Published in final edited form as:
Cancer. 2011 March 1; 117(5): 925–930. doi:10.1002/cncr.25651.

Combined Modality Therapy of cT2N0M0 Esophageal Cancer: UT M. D. Anderson Cancer Center Experience

P. Kountourakis, **A. M. Correa**, **W. L. Hofstetter**, **J. H. Lee**, **M. S. Bhutani**, **D. C. Rice**, **R. Komaki**, **D. M. Maru**, **W. A. Ross**, **A. Vaporciyan**, **S. G. Swisher**, and **J. A. Ajani**
Departments of Gastrointestinal Medical Oncology (PK, JAA) and Gastroenterology, Hepatology, and Nutrition (JHL, MSB, WAR), and Thoracic and Cardiovascular Surgery (AMC, WLH, DCR, AV, SGW), Pathology (DMM), and Radiation Oncology (RK) at the University of Texas M. D. Anderson Cancer Center, Houston, Texas

Abstract

Background—Treatment strategy for patients with adequately staged cT2N0M0 carcinoma of the thoracic esophagus is a subject of debate. We analyzed the largest series of consecutive cT2N0M0 esophageal cancer patients treated with preoperative chemoradiotherapy.

Methods—All patients with cT2N0M0 (assessment included endoscopic ultrasonography and computed tomography of the chest and abdomen) thoracic esophageal cancer treated with preoperative chemoradiation between 1997 and 2009 were analyzed. We used the Cox regression model and Kaplan-Meier plots to analyze the data.

Results—Forty-nine patients were analyzed. The median follow-up was 28.46 months. Men and adenocarcinoma histology predominated. Pathologic complete response was observed 19 (39%) patients. Ten-year actuarial overall survival (OS) for adenocarcinoma patients was >60%. In the univariate analysis for OS, squamous histology (p=0.006), smoking (p=0.015), and alcohol consumption (p=0.032) were associated with poor OS. In the univariate analysis for disease-free survival (DFS), squamous histology (p=0.009) and smoking (p=0.014) were associated with poor DFS. In the multivariate analysis for OS, smoking was an independent prognosticator (p=0.02). In the multivariate analysis for DFS, advanced yp stage (p=0.05) and nodal metastases (p=0.006) were independent prognosticators. Patients with adenocarcinoma (p=0.002) and those with ypN0 had better OS and DFS. Upward stage migration occurred in only 10% of patients.

Conclusions—Our data suggest that smoking and alcohol influence the long-term outcome of cT2N0M0 patients. Adenocarcinoma patients treated with trimodality therapy had an excellent actuarial 10-year OS and a high rate of pathologic complete response. Trimodality therapy should be prospectively compared with primary surgery in these patients.

Keywords

esophageal cancer; cT2N0M0; preoperative chemoradiotherapy; prognostic factors

Esophageal carcinoma is an aggressive malignancy and a major cause of cancer–related deaths worldwide.1 The incidence of esophageal adenocarcinoma has been rising faster than that of any other cancer in the western world for several decades2, 3 and in 2009, a total of 16,470 new cases and 14,530 deaths were estimated in the United States.4 Therapy options available to patients with localized ≥cT1b esophageal cancer located in the thoracic cavity

Address Correspondence to: Jaffer A. Ajani, MD, Department of GI Medical Oncology, UT M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, 713-792-2828, Jajani@mdanderson.org.

include primary surgery, preoperative therapy, or definitive chemoradiation therapy.5 Patients with cT1a cancer are best treated by an endoscopic mucosal resection and cT1bN0 by primary surgery but surgery for cT2-3 N1 or N0 cancer leads to poor survival at 5 years and preoperative therapy is often utilized without unequivocal level 1 evidence.6 Preoperative chemoradiation is preferred in the USA7, 8 and preoperative chemotherapy is less preferred as two randomized trials are essentially negative.9, 10

cT2N0 is a particularly interesting entity and its primary treatment remains a subject of debate. Only limited information is available in the literature.11 Rice et al. made a number of important observations that have implications on potential therapeutic strategies. All their 53 cT2N0M0 patients, who underwent surgery as primary therapy, were staged by computerized tomographic scans and endoscopic ultrasonography, however, only 7 (13%) had ypT2N0M0 and 17 (32%) had a higher yp stage than the clinical stage. The overall 10-year survival of 53 patients was approximately 30%. The authors also reported on 8 patients who had preoperative chemoradiation therapy, they all did poorly. It would appear from this solitary experience that there is considerable stage migration (in both directions) and that the outcome of patients with surgery alone is poor. Nevertheless, surgery as primary therapy for this group of patients is not ruled out.

Clearly, cT2N0M0 esophageal cancer is not a common entity and there is no agreement as to how these patients should be treated. Rice et al. recommended surgery first as their preference and postoperative adjuvant therapy if needed. They also emphasized the need for more accurate clinical staging methods. In this manuscript, we present our experience with 49 patients who were fully staged and received preoperative chemoradiation therapy.

Patients and Methods

Patients

We searched the Thoracic and Cardiovascular Department's esophageal cancer database at the University of Texas MD Anderson Cancer Center between January of 1997 and March of 2009 to find 49 consecutive patients who were fully staged and designated as cT2N0M0 and all had received preoperative chemoradiation.

Patients were included if they had upper gastrointestinal endoscopy with biopsy and adenocarcinoma or squamous carcinoma histology, cT2N0M0 staging by endoscopic ultrasonography and computed tomography of the chest and abdomen. All eligible patients were aged ≥ 18 years. No other selection criteria were implemented. Positron emission tomography scans were performed when available (n=34). Staging was determined based on the American Joint Committee on Cancer TNM staging.12 This analysis was approved by the Institutional Review Board of U. T. M. D. Anderson Cancer Center.

Therapy

Preoperative chemotherapy consisted of a fluoropyrimidine and the second drug was either a platinum compound or a taxane. Radiation dose varied from 45 to 50.4 Gy, in daily fractions of 1.8 Gy. The details of radiation therapy are similar to those published recently from our institution.13–15

Approximately 5-6 weeks after the completion of chemoradiation, all 49 patients underwent esophagectomy with lymph node dissection with curative intent. The types of surgery were: transthoracic (Ivor-Lewis), 35 patients; transhiatal esophagectomy, 8 patients; total esophagectomy (three-field techniques), 2 patients; and minimally invasive esophagectomy, 4 patients.

Follow-up and Survival

Patients were followed periodically until 10 years or until death. Additional follow-up data were obtained from review of MDACC tumor registry and the hospital records or social security database. Follow-up time was calculated from the date of surgery to the event or to the date of the last contact.

Statistical Analysis

Data were collected in prospective manner with a standardized protocol. All statistical analyses were performed using the SPSS Statistical Software Package, version SPSS 15.0 (SPSS Inc, Chicago, Ill). The differences between groups were tested for significance by student's t test for continuous variables and Fisher's exact test or X^2 test for categorical variables. Univariable Cox regressions analyses were performed using death and recurrence or death as the outcomes with a significance level of $p<0.05$. Covariates that were significant at $p<0.25$ were included into the multivariable Cox regressions. Backward stepwise Wald elimination at $p=0.10$ was used to find a final model. Death and recurrence or death functions were calculated according to the Kaplan-Meier method and differences were assessed using the log-rank test.

Results

Patient Characteristics

Patients and tumor characteristics are summarized in Table 1. Median age was 58 years (range, 33-77 years). Of 49 patients, 45 were men and 4 were women and the majority were Caucasians (n=47). Adenocarcinoma was found in 44 patients and squamous cell cancer in 5 patients. Histology was poorly differentiation in 17 patients. The tumor location had been principally at the lower esophagus and/or gastroesophageal junction (46/49).

Outcomes

The median follow up was 28.46 months (range, 1.6-141.07). Thirty-four patients (69.38%) were alive and thirty-two patients (65.3%) were free of disease at last contact. The 5-year rates for overall survival (OS) and disease-free survival (DFS) were 64.1% and 58.4%, respectively. Mean OS was 92.617 months (*95 CI%:* 72.921-112.314). In the univariable analysis for overall survival: squamous histology (p=0.006), smoking (p=0.015), and alcohol consumption (p=0.032) were identified as significant factors for poorer prognosis (Table 1). The mean disease-free survival was 86.327 months (*95 CI*%: 66.316-106.339). Moreover, in the univariable analysis for disease-free survival: squamous histology (p=0.009) and smoking (p=0.014) were identified as adverse prognostic factors (Table 2).

However, in the multivariable analysis for overall survival, only smoking retained its significance (p=0.02). In addition, advanced pathological (yp) stage (p=0.05) and lymph node metastases (p=0.006) were predictive for worse DFS in the multivariable analysis (Table 3).

Pathologic stage assessed in the surgical specimen by histology subtypes is shown in Table 4. Only 5 (10%) of patients had higher yp stage than cT2N0M0. Pathologic complete response occurred in 15 (34%) of 44 adenocarcinoma patients compared to 3 (60%) of 5 squamous cell carcinoma patients (p=0.342). In addition, 12 (27%) patient had yp stage I adenocarcinoma.

Discussion

Lifestyle factors such as cigarette smoking, alcohol consumption, and body mass index (BMI) have been identified as contributors to the risk of esophageal carcinoma.16 However, it is unclear if such factors influence prediction of response to therapy or prognosis in general of patients with esophageal carcinoma. In a 618-patient study conducted in Sweden17, increased BMI was a favorable prognostic factor for patients with adenocarcinoma but tobacco use and low levels of education were associated with poor outcome in patients with squamous cell carcinoma. Although, in our small study, smoking and alcohol appear prognostic, a considerably larger effort is needed to determine the role various lifestyle elements.

Whether the prognosis of patients with similar clinical stage but with either adenocarcinoma or squamous cell carcinoma is different remains an unresolved issue. Published literature suggests that patients with adenocarcinoma might fare better than those with squamous cell carcinoma.18, 19 Our study cannot adequately address this issue as it had only 5 patients with squamous cell carcinoma, albeit their prognosis and despite non-significantly higher pathologic complete response rate, was unfavorable compared to the larger cohort of adenocarcinoma patients. Since biologically these two histologies are quite different and one could anticipate different clinical behavior but this needs further elucidation with larger number of patients.

Our study provides the only large series of adequately staged cT2N0M0 patients treated with preoperative chemoradiation therapy. Our findings demonstrate that post-surgical upstaging is uncommon compared to a report of patients who received surgery as primary therapy and had considerable upstaging but we anticipated downstaging in our cohort because of the use of preoperative chemoradiation. Our study also demonstrates that the actuarial 10-year survival rate of patients with cT2N0M0 adenocarcinoma is 60% and although our results cannot be compared to those by others, they are encouraging. Our study also suggests that the pathologic complete response rate is quite decent in patients with adenocarcinoma.

Our study also suffers from a number of drawbacks and these include: (1) retrospective nature of the analysis, (2) small number of patients with squamous histology, and (3) small number of overall sample size resulting in questionable results such as yp stage not correlating significantly with overall survival and lifestyle elements emerging as independent prognosticators. Our study cannot resolve the issue of what would be the best therapy for patients with adequately staged cT2N0M0 esophageal cancer but suggests that a prospective evaluation may be warranted. It is acknowledged that a prospective randomized phase III trial is likely not possible because of the paucity of patients with this stage of esophageal cancer but a creative phase II randomized trail is a possibility.

In conclusion, our study demonstrates that cT2N0M0 patients treated with preoperative chemoradiation have an excellent overall survival and disease-free survival. These results provide support for multimodality therapy of this group of patients but with recognition that further research is necessary to establish the most effective therapeutic algorithm.

Acknowledgments

Supported in part by Dallas, Park, Smith, and Cantu Family funds and by the Reivercreek Foundation. Also supported by the Multidisciplinary Research Program Grant from UT M. D. Anderson Cancer Center, and the NCI Grants (CA142072, CA127672, and CA129906)

Bibliography

1. Parkin, DM.; Bray, F.; Ferlay, J.; Pisani, P. Global cancer statistics, 2002; CA Cancer J Clin. 2005. p. 74-108.http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15761078
2. Oesophageal (gullet) cancer. [October 14, 2008]. 2008 Available from URL: http://info.cancerresearchuk.org/cancerstats/types/oesophagus/incidence/
3. Brown, LM.; Devesa, SS.; Chow, WH. Incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, and age; J Natl Cancer Inst. 2008. p. 1184-7.http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18695138
4. Jemal, A.; Siegel, R.; Ward, E.; Hao, Y.; Xu, J.; Thun, MJ. Cancer statistics, 2009; CA Cancer J Clin. 2009. p. 225-49.http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19474385
5. Ajani, JA.; Barthel, JS.; Bekaii-Saab, T.; Bentrem, DJ.; D'Amico, TA.; Fuchs, CS.; Gerdes, H.; Hayman, JA.; Hazard, L.; Ilson, DH.; Kleinberg, LR.; McAleer, MF.; Meropol, NJ.; Mulcahy, MF.; Orringer, MB.; Osarogiagbon, RU.; Posey, JA.; Sasson, AR.; Scott, WJ.; Shibata, S.; Strong, VE.; Swisher, SG.; Washington, MK.; Willett, C.; Wood, DE.; Wright, CD.; Yang, G. Esophageal cancer; J Natl Compr Canc Netw. 2008. p. 818-49.http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18926093
6. Ajani, JA. Resectable Esophageal Cancer: Surgery As Primary Therapy Is Not the Answer, but Then, What Is and Why?. J Clin Oncol. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20368554
7. Suntharalingam, M.; Moughan, J.; Coia, LR.; Krasna, MJ.; Kachnic, L.; Haller, DG.; Willett, CG.; John, MJ.; Minsky, BD.; Owen, JB. The national practice for patients receiving radiation therapy for carcinoma of the esophagus: results of the 1996-1999 Patterns of Care Study; Int J Radiat Oncol Biol Phys. 2003. p. 981-7.http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12829133
8. Suntharalingam, M.; Moughan, J.; Coia, LR.; Krasna, MJ.; Kachnic, L.; Haller, DG.; Willet, CG.; John, MJ.; Minsky, BD.; Owen, JB. Outcome results of the 1996-1999 patterns of care survey of the national practice for patients receiving radiation therapy for carcinoma of the esophagus; J Clin Oncol. 2005. p. 2325-31.http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15800323
9. Kelsen, DP.; Ginsberg, R.; Pajak, TF.; Sheahan, DG.; Gunderson, L.; Mortimer, J.; Estes, N.; Haller, DG.; Ajani, J.; Kocha, W.; Minsky, BD.; Roth, JA. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer; N Engl J Med. 1998. p. 1979-84.http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9869669
10. Allum, WH.; Stenning, SP.; Bancewicz, J.; Clark, PI.; Langley, RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer; J Clin Oncol. 2009. p. 5062-7.http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19770374
11. Rice, TW.; Mason, DP.; Murthy, SC.; Zuccaro, G., Jr; Adelstein, DJ.; Rybicki, LA.; Blackstone, EH. T2N0M0 esophageal cancer; J Thorac Cardiovasc Surg. 2007. p. 317-24.http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17258554
12. Greene, FL. AJCC cancer staging atlas / American Joint Committee on Cancer. New York, NY: Springer; 2006. c2006

13. Ajani, JA.; Correa, AM.; Walsh, GL.; Komaki, R.; Lee, JH.; Vaporciyan, AA.; Rice, DC.; Yao, JC.; Maru, DM.; Hofstetter, WL.; Phan, AT.; Swisher, SG. Trimodality therapy without a platinum compound for localized carcinoma of the esophagus and gastroesophageal junction; Cancer. p. 1656-63.http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20143431

14. Javeri, H.; Arora, R.; Correa, AM.; Hofstetter, WL.; Lee, JH.; Liao, Z.; McAleer, MF.; Maru, D.; Bhutani, MS.; Swisher, SG.; Izzo, JG.; Ajani, JA. Influence of induction chemotherapy and class of cytotoxics on pathologic response and survival after preoperative chemoradiation in patients with carcinoma of the esophagus; Cancer. 2008. p. 1302-8.http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18623381

15. Javeri, H.; Xiao, L.; Rohren, E.; Lee, JH.; Liao, Z.; Hofstetter, W.; Maru, D.; Bhutani, MS.; Swisher, SG.; Macapinlac, H.; Wang, X.; Ajani, JA. The higher the decrease in the standardized uptake value of positron emission tomography after chemoradiation, the better the survival of patients with gastroesophageal adenocarcinoma; Cancer. 2009. p. 5184-92.http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19685531

16. Vaughan, TL.; Davis, S.; Kristal, A.; Thomas, DB. Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma; Cancer Epidemiol Biomarkers Prev. 1995. p. 85-92.http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7742727

17. Sundelof, M.; Lagergren, J.; Ye, W. Patient demographics and lifestyle factors influencing long-term survival of oesophageal cancer and gastric cardia cancer in a nationwide study in Sweden; Eur J Cancer. 2008. p. 1566-71.http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18434132

18. Holscher, AH.; Bollschweiler, E.; Schneider, PM.; Siewert, JR. Prognosis of early esophageal cancer. Comparison between adeno- and squamous cell carcinoma; Cancer. 1995. p. 178-86.http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8625089

19. Siewert, JR.; Stein, HJ.; Feith, M.; Bruecher, BL.; Bartels, H.; Fink, U. Histologic tumor type is an independent prognostic parameter in esophageal cancer: lessons from more than 1,000 consecutive resections at a single center in the Western world; Ann Surg. 2001. p. 360-7.discussion 68-9. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11524589

Table 1
Patient and treament characteristics and univariable Cox regression for overall survival

Characteristic	No	HR	95% CI	*p*-value
Gender				
Male	45	1		
Female	4	0.045	0-864.924	0.539
Age	49	1.009	0.961-1.059	0.726
Histology (Carcinoma)				
Adenocarcinoma	44	1		
Squamous Cell	5	6.839	1.719-27.211	0.006
Grade				
Moderate differentiated	23	1	0.214-2.194	0.524
Poorly Differentiated	17	0.685		
Tumor location				
Middle	3	1		
Lower/GEJ	46	0.27	0.058-1.253	0.095
Type of esophagectomy				0.07
Transthoracic (Ivor-Lewis) (reference)	35	1		
Transhiatal	8	0.603	0.132-2.759	0.514
Total (3-field technique)	2	1.309	0.167-10.285	0.798
Minimally invasive	4	8.752	1.567-48.893	0.013
Tumor size(cm)				
<3	41	1		
≥3	3	0.042	0-117.881	0.435
Pathological stage				0.644
Stage 0 (reference)	19	1		
Stage I	13	0.737	0.176-3.092	0.676
Stage II	5	1.681	0.533-5.303	0.376
Stage III	2	0	0 - ---	0.452
BMI				
<25	17	1		
≥25	31	0.436	0.151-1.261	0.125
Alcohol use(≥4oz/day)				
No	36	1		
Yes	13	3.038	1.1-8.388	0.032
Smoking				
No	27	1		
Yes	22	6.411	1.444-28.469	0.015

HR denotes hazard ration; CI denotes confidence interval.

Table 2
Univariable Cox regression for disease-free survival

Characteristic	No	HR	95% CI	*p*-value
Gender				
Male	45	1		
Female	4	0.045	0-421.884	0.507
Age	49	1.015	0.969-1.063	0.54
Histology (Carcinoma)				
Adenocarcinoma	44	1		
Squamous Cell	5	6.164	1.586-23.962	0.009
Grade				
Moderate differentiated	23	1	0.255-2.122	0.569
Poorly Differentiated	17	0.735		
Tumor location				
Middle	3	1		
Lower/GEJ	46	0.295	0.064-1.353	0.116
Type of esophagectomy				0.146
Transthoracic (Ivor-Lewis) (reference)	35	1		
Transhiatal	8	0.501	0.112-2.244	0.366
Total (3-field technique)	2	1.077	0.139-8.323	0.943
Minimally invasive	4	5.195	1.050-25.705	0.043
Tumor size(cm)				
<3	41	1		
≥3	3	0.042	0-56.342	0.388
Pathological stage				0.410
Stage 0 (reference)	19	1		
Stage I	13	0.728	0.174-3.052	0.664
Stage II	5	1.926	0.629-5.894	0.251
Stage III	2	2.304	0.262-20.238	0.452
BMI				
<25	17	1		
≥25	31	0.434	0.161-1.168	0.098
Alcohol use(≥4oz/day)				
No	36	1		
Yes	13	2.462	0.948-6.396	0.064
Smoking				
No	27	1		
Yes	22	4.818	1.381-16.814	0.014

HR denotes hazard ration; CI denotes confidence interval.

Table 3
Multivariable Cox regressions for overall survival and disease free survival

Characteristic	No	HR	95% CI	p-value
Overall Survival				
Smoking				
No	27	1		
Yes	21	5.932	1.324-26.567	0.02
Disease-Free Survival				
Lymph nodes involvement				
No	46			
Yes	3	9.034	1.863-43.811	0.006
Pathological stage				0.050
Stage 0 (reference)	19	1		
Stage I	13	0.789	0.166-3.752	0.766
Stage II	15	1.077	0.301-3.856	0.909
Stage III	2	0	0-0.013	0.011

HR denotes hazard ration; CI denotes confidence interval.

Table 4
Pathologic stage following surgery by histologic types (n=49)

Pathologic Stage	Adenocarcinoma	Squamous cell carcinoma	Total
0	16	3	19
I	12	1	13
IIA	13	1	14
IIB	1	0	1
III	2	0	2
Totals	44	5	49