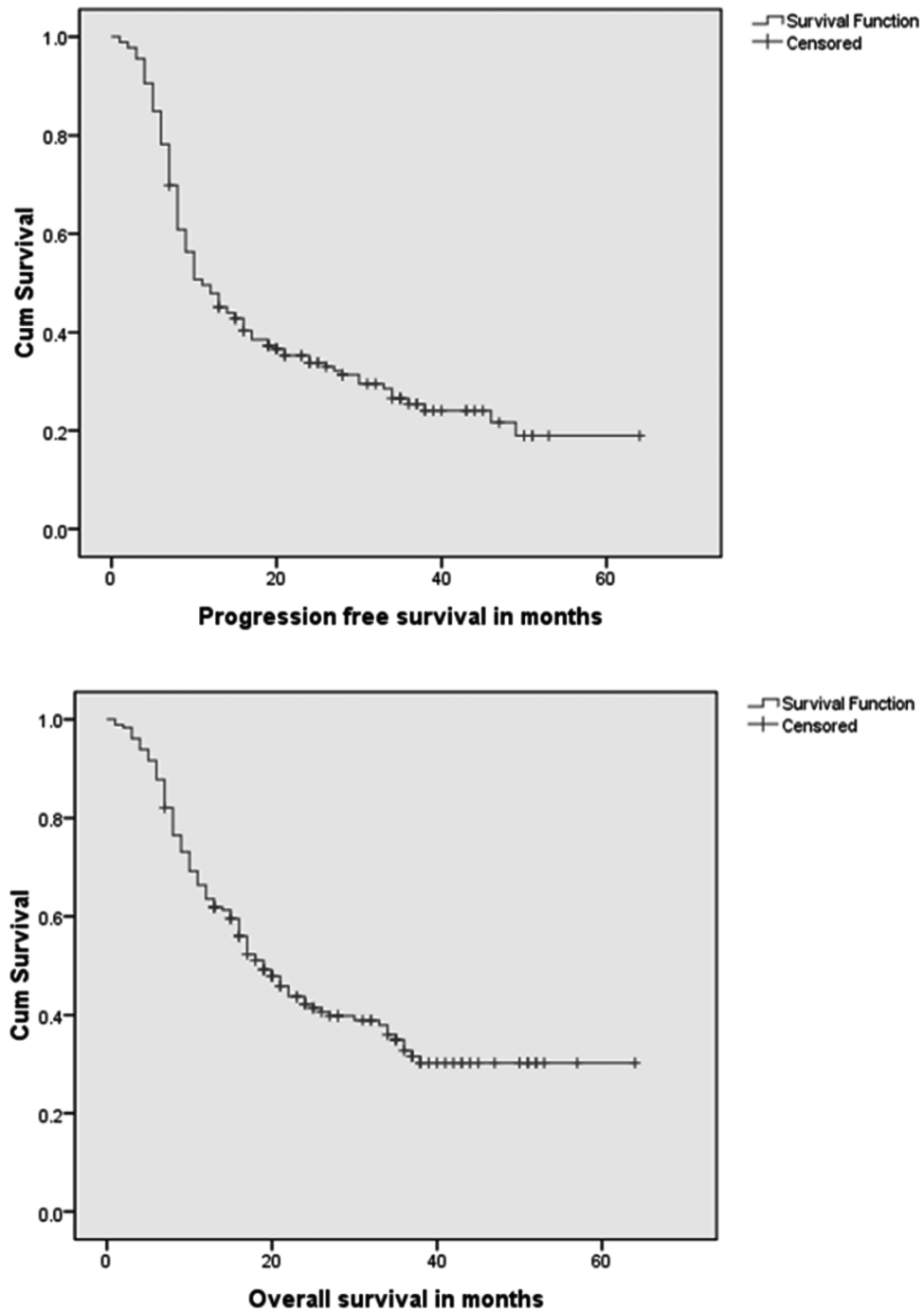
Figure 1. Survival curves. (Top) Progression-free survival in months, calculated as the time period between the date of diagnosis to the date of persistence or progression of disease, lost to follow-up, or death from any cause. One hundred twenty-eight events have occurred for PFS, including 74 relapses and 47 deaths without obvious relapses. The median PFS was 11 months, with an SE of 1.5 months and a 95% CI of 8 to 13.9 months. (Bottom) Overall survival in months from the date of diagnosis to the date of death from any cause or lost to follow-up. Ninety-nine patients have died, and 12 are lost to follow-up. The estimated 1-year, 2-year, and 3-year survivals were 70%, 47%, and 39%, respectively. The estimated median OS was 19 months with an SE of 1.9 months and 95% CI of 15.4 to 22.6 months.

Table 5. Univariate Analysis to Evaluate Which Factors Affect the Overall Survival (OS) of Patients Treated With Paclitaxel and Carboplatin-Based CRT for Locally Advanced Esophageal/GEJ Cancer

| Factor/Subtypes	Median OS in Months (95% CI)	p Value
Adequacy of CRT		p=0.000
Adequate (≥50 Gy and ≥5 chemo cycles)	24 (14.4–33.6)	
Inadequate	9 (6.7–11.3)	
Gender		p=0.101
Male (n=107)	22 (17.2–26.8)	
Female (n=72)	14 (10–17.9)	
Histopathology		p=0.032
Squamous cell carcinoma (n=165)	20 (14.5–25.5)	
Adenocarcinoma (n=14)	15 (7.7–22.3)	
Site of origin in the esophagus		p=0.013
Cervical and upper third thoracic (n=98)	24 (10.8–37.2)	
Mid-third thoracic (n=55)	17 (8.9–25.1)	
Lower third thoracic and GEJ (n=26)	16 (11.1–20.9)	
Baseline hemoglobin		p=0.309
≥10 mg/dl (n=155)	20 (14.4–17.6)	
<10 mg/dl (n=23)	16 (5.5–16.5)	
Performance status		p=0.074
ECOG PS 0, 1 (n=154)	21 (15–26.9)	
ECOG PS 2 (n=25)	16 (11.4–20.6)	
Tumor length		p=0.121
<5 cm (n=55)	27 (13.9–40)	
≥5 cm (n=124)	17 (13.4–20.6)	
Induction chemotherapy		p=0.311
Not given (n=104)	22 (8.6–35.3)	
Given (n=75)	17 (13.7–20.3)	
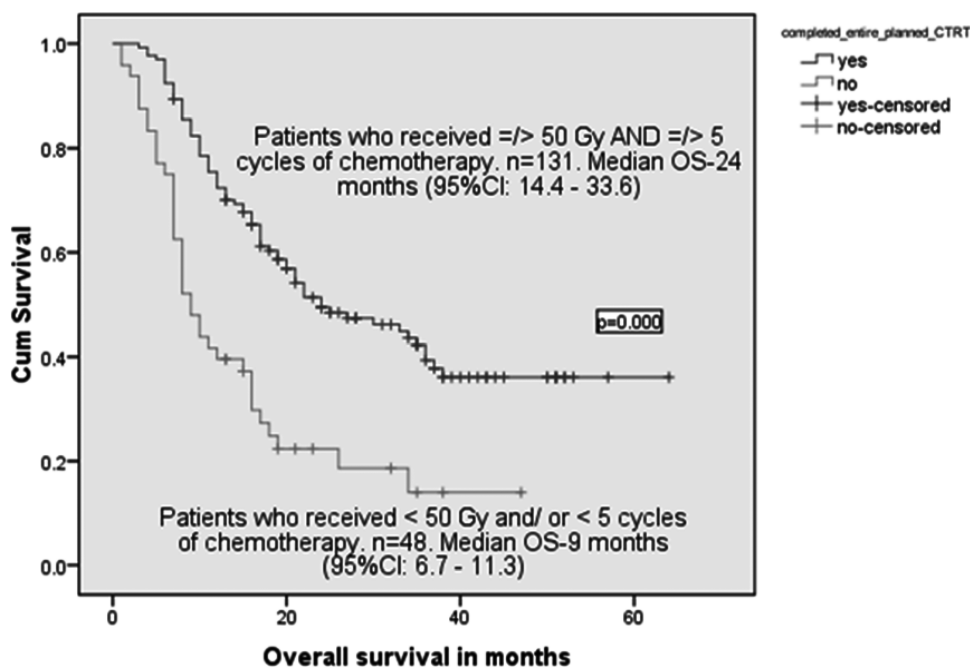
Figure 2. Overall survival of the patients who received adequate doses of both chemotherapy and radiotherapy compared to the patients who did not receive adequate dose of either chemotherapy or radiotherapy.

Table 6. Multivariate Analysis to Evaluate Which Factors Affect the Overall Survival of Patients With Locally Advanced Esophageal/GEJ Cancer Treated With Paclitaxel and Carboplatin-Based CRT

Factor	Hazard Ratio	95% CI for Hazard Ratio	p Value
Received adequate dose of CRT	0.424	0.283–0.637	0.000
Histopathology	1.064	0.509–2.224	0.868
Site of origin in esophagus	0.63	0.344–1.556	0.126
Performance status	0.788	0.475–1.306	0.355

of patients failed locoregionally: 25% of patients had persistent disease, 13% had locoregional, 8% distant, and 8% had both locoregional and distant failure (23). Attempts at improvement on the results of definitive CRT must target this locoregional failure. It appears that the use of taxane and platinum CRT may improve locoregional control, which needs to be confirmed in a randomized trial.

Our article has all the usual drawbacks of a retrospective analysis. There is the obvious selection bias, since the choice of therapy at our center is surgery, and only patients who are not fit for curative surgery or whose disease is very extensive are considered for definitive CRT. Since the majority of the patients in our study had squamous histology, our results and conclusions may not be readily applicable for patients with adenocarcinoma. However, we present data from the largest group of patients treated with pacli-carbo in combination with radical RT for locally advanced esophageal and GEJ cancer. All data were collected prospectively. All patients who received pacli-carbo at TMH as radical definitive CRT for esophageal and GEJ cancer were included in the analysis, without stringent inclusion and exclusion criteria. Hence, the results are applicable to the usual patients seen daily in the clinic and give useful information for day-to-day practice. Since all patients received chemotherapy at our institution and data were prospectively recorded, we have meticulously recorded toxicity details, both acute and chronic. We have also attempted to assess the response to definitive CRT with radiologic scans and through endoscopy. Few papers have reported on the radiologic response to CRT, since response assessment in CA esophagus is often difficult. Finally, our data are relatively mature with a median follow-up for surviving patients of 28 months. Most events had already occurred by 28 months since relapses occurred early, with 121 of the 128 events for relapse occurring by 28 months; the estimated median overall survival of our patients was 19 months.

CONCLUSIONS

Weekly pacli-carbo in combination with radical RT for locally advanced esophageal and GEJ cancer is efficacious with substantial but manageable toxicity. Infectious and hematologic toxicities are the most common. Appropriate patient selection and good supportive care are essential.

REFERENCES

1. D'Amico, T. A. Outcomes after surgery for esophageal cancer. Gastrointest. Cancer Res. 1:188–196; 2007.
2. Siegel, R.; Naishadham, D.; Jemal, A. Cancer statistics, 2013. CA Cancer J. Clin. 63:11–30; 2013.
3. Walsh, T. N.; Noonan, N.; Hollywood, D.; Kelly, A.; Keeling, N.; Hennessy, T. P. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N. Engl. J. Med. 335:462–467; 1996.
4. Kelsen, D. P.; Ginsberg, R.; Pajak, T. F.; Sheahan, D. G.; Gunderson, L.; Mortimer, J.; Estes, N.; Haller, D. G.; Ajani, J.; Kocha, W.; Minsky, B. D.; Roth, J. A. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N. Engl. J. Med. 339:1979–1984; 1998.
5. Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: A randomised controlled trial. Lancet 359:1727–1733; 2002.
6. Hulscher, J. B.; van Sandick, J. W.; de Boer, A. G.; Wijnhoven, B. P.; Tijssen, J. G.; Fockens, P.; Stalmeier, P. F.; ten Kate, F. J.; van Dekken, H.; Obertop, H.; Tilanus, H. W.; van Lanschot, J. J. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N. Engl. J. Med. 347:1662–1669; 2002.
7. Van Hagen, P.; Hulshof, M. C.; van Lanschot, J. J.; Steyerberg, E. W.; van Berge Henegouwen, M. I.; Wijnhoven, B. P.; Richel, D. J.; Nieuwenhuijzen, G. A.; Hospers, G. A.; Bonenkamp, J. J.; Cuesta, M. A.; Blaisse, R. J.; Busch, O. R.; ten Kate, F. J.; Creemers, G. J.; Punt, C. J.; Plukker, J. T.; Verheul, H. M.; SpillenaarBilgen, E. J.; van Dekken, H.; van der Sangen, M. J.; Rozema, T.; Biermann, K.; Beukema, J. C.; Piet, A. H.; van Rij, C. M.; Reinders, J. G.; Tilanus, H. W.; van der Gaast, A.; CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. N. Engl. J. Med. 366:2074–2084; 2012.
8. Health and Social Care Information Centre. National oesophago-gastric cancer audit 2013. Retrieved from http://www.hscic.gov.uk/catalogue/PUB11093/clin-audi-supp-prog-oeso-gast-2013-rep.pdf
9. Herskovic, A.; Martz, K.; al-Sarraf, M.; Leichman, L.; Brindle, J.; Vaitkevicius, V.; Cooper, J.; Byhardt, R.; Davis, L.; Emami, B. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N. Engl. J. Med. 326:1593–1598; 1992.
10. al-Sarraf, M.; Martz, K.; Herskovic, A.; Leichman, L.; Brindle, J. S.; Vaitkevicius, V. K.; Cooper, J.; Byhardt, R.; Davis, L.; Emami, B. Progress report of combined chemoradiotherapy

versus radiotherapy alone in patients with esophageal cancer: An intergroup study. J. Clin. Oncol. 15:277–284; 1997.

11. Meerten, E. V.; van Rij, M. E.; Tesselaar, K.; Neelis, K.; Richel, D.; Hulshof, M.; Gaast A. V. Definitive concurrent chemoradiation (CRT) with weekly paclitaxel and carboplatin for patients (pts) with irresectable esophageal cancer: A phase II study. J. Clin. Oncol. 28(Suppl; abstract e14508); 2010.

12. Haj Mohammad, N.; Hulshof, M. C.; Bergman, J. J.; Geijsen, D.; Wilmink, J. W.; van Berge Henegouwen, M. I.; van Laarhoven, H. W. Acute toxicity of definitive chemoradiation in patients with inoperable or irresectable esophageal carcinoma. BMC Cancer 14:56; 2014.

13. Ruppert, B. N.; Watkins, J. M.; Shirai, K.; Wahlquist, A. E.; Garrett-Mayer, E.; Aguero, E. G.; Sherman, C. A.; Reed, C. E.; Sharma, A. K. Cisplatin/Irinotecan versus carboplatin/paclitaxel as definitive chemoradiotherapy for locoregionally advanced esophageal cancer. Am. J. Clin. Oncol. 33:346–352; 2010.

14. Honing, J.; Smit, J. K.; Muijs, C. T.; Burgerhof, J. G.; de Groot, J. W.; Paardekooper, G.; Muller, K.; Woutersen, D.; Legdeur, M. J.; Fiets, W. E.; Slot, A.; Beukema, J. C.; Plukker, J. T.; Hospers, G. A. A comparison of carboplatin and paclitaxel with cisplatinum and 5-fluorouracil in definitive chemoradiation inesophageal cancer patients. Ann. Oncol. 25:638–643; 2014.

15. Battley, J. E.; O'Keeffe, M.; Mulvihill, E.; O'Reilly, S.; Bennett, M. W.; Suilleabhain, O. C.; Flavin, A.; Murphy, T. J.; Power, D. G. Chemoradiotherapy for locally advanced esophageal cancer using carboplatin, paclitaxel. J. Clin. Oncol. 30(Suppl; abstract e14666); 2012.

16. Doherty, M.; Cowzer, D.; Kelly, C. M.; Battley, J. E.; Leonard, G.; Power, D. G. Combination therapy with radiation and weekly paclitaxel/carboplatin as definitive treatment for locally advanced esophageal cancer. J. Clin. Oncol. 31(Suppl 4; abstract 133); 2013.

17. Minsky, B. D.; Pajak, T. F.; Ginsberg, R. J.; Pisansky, T. M.; Martenson, J.; Komaki, R.; Okawara, G.; Rosenthal, S. A.; Kelsen, D. P. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: High-dose versus standard-dose radiation therapy. J. Clin. Oncol. 20:1167–1174; 2002.

18. Bedenne, L.; Michel, P.; Bouché, O.; Milan, C.; Mariette, C.; Conroy, T.; Pezet, D.; Roullet, B.; Seitz, J. F.; Herr, J. P.; Paillot, B.; Arveux, P.; Bonnetain, F.; Binquet, C. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J. Clin. Oncol. 25:1160–1168; 2007.

19. National Comprehensive Cancer Network guidelines for treatment of cancer by site: Esophageal and esophagogastric junction cancer. Retrieved from http://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf

20. Golden, E. B.; Formenti, S. C.; Schiff, P. B. Taxanes as radiosensitizers. Anticancer Drugs 25:502–511; 2014.

21. Noronha, V.; Patil, V.; Bhosale, B.; Joshi, A.; Purandare, N.; Prabhash, K. Metronomic weekly paclitaxel in advanced unresectable esophageal cancer. Indian J. Cancer 50:128–134; 2013.

22. D'Journo, X. B.; Thomas, P. A. Current management of esophageal cancer. J. Thorac. Dis. 6:S253–264; 2014.

23. Cooper, J. S.; Guo, M. D.; Herskovic, A.; Macdonald, J. S.; Martenson, J. A. Jr.; Al-Sarraf, M.; Byhardt, R.; Russell, A. H.; Beitler, J. J.; Spencer, S.; Asbell, S. O.; Graham, M. V.; Leichman, L. L. Chemoradiotherapy of locally advanced esophageal cancer: Long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA 281:1623–1627; 1999.