RESEARCH ARTICLE

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Factors Affecting Long-Survival of Patients with Esophageal Cancer Using Non-Mixture Cure Fraction Model

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Abstract

Objective: Esophageal cancer (EC) is one of the gastrointestinal malignancies with a very high morbidity and mortality rate due to poor prognosis. This study aims to assess the effects of risk factors on survival and cure fraction of patients with EC in a population of Iranian patients using a non-mixture cure fraction model. **Methods:** This retrospective cohort study was conducted on 127 patients with EC who were diagnosed during 2009-2010 and were followed up for 5 years in East-Azarbaijan, Iran. Stepwise selection and non-mixture cure fraction model were used to find the risk factors of EC survival patients. **Results:** The mean (±standard deviation) diagnosis age of the EC was 66.92(±11.95). One, three and five-year survival probabilities were 0.44 (95% confidence interval (CI): 0.36-0.54), 0.2 (95% CI: 0.14-0.28) and 0.13 (95% CI: 0.08-0.2) respectively. Female sex (Estimate=-0.99; 95% confidence interval (CI): -1.41,-0.58; p-value<0.001), low level socioeconomic status (Estimate=0.39; 95%CI: 0.12,0.66; p-value=0.043), the group who did not do esophagectomy surgery (Estimate=0.58; 95%CI: 0.17,0.99; p-value=0.005) and unmarried group (Estimate=0.58; 95%CI: 0.11-1.05; p-value=0.015) were found as the significant predictor of survival and cure fraction of the EC patients. Population cure rate was 0.11 (95%CI: 0.07-0.19) and Cure fraction was estimated 5.11 percent. **Conclusion:** This study found gender, socioeconomic status, Esophagectomy surgery and marital status as the potential risk factors for survival and cure fraction of Iranian EC patients. Moreover, non- mixture cure fraction provides more accurate and more reliable insight into long-term advantages of EC therapy compared to standard classic survival analysis alternatives.

Keywords: Esophageal neoplasms- survival analysis- non-mixture cure fraction models

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Introduction

Chronic disease such as cardiovascular disease and cancer are the leading causes of death worldwide. Recent studies indicate that over the past two decades the number of new cancer cases has increased. Currently, cancer is known as a major public health problem and as the second leading cause of death worldwide (Siegel et al., 2016, Oschman, 2011). Although the incidence rate of cancer in developed countries is 2-folds more than in developing countries, according to the International Agency for Research on Cancer (IARC) reports, cancer is recognized as the most important leading cause of death in developing countries (Torre et al., 2015). In Iran, based on the National Cancer Registry (NCR), cancer is reported as the third most common cause of death after coronary heart disease and accidents. The mortality rate of cancer in Iran has been reported as 41 and 65 per 100,000 in men and women respectively (Mousavi et al., 2009).

Esophageal cancer (EC) is defined as one of the gastrointestinal malignancies with a very high morbidity and mortality rate and low survival probability. EC is the sixth most common cancer related to death and also is the eighth most prevalent cancer in the world (Alsop and Sharma, 2016, Domper Arnal et al., 2015). EC is classified into main histological types including squamous cell carcinoma and adenocarcinoma. Multiple epidemiological studies indicated that the incidence of esophageal squamous cell cancer is decreasing whereas the incidence of esophageal carcinoma is rapidly increasing. This type of EC affects more than 45000 people across the world (Blot et al., 1991, Zhang et al., 2012). The survival rate of EC varies extensively around the world. Some

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of the highest rates of esophageal cancer worldwide are seen in the ‘central Asian esophageal cancer belt’. This region includes the countries of the Caspian littoral, the central Asian republics, Mongolia and north-western China (Islami et al., 2004). Also South Africa and some European countries such as France and Italy have the high incidence rates (Lu et al., 1999, Eslick, 2009). EC death rate was reduced in women between 1990 and 2004, however, for males there has been no such decrease in the world (Jemal et al., 2008). The survival rate of esophageal cancer is poor. In the United States, the 5-year survival rate for people with EC has been reported as 18% (Siegel et al., 2016). In Iran, the esophageal cancer is the second and third common malignancy in males and females, respectively (Sadjadi et al., 2010). Most patients with EC have been identified as being from the North and Northeast regions of the country (Ghavamzadeh et al., 2001). Among 35,000 deaths reported due to cancer in Iran, 5800 cases were attributed to esophageal cancer (Sadjadi et al., 2005). However, limited studies have been done regarding the survival of patients with EC in Iran (Somi et al., 2008). Therefore, the survival analysis of patients with esophageal cancer is very important and appropriate statistical models can better introduce the important prognostic factors to improve the survival of patients.

In the last few decades, clinical researchers have achieved progress in the treatment of chronic diseases. These achievements have increased the proportion of cured patients from many types of cancers. In this circumstances, the population consists of two groups of cured (or long-term survivors) and non-cured. In such situation, routine survival analysis approaches such as Cox proportional hazard model does not perform well due to the high number of censorings at the end of the follow-up period, and disability in considering the possibility of long-term survivors. Since a proportion of individuals will survive, cure model can be an appropriate and useful method to estimate cure fraction (Sy and Taylor, 2000; Lambert et al., 2007; Farewell, 1986). In the Current study, a non-mixture cure fraction model is utilized to determine the effects of risk factors on the survival and cure fraction of patients with esophageal cancer.

Materials and Methods

This retrospective cohort study enrolled a total of 127 patients with esophageal cancer who lived in East-Azarbaijan Province and were registered in Iran Registration Cancer during 2009-2010. These patients were followed up for a period of 5 years from 2010 to 2015. Data were sourced mainly from the patient reports of hospitals and pathology laboratories. The socio-demographic and clinical data were obtained using structured questionnaire and the patients’ clinical records. Survival information was collected through telephone interviews with the patients and/or their family members who were at home at the time of the interview. The beginning of the study was assumed as the pathologic diagnosis of cancer. Death due to esophageal cancer was regarded as the failure and survival time was calculated as the time interval between the date of cancer diagnosis and date of death due to esophageal cancer (for those who died) and the date of the last follow up (for those who were alive).

The risk factors which were recorded in the patients’ clinical data and were assessed in this study were the age at diagnosis, gender, education, job, marital status, smoking habit, non-communicable disease (NCD) affected status, Esophagectomy surgery, radiotherapy and chemotherapy.

In addition, wealth index patients’ socioeconomic status (SES) was identified based on a checklist of economic characteristics such as household fuel consumption, residential facilities, personal family facilities, household appliances used by the family, the source of household income, and total monthly household income. Principle component factor analysis was applied to obtain the socioeconomic status (low level/ high level). The Varimax approach to factor axes rotation was used in this study to determine the factor loading. After the factors was interpreted, the ones which their variances were greater than one and had high loadings were retained. The extracted factor called SES was transformed into an ordinal variable using visual Binnig and divided into two interval cut points based on median of extracted factor. According to the questionnaire and the responses of variables as considered for wealth index, the cut points were labeled as low level and high level.

Statistical analysis

Descriptive characteristics of the patients were expressed as the mean ± standard deviation (SD) and frequency (percentage) for continuous and categorical variables, respectively. The log-rank test was applied to assess the unadjusted effect of variables on the survival time. The stepwise variable selection was used to investigate the best subset of variables in which the best fit on Cox proportional hazards model could be achieved. According to the stepwise method, this subset was obtained based on the variables which they had p-values less than 0.2 and more than 0.1 in this study. Variance inflation factor (VIF) was used to check the presence of multicollinearity between the covariates. The best subset of variables which resulted from the Cox proportional hazards model were assessed in the non-mixture cure fraction fitting.

The Kaplan-Meier survival plot was used to reveal whether the plot reached zero with the current amount of follow up time. The plot contributed to finding the proportion of survival cases. In the case of high survival rate, Cox regression model will lead to bias estimates. Cure models allow us to investigate what risk factors are associated with survival of cured and uncured patients. These models are a composition of incidence, which demonstrate whether the event of interest could eventually be experienced and a latency part, which demonstrates whether the event will occur for those subjects who are more prone to the event. The mixture and non-mixture cure fraction models are two major forms of cure fraction models. Non-mixture cure model or bounded cumulative hazard model uses particular approaches to model the survival and cure fraction parts of the model (Lambert et al., 2007, Maetani and Gamel, 2013).

In this model, a log-log link function was used and the survival function can be written as follows:

$$S_p(t)=\exp(-\theta * F(t));$$

where $\theta=\exp(\beta' X)$ and F(t) is expressed as the cumulative distribution function for the non-cured group (Sposto, 2002; Rahimzadeh et al., 2014; Lambert et al., 2007).

The results were presented as point estimate from non-mixture cure fraction model. The sign of point estimate in non-mixture cure fraction with log-log link function shows in which groups of variable the probability of cure is more than the other one. If the sign of point estimate is positives, the cure probability of baseline group is more than the other one and vice versa (Sposto, 2002). Moreover, the 95% confidence intervals for the estimated effect sizes were demonstrated as 95% CI. The statistical programming R software, version 3.4.2 was used to perform the models and the p-value<0.05 was considered statistically significant.

Results

Our study was performed on 127 esophageal cancer patients, 35-88 years old. The mean (± standard deviation) age was 66.92 (± 11.95) years old. A total of 113 (89%) cases experienced the death due to esophageal cancer and 14 (11%) were alive by the end of the study. One, three and five-year survival probabilities were 0.44 (95% CI: 0.36-0.54), 0.2 (95% CI: 0.14-0.28), and 0.13 (95% CI: 0.08-0.2) respectively. The survival time ranges were from 0.10 to 69.03 months. The mean and median survival time for the uncured group were 16.99 (95% CI: 13.46-20.52) and 10.06 (95% CI: 6.49-13.63) months respectively. The patients' characteristics and Log-rank results are shown in Table 1.

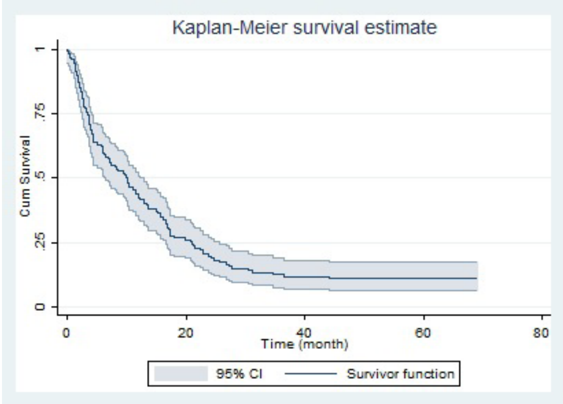

Figure 1. The Kaplan-Meier Curve of Patients with Esophageal Cancer

The stepwise selection indicated that sex, Esophagectomy surgery, marital status, SES, and radiotherapy had the best fit on the Cox proportional hazards model while the presence of multicollinearity between covariates was considered based on the VIF values.

We checked the PH assumption in the Cox regression model and the assumption was rejected (p-value=0.035). Therefore the Cox proportional hazards model was not appropriate for the dataset. As shown in Figure 1, the Kaplan-Meier curve is stabled at the probability of almost 0.11 (Standard Deviation=0.01,95% CI: 0.07-0.19) which implies that the population cure rate is 11 percent.

Table 2 demonstrates the results of non-mixture cure fraction model results. According to the

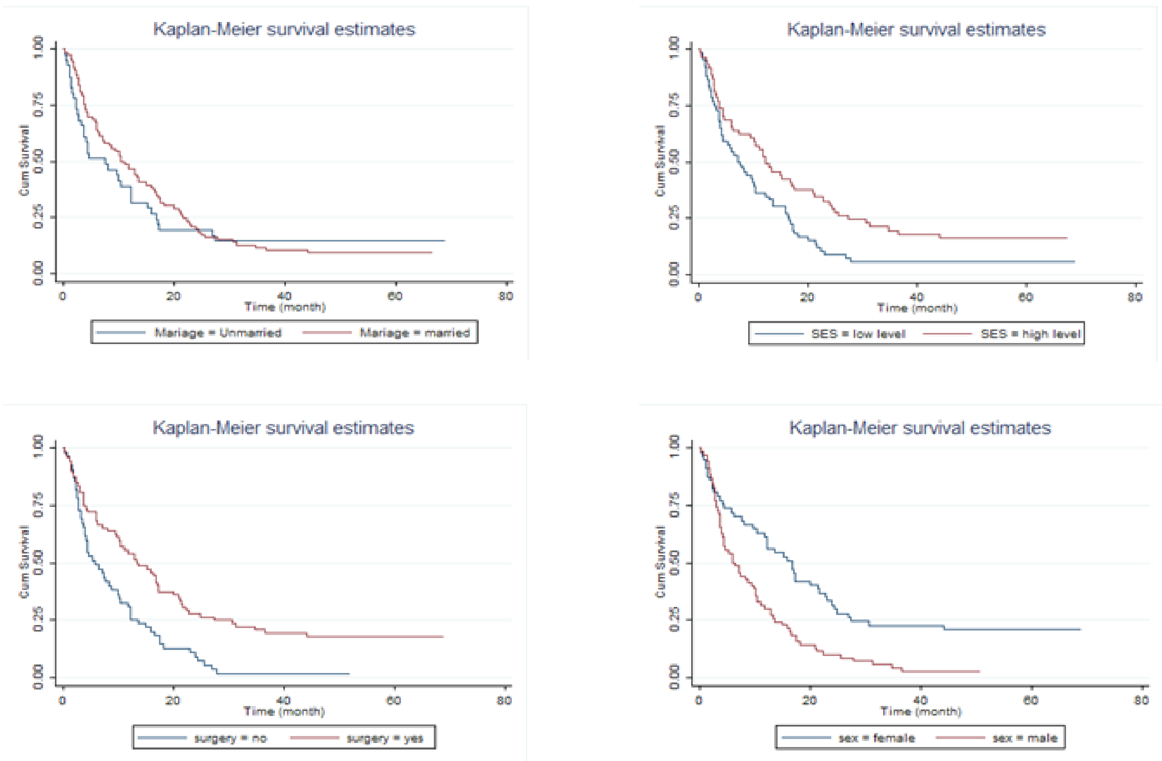

Figure 2. Kaplan-Meier Survival Curves of Covariates which Had Significant Effect on Non-mixture Cure Fraction Model

Table 1. The Esophageal Cancer Patients' Characteristics and the Results of Log-rank

Variable	n (%)	Death 113 (89%)	Log-Rank Test		
			mean survival time	SE*	p-value
Age					0.384
≥50	113 (89)	101 (89.4)	16.52	1.89	
<50	14 (11)	12 (85.7)	19.71	5.02	
Gender					<0.001
male	70 (55.1)	68 (97.1)	10.4	1.29	
female	57 (44.9)	45 (78.9)	24.45	3.27	
Education					0.989
illiterate	98 (77.2)	87 (88.8)	17.14	2.08	
literate	29 (22.8)	26 (89.7)	16.21	3.43	
Marital Status					0.524
married	86 (67.7)	35 (85.4)	16.96	1.98	
unmarried	41 (32.3)	78 (90.7)	16.56	3.55	
Job Status					0.004
unemployed	79 (62.2)	67 (84.8)	20.61	2.52	
employed	48 (37.8)	46 (95.8)	10.70	1.87	
Smoking Habit					0.554
yes	42 (33.1)	40 (95.2)	14.39	2.21	
no	85 (66.9)	73 (85.9)	18.07	2.40	
NCD affected Status					0.503
no	103 (81.1)	93 (90.3)	16.30	1.92	
yes	24 (18.9)	20 (83.3)	18.51	4.15	
Esophagectomy Surgery					<0.001
yes	72 (56.7)	59 (81.9)	22.48	2.80	
no	55 (43.3)	54 (98.2)	9.49	1.28	
Chemotherapy					0.528
yes	55 (43.3)	51 (92.7)	16.80	2.10	
no	72 (56.7)	62 (86.1)	16.52	2.62	
Radiotherapy					0.263
yes	43 (33.9)	39 (90.7)	18.08	2.60	
no	84 (66.1)	74 (88.1)	16.22	2.31	
SES					0.008
high level	66 (52)	62 (93.9)	21.57	2.90	
low level	61 (48)	51 (83.6)	12.55	1.97	

*, Standard Error

estimations, Females had more probability to cure of EC in comparison to males (Estimate= -0.99; 95% CI:-1.41,-0.58; p-value<0.001). Patients in low level SES had less probability to cure of EC in comparison to patients in high level SES (Estimate=0.39; 95% CI: 0.12,0.66; p-value=0.043). Those who didn't do Esophagectomy surgery were less likely to be cured death (Estimate= 0.34; 95% CI: 0.17,0.99; p-value= 0.005). Moreover, unmarried cases had less likelihood of cure (Estimate=0.58; 95%CI: 0.11,1.05; p-value=0.015). In addition, the obtained cure fraction was estimated 5.11% from model which was reasonable compared to population cure rate.

Figure 2 shows the Kaplan-Meier survival graph of covariates which had a significant effect on non-mixture cure fraction model. Kaplan-Meier curves for gender, SES, Esophagectomy surgery, and marital status demonstrated that the probability of cure in the female sex, high level, surgery and the married group was more than that of the males , low level, no Esophagectomy surgery and unmarried group respectively.

Discussion

Our study demonstrated that factors such as sex, socioeconomic status, Esophagectomy surgery and martial status can be determining risk factors for esophageal cancer. In our data, a high proportion of patients died before the end of the study and a relatively short survival time was observed.

The results of our study showed that females have higher odds of cure than males. Assessing the association between gender and EC, lots of confounding

Table 2. Estimation Based on Non-mixture Cure Fraction Model with Log (-log) Link Function

Variable	Estimate	SE	95% CI**		p.value***
			lower	upper	
Gender					
Male	*				
Female	-0.99	0.21	-1.41	-0.58	<0.001
SES					
High level	*				
Low level	0.39	0.14	0.12	0.66	0.043
Esophagectomy Surgery					
Yes	*				
No	0.58	0.21	0.17	0.99	0.005
Radiotherapy					
Yes	*				
No	0.34	0.20	-0.06	0.73	0.093
Martial status					
Married	*				
Unmarried	0.58	0.24	0.11	1.05	0.015

*, Stands for a baseline group;**, 95% confidence interval;***, Significant at the 5% level

variables interfere. Generally, women's lifestyle is less correlated with smoking habits and tobacco use, alcohol consumption, and other health risk behaviors. Melhado et al., (2010) investigated the changing face of esophageal cancer and showed that women are at a lower risk of EC. Bohanes et al., (2012) assessed the difference between the genders regarding the survival after positive diagnosis of esophageal cancer. They revealed that men have shorter survival rates in both metastatic and loco-regional esophageal cancer. The difference between the genders survival time was justified due to the differences in hormones and women going through menopause. The same question was addressed by Mathieu et al., 2012) and it was observed that higher estrogen levels protect women against this cancer. It was revealed that the same behavior between the two genders happen after menopause among women.

In line with the expectations, a higher level of socioeconomic status was directly associated with the longer survival time of EC. Socioeconomic status is an accelerator of shorter survival time for various types of diseases including EC. The preparation of many cancer-related facilities including chemotherapy, hormone therapy, Esophagectomy surgery and other potential treatments is not straightforward for low-income patients and those with lower levels of socioeconomic status. In other words, the adverse outcomes of esophageal cancer are strongly associated with the negative consequences followed by the low socioeconomic status of the patients. Louwman et al., (2010) evaluated the frequency and prevalence of life-shortening factors for several cancers such as esophageal cancer among low socioeconomic status patients. Their study showed that the risk of suffering from another serious disease among cancer patients with low SES was 1.5 times greater than those with high SES levels. Tran et al., (2017) assessed the impact of sex, race, socioeconomic status, and treatment on the survival of esophageal cancer patients. They found that low SES can affect the likelihood of receiving Esophagectomy surgery which then results in shorter survival time. Relatedly, Dar et al., (2013) also demonstrated a negative relationship between the risk of esophageal squamous cell carcinoma and SES.

Our study also showed that Esophagectomy surgery is an effective factor for improving the survival time of patient's with esophageal cancer. Esophagectomy surgery is known as one of the best potential tools for the management of esophageal cancer. The positive and more efficient effect of Esophagectomy surgery can be observed in the early stages of cancer. In contrast, the other options such as chemotherapy and radiation therapy are suggested for later-stages. The outcomes after Esophagectomy surgery were investigated by D'Amico and it was shown that a combination of chemotherapy and Esophagectomy surgery results in a longer survival time for patients with EC (D'Amico, 2007). Lagergen et al., (2007) suggested the quality of life factors after Esophagectomy surgery as treatment for esophageal cancer. They exposed that the combination of Esophagectomy surgery and improved quality of life can extend the survival time of EC patients for at least 3 years.

Identifying any progress in cancer therapy depends on monitoring the trends of patients' survival over time (Baghestani et al., 2015). The valuable measure of care for patients and clinician is the time from diagnosis of the disease until symptom occurrence (Andersson et al., 2011). In the recent years, the therapy for various types of cancers has been improved significantly. Therefore, the proportion of patients who are not susceptible to the occurrence of the study event (cure fraction) has increased (Asano et al., 2014). Furthermore, most of the cure rate models have been applied to cancer cases (Ortega et al., 2008). Since some cancer-related subjects may have long-term survival, cure rate models can be an appropriate method to characterize and study the patients' survival (Akhlaghi et al., 2013). Mixture and non-mixture are two general forms of cure models and the use of each model depends on data (Baghestani et al., 2015). In the current study, non-mixture cure fraction model was used to estimate the effect size of potential risk factors that affect patients' survival.

However, there are lots of other factors related to the esophageal cancer lifetime such as metastatic status, tumor size, and stage of disease and the certain type of esophageal cancer (adenocarcinoma and squamous). These prognostic factors were not assessed because of the lack of access to the medical records of patients and the unavailability of the data in the East-Azarbayjan cancer registry.

In conclusion, although esophageal cancer is known as a fatal disease with a low survival rate,significant improvement of therapies for this cancer have been identified in the recent years. Moreover, using appropriate survival analysis can help the clinicians and researchers to determine potential risk factors which can affect the survival of patients who are not susceptible to EC. In this study, gender, SES, Esophagectomy surgery, and marital status are determined as risk factors that affect both survival and cure fraction of patients with EC. Non- mixture cure fraction provides more accurate and more reliable insight into long-term advantages of EC therapy compared to standard classic survival analysis alternatives.

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References

Akhlaghi AA, Najafi I, Mahmoodi M, et al (2013). Survival analysis of Iranian patients undergoing continuous ambulatory peritoneal dialysis using cure model. *J Res Health Sci*, **13**, 32-6.

Alsop BR, Sharma P (2016). Esophageal cancer. *Gastroenterol Clin*, **45**, 399-412.

Andersson TM, Dickman PW, Eloranta S, Lambert PC (2011). Estimating and modelling cure in population-based cancer studies within the framework of flexible parametric survival models. *BMC Med Res Methodol*, **11**, 96.

Arnal MJD, Arenas ÁF, Arbeloa ÁL (2015). Esophageal cancer: Risk factors, screening and endoscopic treatment in Western and Eastern countries. *W J Gastroenterol*, **21**, 7933.

Asano J, Hirakawa A, Hamada C (2014). Assessing the prediction accuracy of cure in the Cox proportional hazards cure model: an application to breast cancer data. *Pharm Stat*, **13**, 357-63.

Baghestani AR, Moghaddam SS, Majd HA, et al (2015). Application of a non-mixture cure rate model for analyzing survival of patients with breast cancer. *Asian Pac J Cancer Prev*, **16**, 7359-63.

Blot WJ, Devesa SS, Kneller RW, Fraumeni Jr JF (1991). Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA*, **265**,1287-89.

Bohanes P, Yang D, Chhibar RS, et al (2012). Influence of sex on the survival of patients with esophageal cancer. *J Clin Oncol*, **30**, 2265.

D'Amico TA (2007). Outcomes after surgery for esophageal cancer. *Gastrointestinal Cancer Res*, **1**, 188.

Dar NA, Shah IA, Bhat GA, et al (2013). Socioeconomic status and esophageal squamous cell carcinoma risk in Kashmir, India. *Cancer Sci*, **104**, 1231-6.

Eslick GD (2009). Epidemiology of esophageal cancer. *Gastroenterol Clin*, **38**, 17-25.

Farewell VT (1986). Mixture models in survival analysis: Are they worth the risk?. *Canadian J Stat*, **14**, 257-62.

Forouzanfar MH, Afshin A, Alexander LT, et al (2016). Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*, **388**, 1659-1724.

Ghavamzadeh A, Moussavi A, Jahani M, Rastegarpanah M, Iravani M (2001). Esophageal cancer in Iran. *Semin Oncol*, **28**, 153-7.

Islami F, Kamangar F, Aghcheli K, et al (2004). Epidemiologic features of upper gastrointestinal tract cancers in Northeastern Iran. *Br J Cancer*, **90**, 1402.

Jemal A, Siegel R, Ward E, et al (2008). Cancer statistics, 2008. *CA Cancer J Clin*, **58**, 71-96.

Lagergren P, Avery KN, HughesR, et al (2007). Health-related quality of life among patients cured by surgery for esophageal cancer. *Cancer*, **110**, 686-93.

Lambert PC, Thompson JR, Weston CL, Dickman PW (2006). Estimating and modeling the cure fraction in population-based cancer survival analysis. *Biostatistics*, **8**, 576-94.

Louwman WJ, Aarts MJ, Houterman S, et al (2010). A 50% higher prevalence of life-shortening chronic conditions among cancer patients with low socioeconomic status. *Br J Cancer*, **103**, p.1742.

Lu S, Lin P, Wang G, Luo X, Wu M (1999). Comprehensive prevention and treatment for esophageal cancer. *Chin Med J*, **112**, 918-23.

Maetani S, Gamel JW (2013). Parametric cure model versus proportional hazards model in survival analysis of breast cancer and other malignancies. *Adv Breast Cancer Res*, **2**, 119.

Mathieu LN, Hooker C, Kanarek N, et al (2010). The changing face of esophageal cancer. *Cancers*, **2**, 1379-1404.

Mousavi SM, Gouya MM, Ramazani R, et al (2008). Cancer incidence and mortality in Iran. *Ann Oncol*, **20**, 556-63.

Ortega EM, Cancho VG, Lachos VH (2008). Assessing influence in survival data with a cure. *Sort-Stat Oper Res T J*, **32**, 115-40.

Oschman JL (2011). Chronic disease: are we missing something?, pp 283-5. https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=Oschman+JL+%282011%29.+Chronic+disease&btnG=.

Rahimzadeh M, Kavehie B, Zali MR (2014). Cure models in analyzing long-term survivors. *Translational Gastrointestinal Cancer*, **3**, 149-54.

Sadjadi A, Marjani H, Semnani S, Nasseri-Moghaddam S (2010). Esophageal cancer in Iran: A review. *Middle East J Cancer*, **1**, 5-14.

Sadjadi A, Nouraie M, Mohagheghi MA, et al (2005). Cancer occurrence in Iran in 2002, an international perspective. *Asian Pac J Cancer Prev*, **6**, 359.

Siegel RL, Miller KD, Jemal A (2016). Cancer statistics, 2016. *CA Cancer J Clin*, **66**, 7-30.

Somi MH, Farhang S, Mirinezhad SK, et al (2008). Cancer in East Azerbaijan, Iran: results of a population-based cancer registry. *Asian Pac J Cancer Prev*, **9**, 327-30.

Sposto R (2002). Cure model analysis in cancer: an application to data from the Children's Cancer Group. *Stat Med*, **21**, 293-312.
Sy JP, Taylor JM (2000). Estimation in a Cox proportional hazards cure model. *Biometrics*, **56**, 227-36.
Torre LA, Bray F, Siegel RL, et al (2015). Global cancer statistics, 2012. *CA Cancer J Clin*, **65**, 87-108.
Tran PN, Taylor TH, Klempner SJ, Zell JA (2017). The impact of gender, race, socioeconomic status, and treatment on outcomes in esophageal cancer: A population-based analysis. *J Carcinog*, **16**, 2017.
Zhang HZ, Jin GF, Shen HB (2012). Epidemiologic differences in esophageal cancer between Asian and Western populations. *Chin J Cancer*, **31**, 281.