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Is Aggressive Mediastinal Control Needed After Neoadjuvant Therapy For Distal Esophagus Carcinomas?

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Is aggressive mediastinal control needed after neoadjuvant therapy for distal esophagus carcinomas?

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Abstract

The pattern of recurrence after neoadjuvant chemoradiotherapy followed by transhiatal esophagectomy with limited mediastinal lymphadenectomy among 73 patients with carcinoma of the distal esophagus, gastroesophageal junction (GEJ) and/or gastric cardia, was investigated in this retrospective study. Results indicate that among the 30 patients with recurrence, distant sites (n = 24) were more common than local sites (n = 6) and this difference was statistically significant (P = 0.001). Lungs and liver were the most common sites of first recurrence, 51%, while mediastinal nodes were the sites of first recurrence in 6% of cases. Twenty patients (27.4%) had pathologic complete response, 20 patients (27.4%) had disease downstaging, 17 patients (23.3%) had no response, and 12 (16.4%) had disease progression. Time to first recurrence was significantly reduced in patients with pathologic stage III disease (P = 0.044). Patients receiving 50 Gy of neoadjuvant radiotherapy had lower rates of recurrence than patients receiving 45 Gy (P = 0.025). Five-year disease-free survival and overall survival were 61.6% and 60.3%, respectively. Since mediastinal failure rates were significantly lower than distant failure rates in this study, it appears that aggressive mediastinal control at the time of esophagectomy in patients with carcinoma of the distal esophagus, GEJ and/or gastric cardia, who have received neoadjuvant chemoradiotherapy, is unnecessary. Furthermore, since pathologic stage of disease is significantly associated with disease recurrence, more efforts should be made to improve systemic therapy prior to and/or after resection.

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Chantae Sullivan

Table of Contents

Introduction

Esophageal cancer is the seventh leading cause of cancer death among American men and is the sixth leading cause of cancer death worldwide, responsible for 286,000 deaths (R. A. Malthaner, Collin, & Fenlon, 2006). The National Cancer Institute estimates that in the United States 16,640 new cases arose in 2010 leading to 14,500 deaths ("Esophageal Cancer," 2010). The lifetime risk is 0.8% for men and 0.3% for women and the risk increases with age with mean age at diagnosis being 67 years. More than 90% of esophageal cancers are either squamous cell carcinomas or adenocarcinomas while other carcinomas, including melanomas, leiomyosarcomas, carcinoids, and lymphomas are far less common. Approximately three quarters of adenocarcinomas are found in the distal esophagus whereas squamous cell carcinomas are more evenly distributed between the middle and lower thirds, while cancers of the cervical esophagus are uncommon. The demographics of esophageal cancer in the United States are changing as, in 1975, squamous cell carcinoma accounted for 75% of esophageal cancer while adenocarcinoma accounted for 25% while, over the past 20 years, the incidence of squamous cell carcinoma has decreased and the incidence of adenocarcinoma has increased by up to 450% in white men and 50% among black men (Enzinger & Mayer, 2003; R. A. Malthaner, et al., 2006). The pathogenesis of esophageal carcinoma remains unclear but animal studies suggest that “oxidative damage, from factors such as smoking and gastroesophageal reflux, which causes inflammation, esophagitis, and increased cell turnover, may initiate the carcinogenic process” (Enzinger & Mayer, 2003).

Despite its relatively low incidence, esophageal cancer is a deadly disease with more than 50% of patients having unresectable or metastatic disease at the time of diagnosis. In fact, 14% to 21% of submucosal cancers (T1 lesions) and 38% to 60% of cancers invading the muscularis propria (T2 lesions) are associated with spread to lymph nodes, which is a poor prognostic indicator. Other independent indicators of poor prognosis are the tumor-node-metastasis (TNM) stage, weight loss of greater than 10% of body mass, dysphagia, large tumors, and advanced age. The overall survival rate is poor but has increased from 4% in the 1970s to 14% in 2003 (Enzinger & Mayer, 2003). Stage IV disease is treated with palliative chemotherapy, however, it is controversial as to whether the optimal treatment strategy for patients with low stage locally resectable disease should be surgery alone with extensive lymphadenectomy or using neoadjuvant chemoradiotherapy or chemotherapy followed by surgery with limited lymph node dissection.

As previously mentioned, lymph node metastasis is a poor prognostic indicator in esophageal cancer. There is however significant controversy among surgeons as to the extent of lymphadenectomy to be performed during esophagectomy (Altorki, et al., 2008; Schipper, 2009). The prevailing view contends that the disease is systemic at the time of diagnosis and that extensive lymph node dissection only adds to the postoperative morbidity and so lymph node dissection is limited to periesophageal and perigastric nodes only. The opposing view supports extensive lymph node dissection to enhance accuracy of staging, improve local disease control and possibly improve survival (Altorki, et al., 2008). Multiple authors have shown an improvement in overall survival (OS) when extensive lymph

node dissection is performed, with greater than 25 lymph nodes in node-positive cancer showing improvement in OS, and greater than 40 lymph nodes in node-negative cancer (Altorki, et al., 2008; Lee, Port, Paul, Stiles, & Altorki, 2009; Peyre, et al., 2008; Schipper, 2009; Stiles, et al., 2009). Other authors have demonstrated increased incidence of tracheobronchial lesions including fistulae, ulcers, and erosions that complicate esophagectomies with extensive lymphadenectomy of over 60 lymph nodes (Maruyama, et al., 2009; Schipper, 2009). There is apparently a large gap between the number of nodes needed to achieve a survival benefit, and the number of nodes needed to be removed to increase the risk of tracheoesophageal lesions. However, Schipper pointed out that inconsistencies in the way lymph nodes are counted in different centers may account for this perceived gap (Schipper, 2009).

The two main techniques of surgical resection utilized for esophageal cancer are the transhiatal esophagectomy and the transthoracic esophagectomy. The transhiatal approach involves dissection of the esophagus under direct visualization through the widened hiatus of the diaphragm up to the pulmonary vein and the tumor is removed along with its adjacent lymph nodes (Hulscher, et al., 2002). Transthoracic en bloc resection involves a posterolateral thoracotomy and midline laparotomy along with extensive lymphadenectomy of mediastinal and abdominal nodes (two-field dissection). In both procedures, the esophagogastrostomy is performed either in the chest (Ivor-Lewis technique) or the neck (Enzinger & Mayer, 2003; Hulscher, et al., 2002). The transthoracic en bloc resection may at times be accompanied by a three-field dissection (3-FL), which includes cervical node

dissection along with mediastinal and abdominal nodes (Stiles, et al., 2009). In Japan, three-field dissection is routinely performed because there is a high rate of cervical node involvement in this population. However, Law et al. discourages the practice of 3-FL as they have found that the rate of recurrence of cervical node involvement is uncommon and similar in both the three-field and two-field dissection groups and that there is no survival advantage (Law & Wong, 2001). The authors also indicate that radical lymphadenectomy of the superior mediastinum may improve local disease control at the expense of increased postoperative morbidity and impaired quality-of-life (Law & Wong, 2001).

While the transhiatal and transthoracic surgical approaches to esophageal cancer are most commonly employed, minimally invasive esophagectomy is a newer technique used in a few centers worldwide. In 1993, Collard and colleagues demonstrated that esophageal dissection could be carried out thoracoscopically, when combined with laparotomy for gastric mobilization. There have been multiple subsequent reports of esophagectomy for cancer, performed by thoracoscopy and open laparotomy, which have demonstrated the feasibility of thoracoscopic-assisted esophagectomy, but the overall benefit was not well established. The current approach combines thoracoscopy and laparoscopy because laparoscopic esophageal mobilization by itself can be tedious and cumbersome via a completely laparoscopic approach and visualization of paraesophageal structures (such as the inferior pulmonary vein and the mainstem bronchi) and the performance of mediastinal lymph node dissection can be very limited (Schuchert, Luketich, & Landreneau). Pennathur and colleagues reported a series of 222 consecutive minimally invasive

esophagectomies (MIE) in which minimally invasive esophagectomy was successfully completed in 206 (92.8%) patients. The median intensive care unit stay was 1 day, and the hospital stay was 7 days. The operative mortality was 1.4%. The oncologic results, per stage, were similar to historic series of open esophagectomy (Pennathur, Zhang, Chen, & Luketich).

Hulscher et al. compared survival outcomes of patients with resectable adenocarcinoma of the mid-to-distal esophagus or adenocarcinoma of the gastric cardia involving the distal esophagus according to whether they underwent transhiatal esophagectomy or transthoracic esophagectomy with extended en bloc lymphadenectomy (Hulscher, et al., 2002). The authors found a higher rate of perioperative morbidity among patients who underwent transthoracic esophagectomy although there was no significant difference in in-hospital mortality (P=0.45). After a median follow-up of 4.7 years, 70% of patients in the transhiatal group had died compared to 60% of patients in the transthoracic group (P=0.12). The disease-free survival was 27% for the transhiatal group versus 39% for the transthoracic group, while the overall survival was 29% for the transhiatal group versus 39% for the transthoracic group. The differences in the median, disease-free, and overall survival were not statistically significant, but the trend shows an improved long-term survival at 5 years of the transthoracic approach over transhiatal approach (Hulscher, et al., 2002). The postoperative morbidity associated with extensive lymphadenectomy, however, leads other surgeons to consider alternative options.

As an alternative to extensive lymphadenectomy at the time of

esophagectomy, preoperative chemoradiation is becoming increasingly common in North America and Europe (Ku & Ilson, 2009; Liu, Zhang, & Sun, 2008; R. Malthaner & Fenlon, 2001; Matsubara, 2008; Urschel, Vasan, & Blewett, 2002). In fact, Knisely et al. argue that the need for extensive lymphadenectomy may be obviated by the use of neoadjuvant chemoradiotherapy or chemotherapy and eliminate the associated perioperative morbidity (Knisely, Burtness, & Salem, 2003). The theoretical advantages of neoadjuvant chemotherapy and/or chemoradiotherapy include improvement in baseline dysphagia, downgrading of primary tumor, increased resection rates, and the treatment of micrometastatic disease (Ku & Ilson, 2009). In addition, patients with a complete pathologic response (pCR) typically fare better than patients who do not, but the pCR rate is 2.5 to 5% of patients who receive neoadjuvant chemotherapy alone and in 16% to 51% of patients who receive neoadjuvant chemoradiation (Ku & Ilson, 2009; Stiles, et al., 2009).

Kleinberg et al assessed the long-term survival results after cisplatin, protracted 5-fluorouracil infusion, and concurrent radiotherapy followed by surgical resection of esophageal cancer (Kleinberg, et al., 2003). The authors found a pathologic complete response (pCR) rate of 33% among the study participants. The 5-year survival and disease-free survival rates were 40% and 49%, respectively. Patients with a pCR had an overall 5-year survival rate of 67%, while the remainder of patients had an overall survival rate of 21%. These promising 5-year survival rates suggest that these intensive chemoradiotherapy regimens may improve the cure rate. Patients with Stage I tumors at the time of surgery had survival rates similar to patients with pCR, while patients with Stage IIA and higher disease had

lower rates of median survival. This suggests that pathologic stage after neoadjuvant therapy is an important predictor of survival. The authors also found that isolated local recurrence is uncommon suggesting that efforts to improve neoadjuvant therapy should focus on improving systemic therapy rather than intensifying the radiation therapy (Kleinberg, et al., 2003).

Furthermore, in 2004, Malthaner et al published a systematic review and meta-analysis pooling one-year mortality from six randomized trials and found no statistically significant difference in mortality of neoadjuvant chemotherapy over surgery alone (R. A. Malthaner, Wong, Rumble, & Zuraw, 2004b; Raja, Salhiyyah, & Nagarajan, 2007). Based on this systematic review, subsequent external review, Practice Guidelines Coordinating Committee revision suggestions, and final approval, the Gastrointestinal Cancer Disease Site Group recommended that for adult patients with resectable thoracic esophageal cancer for whom surgery is considered appropriate, surgery alone be the standard of care (R. A. Malthaner, Wong, Rumble, & Zuraw, 2004a; Raja, et al., 2007). Noting the conflicting results of several later studies investigating whether neoadjuvant chemotherapy provided a survival advantage for patients with resectable esophageal cancer, Malthaner et al later published a Cochrane systematic review of 11 randomized clinical trials and showed a trend toward benefit of neoadjuvant chemotherapy, although the benefit was not statistically significant (HR 0.88, 95% CI 0.75 – 1.04) (R. A. Malthaner, et al., 2006).

More recently, Gebski et al. published a meta-analysis investigating the benefits of neoadjuvant chemoradiotherapy or chemotherapy versus surgery alone

and determined that there is a significant survival benefit at 2 years for neoadjuvant chemoradiotherapy and, to a lesser extent, chemotherapy in patients with carcinoma of the esophagus (Gebski, et al., 2007). The authors found a relative reduction in all-cause mortality for patients receiving neoadjuvant chemoradiotherapy versus surgery alone after pooling results from ten trials (hazard ratio 0.81 [95% CI 0.70 – 0.93]; p=0.002) corresponding to a 13% absolute difference in survival at 2 years. Among eight reports comparing all-cause mortality in patients treated with neoadjuvant chemotherapy versus surgery alone, there was a relative benefit in favor of chemotherapy, which just reached significance (0.90 [0.81 – 1.00]; p=0.05), corresponding to a 7% absolute survival benefit at 2 years. The authors also assessed survival benefit of neoadjuvant therapies based on histological type of tumor. Patients with squamous cell carcinoma did not have a survival benefit from neoadjuvant chemotherapy (0.88 [0.75-1.03]; p=0.12). One large study, the UK Medical Research Council (MRC) trial, showed a significant benefit to using neoadjuvant chemotherapy for patients with adenocarcinoma (0.78 [0.64-0.95]; p=0.014), while another large study, the North American Intergroup 113 trial, using the same chemotherapy agents at higher doses did not show a benefit (Kelsen, et al., 1998; Ku & Ilson, 2009; Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial," 2002). Chemoradiotherapy was beneficial over surgery alone for both patients with squamous cell carcinoma (0.84 [0.71-0.99; p=0.04) and adenocarcinoma (0.75 [0.59-0.95]; p=0.02).

Meguid et al, studied the pattern of recurrence among patients with esophageal cancer who had either a complete, partial, or no response to chemoradiotherapy before esophagectomy (Meguid, et al., 2009). The authors found that of 267 patients studied, 30.7% had a complete response, while 40.4% had partial response, and 28.8% had no response. Of the patients who had a complete response, 21.4% had recurrence of disease, while recurrence occurred in 36.1% of patients with partial response and 35.1% of patients with no response. Most recurrences occurred at distant sites (77.4%) regardless of pathologic response, and subsequent survival was brief (median 8.37 months). Disease-free survival was longer for patients who had complete response to neoadjuvant therapy (median 27.3 months) compared to those who had a partial or no response to neoadjuvant therapy (median 10 months). Since it appears that it is the pathologic response of the tumor that determined recurrence rates in this population of patients, and most of the sites of first recurrence were distant from the location of the primary tumor, it is doubtful whether aggressive mediastinal control with lymphadenectomy at the time of esophagectomy is beneficial for patients who have had neoadjuvant chemoradiotherapy. As already mentioned, lymphadenectomy is associated with increased morbidity after surgery, which may affect patients' overall survival. Perhaps mediastinal control, if needed, may be achieved with neoadjuvant chemoradiotherapy.

Statement of Purpose

The aim of the current study is to determine the patterns of recurrence of esophageal carcinoma after neoadjuvant chemoradiotherapy followed by transhiatal esophagectomy with minimal mediastinal lymph node dissection. We hypothesize that distant recurrence will be more common than local or mediastinal recurrence in patients who received trimodality therapy, thus obviating the need for aggressive mediastinal control with extensive lymph node dissection at the time of surgery.

Materials and Methods

Study Population

A database of 150 patients who underwent transhiatal esophagectomy at the Yale New Haven Hospital between September of 1995 and June of 2009 was searched to identify patients who underwent neoadjuvant chemoradiotherapy prior to transhiatal esophagectomy. Patients were included in the study if they were diagnosed with either adenocarcinoma or squamous cell carcinoma of the distal esophagus, gastroesophageal junction (GEJ), or the gastric cardia. Patients were excluded if they had tumor histology other than adenocarcinoma or squamous cell carcinoma. Patients who did not have neoadjuvant chemoradiotherapy prior to surgery were also excluded. After applying inclusion and exclusion criteria, 73 patients remained in the study. 95% of patients in the study had complete preoperative clinical staging with endoscopic ultrasound (EUS). Staging was determined using the American Joint Commission (AJCC) 2010 TNM staging system. The study was approved by the Institutional Review Board (IRB) at the Yale School of Medicine.

Treatment

Neoadjuvant chemoradiotherapy varied by patient as some patients received medical and radiation oncology treatment at sites external to the Yale New Haven Hospital. However, for the majority of patients (n = 54/73), chemotherapy consisted of 5-fluoropyrimidine (5-FU), a platinum agent (either cisplatin or carboplatin), and/or a taxane (Table 1). In addition, most patients had external beam radiation to

the diseased portion of the esophagus to a dose between 45 Gy – 50 Gy (n = 60/73; Table 1). All patients underwent restaging EUS after neoadjuvant chemoradiotherapy and were taken to the operating room where they underwent transhiatal esophagectomy with limited lymph node dissection. In most cases, patients who had residual disease at the time of surgical resection were offered adjuvant therapy by their medical oncology providers.

Follow-up and Recurrence

Follow-up time was calculated to be the number of months from the date of surgery to the date of last contact or death. The time to first recurrence was calculated to be the time from the date of surgery to the date of the first recurrence documented in the medical records. Follow-up information was complete in 60/73 charts.

Statistical Analysis

Data was collected in a retrospective manner and all analyses were performed using SPSS Analytical Software Package Version 18.0 (SPSS, Chicago, IL). The differences between groups were tested for significance by the Student *t* test for continuous variables and Fisher exact test or Pearson's chi-squared test for categorical variables. Binomial testing was used to determine the statistical difference between the groups of patients with local versus distant recurrence. Univariable Cox regression analyses were performed with disease recurrence or death as the outcomes with a significance level of $P<0.05$. Covariates that were

significant at P <0.25 were included in the multivariable Cox regression analyses. Kaplan-Meier analysis was used to calculate disease recurrence functions and differences were assessed using the log-rank test.

Results

Patient Characteristics

Patient demographics along with clinical and pathological characteristics of the tumors are presented in Table 1. Of the 73 patients in the population, 63 were male and 10 were female. The mean age was 58.63 (SD 9.082; range, 27 years – 74 years). The majority of the patients were Non-Hispanic White, accounting for 87.7% of the study population. 8.2% of the population was Non-Hispanic Black and the remaining 4.1% were either Hispanic or other unspecified race. Forty-seven patients had a history of alcohol use and 63 had a tobacco use history. Sixty-four patients were diagnosed with adenocarcinoma, while 9 had squamous cell carcinoma. At the time of diagnosis, the majority of patients had stage II or III disease (n = 63/73). After trimodality therapy, 20 patients (27.4%) had a complete response (CR) and were noted to have stage 0 disease at the time of surgery. Twenty patients (27.4%) had the stage of their disease lowered but had residual disease on surgical pathology. Seventeen patients (23.3%) had the same pathologic stage as clinical stage after trimodality therapy and 12 patients (15.4%) had disease upstaging after therapy. It was not possible to quantify response to therapy for 4 patients who either did not have a recorded clinical stage or pathological stage. After trimodality therapy, 20 patients (27.4%) had stage 0 disease, 12 patients (16.4%) had stage I disease, 23 patients (31.5%) had stage II disease, and only 3 patients (4.1%) had stage IV disease.

Table 1 Patient Characteristics and Univariable Cox Regression Analysis for Disease-Free Survival

Characteristic	**No. (std dev)**	**%**	**HR**	**95% CI**	***P***
Gender					
Male	63	86.3	1		
Female	10	13.7	1.565	0.358-6.843	0.552
Age	58.63 (9.082)	100.0	0.989	0.937-1.044	0.691
Race					
Non-Hispanic White	64	87.7	1		
Non-Hispanic Black	6	8.2	1.886	0.430-8.276	0.400
Other	3	4.1	1.795	0.233-13.841	0.575
Alcohol use history					
No	25	34.2	1		
Yes	47	64.4	0.963	0.422-2.199	0.929
Unknown	1	1.4			
Tobacco Use history					
No	9	12.3	1		
Yes	63	86.3	0.913	0.210-3.968	0.903
Unknown	1	1.4			
Histology					
Adenocarcinoma	64	87.7	1		
Squamous Cell Carcinoma	9	12.3	3.362	0.704-16.068	0.129
Response to treatment					
No response	17	23.3	1		
Downstaging without complete response	20	27.4	0.986	0.350-2.781	0.979
Downstaging with complete response	20	27.4	1.241	0.382-4.029	0.719
Disease progression	12	16.4	1.544	0.461-5.172	0.481
Unknown	4	5.5			
Clinical Stage					
Stage I	5	6.8	1		
Stage II	36	49.3	0.103	0.009-1.212	0.071
Stage III	27	37.0	0.092	0.008-1.083	0.058
Stage IV	1	1.4	0.208	0.009-4.614	0.322
unstaged	4	5.5			
Pathologic Stage					
Stage 0	20	27.4	1		

Stage I	12	16.4	0.489	0.094-2.539	0.395
Stage II	23	31.5	0.469	0.153-1.440	0.186
Stage III	14	19.2	2.442	0.768-7.770	0.131
Stage IV	3	4.1	0.406	0.046-3.562	0.416
unstaged	1	1.4			
Type of Neoadjuvant chemotherapy received					
Cisplatin/5-FU	39	53.4	1		
Cisplatin/5-FU/Taxol	9	12.3	0.949	0.261-3.445	0.937
Cisplatin/Taxol	6	8.2	0.467	0.149-1.465	0.192
Other	15	20.5	0.657	0.254-1.697	0.386
Unknown	4	5.5			
Dose of external beam radiation					
45 Gy	43	58.9	1		
50 Gy	17	23.3	0.370	0.150-0.913	0.031
52 Gy - 60 Gy	4	5.5	5.187	1.031-26.081	0.046
unknown	7	9.6			
None	2	2.7			

Response to Treatment

Seventeen patients (23.3%) in the study did not have a pathological response to trimodality therapy. Of the non-responders, 2 patients (11.8%) had squamous cell carcinoma and 15 patients (88.2%) had adenocarcinoma. Twenty patients (29.0%) had a pathologic complete response and of these, 4 patients (20.0%) had squamous cell carcinoma compared to 16 patients (80.0%) with adenocarcinoma. Twenty patients (29.0%) had a lower stage of disease after trimodality therapy and of these, 2 patients (10.0%) had squamous cell carcinoma and 18 patients (90.0%) had adenocarcinoma. Only 12 patients (16.2%) had disease upstaging during therapy and of these, 1 patient (8.3%) had squamous cell carcinoma and 11 patients (91.7%) had adenocarcinoma (Table 2). Of the patients with squamous cell

carcinoma, 4 (44.4%) had a complete response to treatment and 2 (22.2%) had disease downstaging with treatment. Two patients (22.2%) with squamous cell carcinoma showed no pathologic response to therapy, and 1 (11.1%) had disease progression with therapy. The majority of patients with adenocarcinoma had a pathologic response to therapy, 18 (30.0%) downstaged without complete response while 16 (26.7%) downstaged with complete response. Fifteen patients (25.0%) with adenocarcinoma had the same pathological stage as clinical stage after therapy, and 11 (18.3%) had disease progression with therapy. Chi-squared analysis revealed no significant difference between adenocarcinoma and squamous cell carcinoma in terms of their response to chemoradiotherapy ($P = 0.735$).

Table 2 Response to trimodality therapy by carcinoma histology

Response to Treatment	**Squamous Cell Carcinoma**	**Adenocarcinoma**	**Total**
No response	2 (22.2%)	15 (25.0%)	17 (24.6%)
Downstaged without complete response	2 (22.2%)	18 (30.0%)	20 (29.0%)
Downstaged with complete response	4 (44.4%)	16 (26.7%)	20 (29.0%)
Disease progression	1 (11.1%)	11 (18.3%)	12 (17.4%)
Total	9 (100%)	60 (100.0%)	69 (100.0%)

Recurrence of Esophageal Carcinoma

At our significance level of 0.05, there is no evidence to suggest that there is a relationship between age, gender, tobacco use history, tumor histology, clinical stage, pathologic stage, or response to therapy, with recurrence of esophageal carcinoma after trimodality therapy ($P > 0.05$; Table 3).

Table 3 Statistical relationship between the independent variables and the incidence of recurrence independent of time

Variable	**Number with recurrence**	**Number without recurrence**	***P***
Age	30	43	0.085
Gender			0.144
M	28	35	
F	2	8	
Tobacco Use History			0.238
No	2	7	
Yes	27	36	
Alcohol Use History			0.589
No	9	16	
Yes	20	27	
Histology			0.219
Adenocarcinoma	28	36	
Squamous Cell Carcinoma	2	7	
Clinical stage			0.096
I	1	4	
II	11	25	
III	15	12	
IV	1	0	
Pathological Stage			0.147
0	6	14	
I	2	10	

II	13	10	
III	7	7	
IV	1	2	
Response to Treatment			0.789
No response	7	10	
Downstaging without complete response	9	11	
Downstaging with complete response	6	14	
Disease progression	5	7	
Type of Neoadjuvant chemotherapy received			0.550
Cisplatin/5-FU	15	24	
Cisplatin/5-FU/Taxol	3	6	
Cisplatin/Taxol	4	2	
Other	7	8	
Dose of external beam radiation			0.904
45 Gy	18	25	
50 Gy	8	9	
52 Gy - 60 Gy	2	2	

The mean follow-up time was 40.90 ± 38.76 months (range, 0 months-153 months). At the time of the last follow-up, 30 patients (41.1%) had recurrent disease, while 43 patients (58.9%) remained disease-free. The majority of patients with recurrence (n=24/30; 80.0%), had disease distant from the site of origin of the tumor (Table 4).

Table 4 Patients with recurrent disease at last follow-up

Recurrence	**No.**	**%**
Yes	30	41.1
No	43	58.9
Local	6	20.0
Distant	24	80.0

Binomial testing further revealed that the difference between the number of patients with local recurrence and those with distant recurrence is statistically significant ($P = 0.001$; Table 5).

Table 5 Binomial Test of Local versus Distant Recurrence

		Category	N	Observed Prop.	Test Prop.	*P*
Site of first recurrence	Group 1	Distant	24	.80	.50	.001
	Group 2	Local	6	.20		
	Total		30	1.00		

Local recurrence was defined as recurrence at the site of anastomosis, in the stomach, or in the celiac, paraaortic, paratracheal, or mediastinal lymph nodes. Celiac nodes are the nodes located at the base of the celiac artery and paraaortic nodes are located lateral to the ligamentum arteriosum. Paratracheal lymph nodes are divided into right and left upper paratracheal nodes as well as right and left lower paratracheal nodes. Right upper paratracheal nodes are located between the intersection of the caudal margin of the innominate artery with trachea and the lung apex; left upper paratracheal nodes are located between the top of the aortic arch and the lung apex. Right lower paratracheal nodes are located between the intersection of the caudal margin of the innominate artery with the trachea and cephalic border of the azygous vein; left lower paratracheal nodes are located between the top of the aortic arch and the carina. Mediastinal nodes are divided

into anterior mediastinal nodes, located anterior to the ascending aorta or the innominate artery, and posterior mediastinal nodes, located above the tracheal bifurcation ("Esophagus and Esophagogastric Junction," 2009). Distant recurrence was defined as any site distant from the location of the original tumor. The lungs and liver combined were the most common sites of first recurrence in this group of patients, accounting for 51% of cases (Figure 1). The central nervous system (CNS), including the brain and leptomeninges, was the site of first recurrence in 8% of cases. The bones and abdominal wall were each the site of first recurrence 6% of the time. The small bowel, omentum, and serosa were the sites of first recurrence in 5% of cases, while the adrenal accounted for only 3%. The stomach, anastomosis, celiac nodes, paraaortic lymph nodes, and paratracheal nodes combined accounted for 15% of the sites of first recurrence (Figure 1). However, the mediastinal lymph nodes were the site of first recurrence in only 6% of cases. The Fisher exact test revealed a statistically significant relationship between the site of first recurrence of esophageal carcinoma and tumor histology ($P = 0.034$; Table 6).

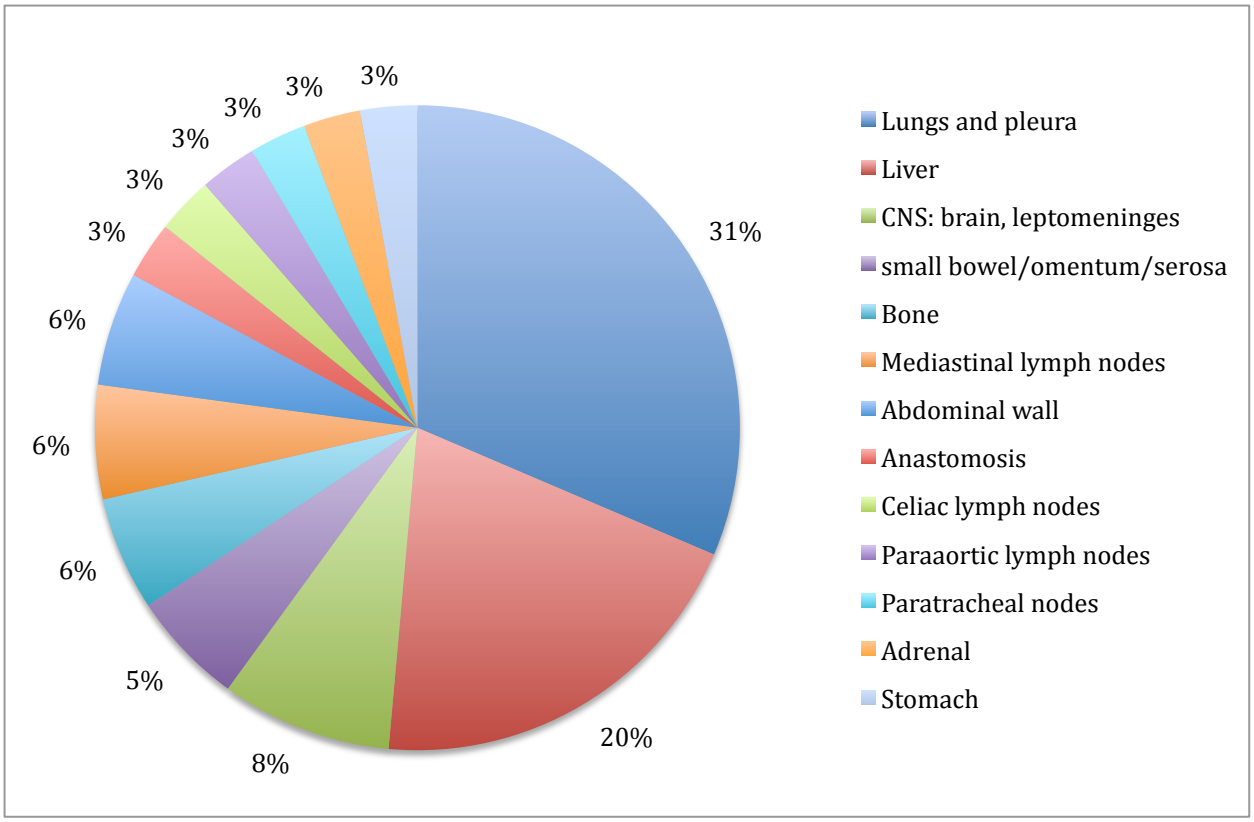

Figure 1 Patterns of First Recurrence of Esophageal Cancer

Table 6 Site of First Recurrence based on tumor histology

Tumor Histology	No recurrence	Local recurrence	Distant recurrence	Total
Squamous Cell Carcinoma	7 (77.8%)	2 (22.2%)	0	9
Adenocarcinoma	36 (56.3%)	4 (6.3%)	24 (37.5%)	64
Total	43	6	24	73

Distant recurrence is also more common than local recurrence when a patient has further disease progression beyond the site of first recurrence. Local sites accounted for only 14% of cases of later disease progression (Figure 2). The lungs were the most common site of later recurrence (33%), followed by the liver and bone at 14%

each, the CNS was involved in 10% of cases, and the gluteal muscles, chest wall, and omentum were each involved in 5% of these cases, respectively.

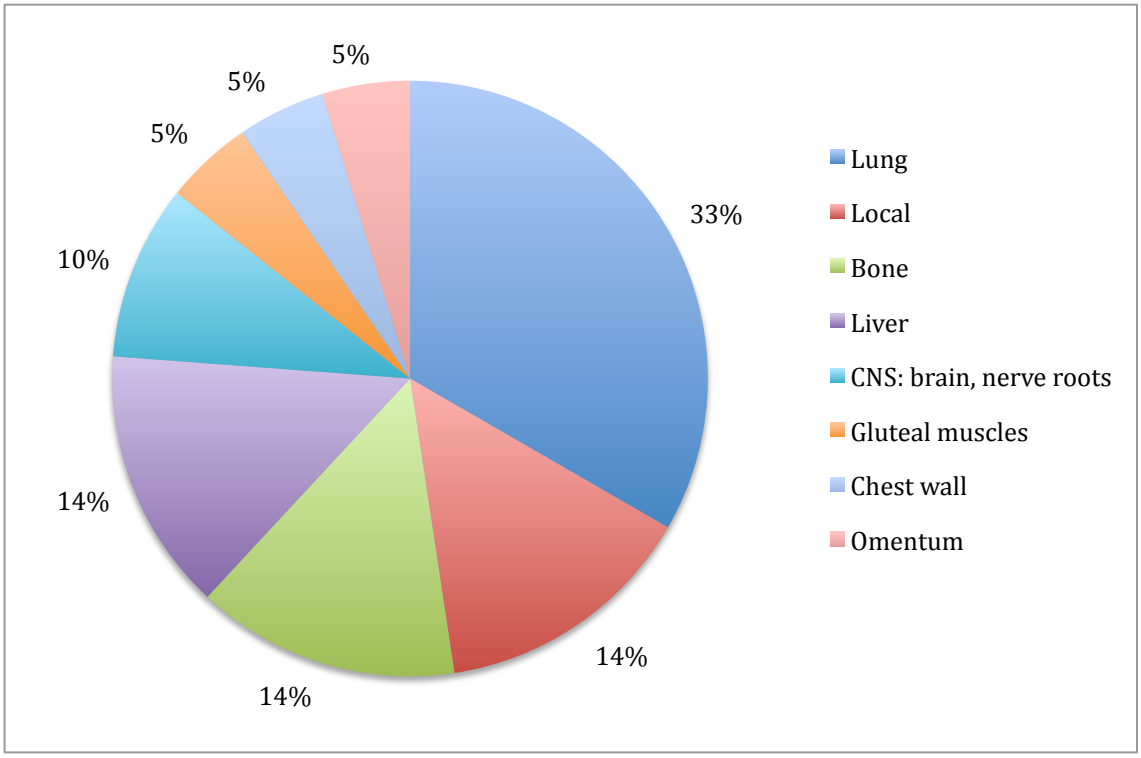

Figure 2 Patterns of Secondary Recurrence of Esophageal Cancer

In the univariable analysis for disease-free survival, the only significant factors were treatment with a dose of external beam radiation to 50 Gy, which is associated with a significant decrease in the time to recurrence (HR = 0.370, P = 0.031; Table 1), while a dose of 52 Gy to 60 Gy is associated with a poorer prognosis (HR = 5.187, P = 0.046; Table 1). The type of chemotherapy used was not a significant factor in the time to recurrence ($P > 0.05$; Table 1). In the multivariable analysis, treatment with external beam radiation therapy retained its significance with a dose of 50 Gy being associated with a significant reduction in the time to

recurrence (HR = 0.202, *P* = 0.025; Table 7), and a significant increase in time to recurrence with radiation dose of 52 Gy to 60 Gy (HR = 8.880, *P* = 0.029; Table 7). The multivariable analysis for time to recurrence also revealed that pathologic stage III disease is significantly associated with a poorer disease-free survival (HR = 4.200, *P* = 0.044; Table 7).

Table 7 Multivariable Cox Regression Analysis for Time to Recurrence

Characteristic	**No. (std dev)**	**HR**	**95% CI**	***P***
Histology				
Adenocarcinoma	54	1		
Squamous Cell Carcinoma	7	2.189	0.204-23.485	0.518
Clinical Stage				
Stage I	5	1		
Stage II	32	0.081	0.005-1.368	0.081
Stage III	24	0.243	0.017-3.527	0.300
Pathologic Stage				
Stage 0	18	1		
Stage I	10	0.508	0.053-4.885	0.558
Stage II	17	0.673	0.180-2.512	0.555
Stage III	13	4.200	1.043-16.920	0.044
Stage IV	3	0.147	0.013-1.661	0.121
Dose of external beam radiation				
45 Gy	42	1		
50 Gy	15	0.202	0.050-0.816	0.025
52 Gy - 60 Gy	4	8.880	1.248-63.183	0.029

Kaplan-Meier analysis also revealed that disease-free survival was significantly associated with the pathologic stage of the patient's tumors after chemoradiotherapy (*P* = 0.034; Figure 4).

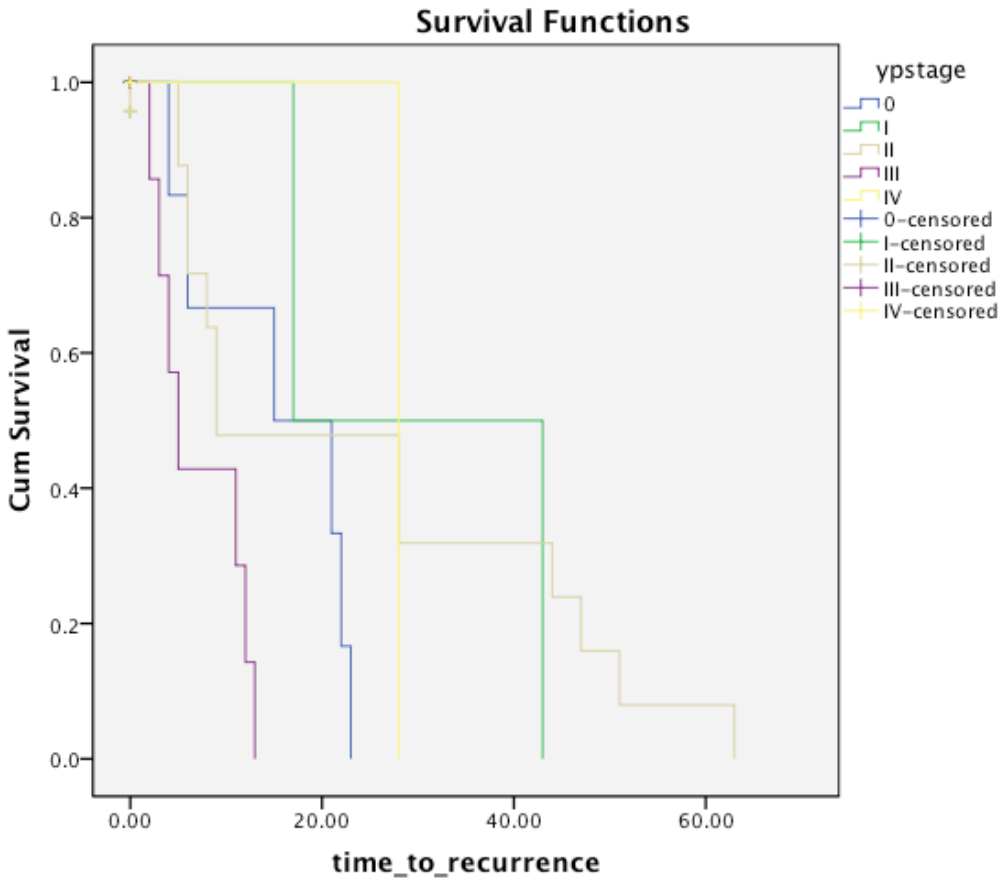

Figure 1 Kaplan-Meier Analysis showing the difference in disease free survival according to pathological stage

Kaplan-Meier analysis of disease-free survival according to the dose of neoadjuvant radiotherapy patients received also showed a significant difference in disease-free survival, with patients receiving 50 Gy having a longer disease-free period than patients receiving 45 Gy or 52 Gy to 60 Gy (P = 0.002; Figure 5). The 5-year disease-free survival was 61.6%.

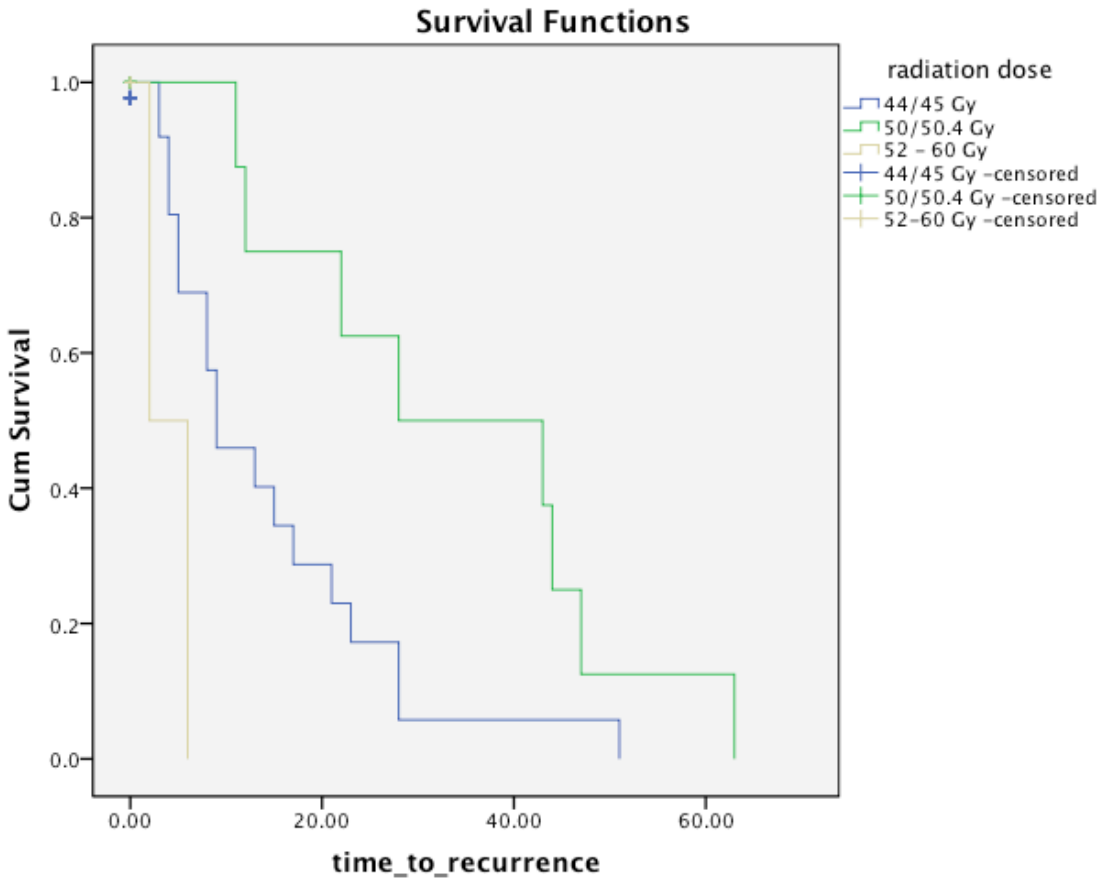

Figure 2 Kaplan-Meier Analysis showing the difference in disease-free survival according to dose of radiation therapy administered

Overall Survival

There were no significant factors in the univariable analysis for overall survival (Table 8). Likewise, in the multivariable analysis, there were no factors emerged as significantly influencing the overall survival (Table 9). The 5-year overall survival was 60.3%.

Table 8 Univariable analysis for overall survival

Characteristic	No. (std dev)	HR	95% CI	*P*
Gender				
Male	63	1		
Female	10	0.697	0.212-0.295	0.553
Age	58.63	1.016	0.976-1.058	0.439
Race				
Non-Hispanic White	64	1		
Non-Hispanic Black	6	0.518	0.121-2.230	0.378
Other	3	0.849	0.115-6.258	0.872
Alcohol use history				
No	25	1		
Yes	47	0.514	0.253-1.047	0.067
Tobacco Use history				
No	9	1		
Yes	63	3.910	0.533-28.690	0.180
Histology				
Adenocarcinoma	64	1		
Squamous Cell Carcinoma	9	2.155	0.877-5.299	0.094
Clinical Stage				
Stage I	5	1		
Stage II	36	0.474	0.105-2.137	0.331
Stage III	27	0.807	0.182-3.585	0.778
Stage IV	1	1.545	0.139-17.183	0.723
Pathologic Stage				
Stage 0	20	1		
Stage I	12	0.262	0.031-2.189	0.217
Stage II	23	2.246	0.854-5.911	0.101
Stage III	14	2.351	0.811-6.811	0.115
Stage IV	3	2.102	0.418-10.567	0.367
Response to treatment				
No response	17	1		
Downstaging without complete response	20	0.717	0.283-1.818	0.484
Downstaging with complete response	20	0.481	0.173-1.334	0.160
Disease progression	12	0.838	0.304-2.310	0.732

Type of Neoadjuvant chemotherapy received				
Cisplatin/5-FU	39	1		
Cisplatin/5-FU/Taxol	9	0.436	0.130-1.461	0.178
Cisplatin/Taxol	6	0.235	0.031-1.753	0.158
Other	15	0.528	0.199-1.399	0.199
Dose of external beam radiation				
45 Gy	43	1		
50 Gy	17	0.457	0.157-1.331	0.151
52 Gy - 60 Gy	4	0.969	0.228-4.124	0.966

Table 9 Multivariable analysis for overall survival

Characteristic	**No.**	**HR**	**95% CI**	***P***
Alcohol use history				
No	21	1		
Yes	39	0.547	0.214-1.395	0.207
Tobacco Use history				
No	8	1		
Yes	52	3.499	0.415-29.472	0.249
Histology				
Adenocarcinoma	54	1		
Squamous Cell Carcinoma	6	1.466	0.375-5.730	0.583
Pathologic Stage				
Stage 0	17	1		
Stage I	10	0.281	0.027-2.929	0.289
Stage II	18	2.024	0.524-7.812	0.306
Stage III	12	1.570	0.398-6.198	0.520
Stage IV	3	5.164	0.624-42.734	0.128
Type of Neoadjuvant chemotherapy received				
Cisplatin/5-FU	36	1		
Cisplatin/5-FU/Taxol	7	0.763	0.171-3.403	0.723
Cisplatin/Taxol	5	0	0--	0.983
Other	12	0.595	0.199-1.781	0.353
Dose of external beam radiation				
45 Gy	42	1		
50 Gy	14	0.477	0.144-1.579	0.226
52 Gy - 60 Gy	4	0.762	0.107-5.442	0.786

Discussion

In this study, we investigated a group of 73 patients diagnosed with either adenocarcinoma or squamous cell carcinoma of the distal esophagus, gastroesophageal junction, or the gastric cardia. All patients received neoadjuvant chemoradiotherapy before undergoing a transhiatal esophagectomy with minimal mediastinal lymph node dissection. We hypothesized that aggressive mediastinal control at the time of surgery may be obviated by the use of neoadjuvant chemoradiotherapy.

Although the transthoracic esophagectomy has been associated with improved disease-free and overall survival compared to the transhiatal approach, it is also associated with greater perioperative morbidity partly due to the extensive lymph node dissection involved (Altorki, et al., 2008; Hulscher, et al., 2002; Lee, et al., 2009; Maruyama, et al., 2009; Peyre, et al., 2008; Schipper, 2009; Stiles, et al., 2009). Having neoadjuvant chemoradiotherapy before transhiatal esophagectomy has been shown to improve overall survival and patients also have a lower overall morbidity compared to their counterparts who have the more extensive surgery without neoadjuvant therapy (Gebski, et al., 2007; R. A. Malthaner, et al., 2006; Meguid, et al., 2009). It is therefore conceivable that improving neoadjuvant therapy at the time of transhiatal esophagectomy may further improve disease-free survival and overall survival without increasing moribidity.

Thirty patients in this study had recurrence of disease after trimodality therapy. The data further showed that in carcinomas of the distal esophagus, GEJ, and gastric cardia, distant recurrence is significantly more common than local

recurrence after trimodality therapy, regardless of tumor histology. Given the sample size of 30 recurrence events, in a post-hoc power calculation in which the power is set to 80%, and at a 0.05 significance level, compared to the null proportion of 0.5 (representing equal proportions of both local recurrences and distant recurrences), the minimum change detectable in either group is 0.21. This corresponds to a proportion of 0.71 in one group and 0.29 in the other, that is, 9 recurrences in one group and 21 in the other group. In this study, the differences in proportion of each group were 0.80 in the distant recurrence group, and 0.20 in the local recurrence group, both of which are greater than the minimum difference required for 80% power. It has also been shown previously that distant recurrence is more common than local recurrence (Kleinberg, et al., 2003). The most common sites of first recurrence as well as later recurrence in this study were the lungs and liver, followed by the bones and the central nervous system. Since the sites of failure after transhiatal esophagectomy are more likely to be distant from the site of the primary tumor than in the mediastinal lymph nodes or even locally at the anastomosis, this obviates the need for extensive mediastinal lymph node dissection at the time of surgery and suggests the need for improved systemic therapy. Although other studies have shown a trend toward improved disease-free and overall survival with chemotherapy, in the current study, the neoadjuvant chemotherapy regimen did not significantly impact disease-free survival (Kleinberg, et al., 2003; R. A. Malthaner, et al., 2006). However, in this retrospective study, the type of neoadjuvant chemotherapy as well as the duration of administration was not controlled and a randomized controlled trial comparing standard chemotherapy

regimens with regard to disease-free survival in this patient population is needed to determine how neoadjuvant chemotherapy affects disease recurrence.

The rates of failure were significantly associated with the pathologic stage of the disease as patients who had stage III disease after chemoradiotherapy tended to have recurrence earlier than their counterparts who had either no residual disease after therapy or those who had residual disease but stage lower than III. The pathological response to therapy and pathologic stage after therapy have also been shown to be important predictors of survival (Kleinberg, et al., 2003; Meredith, et al.). Only 3 patients in the study had stage IV disease after therapy and with this small sample of patients, there was no significant association of having pathologic stage IV disease after trimodality therapy and the time to recurrence. Although many patients who had residual disease in the study were treated adjuvantly, these regimens varied with the provider and the numbers were too small to include in the analysis. However, since sites of failure are predominantly distant, a goal for future study may be to investigate how systemic adjuvant chemotherapy affects disease-free survival in patients with residual disease after trimodality therapy.

Failure rates were reduced with a dose of neoadjuvant radiotherapy of 50 Gy compared to a dose of 45 Gy. The improvement in disease-free survival with a slightly higher dose of radiation may be related to enhanced tumor downstaging leading to a lower pathological stage of disease, which was also shown to be associated with risk of disease recurrence. However, the number of patients who received 50 Gy radiation was small (n = 17) compared to those who received 45 Gy (n = 43) and there may be confounding factors such as the difference in disease

burden before therapy that may be masked by this small number. Given the sample sizes in the 45 Gy and 50 Gy groups, a post-hoc power calculation in which power is set to 80% will detect a minimum difference in hazard ratio of 0.5. This corresponds to a 50% difference in risk of recurrence. The hazard ratio obtained in this case was 0.202, which is a difference in hazard ratio of 1.798, which is greater than the minimum difference of 0.5.

On the other hand, rates of failure appeared to increase with radiation dose between 52 Gy and 60 Gy (P = 0.029) but the confidence interval was large (1.248-63.183) and the result is limited by both the small number of patients (n = 4) who received a dose in this range as well as the disease burden of the patients before therapy that may have influenced the decision to treat with a higher radiation dose. Given the sample sizes of patients who received 45 Gy and those who received 52-60 Gy, a post-hoc power calculation in which power is set to 80% will detect a minimum difference in hazard ratio of 1.5. This corresponds to a 150% difference in risk of recurrence. The hazard ratio obtained in this case was 8.880, which is greater than the minimum difference of 1.5. A randomized controlled trial comparing different doses of radiation with respect to rates of recurrence would limit the confounding and determine how radiation doses above 50 Gy affect disease-free survival, bearing in mind patient safety as the risk of esophagitis increases with radiation doses above 40-50 Gy (Werner-Wasik, Yorke, Deasy, Nam, & Marks).

Demographic factors, lifestyle factors, as well as tumor histology and clinical stage did not significantly affect disease-free survival. However, lifestyle factors

have been implicated in previous studies (Kountourakis, et al.; Vaughan, Davis, Kristal, & Thomas, 1995). The reasons for the difference may include sample size and differences in the quantification of alcohol of tobacco use. In the current study, it was not possible to quantify the quantity of alcohol a patient consumed daily as this information was not necessarily present in the patients' medical record.

It has been shown previously that overall survival improves in patients who have a pathologic complete response after receiving neoadjuvant chemoradiotherapy (Kleinberg, et al., 2003; Slater, Holland, Faigel, Sheppard, & Deveney, 2001). Although dose of neoadjuvant radiotherapy and pathologic stage impacted disease-free survival, neither impacted overall survival. Furthermore, no other factor emerged as significantly affecting overall survival. This may be due to the fact that patients in the study died from multiple causes including metastatic esophageal carcinoma, perioperative complications, and multiple other causes.

There are several limitations in this study: (1) small sample size, (2) lack of a control group, and (3) the retrospective nature of the study. The small sample size increases the probability that observations made are by chance, thus limiting our ability to find significant relationships that may actually exist. In particular, the small number of patients with squamous cell carcinoma and the small number of female patients makes observations about relationships of these groups to disease recurrence difficult to determine statistically. Achieving a large sample size is a challenge since esophageal carcinoma is relatively rare, so multicenter studies would be necessary to achieve a large sample size. The study did not have a control group of patients who did not have neoadjuvant chemoradiotherapy before surgery,

or patients who had chemoradiotherapy with transthoracic esophagectomy thus direct comparisons of the impact of the therapy versus other treatment options cannot be made, and a prospective randomized controlled study would be useful for that purpose. Finally, the retrospective nature of the study limits the ability to control for confounding factors although it enables us to determine significant relationships.

Since local failure rates were significantly lower than distant failure rates in this study, it appears that aggressive mediastinal control at the time of esophagectomy in patients with adenocarcinoma or squamous cell carcinoma of the distal esophagus, GEJ and/or gastric cardia, who have received neoadjuvant chemoradiotherapy, is unnecessary. Furthermore, since pathologic stage of disease is significantly associated with disease recurrence, more efforts should be made to improve systemic therapy prior to and/or after resection.

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