

Improvement in the Survival of Esophageal Cancer Patients at Cancer Institute of Iran after Implementation of the Neo-adjuvant Chemo-radiation: Retrospective Cohort Study

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Abstract

Background: Iran is a high-risk area with a poor prognosis for esophageal cancer. We conducted the present study to evaluate the survival rate of esophageal cancer after the introduction of neo-adjuvant chemo-radiation at the Cancer Institute of Iran.

Method: We performed a retrospective cohort study and abstracted the data of 421 patients who referred to the Cancer Institute of Iran between 2007 and 2011. Life table and Kaplan-Meier approaches were applied to estimate 1-, 3-, and 5-year survival rates and corresponding 95% confidence intervals (CI). Multiple Cox regression model was recruited for investigating the association between 5-year survival rate and prognostic factors.

Results: We found that 1-, 3-, and 5-year survival rates were 66.7%, 28.2, and 20.9%, respectively. The hazard ratio (HR) was significantly higher among the patients who has received definitive chemo-radiation therapy (Hazard ratio (HR) = 2.2, 95% confidence interval (CI): 1.1, 4.2), surgery (HR= 2.0 95% CI: 1.0, 3.7), and palliative care (HR= 4.2, 95% CI: 2.1, 1.8) compared with those who received neo-adjuvant chemo-radiation and surgery. We also found that the 5-year survival rate was doubled in the current study conducted between 2007 and 2011 (20.9%) compared with the previous one conducted between 1997 and 2006 (10.0%). Additionally, a considerable improvement was observed in 1- and 3-year survival rate of esophageal cancer at the Cancer Institute of Iran.

Conclusion: Following the administration of neo-adjuvant chemo-radiation therapy, the prognosis of esophageal cancer has improved significantly at the Cancer Institute of Iran during the last decade. More data from other cancer centers and provinces of Iran are required.

Keywords: Esophagus, Neoplasms, Staging, Chemoradiation, Survival

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Introduction

Esophageal cancer has a poor prognosis and known as the sixth leading cause of cancer death worldwide.¹ Despite the recent increase in the incidence of adenocarcinoma, squamous cell carcinoma of esophagus remained as the most prevalent histopathology in esophageal cancer.¹ Tumor locations, stage at diagnosis, tumor histology, age at diagnosis, and treatment protocol are the main prognostic factors affecting esophageal cancer survival.² Although there is a considerable variation in 5-year relative survival of esophageal cancer worldwide, several studies from China (11.0%), the UK (15%), and the USA (20.6%) have reported a quite poor prognosis for esophageal cancer patients.³⁻⁵

Iran is located in a high incidence area called "the esophageal cancer belt", stretching from the Caspian littoral area in Iran to northern China and including areas with incidence rates >100/100000.⁶ According to national estimates

incidence of esophageal cancer is increasing in Iran and the ASR reached from 6.8 in 2008 to 8.4 in 2012 and it is projected that by continuing the same pattern the incidence of esophageal cancer will increase by three times in 2035.^{7,8} Few studies have evaluated the 5-year survival of esophageal in Iran, in which poor prognosis and extremely low survival rate have been reported,⁹ specifically in northern provinces, such as Golestan (14.0%) and Ardabil (1%).^{9,10} In our previous study, we reported that 5-year survival of esophageal cancer was about 10% at the Cancer Institute of Iran.¹¹ We hypothesized that the low survival could be linked to the delays in the diagnosis and lack of neo-adjuvant chemo-radiation therapy.

In the current study, we updated the analysis and examined survival rate and prognostic factors of esophageal cancer patients admitted to the Cancer Institute of Iran from 2007 to 2011.

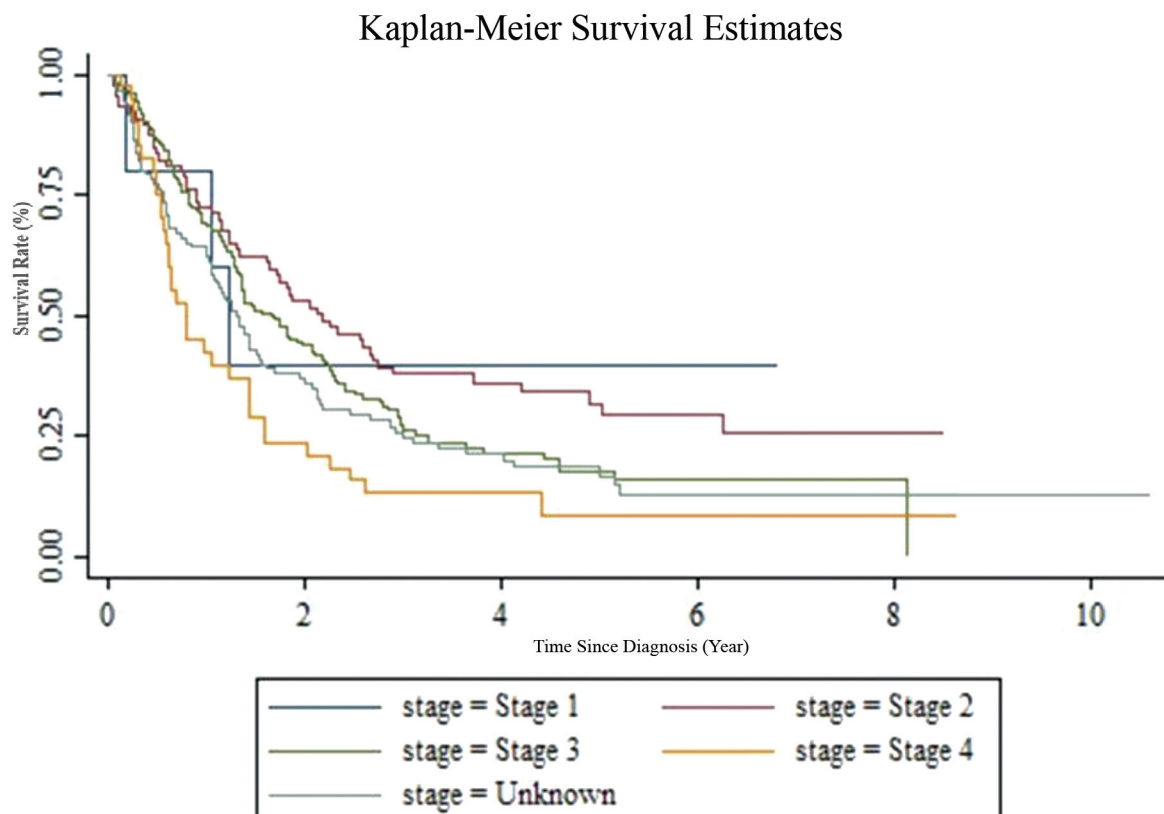


Figure 1. This figure displays the survival of esophageal cancer patients at the Cancer Institute of Iran by type of treatment in 2007-2011.

Table 1. The 1-, 3-, and 5-year survival rates and corresponding 95% CI by different prognostic factors among esophageal cancer patients at Cancer Institute of Iran in 2007-2011

Variables	n (%)	1 Year	95% CI	3 Year	95% CI	5 Year	95% CI
Gender							
Female	207 (49.0)	68.4	61.4, 74.3	29.9	23.3, 36.6	20.8	14.8, 27.5
Male	214 (50.9)	65.0	58.1, 71.1	26.6	20.4, 33.2	21.0	15.0, 27.6
Age at diagnosis							
<50	44 (10.4)	67.0	50.8, 78.9	34.6	20.5, 49.0	27.3	14.0, 42.5
50-59	97 (23.0)	73.5	63.4, 81.2	35.6	25.6, 45.7	31.0	21.2, 41.3
60-69	113 (26.8)	68.4	58.5, 76.4	22.5	14.4, 31.8	16.0	8.3, 25.9
+70	167 (39.7)	61.9	53.8, 68.9	25.8	18.9, 33.2	15.8	10.0, 22.8
Type of treatment							
Neoadjuvant Chemoradiation+surgery	55 (13.0)	88.6	76.5, 94.7	46.0	31.4, 59.4	42.0	26.9, 56.3
Chemoradiation	109 (25.8)	64.7	54.8, 73.0	27.7	19.0, 37.1	24.1	15.6, 33.8
Adjuvant surgery	133 (31.5)	70.0	61.3, 77.2	32.9	24.5, 41.5	21.3	14.1, 29.6
Sedative chemo/ radiotherapy	85 (20.1)	43.9	33.0, 54.2	12.1	5.9, 20.7	10.4	4.6, 18.8
Unknown	39 (9.2)	79.2	62.7, 89.0	26.2	13.2, 41.2	8.4	1.7, 22.3
Stage at diagnosis							
Early	95 (22.5)	73.4	63.1, 81.3	38.3	27.8, 48.7	32.8	22.4, 43.6
Advanced	213 (50.6)	64.8	57.9, 70.9	24.9	18.9, 31.4	16.8	11.3, 23.2
Unknown	113 (26.8)	64.5	54.8, 72.6	26.1	17.9, 35.0	18.4	11.2, 27.1
SES							
High	140 (33.3)	77.3	67.6, 84.4	39.2	29.1, 49.0	31.1	21.3, 41.5
Middle	116 (27.5)	64.5	53.3, 73.6	35.4	24.9, 46.0	26.2	16.3, 37.1
Low	165 (39.2)	59.1	49.7, 67.4	22.3	26.9, 44.0	14.8	8.7, 22.4
Calendar period at diagnosis							
2007-2009	192 (45.6)	63.7	56.4, 70.2	26.6	20.2, 33.4	19.7	14.0, 26.0
2010-2011	229 (54.3)	69.1	62.6, 74.8	29.5	23.2, 36.1	22.2	15.9, 29.3
Overall	421 (100)	66.7	61.8, 71.0	28.2	23.3, 33.0	20.9	16.6, 25.5

CI= Confidence interval, SES: Socio-economic status

Material and Methods

Source of data

The current study was a retrospective cohort study carried out on 421 esophageal cancer patients admitted to the Cancer Institute of Iran between 2007 and 2011. The follow-up information was gathered through the medical records and telephone interviews with patients or their next of kin. Informed consent was taken from each participant during the telephone interviews. All the interviews were performed by a trained interviewer from 1st January 2015 to 15th March 2015. In general, we could not contact 232 patients (response rate 64.4%) during our active follow-up process. We compared the baseline information of the study participants to censored cases to make sure whether any systematic errors have occurred. Information on age at diagnosis time, sex, date of diagnosis, type

of treatment, tumor histopathology, types of treatment, tumor histopathology, and residence of the area were extracted from the medical records. Moreover, they were also asked about socio-economic status (SES) at diagnosis time and filled an SES questionnaire, including the following items: personal car, television, vacuum cleaner, washing machine, dish machine, personal computer or laptop, side-by-side refrigerator, and air conditioner during the interview. Study participants were also asked about their house size and their education level at diagnosis time of esophageal cancer. Moreover, an oncosurgeon (M. Sh.) reviewed and confirmed tumor stage based on pathology reports and available clinical data. We used AJCC 7th edition cancer staging manual. We also used the AJCC clinical staging system for patients who did not undergo surgery. Due to lack of enough power and according to

Table 2. Hazard ratios and corresponding 95% CIs for different prognostic factors among esophageal cancer patients at Cancer Institute of Iran in 2007-2011

Variables	Hazard ratio	95% CI	P- value
Gender			
Female	Reference		
Male	1.0	0.7, 1.3	0.937
Age at diagnosis			
<50	Reference		
50-59	1.0	0.6, 1.8	0.838
60-69	1.2	0.7, 2.1	0.467
+70	1.2	0.7, 2.2	0.353
Treatment			
Neoadjuvant Chemoradiation +surgery	Reference		
Chemoradiation therapy	2.0	1.0, 3.8	0.025
Adjuvant surgery	1.8	1.0, 3.2	0.043
Palliative chemo/radiotherapy	3.8	2.0, 7.1	<0.001
Unknown	2.2	1.1, 4.4	0.024
Stage at diagnosis			
Early	Reference		
Advanced	1.7	1.0, 2.6	0.018
Unknown	1.4	0.8, 2.4	0.196
SES			
High	Reference		
Middle	0.9	0.6, 1.4	0.812
Low	1.1	0.7, 1.7	0.424
Calendar time			
2007-2009	Reference		
2010-2011	0.7	0.5, 1.0	0.160
Tumor histology			
SCC ¹	Reference		
ADC	1.1	0.6, 1.8	0.686
Area of residence			
Urban	Reference		
Rural	1.2	0.8, 1.7	0.284

CI: Confidence interval; SES: Socio-economic status; SCC: Squamous cell carcinoma; ADC: Adenocarcinoma; Reference: Reference group

our previous study, we classified stages I and II as early stages, and stages III and IV as advanced stages.⁹

Ethics approval

The current study was approved by the Ethics Committee of Tehran University of Medical Sciences with the ethics code of 93-02-51-26069.

Statistical analysis

First, we excluded the cases whom we could not follow up after diagnosis. We also censored the patients if they died due to other causes than esophageal cancer. Comparison of the baseline characteristics between the excluded cases and complete followed up patients indicated that loss to follow-up was random and we did not face a

selection bias. Afterward, we applied life-table and Kaplan-Meier approaches to calculate 1-, 3-, and 5-year survival rates and corresponding 95% confidence interval (CI). Survival rates were calculated by the demographic and clinical characteristics of the study participant. We also utilized weights of the highest representative component of a Principal Component Analysis (PCA), including asset variables plus the size of house and level of education to categorize the subjects into three socio-economic quantiles. To assess the association between the 5-year net survival rate and the studied variables, a multiple Cox-regression estimated hazard ratios (HR) and the associated 95% CI for all the investigated

Table 3. Comparison of 1-, 3- and 5-year esophageal cancer survival at Cancer Institute of Iran between two periods (i.e. 2007-2011 vs. 1997-2006).

Time since diagnosis	1997-2006 (95% CI)	2007-2011 (95% CI)
1 year	51.0 (46.0, 56.0)	66.7 (61.8, 71.0)
3 year	17.0 (13.0, 22.0)	28.2 (23.3, 33.0)
5 year	10.0 (6.0, 14.0)	20.9 (16.6, 25.5)

CI: Confidence interval

prognostic factors. Besides, we compared the 5-year survival of esophageal cancer patients from present study with the results that we have reported previously from the patients admitted at the Cancer Institute of Iran in 1997-2006. We used Stata for the statistical analyses (Ver. 14.1, College Station, Texas, USA).

Results

As a whole, 49% of our participants comprised women and the mean of age (\pm SD) for men and women was 65.2 (\pm 12.2) and 63.6 (\pm 11.7), respectively. The proportion of patients with advanced stages of esophageal cancer was

(50.6%) and 62.6% of the study participants were urban dwellers (Table 1).

Overall, 1-, 3-, and 5-year survival rates were estimated 66.7%, 28.2%, and 20.9%, respectively. The highest 5-year survival rate belonged to the age group of 50-59 (31.0 95% CI: 21.2, 41.3). However, 5-year survival was 15.8% (95% CI 10.0, 22.8) among whom were diagnosed at the age of 70 or more (Table 1). In addition, those who received neo-adjuvant chemo-radiation had a considerably higher 5-year survival rate than other treatment groups. Based on the multiple Cox regression model, HR was significantly higher among the patients who received definitive

Kaplan-Meier Survival Estimates

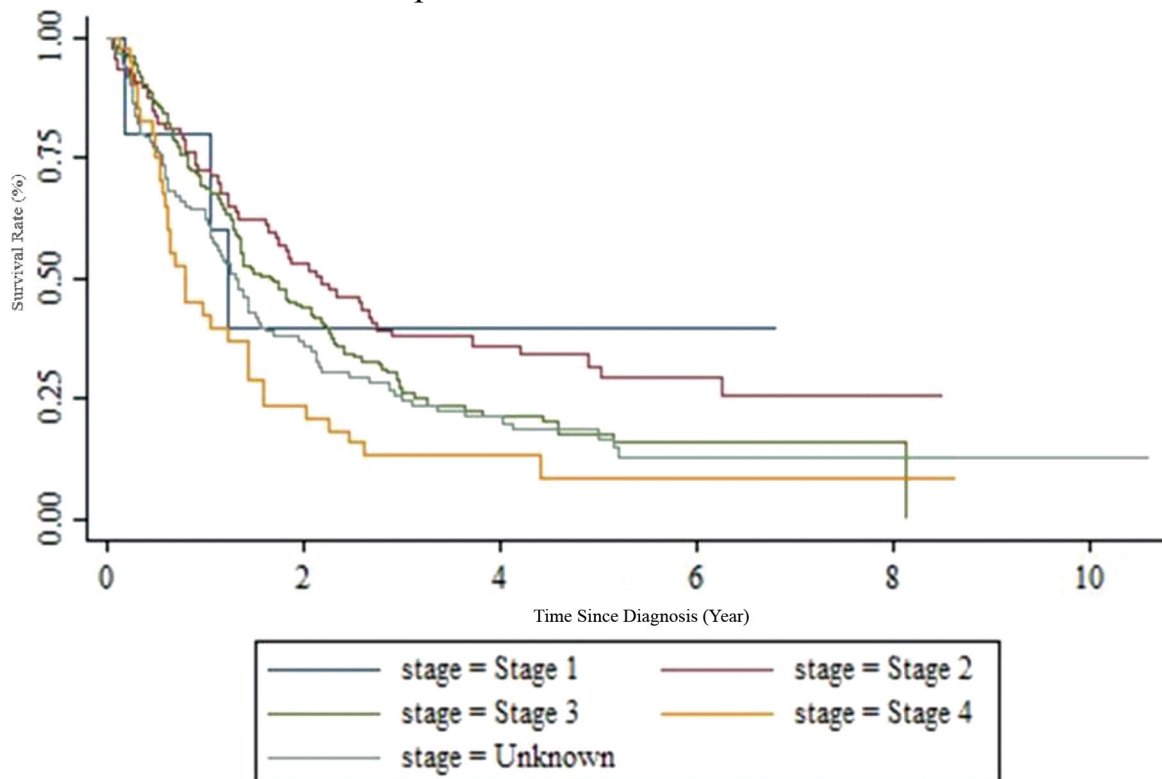
**Figure 2.** This figure displays esophageal cancer patients at cancer institute of Iran by stage at diagnosis time in 2007-2011.

Table 4. Frequency and percentage of recruited treatments for esophageal cancer patients by stage at diagnosis time at Cancer Institute of Iran in 2007-2011

Stage at diagnosis	Treatment				
	Neoadjuvant	Chemoradiation therapy	Surgery	Palliative	Unknown
Early stage	13 (13.6%)	10 (10.5%)	65 (68.4%)	2 (2.1%)	5 (5.2%)
Advanced	36 (16.9%)	62 (29.1%)	57 (26.7%)	45 (21.1%)	13 (6.1%)
Unknown	6 (5.3%)	37 (32.7%)	11 (9.7%)	38 (33.6%)	21 (18.5%)

chemoradiation (HR= 2.0, 95% CI: 1.0, 3.8, $P = 0.025$), surgery (HR= 1.8 95% CI: 1.0, 3.2, $P = 0.043$), and palliative care (HR= 3.8, 95% CI: 2.0, 7.1, $P < 0.001$) compared with the neo-adjuvant chemo-radiation treatment group (Table 2) (Figure 1).

We also found a higher 5-year survival rate among the patients in early stages (5-year survival rate= 32.8, 95% CI: 22.4, 43.6) compared with those who were diagnosed at advanced stages (5-year survival rate= 16.8, 95% CI: 11.3, 23.2) (Table 1). Based on multivariate analysis, we found a 70% higher risk of death in patients diagnosed at the more advanced stages (stage III, VI) (HR= 1.7, 95% CI: 1.0, 2.7, $P = 0.018$) (Table 2) (Figure 2).

We observed a positive association between SES and 5-year survival rate, where high SES patients survived longer (5-year survival rate=31.1, 95% CI: 21.3, 41.5) than the low SES ones (5-year survival rate= 14.8, 95% CI: 8.7, 22.4) (Table 1). However, the association disappeared after adjustment for confounding variables (HR= 1.1, 95% CI: 0.7, 1.7, $P = 0.424$) (Table 2).

We also observed that the 5-year survival rate was doubled in the present study (20.9%, 95% CI: 16.6, 25.5) compared with our previous study conducted in 1997-2006 (10.0%, 95% CI: 6.0%, 14.0%). Besides, we observed a considerable improvement in 1- and 3-year survival rates (Table 3). Table 4 summarizes the treatments of the patients based on the stage at diagnosis.

Discussion

The 1-, 3-, and 5-year survival rates of esophageal cancer patients who were treated at the Cancer Institute of Iran in 2007-2011 was 66.7%, 28.2%, and 20.9%, respectively. The stage

at diagnosis, treatment approach and calendar time were statistically significant predictors for the 5-year survival rate. We also found that the 5-year survival rate of esophageal cancer at the Cancer Institute of Iran was doubled among patients admitted in 2007-2011 (20.9%, 95% CI: 16.6, 25.5%) in comparison with the patients treated at the Cancer Institute in 1997-2006 (10%, 95% CI: 6.0%, 14.0%).

We observed the highest 5-year survival rate among the subjects receiving neo-adjuvant chemo-radiation therapy. In addition, the notable improvement in the survival of esophageal cancer during this time could be linked to the percentage of early stages diagnosis patients in the recent data compared with the previous period. In the current study, 20% of the participants were diagnosed at early stages, while it was only 10% in the older series. Even though the association between the stage at diagnosis and the survival rate was statistically significant, the association between neo-adjuvant chemo-radiation and survival rate was stronger. It seems that using the neo-adjuvant therapy played the most important role in the observed improvement of cancer survival in the Cancer Institute of Iran. Several observational studies and clinical trials^{12,13} supported our findings, indicating that the neo-adjuvant chemo-radiation was significantly associated with higher survival in esophageal cancer. Although some studies reported no statistical differences between neo-adjuvant treatment and chemotherapy,^{14,15} we believe that the neo-adjuvant chemo-radiation is the main contributing factor in the improvement of esophageal cancer outcome in the present series.

A similar improvement in the survival of esophageal cancer has been reported by a study

in the United States, where the 5-year survival of esophageal cancer patients increased from 9.0% in 1973 to 22% in 2009.¹⁶ Similar results were reported in the UK¹⁷ and Canada.¹⁸ It is noteworthy that we analyzed the data from the Cancer Institute of Iran, which is the center of excellence for cancer care in Iran, and the survival of esophageal cancer in this center is supposed to be higher than the published reports based on population-based cancer registries even from high-income countries. Estimation of population-based survival is needed to make us capable to compare the results obtained in Iran with those in other high and low-income countries. Besides, we suggest estimation of survival in different provinces to be able to generalize the results to the entire Iranian cancer population. The survival may be lower in other provinces, where there is limited access to proper diagnostic and treatment facilities.^{19,20} Comparison of our findings with the only published population-based study regarding esophageal cancer survival in Golestan province indicates pretty higher survival rate among our patients. We spotted a wide gap in esophageal cancer outcome between our findings and the reported values in Golestan province, where only 7.4% of esophageal cancer patients have experienced a 5-year survival.²¹

The current study had several strengths, including a reasonable power and large sample size. Also, it was the first attempt to assess the impact of neo-adjuvant therapy on esophageal cancer survival in Iran. However, we faced certain limitations. The retrospective design was the main limitation of our study, which led to losing some patients in the follow-up. Moreover, the data from the Cancer Institute may not be generalized to the entire country. Therefore, further researches are required in other provinces employing population-based cancer registries.

Conclusion

In conclusion, the survival rate of esophageal cancer has improved during the last decade at the Cancer Institute of Iran. The stage at diagnosis and administration of neo-adjuvant chemo-

radiation were the main contributing factors for the observed improvement. We suggest population awareness and early diagnosis program, improvement of the access to therapeutic facilities to increase the survival of esophageal cancer in Iran. The survival reports from different cancer centers and provinces are needed.

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Conflict of Interest

None declared.

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