Treatment outcome and prognostic factors in non-metastatic esophageal carcinoma

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ABSTRACT

Objectives: To investigate the therapeutic outcome and prognostic factors in patients with non-metastatic esophageal carcinoma.

Methods: Between January 1989 and December 2003, 171 patients with non-metastatic esophageal carcinoma patients were retrospectively assessed in the Department of Radiation and Oncology, Institute of Oncology, Turkey.

Results: The distribution of the stage at presentation designated 39 stage II patients (23%) and 132 stage III patients (77%). The primary tumors were treated with surgery and postoperative radiotherapy (RT) in 29 patients (17%), with surgery, postoperative RT and chemotherapy (CT) in 17 patients (10%), with radical RT in 40 patients (23%), and with RT and CT in 47 patients (27%). Fourteen patients (8%) did not receive any postoperative adjuvant treatment. Two and three-year survival rates of the whole group were 27.0% and 14.8%, respectively. Clinical staging was the only statistically significant prognostic factor by multivariate analyses (p=0.04). Median survivals by the treatment groups were 12.5 months for surgery alone, 16 months for surgery plus postoperative RT, 15 months in surgery plus postoperative chemoradiotherapy, 9 months in radical RT alone and 17 months in chemoradiotherapy group. Survival advantage was not demonstrated for postoperative RT or RT plus CT. Outcomes were similar between the patients treated with surgery and with chemoradiotherapy (p=0.54). Patients treated with chemoradiotherapy had a longer survival than patients treated with only RT (p=0.05).

Conclusion: The most important prognostic factor was the stage of the disease. Survival advantage was not demonstrated for postoperative RT or RT plus CT. Outcomes were similar between patients treated by surgery and by chemoradiotherapy.

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Carcinoma of the esophagus has been considered as a neoplasm with poor prognosis. Most of the patients present at an advanced stage of disease and with dysphagia. Esophageal obstruction may also cause weight loss, regurgitation and pulmonary damage. The incidence of esophageal cancer has risen in recent decades and its epidemiology has changed during the past decade.[1,2] Adenocarcinoma is seen more frequently in middle-aged males with a history of gastroesophageal reflux, whereas squamous cell cancer occurs more commonly in the proximal and middle esophagus of older patients who have history of smoking and alcohol abuse.[3] There are many prognostic factors for esophageal cancer. Weight loss and low performance status indicate poor prognosis. Tumor size is also important and the extent of a tumor is correlated with its size. Additional prognostic factors, which are found significant, are gender and age.[4-6] Nowadays, the most important factor determining the treatment intent (either curative or palliative) is the stage of the disease. There are number of approaches to the treatment of esophageal cancer. These include surgery alone, surgery plus preoperative or postoperative radiation therapy (RT) and/or chemotherapy (CT), preoperative combined modality therapy, radiation alone, or combined modality therapy.[3] Although the overall results of surgery and non-surgery approaches are similar, it must be emphasized that the patient population selected for treatment with each modality is quite different. The aim of this study was to investigate the demographic features, prognostic factors and therapeutic outcome in patients with non-metastatic esophageal carcinoma.

Methods. One hundred and seventy-one patients were referred to the Department of Radiation and Oncology, Institute of Oncology, Turkey, between January 1989 and December 2003. Patients who had histologically confirmed non-metastatic esophageal carcinoma were retrospectively assessed. Diagnosis was made with endoscopy and biopsy. Clinical staging was made according to American Joint Committee on Cancer (AJCC).[7] The treatment modalities were surgery only, surgery and adjuvant RT, surgery and adjuvant RT + CT, only RT, RT + CT, and palliative RT. The effect of RT and RT + CT administration on survival was assessed in postoperative patients. Radiotherapy was applied with parallel-opposed Co-60 fields by delivering 1.8-2 Gy daily fractions (according to the treatment field size). Initial 44-46 Gy was given using parallel opposed AP/PA fields and was followed by treatment with 2 anterior oblique fields sparing the spinal cord The total dose was 45-50.4 Gy in postoperative RT and 54-60 Gy in radical RT. Chemotherapy regimen, which consisted of 5-fluorouracil (600 mg /m^2 intravenously on days 1-5 of the cycle per 28 days) and cisplatin (60 mg/m^2 intravenously on day one of the cycle) was combined with RT. Chemotherapy regimen was begun on the first day of RT period concomitantly and administrated in the 1st and 5th, 9th, 13th weeks of treatment period. The median number of CT cycles was 3 (minimum 1- maximum 4). The potential prognostic factors evaluated for tumor related mortality (overall survival) were age (≤60 years or >60 years), gender (male/female), localization (cervical/thoracic/distal), histological subtypes (well differentiated/moderately differentiated/poorly differentiated squamous cell/ adenocarcinoma), stage (II/III), nodal stage (N0/ N1), weight loss (<10%/>10%) and treatment modality. The treatment modalities compared as prognostic factors were surgery versus surgery, adjuvant RT+ CT; surgery versus surgery, adjuvant RT; surgery versus RT + CT; RT versus RT + CT. The date of diagnosis was accepted as the beginning date for the calculation of the survival. The last follow up date has been accepted as the end point for the assessment of overall survival. The overall survival was calculated according to the method of Kaplan-Meier and the differences were estimated by the Long-rank test to analyze the significant prognostic factors. Multivariate analysis of these prognostic factors was then performed using the Cox proportional hazards model.

Results. The patients' age ranged were from 21 to 87 years with a median age of 56 years. The male to female ratio was 1:2. Seventy-seven percent of patients referred to the hospital with dysphagia and weight loss. Thirty- four percent of the patients with weight loss had lost over 10% of their weight. The most frequent tumor location was distal esophagus (46%). With the help of the radiological findings, clinical staging was performed according to American Joint Committee on Cancer (AJCC).[7] Diagnosis was made with endoscopic biopsy in 55% of the patients. Most of the cases were at stage III (77%) according to radiological findings. The most common histological type was squamous cell carcinoma (95%). The types of surgery in 60 operated patients were total esophagectomy (68%), distal esophagectomy (20%) and transhiatal esophagectomy (12%). In 6 patients (5%) stent was applied into the esophagus. Patients' characteristics were reported in **Table 1**. Sixty-four patients (37.5%) received CT. The treatment groups were presented in **Table 2**. The median follow-up of patients was 24 months (range: 8-63 months). The 2 and 3-year overall survival rates were 27.0% and 14.8%, respectively and the median survival was 12.5 ± 1.2 months (95% CI: 10.09-14.91). Twenty-two (13%) patients were alive at the time of the analysis. Distant metastases had developed in 40 patients. The most common metastatic region was lung (20 patients),

Table 1 - Patients characteristics.

Characteristics	No. of patients	(%)
Gender		
Male	94	(55)
Female	77	(45)
Symptoms		
Dysphagia	40	(23)
Dysphagia + weight lost	131	(77)
Weight lost		
<10%	73	(43)
>10%	58	(34)
Localization		
Cervical	42	(25)
Thoracic	50	(29)
Distal	79	(46)
Histology		
Well diff. squa. cell	50	(40)
Moderately diff. squa. cell	44	(35)
Poorly diff. squa. cell	24	(20)
Adenocarcinoma	7	(5)
Stage		
II	39	(23)
III	132	(77)
Nodal stage		
N0	33	(19)
N1	91	(53)
NX	47	(28)
Surgery		
Total	41	(24)
Transhiatal	7	(4)
Distal	12	(7)

D - dysphagia, W - weight lost, diff - differentiation, squa - squamous

followed by liver (12 patients), brain (4 patients), surrenal gland (3 patients) and bone (3 patients). The overall survival rates according to various prognostic factors were shown in **Table 3**. In univariate analysis, the overall survival rate was significantly higher in stage II patients (17 months) than stage III patients (11 months) (log-rank = 3.37; degree of freedom (df) =1; p=0.05). Nodal stage was also determined as a statistically significant prognostic factor for survival (log-rank=8.06; df =2; p=0.01). Other factors had no effect on overall survival. The only factor, which predicted the overall survival, was by staging and by multivariate analyses. Risk of death was 1.65 times higher in stage III patients than stage II patients (95% CI: 1.04-2.50; SD: 1; p=0.03) (**Figure 1**). In the surgery alone group (13 patients were stage II and one patient was stage III), the median survival was 12.5 months. The median survival was 16 months in patients who were treated with postoperative RT and 15 months in patients who were treated with postoperative RT + CT. In these 2 postoperative groups, median survival times were almost equal and the difference was not statistically significant (log rank=0.37; df= 1; p=0.54). In our series, there is no clear demonstration for the survival advantage for postoperative RT + CT or RT. When survival of the surgery alone group (median 12.5 months) was compared with the non-surgery RT + CT group (median 17 months), no significant differences were found (log-rank= 0.17; df=1; p=0.67). In the non-surgical treatment group, there were statistically significant difference only between RT and RT + CT (median 9 months versus 17 months, respectively) (log-rank=6.01; df=1; p=0.01). The median survival times of therapy groups were shown in **Table 2**.

Discussion. At present, esophageal carcinoma is among the first 5 cancer types responsible for cancer related death.[3] Stage II and stage III patients with esophageal carcinoma apply to the clinics more than stage I patients. This can be explained by both late diagnosis and advanced stage. In a retrospective analysis, to evaluate patient characteristics and treatment factors influencing outcome of patients treated with definitive

Table 2 - Treatment groups.

Treatment groups	No. of patient (%)	Median survival (months)
Surgery	14 (8)	12.5
Surgery + RT	29 (17)	16
Surgery + RT + CT	17 (10)	15
RT	40 (23)	9
RT + CT	47 (27)	17
Palliative RT	24 (15)	7.5

RT - radiotherapy, CT - chemotherapy

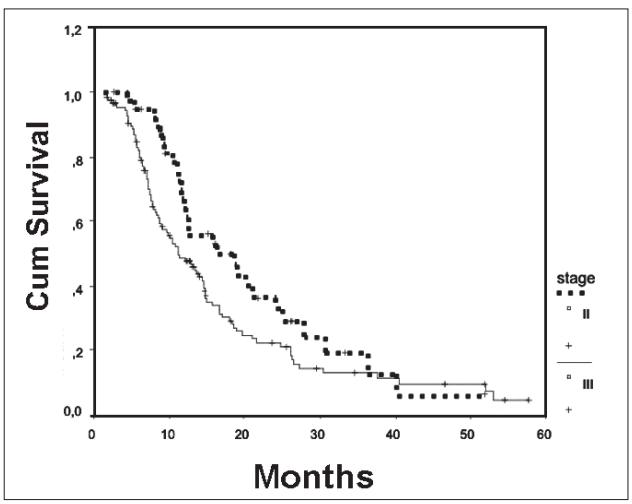

Figure 1 - The survival analyses according to stage II and stage III.

Table 3 - The overall survival rates according to various prognostic factors.

Parameters	2 years survival (%)	Median survival (month)	*P* value (Log Rank - SD)
Age			
≤60	26	13	NS
>60	27	13	
Gender			
Male	22.5	13	NS
Female	31	15	
Weight lose			
<10%	24.5	12	NS
>10%	18	11	
Localization			
Cervical	16	9	NS
Thoracic	32	14	
Distal	28	16	
Histology			
Well diff. squamous cell	25	17	NS
Moderately diff. squamous	32	20	
Poorly diff. squamous	32	19	
Adenocarcinoma	45	16	
Stage			
II	37	17	0.05
III	22.5	11	(3.37 - 1)
Nodal stage			
N0	42	14	0.01
N1	14	11	(8.06 - 1)
NX	42	14	

NS - Non significant, diff - differentiation

radiotherapy, the pretreatment T stage showed the most powerful influence on both survival and local control[5] Lymphatic spread is an independent prognostic factor.[8] Age >65 years, weight loss and low overall performance status also indicate poor prognoses.[8] Patients with lesions in upper third of esophagus carry out better than those with lesions in the lower two-thirds of esophagus.[8] The retrospective analysis of our series revealed that in esophageal carcinomas the most important prognostic factor was staging. In operated patients, the effect of adjuvant therapy for local relapse and survival is controversial. Although, non-randomized studies supported the postoperative RT,[9] these results have not been verified by the randomized studies.[10,11] In the first published randomized study, adjuvant postoperative RT had also showed no advantage for survival. But in this trial, local relapse decreased from 35-10% in patients with nodes spared and treated with postoperative RT.[11] The study of Fok et al[11] have shown no significant overall survival benefit for postoperative radiation therapy over surgery in esophagus squamous cell and adenocarcinoma patients. In our study, 14 patients were treated with surgery only, 29 patients were treated with adjuvant RT and 17 patients were treated with postoperative RT + CT. Due to small number of patients, 3 therapy groups did not statistically significant difference (median survival 12.5 months, 16 months, 15 months). Also it should be noted that the total doses and techniques of radiotherapy have changed to a great extent since 1989. As in the other studies in the literature, the poor prognostic patients were more commonly selected for nonsurgical therapy.[3] Besides, non-surgical series report results based on clinically staged patients, whereas surgical series report results based on pathologically staged patients. Pathological staging has the advantage of excluding some patients with metastatic disease. Furthermore, some of the patients treated without surgery are approached in a palliative rather than potentially curative fashion, thus the intensity of CT and the doses and techniques of RT are frequently suboptimal.[3] Postoperative combined RT and CT especially have been examined in lymph node positive patients. Bedard et al showed that local relapse had decreased in node positive patients with postoperative RT and CT. But the real advantage was observed in overall survival (median survival 14.1 months versus 47.5 months, p=0.001).[12] In our study, only 4 of 17 patients who were treated with postoperative RT and CT were node negative, the others were node positive. Since the patient numbers were small, no statistical analysis was performed. So, concomitant RT + CT regimens did not show any survival difference. Although there are no randomized studies that compare surgical therapy with combined RT + CT regimes, many non-randomized trials have shown that comparable local control and survival rates could be obtained with combined modality non-surgical treatment and with surgery.[13-19] Combined modality treatments are given to the patients with advanced stage and/or poor performance status, which are known to be the most important factors for the outcome in these studies. Chan et al[15] compared surgery and combined RT + CT group retrospectively. Median survival of the combined treatment group (15 months) and surgery group (16 months) were almost the same although early stage patients were more in the surgery group. In our study even though the stage distribution of the treatment groups were not homogeneous in favor of surgery alone group, patients treated with combined RT + CT had a longer survival than the patients treated with the surgery (17 months versus 12.5 months). There was no statistical difference between the 2 groups. So combined RT and CT regime can be a strong alternative to surgery. In our study, for non-surgery group (87 patients), radical RT (40 patients) or combined RT + CT (47 patients) were administered. In the literature in order to avoid perioperative mortality and to relieve dysphagia, definitive radiation therapy in combination with chemotherapy has been studied.[16] An Intergroup Randomized Trial, Radiation Therapy Oncology Group (RTOG) 85-01, of chemotherapy and radiation therapy versus radiation therapy alone resulted in an improvement in 5-year survival for the combined modality group (27% versus 0%).[16] An Eastern Cooperative Oncology Group trial of 135 patients showed that chemotherapy plus radiation provided a better 2-year survival rate than radiation therapy alone,[20] which was similar to that shown in the Intergroup Trial.[20] Chemotherapy regimes and RT doses of our series are similar to Radiotherapy Oncology Group (RTOG 85-01) study.[8] But in our study, radical RT doses were heterogeneous between 52 Gy and 60 Gy and did not reach to 64 Gy. In our series, the median survival of the concomitant therapy group and radical RT group were 17 months and 9 months, respectively (p=0.01). After this study, concomitant RT + CT has become the standard therapy of locally advanced esophageal carcinoma in our clinic. However, concomitant therapy regimes have not been used in patients with low performance status (Karnowsky PS <70).

In conclusion, the retrospective analysis of our series revealed that in esophageal carcinomas the most important prognostic factor was clinical staging. Survival advantage was not demonstrated for postoperative RT or RT + CT. Outcomes were similar between the patients treated by surgery and by chemoradiotherapy. Patients treated with chemoradiotherapy had a longer survival than the patients treated with RT only. Even with the current treatment, survival of esophageal cancers is quite low, and the first relapse areas are mostly

the primary disease area. The insufficiency of single treatment modalities has moved the treatment trends to concomitant RT and CT and using surgery schemes with the aim of increasing local control and survival.[21-24] Also special attention to nutritional support is indicated in any patient undergoing treatment of esophageal cancer.

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