RESEARCH ARTICLE

Impact of Tumor Length on Survival for Patients with Resected Esophageal Cancer

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Abstract

Background: Tumor length in patients with esophageal cancer (EC) has recently received great attention. However, its prognostic role for EC is controversial. The purpose of our study was to characterize the prognostic value of tumor length in EC patients and offer the optimum cut-off point of tumor length by reliable statistical methods. Materials and Methods: A retrospective analysis was conducted on 71 consecutive patients with EC who underwent surgery. ROC curve analysis was used to determine the optimal cut-off point for tumor length, measured with a handheld ruler after formalin fixation. Correlations between tumor length and other factors were surveyed, and overall survival (OS) rates were compared between the two groups. Potential prognostic factors were evaluated by univariate Kaplan-Meier survival analysis. A P value less than 0.05 was considered significant. Results: There were a total of 71 patients, with a male/ female divide of 43/28 and a median age of 59. Characteristics were as follows: squamous/adenocarcinoma, 65/6; median tumor length, 4 (0.9–10); cut-off point for tumor length, 4cm. Univariate analysis prognostic factors were tumor length and modality of therapy. One, three and five year OS rates were 84, 43 and 43% for tumors with ≤4cm length, whereas the rates were 75, 9 and 0% for tumors >4 cm. There was a significant association between tumor length and age, sex, weight loss, tumor site, histology, T and N scores, differentiation, stage, modality of therapy and longitudinal margin involvement. Conclusions: Future studies for modification of the EC staging system might consider tumor length too as it is an important prognostic factor. Further assessment with larger prospective datasets and practical methods (such as endoscopy) is needed to establish an optimal cut-off point for tumor length.

Keywords: Survival - esophageal cancer - tumor length - ROC curve - postoperative chemo radiotherapy - Iran

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Introduction

Esophageal cancer (EC) is the fifth most common cause of cancer-related death in the East Azerbaijan province, north-west of Iran (Somi et al., 2008). The prognosis in this region still remains poor with a 5-year survival of around 12% and a median survival of 13 months (mirinezhad et al., 2012). Studies are needed to define the prognostic factors to delineate more effective interventions.

Tumor length is still a controversial prognostic factor in EC patients (Feng et al., 2013). Before 1987, the American Joint Committee on Cancer (AJCC) staging system used tumor length to predict patients' prognosis (Beahrs et al., 1983; Sobin et al., 1988); however, the current TNM classification system does not consider a prognostic role for tumor length in the staging of EC (Edge et al., 2010). Controversy exists concerning the optimal cut-off points for tumor length to predict overall survival. Different sample sizes, different histological types, variable inclusion criteria, and most importantly unreliable statistical methods used to determine the cut-off points have contributed to this controversy (Wang et al., 2011). In current study, patients with EC who underwent surgery without receiving preoperative chemotherapy or radiotherapy were enrolled to illuminate the prognostic effect of tumor length in these patients. The purpose of our study was to characterize the prognostic value of tumor length and offer the optimum cut-off point by reliable statistical methods for tumor length in EC patients.

Materials and Methods

From March 2006 to March 2011, a retrospective analysis was conducted on 71 consecutive patients with EC who underwent curative surgery. The pathology

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examination was done after preservation of the tissue in 10% neutral buffered formalin .Tumor length was measured with a handheld ruler and was recorded in the results of all pathologic reports. The histological details of tumor in all the patients in the study were achieved from the pathology records. Staging of the tumor was performed using the standard guidelines and the AJCC esophageal cancer staging system. As any intervention prior to surgery may shrink the tumor length and confound the data of tumor length, patients who received preoperative chemotherapy or radiotherapy were excluded. Patients with metastatic diseases were also excluded from the current study. Survival status and postoperative data were gained from telephone contacts and hospital records respectively. The survival time was measured as the interval between date of pathological diagnosis, after endoscopy and date of death from any cause.

Statistical analysis

Data analysis was performed using the statistical Package, SPSS version 16.0. The overall survival (OS) rates were computed according to the life-Table method of Kaplan-Meier and compared by the Log-rank test. Data analysis was carried out for demographic, pathology and clinical features. Descriptive statistics were expressed as means±standard deviation and percentage. Grouped data were stated as the median (range) and non-parametric methods were used. The appropriate cut-off point for tumor length predicting 5-year survival was determined using the receiver-operating characteristic (ROC) curve, from which the area under the curve (AUC) was determined and the Youden index corresponding to each length was calculated (Figure 1). $p<0.05$ was considered as statistically significant.

Results

Clinicopathological characteristics of patients

Seventy one patients (28 women and 43 men) were identified as patients who have undergone resection of EC between March 2006 and March 2011. The median age was 59 years (range 29-80). Clinicopathological characteristics of the patients are shown in Table 1. Sixty five squamous-cell carcinomas (91%) and six (9%) adenocarcinomas were included in the study. The most common tumor location was the lower esophagus (54%).

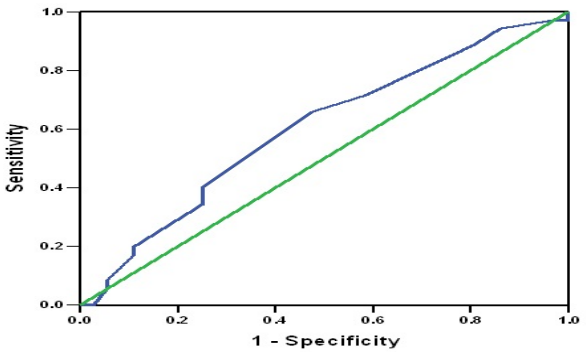

Figure 1. Receiver-Operating Characteristic Curve for an Optimal Cut-off Point of 4 cm

Of the 71 patients, 48 patients had a tumor length of 4 cm or less and 23 patients had a tumor length greater than 4 cm. in 6 patients (9%) out of 71 patients longitudinal margin were involved.

Optimal Cut-off point for the tumor length

Tumor length as measured after fixation diverse, ranged from 0.9 to 10 cm. The mean±SD of the tumor length was 4±1.5 cm and the median tumor length was 4 cm. ROC analysis indicated an optimal cut-off point of 4 cm to have a sensitivity of 65.7% and a specificity of 52.8%, (1-47.2%) in prognostic survival after esophageal surgery (AUC=0.601, 95%CI: 0.469-0.734, p=0.01) (as shown in Figure 1). Based on this cutoff value, the patients were divided into 2 groups, with 23 (32%) having tumor length > 4cm and 48 (68%) having tumor length≤4 cm.

Analyses of prognostic factors

Table 1 shows the results of the Kaplan-Meier univariate survival analysis. For all tumor types (Figure.2), tumor length greater than 4 cm was a significant poor prognostic factor (p=0.01). The 1, 3 and 5 year OS rates were 84%, 43% and 43%, respectively for tumors less than or equal to 4 cm, whereas in tumors greater than 4 cm these rates were 75%, 9% and 0%, in that order. Age, sex, weight loss, tumor location, histology, T stage, N stage, Tumor differentiation, Tumor stage, modality therapy and longitudinal margin involvement were not statistically associated with survival (p>0/05).

Table 2 shows the correlation between tumor length (less than or equal to 4 cm *vs* greater than 4

Table 1. Clinicopathological Characteristics of the patients with Esophageal Cancer

Characteristic		Total =71 No (%)	5- Year Survival (%)	p value (Log-rank)
Age years	<65	51(72)	34	0/71
	65 ≥	20(28)	30	
Sex	Female	28(40)	36	0/63
	Male	43(60)	31	
Tumor length	≤ 4	48(68)	43	0/01
	>4	23(32)	0	
weight loss	No	58(82)	35	0/26
	Yes	13(18)	26	
Tumor Site	Upper/ middle	33(46)	32	0/88
	Lower	38(54)	34	
Histology	SCC	65(91)	37	0/41
	AC	6(9)	0	
T stage	T2	14(20)	49	0/35
	T3	57(80)	29	
N stage	N0	40(56)	40	0/145
	N1	31(44)	22	
Tumor Differentiation	well	52(73)	40	0/77
	Moderate / poor	13(27)	0	
Tumor stage	II	44(62)	41	0/133
	III	27(38)	0	
Modality therapy	S	17(24)	37	0/068
	S/CRT	45(63)	39	
	S/RT	9(13)	0	
Longitudinal margin involvement				
	NO	65(91)	31	0/45
	Yes	6(9)	48	

*S=Surgery, CRT=Chemoradiotherapy, RT=Radiotherapy

Table 2. Characteristics of Patients with Tumor Length more or less than 4 cm

Characteristic		Tumor length N (%)/ Median(moon) ≤4 (cm)	>4 (cm)	p value (Log-rank)
Age	<65	33(65)/ 32	18(35)/ 18	0/01
	65 ≥	15(75)/ 34	5(25)/ 24	
Sex	Female	16(57)/ 48	12(43)/ 17	0/01
	Male	32(74)/ 26	11(26)/ 23	
weight loss	No	42(72)/ 33	16(28)/ 19	0/03
	Yes	6(46)/ 24	7(54)/ 19	
Tumor Site	Upper/ middle	21(64)/ 31	12(36)/ 22	0/02
	Lower	27(71)/ 33	11(29)/ 14	
Histology	SCC	45(69)/ 34	20(31)/ 19	0/01
	AC	3(50)/ 27	3(50)/ 19	
T stage	T2	9(64)/ 48	5(36)/ 23	0/01
	T3	39(68)/ 31	18(32)/ 19	
N stage	N0	26(65)/ 34	14(35)/ 21	0/01
	N1	22(71)/ 28	9(29)/ 13	
Tumor Differentiation	well	33(63)/ 48	19(37)/ 21	0/01
	Moderate/ poor	10(77)/ 30	3(23)/ 18	
Tumor stage	II	30(68)/ 34	14(32)/ 21	0/02
	III	18(67)/ 28	9(33)/ 13	
Modality therapy	S	10(59)/ 34	7(41)/ 19	
	S/CRT	33(73)/ 34	12(27)/ 30	0/008
	S/RT	5(55)/ 30	4(45)/ 16	
Longitudinal margin involvement				
	NO	43(66)/ 31	22(34)/18	0/008
	Yes	5(83)/48	1(17)/30	

*S=Surgery, CRT=Chemoradiotherapy, RT=Radiotherapy

Table 3. Diagnosis Methods and Determine of Cut-off Point

Author/Date	MM	CP
Our study/2013	Formalin fixation	4 cm
Feng JF/2013	After resection	4 cm
Chao IK/2013	Barium swallow (CT)	6 cm
Song Z/2012	After resection	3 cm
Davies L/2012	EUS	10 cm
Wang BY/2011	After resection	3 cm
Gaur P/2011	Endoscopy	2 cm
Sillah K/2010	Formalin fixation	3.5 cm

*MM=Methods of measurement, CP=Cut-off point

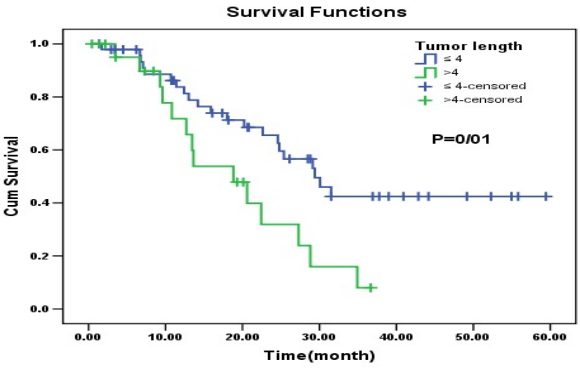

Figure 2.Patients with Tumor Length ≤4.0 cm had a Significantly Better 5-year Survival Rate than Patients with a Tumor Length >4.0 cm (43% versus 0%, p=0.01)

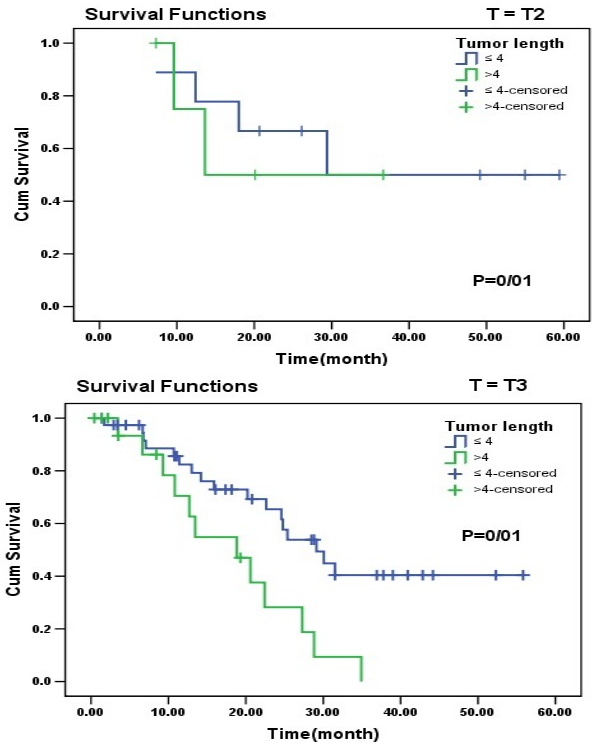

Figure 3. Kaplan–Meier Survival Curves Stratified by Tumor Length in T2 and T3 Patients (p=0.01)

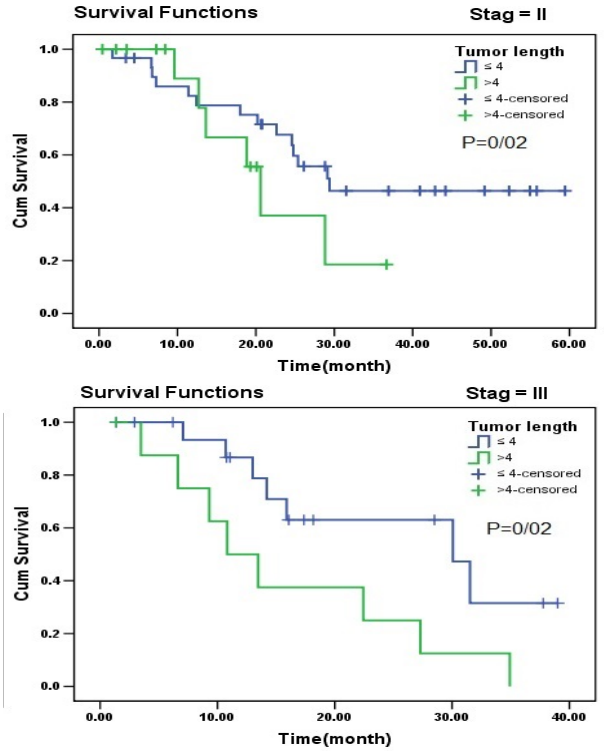

Figure 4. Kaplan-Meier Survival Curves Stratified by Tumor Length in stage II and III Patients (p=0.01)

cm) and other clinico-pathological variables. There was statistical significant association between tumor length and patient age (p=0.01), sex(p=0.01), weight loss(p=0.03), tumor site(p=0.02), histology (p=0.01), tumor differentiation(p=0.01), modality of therapy (p=0.008) and longitudinal margin involvement (p =0/008). Tumor length greater than 4cm was associated with increasing T stage (p=0.01), N stage (p=0.01), and TNM stage (p=0.02). The median survival was 25.37±3.86 (95%CI=17.81-32.93) months with 1, 3 and 5 year OS rates of 81%, 33% and 33%, respectively. Patients with tumor length≤4.0 cm had a significantly better median survival time than patients with a tumor length >4.0 cm (29.4 mo versus 19 mo, p=0.01) (Figure 2). In the group

of T2 and T3 disease, the median survival time of patients with tumor length ≤4.0 cm was better than that of patients with tumor length >4.0 cm (48 mo versus 23 mo, p=0.771 and 31mo versus 19 mo, p=0.035 respectively) (Figure. 3). The median survival time in patients with tumor length≤4.0 cm was better than patients with a tumor length >4.0 cm in stage II and III (34mo versus 21mo, p=0.046 and 28mo versus 13mo, p=0.035 respectively) (Figure 4).

Discussion

This study evaluated the impact of tumor length on survival rate of patients with EC for the first time from the northwest region of Iran. The prognostic role of tumor length in patients with EC has recently received greater attention again; however, an optimal cut-off point for tumor length to predict the overall survival is still controversial.

There are many potential methods of assessing tumor length including barium esophagram, esophago-gastroscopy, computed tomography (CT), EUS, positron emission tomography (pET) imaging and histopathological examination (Table 3). Consequently the optimal cut-off point might be different with the method of diagnosis. Formalin fixation may cause tumor shrinkage and subsequently lead to the small estimation of cut -off point for tumor length. Siu et al. found that esophageal tumors shrink 10% after formalin fixation. Furthermore, the overall shrinkage of the whole esophageal specimen after fixation was 50% (Siu et al., 1986).

Results of the current study indicated that when survival was stratified by the tumor length in T status (T2 and T3), it was a significant prognostic factor (p=0.01-Figure.3). These results are consistent with previous studies (Wang et al., 2011; Song et al., 2012; Feng et al., 2013). In our study, the esophageal tumor length had a significant impact on survival of patients in N0 and N1 (p=0.01-Figure.4) that is contrary to the result reported by Feng et al. (2013) who suggested that tumor length is not a prognostic factor for ESCC patients with N staging (p=0.119). This difference may be explained by a more advanced stage of the tumor at the time of diagnosis in patients of our region.

Similar results were reported by Davies et al. (2012) indicating that tumor length was a prognostic factor for survival in univariate analysis. There are several reports who demonstrated tumor length as a prognostic factor for survival in univariate analysis; as well as a multivariate analysis (Gaur et al., 2011; Wang et al., 2011; Song et al., 2012; Feng et al., 2013). In the current study, tumor length was a prognostic factor after controlling the factor of tumor stage (p=0.02) but a multivariate statistical analysis was not possible for the tumor length. Results of this study had some potential limitations. They include a relatively small number of patients and the nature of the analysis which was retrospective. However the study included all of eth patients in the described period of time in a referral center. In addition, as the study used data from different pathologists, a lack of uniformity in measurement methods may limit the results in some part.

In conclusion, this study introduced the length of the esophageal tumor to be a valuable prognostic factor for survival of patients. Future studies for modification of the EC staging system might consider tumor length too as it is an important prognostic factor. Further assessment with larger prospective datasets and practical methods (such as endoscopy) is needed for an optimal cut-off point for tumor length.

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