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TRIMODALITY THERAPY FOR STAGE II-III CARCINOMA OF THE ESOPHAGUS: A DOSE-RANGING STUDY OF CONCURRENT CAPECITABINE, DOCETAXEL, AND THORACIC RADIOTHERAPY

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Abstract

PURPOSE—This dose escalation study was performed to determine the recommended phase II dose of oral capecitabine to be delivered concurrently with thoracic radiation therapy and weekly docetaxel in patients with locally advanced esophageal carcinoma.

METHODS—Patients with operable stage II or III esophageal carcinoma were staged by endoscopic ultrasonography (EUS) and CT. Two cycles of docetaxel (80 mg/m²) and carboplatin (target area under the concentration curve 6 mg*min/mL) were delivered over 6 weeks. This was followed by concurrent weekly docetaxel (15 mg/m²), thoracic radiotherapy (50.4 Gy in 28 fractions), and increasing doses of capecitabine (500 mg to 3500 mg) given prior to each fraction of radiotherapy. Following re-staging, responding patients continued to esophagectomy within 4–8 weeks of completing chemoradiotherapy.

RESULTS—Forty-four patients (pts) were enrolled and 40 were evaluable for the dose-ranging component of concurrent chemoradiotherapy. EUS stages at enrollment were T3N1 (29 pts), T3N0 (4 pts), T2N1 (6 pts), and T4N0 (1 pts). The maximum tolerated dose of capecitabine was 3500 mg. Thirty-six patients had surgery; 83% had R0 resection and 17% had complete pathological response. Median overall survival was 23.5 months, with 34% and 27% alive at three and five years.

CONCLUSION—The recommended phase II dose of capecitabine is 3500 mg when given concurrently with 50.4 Gy of thoracic radiotherapy in 28 fractions and weekly docetaxel. This trimodality therapy for operable locally advanced esophageal carcinoma was very well-tolerated and remarkably active. This regimen holds promise for treatment of esophageal carcinoma and warrants further investigation.

INTRODUCTION

Esophageal cancer is predicted to afflict 16,980 individuals in 2011, causing 14,710 deaths in that year.¹ The disease has a poor outcome, with a 16.8% five-year survival rate, largely

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because most patients present with regional or distant spread of disease.² Surgical resection is a mainstay of treatment for stage II-III disease, but locoregional and systemic recurrence is common. Consequently, a number of clinical studies have focused on identifying Neoadjuvant therapies to prevent recurrence and improve survival.

Numerous studies have evaluated the role for Neoadjuvant chemotherapy and/or radiotherapy in surgically resectable esophageal carcinoma.³⁻⁵ A recent meta-analysis of Neoadjuvant therapy trials encompassing 4188 patients showed that the hazard ratio for all-cause mortality was 0.78 for Neoadjuvant chemoradiotherapy and 0.87 for Neoadjuvant chemotherapy compared to surgery alone.⁶ As the use of Neoadjuvant chemoradiotherapy gained attention, a series of retrospective analyses indicated that addition of an intensive induction chemotherapy regimen prior to concomitant chemoradiotherapy and surgery further improves outcomes.^{7,8} Numerous phase II trials evaluating induction chemotherapy have shown that such regimens can be well-tolerated and highly active, but results have varied widely due to the variation in agents, schedules, and dosing.⁹⁻¹⁹ In the absence of an accepted optimal approach, one focus for current trials is to identify regimens which maximize quality of life and have minimal toxicity while maintaining acceptable clinical response and overall survival.

The pyrimidine analog 5-fluorouracil (5-FU) is one of the most commonly studied chemotherapeutic agents in esophageal cancer.²⁰ This agent requires central venous access for delivery, which carries a risk of infection, as well as being inconvenient for patients. Capecitabine is an orally bioavailable prodrug of 5'-deoxy-5-fluorouridine (5-DFUR), which is converted to 5-FU in tumor cells due to high expression of the converting enzyme thymidine phosphorylase in human carcinomas.²¹ Capecitabine has shown promise in phase I and phase II studies for the treatment of esophageal cancer.²²⁻²⁵ High expression of thymidine phosphorylase and was associated with therapeutic response to capecitabine/cisplatin combination therapy in patients with esophageal carcinoma, indicating that capecitabine may be a valuable agent for esophageal cancer treatment due to tumor responsiveness and lower general toxicity.²⁶

Docetaxel and paclitaxel are taxane class agents that stabilize microtubules and interfere with cell division. Both agents have a broad spectrum of antitumor activity, and both have been studied in esophageal cancer.²⁷⁻²⁹ Taxane treatment increases expression of thymidine phosphorylase in mouse model systems of breast and colorectal cancer.^{30,31} Therefore, treatment regimens containing docetaxel and capecitabine may have high therapeutic value due to a synergistic effect between these two agents. Preliminary studies of combination capecitabine/docetaxel showed that these agents are well-tolerated and highly active, but the study was limited by a small sample size and limited follow-up.³² The goal of this trial was to integrate oral capecitabine into a trimodal therapeutic regimen including induction chemotherapy followed by combination chemoradiotherapy and surgical resection. Capecitabine dosing was titrated upward during chemoradiotherapy, and patients were monitored for the primary outcome of dose-limiting toxicity. Secondary outcomes were overall survival, relapse-free survival, the rate of complete pathological response, and the rate complete surgical resection.

METHODS

Patient Selection

Previously untreated patients with locally advanced, surgically resectable cancer of the esophagus or gastroesophageal (GE) junction, clinical stage II-III (T2-4N0M0, T1-4N1M0) with histologic or cytologic evidence of adenocarcinoma or squamous cell carcinoma confirmed by the Department of Pathology at Dartmouth-Hitchcock Medical Center were

eligible. Patients having gastric cancer with minor involvement of the GE junction or distal esophagus were not eligible, nor were patients with cancer of the cervical esophagus. Celiac lymph node metastases were considered regional lymph node involvement (N1). Patients were required to be ≥ 18 years of age, with Karnofsky performance status $\geq 70\%$, and with adequate organ function defined by leukocytes $\geq 3,000/\text{mm}^3$, platelets $\geq 100,000/\text{mm}^3$, bilirubin to the upper limit of normal (ULN), serum transaminase (AST or ALT) to five times the ULN, serum creatinine ≤ 1.5 mg/dL or creatinine clearance of ≥ 50 mL/min. Patients were not permitted to have prior chemotherapy, immunotherapy, or chest/abdominal radiotherapy. Patients with any of the following were excluded: clinically apparent metastatic disease (brain, bone, pulmonary, or liver metastases, or positive cytology of the pleura, pericardium, or peritoneum), clinically evident metastatic disease of the cervical or supraclavicular lymph nodes, grade ≥ 2 peripheral neuropathy, serum calcium > 12 mg/dL, recurrent laryngeal or phrenic nerve paralysis, tracheobronchial tree involvement, tracheoesophageal fistula, concurrent active malignancy other than non-melanoma skin cancer or carcinoma-in-situ of the cervix, or uncontrolled intercurrent medical illness. The study was performed in accordance with the Committee for the Protection of Human Subjects (CPHS) at Dartmouth College and monitored by the Data Monitoring Committee of the Norris Cotton Cancer Center at Geisel School of Medicine at Dartmouth. All patients signed a CPHS-approved informed consent prior to enrollment.

Clinical Staging

Initial evaluation included CT scans of the chest and upper abdomen, upper GI endoscopy with endoscopic ultrasonography (EUS), laboratory tests, and radiation therapy simulation, all completed within four weeks of enrollment. A bone scan was performed in patients with abnormal alkaline phosphatase levels in the setting of normal AST, or patients with new-onset bone pain. A screening MRI or CT scan of the brain was performed for a recent history of headache or new focal neurologic findings. EUS was performed with an Olympus gastroscope under conscious sedation in the usual fashion. Biopsies were taken at the initial clinical staging and fixed for evaluation by Pathology. Prior to surgical resection, patients were re-staged by repeat CT scans of the chest and upper abdomen and upper GI endoscopy with EUS.

Treatment Plan

In the induction phase, patients were treated with two cycles of docetaxel (80 mg/m^2) and carboplatin (target area under the concentration curve (AUC) of $6 \text{ mg} \cdot \text{min/mL}$) every 21 days for six weeks. In the concurrent chemoradiotherapy (CCRT) phase, all patients received weekly docetaxel (15 mg/m^2) and external beam radiotherapy (50.4 Gy at 1.8 Gy per fraction in 28 fractions, delivered Monday through Friday). The patients underwent CT simulation, immobilized, arms up using a wing-board combined with a vac-bag. All patients underwent 3 dimensional treatment planning. The dose was calculated using tissue heterogeneity corrections. The planned treatment volume 1 (PTV1) included the gross tumor volume (GTV) with a 4–5 cm margin proximally, distally and 1.5–2 cm circumferentially. The celiac nodes were electively covered in distal and gastro-esophageal junction carcinomas. The planned treatment volume 2 (PTV2) was designed with a 1.5–2 cm margin around the GTV. Margins around the grossly positive nodes were kept at 1–1.5 cm in both PTV1 and PTV2. PTV 1 received 41.4 Gy in 23 fractions. A boost of 9 Gy in 5 fractions was delivered to PTV2. The constraints for the organs at risk were kept under tolerance: less than 32% of the lung volumes received more than 20 Gy , less than 50% of the heart volume received more than 40 Gy , and the maximum dose to any point on the spinal cord was kept less than 45 Gy . Prior to each fraction of radiotherapy, patients took a set dose of oral capecitabine ranging from 500 mg at dose level I to 3500 mg at dose level VII, in 500 mg increments. Dose-limiting toxicity (DLT) was defined as any grade 3 or higher toxicity

which did not return to grade 2 or lower within three weeks from completion of treatment, or any grade toxicity which resulted in a treatment break longer than one week. Initially, three patients were enrolled at dose level I. If one or more patients developed DLT, three more patients were enrolled at the same dose level. If there was no DLT, the next three patients were enrolled at the next incremental dose level. The maximum tolerated dose (MTD) was defined as the dose of capecitabine at which 33% of patients experience a DLT. This experimental design follows the approach outlined by Storer for dose-limiting toxicity studies.³³

Efficacy Analysis

The primary outcome for this study is the occurrence of dose-limiting toxicity during the escalation phase of concomitant chemoradiotherapy treatment. Secondary outcomes include changes in patient weight and performance status after chemoradiotherapy, frequency of minor toxicity, overall survival, relapse-free survival, disease-specific survival, curative surgical resection rate, and pathological complete response rate. All survival outcomes were determined from the date of study enrollment. Relapse-free survival (RFS) was measured to the date of documented disease progression, incomplete surgical resection, or death from any cause. Overall survival (OS) was measured to the date of death from any cause, regardless of disease status. Disease-specific survival (DSS) was measured to the date of death from esophageal cancer or complications of surgery, with other causes of death censored at the time of death. Patients who were living or lost to follow-up without progressive disease were censored at the date of the last documented clinical encounter. Surgical outcomes were defined as: R0, curative resection, all gross disease removed, surgical margins free of tumor; R1, palliative resection, gross tumor left behind, or positive surgical margins on pathology; or R2, no resection, primary tumor could not be removed. Positive radial margins were considered R1 resection. Pathological complete response (pCR) was defined as the absence of residual carcinoma at the primary site on microscopic examination. Microscopic residual disease (MRD) was defined as only single cancer cells or groups of cancer cells present, according to the reporting pathologist. Significant residual disease was defined as residual carcinoma present in the background of fibrosis or as no tumor kill present. All cases that were downstaged to ypT0 or ypT1 had slides reviewed by a pathologist for pCR or MRD, regardless of nodal or distant disease. Surgical mortality was defined as death within 30 days of the surgical procedure.

RESULTS

Patient Characteristics

Forty-four patients were enrolled. Four patients were replaced during the induction phase - two due to discovery of metastatic disease during staging, one due to withdrawal of consent prior to treatment, and one due to death from a non-neoplastic cause (CVA). Demographic and clinical characteristics of the 40 patients who initiated induction are summarized in Table 1. Patients had a median age of 63 years (range 47 to 87 years), 32 (80%) were male, and 36 (90%) had adenocarcinoma. Clinical stages at enrollment were T3N1 (N=29, 72.5%), T2N1 (N=6, 15%), T3N0 (N=4, 10%), and T4N0 (N=1, 2.5%) with disease involving the distal esophagus (N=12, 30%), the distal esophagus and the GE junction (N=19, 47.5%), or both these areas and the cardia of the stomach (N=8, 20%). One patient (2.5%) had disease of the mid-esophagus. The accrual and treatment course of the cohort is summarized in Figure 1. During the concomitant chemoradiotherapeutic (CCRT) phase, one patient died from ARDS, while two patients withdrew consent for low-grade toxicity. Both of these patients later continued to surgery: one had surgical resection, while the other was found to have liver metastases, so no resection was performed. Of 37 patients who completed CCRT, one declined surgery and one transitioned to hospice care, while the remaining 35 patients

proceeded to surgery. The total number of patients having resection was therefore 36 (90% of those who received induction), one of whom did not complete the full course of CCRT. Thirty-three of 36 patients survived the surgical and post-operative period, for a surgical mortality rate of 8.3%. One patient was found to have stage IV disease at the time of surgery.

Safety Parameters

There were seven dose limiting toxicities in CCRT phase, occurring across five different doses of capecitabine (Table 2). Two patients had grade 3 dysphagia (at 500 mg and 1500 mg capecitabine), one patient had thrombocytopenia (at 1500 mg), one had fatigue (at 3000 mg), and one had grade 3 pneumonitis (at 3500 mg). Two patients at 3500 mg withdrew consent for toxicities - one for severe nausea and one for persistent neuropathy. Although these were objectively less than grade 3 or 4 events, the patients were unable to tolerate these toxic effects and declined further participation in the study. Because of the clinical impact of these events and the associated prolonged treatment interruption, we considered them to be dose-limiting. Therefore, from a total of nine patients treated at 3500 mg, three patients (33.3%) had dose-limiting toxicity, meeting the definition for maximally tolerated dose.

All grade 3 or 4 toxicities (including the dose-limiting toxicities) which occurred among patients receiving CCRT are enumerated in Table 3. The most common non-hematologic event was dysphagia, occurring in 6 patients (15%). The most common hematologic toxicity was ANC abnormality during induction, occurring in 10 patients (25%). More than half of the participants had no events of grade 3 or higher (N=23, 58%), and several categories of adverse event never occurred with severity above grade 2.

Efficacy parameters

The median follow-up time was 18.5 months. Overall and relapse-free survivals were computed from 40 patients who started induction therapy, measured from the time of enrollment (Figure 2). The median overall survival was 23.5 months, with 62%, 34%, and 27% of patients alive at one, three, and five years of follow-up. The median relapse-free survival was 15.6 months, with 63% of patients relapse-free at one year. The three- and five-year relapse-free survivals were both 37%. The median disease-specific survival was 28.1 months (Figure 3A).

Thirty-six patients had surgical resection, with the vast majority (30 out of 36, 83%) having R0 resection. One of the patients with R0 resection of the primary tumor was found to have a single nodule of metastatic disease embedded in the abdominal wall, which was completely resected. Five patients had R1 resection, with tumor microscopically present at the proximal, distal, or radial margins. Two of these patients had positive radial margins and two others had isolated tumor cells in lymphovascular spaces. Only one patient had microscopic extension of the primary tumor to a proximal or distal margin. One patient had gross residual disease involving the chest wall, and was classified as R2. Six patients (16.7%, 95% confidence interval 4.5% – 28.8%) had a complete pathological response (pCR) at the primary site, and an additional five patients had microscopic foci of residual tumor cells at the primary site. Based on evidence that microscopically residual disease (MRD) and complete pathological response have identical outcomes with respect to overall survival, we considered these two groups together.³⁴ We found that 11 patients (30.6%, 95% confidence interval 15.5% – 45.6%) who had pCR or MRD had a median survival of 86.6 months, compared to a median survival of 19.1 months for 25 patients who had a greater extent of residual disease. The pCR/MRD group had a 61.4% survival rate at both 3 and 5 years, compared to 27.5% at 3 years and 18.4% at 5 years for patients with significant

residual disease (Figure 3B). This result was statistically significant by the log-rank test, with a p-value of 0.026.

Nineteen of 37 patients who completed CCRT (51%) had a stable or improved Karnofsky performance status, while 13 patients (35%) dropped by ten points and five patients (14%) dropped by twenty points. No patient dropped their performance status dropped below 70%. The average weight loss among CCRT patients was 4.6 kg. Six patients (15%) required a feeding tube prior to surgery, and in 3 of these cases the feeding tube was required because of the tumor causing obstruction of the esophagus rather than toxicity from the chemoradiotherapy.

Discussion

Esophageal cancer presents a therapeutic challenge due to the advanced stage of disease at clinical presentation, and frequent local recurrence. One approach to therapy consists of an intensive chemotherapeutic regimen, followed by lower doses of chemotherapy combined with radiotherapy. This approach may improve local disease control, achieve downstaging for easier surgical resection, and treat occult metastatic disease. However, such regimens can carry significant toxicity. Capecitabine and docetaxel are promising agents for such trimodal therapy, due to potential synergistic effects, reduced toxicity, and easy delivery. We investigated a trimodal regimen including phase 2 dose escalation of capecitabine in patients with resectable esophageal cancer and found that this regimen produced excellent median and five year survival, with a low burden of toxicity.

Several recent phase 2 studies have evaluated trimodal therapies in esophageal carcinoma, included both adenomatous and squamous histology, with a high-intensity induction chemotherapy phase before concomitant chemoradiotherapy (Table 4). The rates of R0 resections have ranged from 76% to 100%. By comparison, our study achieved a reasonable rate of 83% R0 resection. In four out of five R1 resections, disease extended to the radial margins or to the lymphovascular space, while only one case had a microscopically positive margin at the proximal or distal aspect. Thus, even in cases that were strictly defined as R1, the degree of marginal disease was minimal, suggesting a potent therapeutic effect. In the same set of studies, pathologic complete response rates among patients who had resection ranged from 20% to 40%, while our study achieved a pCR rate of 17% and pCR/MRD rate of 30.6%. This may be a result of the sample size, and in fact the 95% confidence interval for our response rate overlaps with many of the response rates in previous studies. This may reflect the range of efficacy for this trimodal regimen, it must be noted that our surgical outcomes are confounded by the dose escalation aspect of the chemoradiotherapy phase. It is possible that using the maximum tolerated dose of capecitabine (3500 mg) would produce better and less variable results. Furthermore, recent reports have found that tumor histology can influence treatment response. Specifically, patients with squamous cell carcinoma are more likely to achieve a pCR, but they are also more prone to distal recurrence.³⁵ Thus, one factor potentially explaining our lower than expected pCR rate may be a higher frequency of adenocarcinoma compared to most other studies (Table 4). In this cohort, 34 patients (85%) had T3 or higher staging at enrollment, which is comparable to other studies. Compared to a landmark clinical trial of 5-FU and cisplatin, this regimen produced a superior median overall survival (23.5 months, versus 18 months) and three-year survival (34% compared to 25%).³⁶

As expected, we observed that patients having either pCR or MRD had a better 5-year survival compared to patients with a greater burden of residual disease. Although there is evidence that these two categories can be considered together, Verlato *et al* recently reported that the prognostic value of absent or scattered residual cancer cells varies depending on

node status.³⁷ Considering that the main goal of this work is to define maximum tolerated dose of capecitabine, and consequently we have a small number of patients in the cohort, we do not believe it is appropriate to draw any firm conclusions on the prognostic value of pCR versus MRD in our population.

One advantage of this regimen is the overall tolerability. Grade 3 or 4 toxicity occurred in a minority of patients, and was largely limited to dysphagia, nausea/vomiting, and laboratory abnormalities. Few patients required a feeding tube prior to surgery, indicating that induction therapy helped to preserve swallowing function, which enabled delivery of oral capecitabine. These results are consistent with data from a smaller set of patients who were treated with a capecitabine/docetaxel-based regimen.³² One limitation of our study is that at the highest tolerated dose level of capecitabine -- 3500 mg -- two of the patients had objectively low-grade toxicities which resulted in withdrawal from the study. It is possible that higher doses of capecitabine might be tolerated without producing grade 3 or higher toxicities, but our study was limited by our definition of DLT to include prolonged treatment breaks. We concluded that 3500 mg capecitabine was the highest practically achievable dose, and an appropriate end point for a MTD study.

In conclusion, a trimodal approach including capecitabine and docetaxel was well-tolerated and produced acceptable overall survival rates, although the pathological response rate was low compared to other studies. The low pCR rate was a surprising result, but we believe the high tolerability and favorable survival outcomes make a strong case for further studies with the maximum tolerated dose of capecitabine, where better pCR rates might be attained. Despite the low pCR rate, overall survival was comparable to other studies and this is a more direct outcome. We identified 3500 mg as the maximum tolerated dose of capecitabine in this regimen. We suggest that survival and response might be further improved by treating with the maximum tolerated capecitabine dose. High-grade toxicity was uncommon. This method of treatment warrants further investigation and has the potential to prolong survival and increase quality of life among patients with resectable esophageal carcinoma.

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Figure 1. Accrual and Treatment Course

Patients accrued and treated throughout the trial are shown. CRT = chemoradiotherapy, pCR = pathological complete response, MRD = microscopically residual disease.

Figure 2. Overall and Relapse-Free Survival

Kaplan Meier curves are shown for overall survival (A) and relapse-free survival (B) among 40 patients who initiated induction therapy. Values for median overall survival and absolute survival at one, three, and five years are indicated on each chart.

Figure 3. Disease-Specific and Subgroup Survival

(A) Disease-specific survival was calculated among enrolled patients. (B) Kaplan Meier curves for overall survival among 36 patients who had surgical resection are shown for patients having complete pathological response or microscopically residual disease (n=11) versus those having a higher level of residual disease (n=25). The p-value represents a log-rank test.

Table 1

Patient Characteristics

	Number	Percent
Patients	40	
Age (years)		
Median	63	
Range	47–87	
Sex		
Male	32	80%
Female	8	20%
Performance Status		
90%	29	72.5%
80%	8	20%
70%	3	7.5%
Sites of Disease		
Distal esophagus (DE)	12	30%
DE and GE junction	19	47.5%
DE, GE junction, and cardia	8	20%
Mid-esophagus	1	2.5%
Histology		
Adenocarcinoma	36	90%
Squamous cell carcinoma	4	10%
Clinical Stage		
T4N0	1	2.5%
T3N1	29	72.5%
T3N0	4	10%
T2N1	6	15%

Table 2

Dose-Limiting Toxicity By Level

Level	Capecitabine	N	Dose-limiting Toxicity	% DLT
I	500 mg	7	One grade 3 dysphagia	14.3%
II	1000 mg	3	None	0%
III	1500 mg	6	One grade 3 dysphagia	16.7%
IV	2000 mg	3	None	0%
V	2500 mg	6	One thrombocytopenia	16.7%
VI	3000 mg	6	One fatigue	16.7%
VII	3500 mg	9	One grade 3 pneumonitis One withdrawal for nausea One withdrawal for neuropathy	33.3%

Table 3

Grade 3 or 4 Toxicity Events By Dose Level

	Level I (N=7)	Level II (N=3)	Level III (N=6)	Level IV (N=3)	Level V (N=6)	Level VI (N=6)	Level VII (N=9)	Total
Cardiac	0	0	0	0	0	1	0	1
Pulmonary	0	0	1	0	0	0	0	1
Dehydration	0	0	0	0	0	0	1	1
Dysphagia	1	0	1	1	0	3	0	6
Odynophagia	0	0	0	0	0	1	0	1
Weight loss	0	0	0	1	0	0	0	1
Nausea/vomiting	0	0	1	0	0	1	1	3
Fatigue	0	0	0	0	0	1	0	1
Pre-radiation therapy								
WBC	4	2	2	0	0	1	0	9
ANC	5	3	2	0	0	0	0	10
Platelets	0	0	0	0	0	0	0	0
Hgb	0	0	0	0	0	0	0	0
During radiation therapy								
WBC	1	0	0	0	0	0	0	1
ANC	0	0	0	0	0	0	0	0
Platelets	0	0	0	0	0	2	0	2
Hgb	0	0	0	0	0	1	1	2
Neutropenic fever	0	0	0	0	0	1	0	1
Lab abnormalities	1	1	0	0	0	4	1	7
Total grade 3-4 events	12	6	7	2	0	16	4	47
Number (%) with any grade 3-4 event	5 (71%)	3 (100%)	3 (50%)	1 (33%)	0 (0%)	4 (67%)	1 (11%)	17 (42.7%)

The following events did not occur above grade 2: diarrhea, constipation, shortness of breath, cough, headache, myalgia/arthralgia, insomnia, alopecia, rash, dermatologic, epistaxis, visual disturbances, taste disturbances.

Table 4

Outcomes of Phase 2 Studies With Trimodal Therapy

Author Year	Induction	CCRT ¹	Resected/Total	Of Resected		Of Total	
				% R0	% pCR	% Adeno	% T3
Ajani 2001 ¹³	5-FU Cisplatin Paclitaxel	45 Gy 5-FU Cisplatin	25/38	100%	30%	82%	87%
Bains 2002 ⁹	Cisplatin Paclitaxel	50.4 Gy Cisplatin Paclitaxel	36/41	92%	22%	61%	83%
Swisher 2003 ¹⁷	5-FU Cisplatin Paclitaxel	45 Gy 5-FU Cisplatin	35/38	100%	23%	84%	87%
Ajani 2004 ¹⁴	Irinotecan Cisplatin	45 Gy 5-FU Paclitaxel	39/43	100%	28%	86%	85%
Henry 2006 ¹⁶	Cisplatin Paclitaxel	45 Gy 5-FU Cisplatin Paclitaxel	16/21	100%	25%	86%	NR ²
Ruhstaller 2009 ¹¹	Cisplatin Docetaxel	45 Gy Cisplatin Docetaxel	57/66	93%	26%	55%	82%
Ajani 2010 ¹⁵	Docetaxel Irinotecan 5-FU	50.4 Gy Docetaxel Irinotecan 5-FU	43/55	76%	20%	98%	96%
Choong 2010 ¹⁸	Docetaxel Cisplatin	50 or 66 Gy Docetaxel	45/78	93%	40%	77%	NR
Eislerer 2011 ¹⁹	Cisplatin Docetaxel 5-FU	40 or 60 Gy Docetaxel 5-FU	16/24	100%	31%	33%	75%
De Vita 2011 ¹⁰	FOLFOX-4 Cetuximab	50.4 Gy Cetuximab	30/41	80%	27%	32%	NR
Ruhstaller 2011 ¹²	Cisplatin Docetaxel Cetuximab	45 Gy Cisplatin Cetuximab +/- Docetaxel	25/28	100%	36%	54%	64%
Wood 2012 (this study)	Docetaxel Carboplatin	50.4 Gy Capecitabine Docetaxel	36/40	83%	17%	90%	85%

¹Concomitant chemoradiotherapy
²Not Reported