

Received: 25 October 2017 • Accepted: 20 December 2017

Research

doi:10.15412/J.JBTW.01070101

# Gastroesophageal Junction Adenocarcinoma in Iran; a Retrospective Study to Investigate Demographic Characteristics and Effect of Multimodality Therapy on Survival Rate

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## ABSTRACT

Gastroesophageal junction (GEJ) carcinoma is a rare but highly aggressive cancer. Adenocarcinomas of the GEJ (GEJAD) represent around 90% of all the GEJ cancers. In recent years, a significant increase in the prevalence of GEJAD has been recorded in many countries. In the current study, it was aimed to investigate the GEJAD in Iran and effect of multimodality therapy on survival rate. 246 patients with GEJAD have been investigated in terms of age, gender, Siewert types, tumor stage and history of cancer. To assess the impact of different types of treatments on survival outcomes, 124 patients that completed their treatment remained in the study. Analyses were performed using SPSS statistical software. Survival rates were estimated by use of the Kaplan-Meier method. All statistical tests were 2-sided, and  $p \leq 0.05$  indicated statistical significance. 198 males (80.5%) and 48 females (19.5 %) with mean ages of 67.52 and 64.23 years were studied respectively. The number of patients with Siewert type I ( $n= 107$ ) was more than types II and III ( $n= 94$  and  $45$  respectively). There was a significant correlation between Siewert types and tumor stage ( $p= 0.032$ ). 15.1 % of patients had the family history of cancer in which 56.7% of them were related to the male first-degree relatives (father, brother). Overall mean and median survival time were 33.5 and 30 months respectively. There were significant differences between survival times based on different kinds of treatments ( $p=0.041$ ). SUR→RT and CHT→SUR→RT, with two years' survival rates of 60% and 100% respectively; in addition, there were the most effective treatments for GEJAD patients. In order to obtain more significant results about the impact of SUR→RT and CHT→SUR→RT on survival time, more patients with long-term assessments need to be studied.

**Key words:** Adenocarcinoma of gastro esophageal junction, Siewert type, Multimodality therapy, Survival time.

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*Journal of Biology and Today's World* is published by [Lexis Publisher](http://www.lexispublisher.com); Journal p-ISSN 2476-5376; Journal e-ISSN 2322-3308.

## 1. INTRODUCTION

Gastroesophageal junction (GEJ) carcinoma is a rare but highly aggressive cancer worldwide with increasing importance as a public health problem in recent years (1). According to recent studies, incidence and distribution of cancers within the esophagus and stomach have been faced with an observed epidemiological shift away from distal gastric cancer and proximal cancer of the esophagus towards the esophagogastric junction (2). The incidence of adenocarcinoma has been increased in comparison to all other types of histology. Adenocarcinomas of the GEJ (GEJAD) represent around

90% of all the GEJ cancers (3). In recent years, a significant increase in the prevalence of GEJAD has been recorded in the west (4, 5). According to the studies, in the United States, an approximately 2.5-fold increase in the incidence of GEJAD from 1973 to 1992, with rates stabilizing in the past 2 decades has been observed (1). In Canada, an increase in incidence of distal esophageal and proximal gastric adenocarcinomas was recorded from 1964 to 2002 (6). Also based on Studies from population-based cancer registries in the United States, the United Kingdom, and Switzerland has indicated a rapid increase in the incidence of GEJAD during last decades (1, 7, 8). Among

eastern Asian countries, there are several reports of a rapid increase in the incidence of GEJAD (9). A study in Japan shows a 2.3% incidence of GEJAD during the 1962-1965 period and a 10% increase during the 2001-2005 period (10). Recent epidemiological shifts have led to controversy about the etiology and treatment of GEJAD (3). Siewert

recognized the need for a tumor classification for GEJ cancer. The Siewert classification conveniently describes the anatomical location of these tumors relative to the GEJ (1). The current Siewert's classification is summarized in Table 1 (1).

**Table 1. Current Siewert's classification**

Siewert Type	Epicenter of the lesion
Type I	Within 1 to 5 cm above the anatomic GEJ
Type II	Within 1 cm above and 2 cm below the GEJ (true carcinoma of the cardia)
Type III	Between 2 to 5 cm below the GEJ, infiltrating GEJ and esophagus from below (subcardial carcinoma)

GEJAD is a complex disease. At present, surgery is the sole curative option for operable GEJAD (11, 12), but long-term outcomes are not satisfactory with resection alone. This poor long-term outcome has prompted an evaluation of neoadjuvant and adjuvant combined modality therapy (13). A number of clinical trials have established various peri- and post-operative treatment options that further improve survival rates of patients with GEJAD in contrast to surgery alone. The best form of multimodality therapy is not established (14). There is a variable incidence of GEJAD in terms of gender, age and geographical areas (15). To the best of our knowledge, in Iran, GEJAD has been studied poorly. In addition, there is a little in the literature about the baseline characteristics and impact of different types of treatments on survival rates in Iranian patients with GEJAD. Hence, in the current retrospective study, it was aimed to investigate the Iranian patients with GEJAD in terms of age, Siewert types, and the impact of multimodality therapy on their survival rates.

## 2. MATERIALS AND METHODS

### 2.1. Demographic studies

#### 2.1.1. Sampling procedure

Here, 246 subjects were included with documented pathology of GEJAD who referred to radiotherapy and oncology center of Reza, Mashhad city, Iran, between years 2009 to 2014.

#### 2.1.2. Evaluation of Demographic characteristics

The population was evaluated in terms of age, gender, Siewert types, tumor stage and also a history of cancer in their families. Tumor classification was performed according to National Cancer Institute (NCI) (16). Local refers to an invasive malignant cancer confined entirely to the organ where cancer began. Locally advanced refer to cancer that has spread from where it started to nearby tissue or lymph nodes. Advanced refers to cancer that has spread to other places in the body and usually cannot be cured or controlled with treatment.

### 2.2. Evaluation of different types of treatments

In order to assess the impact of different types of treatments on survival outcomes, among 246 patients with GEJAD, subjects with metastatic (advanced) GEJAD, and patients with an incomplete period of treatment were

excluded (124 patients remained in the study).

#### 2.2.1. Different types of treatments

All patients were sorted into 12 groups based on different multimodality treatments as they have been shown below. Abbreviations RT, CHT and SUR refer to radiotherapy, chemotherapy and surgery respectively.

1. RT,
2. CHT,
3. RT→CHT,
4. CHT→RT,
5. SUR→CHT,
6. SUR→RT,
7. CHT→SUR→RT,
8. SUR→CHT→RT,
9. CHT→RT→CHT,
10. CHT→RT→SUR,
11. SUR→CHT→RT→CHT,
12. CHT→RT→SUR→CHT.

##### 2.2.1.1. Radiotherapy procedure

For all kinds of treatments, radiotherapy was performed as following: Irradiation consisted of external- beam radiotherapy delivering a mean total dose of 44.5Gy (range, 40–50Gy), at 1.8 to 2Gy per fraction, with a 3- or 4-field technique. The irradiated volume took into account the tumor size and the risk of lymph node involvement.

##### 2.2.1.2. Chemotherapy procedure

All patients received chemotherapy based on cisplatin (Cis, EBWE) and 5-fluorouracil (5FU, Hospira healthcare Corp) regimen according to the following schedules: 2 cycles Cis-80 mg/m<sup>2</sup>, 5FU 1000 mg/m<sup>2</sup> administered during radiotherapy and every 3 weeks for both pre- and post CHTs.

### 2.3. Statistical analysis

All analysis was performed using SPSS statistical software, version 22.0 (SPSS for Windows Inc. Version 22. Chicago, Illinois, USA). The differences between each group were evaluated by use of the chi<sup>2</sup> test. Survival rates were estimated using Kaplan-Meier method (17). Overall survival was defined by the interval between the date of the diagnosis and the date of death or last follow-up. For survival time analysis, the number of events and censored refer to patients dead or alive respectively by the end of the study. All statistical tests were 2-sided, and P ≤ 0.05

indicated statistical significance (17).

### 3. RESULTS AND DISCUSSION

In the present retrospective study, a number of 246 subjects with GEJAD have been studied in terms of gender,

age, Siewert classification, tumor stage and history of cancer in their family members. Among 246 patients, 198 males (80.5%) and 48 females (19.5 %) with mean ages of 67.52 and 64.23 years were categorized respectively (Figure 1).

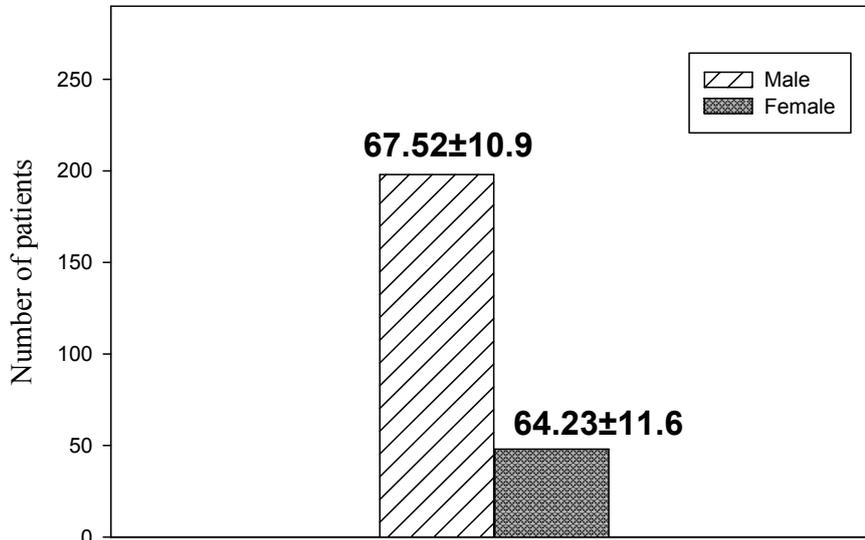


Figure 1. Number of patients based on gender; the mean age has been shown on the bars as mean ±SD

Baseline characteristics of patients have been shown in classification. Table 2 and Table 3 based on the current Siewert

Table 2. Age and number of patients based on Siewert classification; the mean age has been shown as mean ±SD

Siewert classification		No of Patients	Mean age ±SD	Min Age	Max Age
Type I	Male	79	68.62±10.6	30	89
	Female	28	64.71±12.8	29	86
Type II	Male	79	66.82±11.4	37	89
	Female	15	62.40±7.1	47	72
Type III	Male	40	66.72±10.6	42	82
	Female	5	67.00±16.1	39	79

Table 3. Number of patients with different tumor stages based on Siewert types

Siewert Classification	Local	Locally Advanced	Advanced
Type I	54	39	14
Type II	59	21	14
Type III	18	22	5

As it is observed, a number of patients with Siewert type I (n= 107) is more than types II and III (n= 94 and 45 respectively). Table 3 shows classification of patients in term of tumor stage. According to the results, there is a significant correlation between tumor stage and Siewert

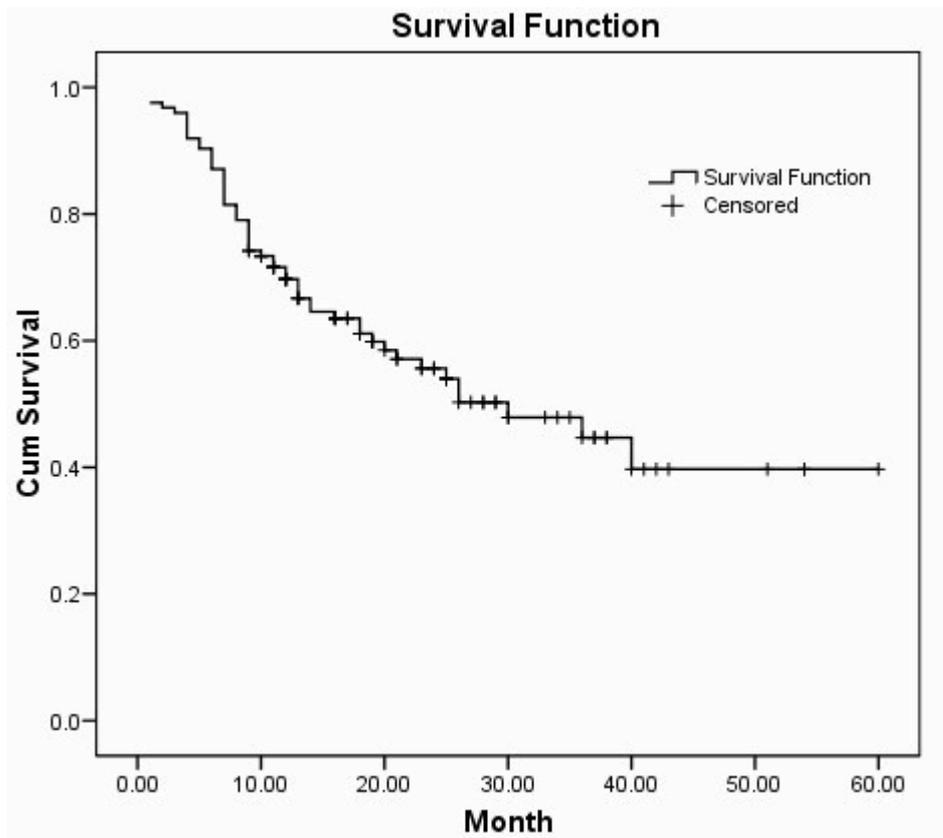
type with obtained Pearson chi-square of 10.56 (p= 0.032). Table 4 shows the information about the patients with a history of cancer for their family members and also shows the involved organs in patients with metastatic GEJAD.

**Table 4. Number of patients with history of cancer in their family members and the location of metastasis as well**

Kind of Relationship		Number of Patients
Immediate family	Father	12
	Mother	5
	Sister	6
	Brother	9
	Daughter	2
Extended family		3
Overall		37
Site of Metastasis		
Liver		28
Pancreas		3
Skin		1
Spleen		1
Overall		33

As it can be observed, among 246 individuals, 37 subjects have a history of cancer in their family members in which father has more frequency. In addition, as it has been shown, the number of patients with metastatic GEJAD has been reported 33 individuals (13.4%) so that liver as the involved organ shows more frequency in contrast to other organs. For the following studies, in order to investigate the effect of different types of multimodality therapy on

survival ratio, 124 subjects were included in the study and patients with metastatic GEJAD, undetermined last condition (dead or alive), and those who uncompleted treatment procedure, were excluded from the study. Then, using kaplen-meier statistic test, Overall survival (Figure 2) has been investigated (no of events=55).



**Figure 2. Overall survival rate; the word censored refers to patients are still alive by the end of the study**

Estimated overall survivals mean and median were obtained as  $33.5 \pm 2.6$  and  $30 \pm 6.7$  months respectively. Also, survival times have been evaluated based on different types of Siewert classification using kaplen- meier statistic

test and to determine whether there is a significant difference between studied groups, log-rank test was employed (Figure 3).

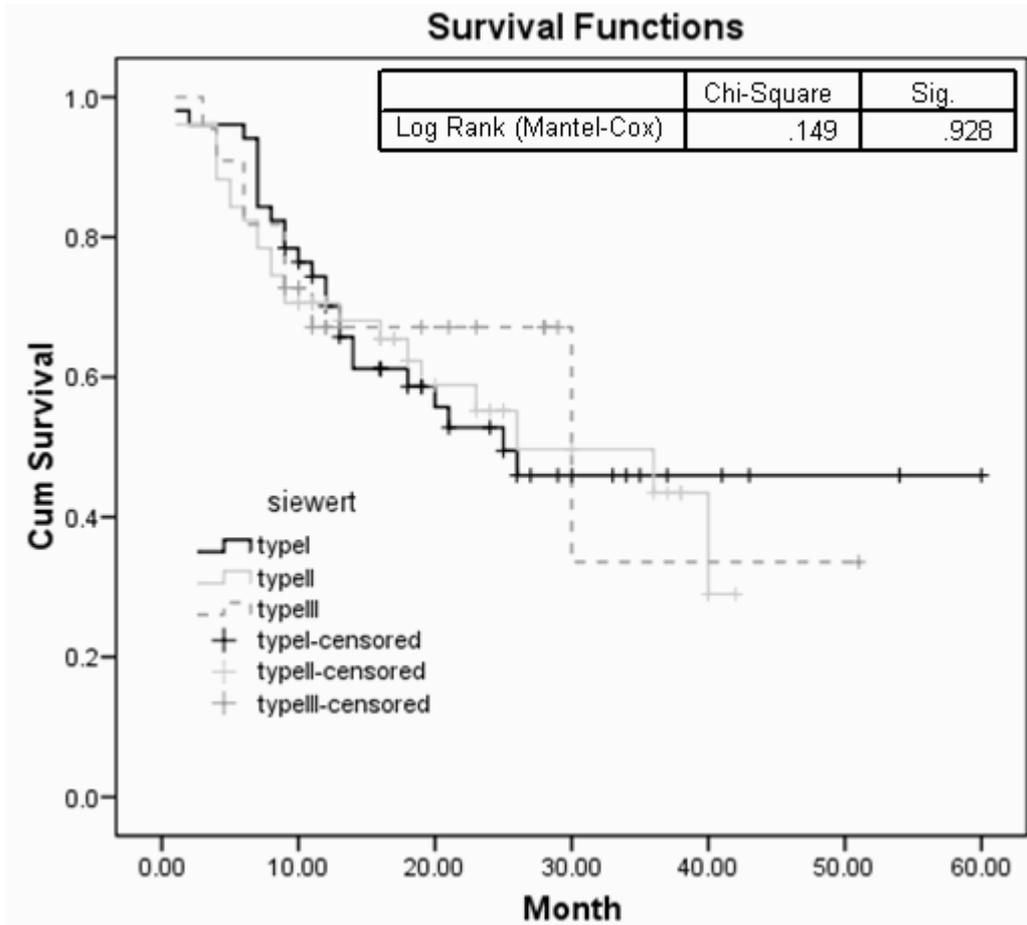


Figure 3. Survival function based on Siewert classification; the word censored refers to patients are still alive by the end of the study

To investigate the impact of different types of treatment on survival times, kaplen-meier and log- rank tests were

employed as described before. Obtained results have been shown in Table 5.

Table 5. Survival rates based on different types of treatments; words event and censored respectively refer to patients experienced death and patients are still alive by the end of the study

Kind of Treatment	No of Events	Censored		Total Number	One year Survival rate (%)	Two years Survival rate (%)
		Number	%			
RT	9	3	25	12	41.6	8.3
CHT	4	1	20	5	40	20
RT→CHT	4	9	69.2	13	76.9	7.7
CHT→RT	13	24	64.9	37	64.9	27.1
SUR→CHT	4	1	20	5	40	20
SUR→RT	1	4	80	5	80	60
CHT→SUR→RT	0	3	100	3	100	100
SUR→CHT→RT	8	11	57.9	19	73.7	57.9
CHT→RT→CHT	5	3	37.5	8	50	12.5
CHT→RT→SUR	2	3	60	5	40	40
SUR→CHT→RT→CHT	4	3	42.9	7	71.4	14.3
CHT→RT→SUR→CHT	1	4	80	5	40	40
Overall	55	69	55.6	124	62.1	29.1

According to the obtained results from log-rank test, different kinds of treatments led to significantly different survival times (p=0.041). In addition, one and two years' survival rates have been shown in Table 5. As it can be observed, the groups SUR→RT, CHT→SUR→RT, and CHT→RT→SUR→CHT had the highest ratio of patients alive in contrast to other groups by the end of the study. Also by comparing one and two years' survival rates, groups SUR→RT and CHT→SUR→RT showed the

highest ratio of survival rates. According to several reports, incidence of GEJAD has been raised fast during recent decades (18, 19). Based on geographical regions, a variety of countries was involved with this cancer (1, 20). As previously reported, gender, breed, Age and geographical situation affect the incidence and distribution of GEJAD (15). At the present, the only method for treatment of GEJAD is surgery (21). Recently, several studies have been reported the effect of combined modality therapy

such as radiotherapy and chemotherapy, on an enhancement of survival time, but there is no conventional method at the present (1). As GEJAD has been studied poorly in Iran, especially based on kinds of modality therapy, so in the present study, data of 246 patients with GEJAD were investigated. According to the obtained results, gender significantly correlates with GEJAD so that 80.5 % of patients were male with mean age of 67.52 years in contrast to 13.7 % female with mean age of 64.23 years. Therefore, the current study confirms that male predominance is particularly strong in this type of cancer and older adults face the higher risk for cancer. Each before the study has reported the distribution of patients based on different Siewert types. In the present study, a number of patients with type I GEJAD was higher than both types II and III. As different treatment guidelines were employed based on different Siewert types (22); so this study suggests more investigation on Siewert types for different populations to recommend more benefit treatment guidelines. Table 3 compares tumor stage based on Siewert types. According to the obtained results, there was a significant correlation between Siewert types and tumor stage. Local tumors were diagnosed in 62.8% of patients with Siewert type II in contrast to 50.5% and 40% of patients with Siewert types I and III respectively. On the other side, tumors with advanced stage were diagnosed for 14.9% of patients with Siewert type II in contrast to 13.1% and 11.1% of patients with Siewert types I and III respectively. Based on these findings, it can be concluded that metastatic GEJAD has been diagnosed for Iranian patients with Siewert type II more than other types. According to previous studies about 5 to 10% all cancer cases can be attributed to inherited gene defects (23). In the present study, 15.1 % of patients had the family history of cancer (Table 4) that was remarkably more than the mentioned range at above. According to the obtained results in this study, among patients with family history of cancer, 91.9% of cases were related to their immediate family in contrast to 8.9% of extended family. Based on other reports, a family history of certain types of cancer can increase the risk of cancer in other first-degree family members (24). This increased risk may be due to genetic factors (known and unknown), shared lifestyle factors or other family traits. Moreover, in this study, among patients with the history of cancer in their family members, 56.7% of cases were related to the male first-degree relatives (father, brother). Based on Table 4, among 246 patients, 13.4 % of subjects were diagnosed as patients with metastatic GEJAD. Among patients with metastatic GEJAD, liver metastasis (84.9%) was reported remarkably higher than other organs (lung, skin and brain). Sometimes the metastatic lesion is identified synchronously as original cancer, but in some cases, the metastatic lesion is discovered later, when original cancer has been treated or surgically removed (25). In this regard, according to the obtained results, it seems in patients with GEJAD, the liver must be considered and monitored more carefully as an

organ with a high risk of metastasis during later stages of cancer. Based on many reports, at the present, surgery is the most effective treatment for GEJAD, but long-term outcomes are not satisfactory with resection alone (26). Hence, many trials have been established to introduce new treatments with better long-term outcomes. Recently several studies were reported multimodality therapy with further improvement of survival rates of patients with GEJAD, but currently, the best form is not established (1). In the current study, it was aimed to evaluate the impact of different types of treatments on survival rates of Iranian patients with GEJAD. Among 246 patients, 124 subjects were included in the study. The time-to-event distributions were estimated using the method of Kaplan-Meier and to test the equality of the survival distributions for different groups, log-rank test was performed (17). According to Figure 2, overall mean and median survival rates were 33.5 and 30 months respectively. Based on Figure 3, there was no significant difference between Siewert types in term of survival time ( $p=0.928$ ). To assess the impact of different types of treatments on survival rates, Kaplan-Meier test was employed as well. According to the obtained results based on log-rank test ( $\chi^2=20.335$ ,  $\text{sig}=0.041$ ) there were significant differences between survival times based on different types of treatments. According to Table 5, groups SUR→RT, CHT→SUR→RT, and CHT→RT→SUR→CHT showed the highest ratio of patients alive in contrast to other groups by the end of the study. By comparing two years' survival rates, SUR→RT, CHT→SUR→RT were more effective multimodality therapies in contrast to other types. CHT→SUR→RT was the most effective multimodality therapy with 100% survival rate after two years of treatment. Since in this study, only three patients have been investigated with this kind of treatment, in order to evaluate the impact of this kind of treatment on survival rate more remarkably, more number of patients suggested to be studied long-term in the future.

#### 4. CONCLUSION

GEJAD is a complex disease. There is a variable incidence of GEJAD in terms of gender, age and geographical areas of incidence. Careful monitoring and treatment may help prevent developing this cancer. At the present, International Guidelines do not completely agree on the standard treatment approach for GEJAD. The National Comprehensive Cancer Network (NCCN) recommends surgery alone for the very early stages of ADGE and preoperative RT, CHT for all the others. The European Society for Medical Oncology (ESMO) indicates: surgery for local disease, perioperative chemotherapy for localized disease or alternatively, preoperative RT, CHT and perioperative CHT are recommended for the locally advanced disease. In the current study, SUR→RT, CHT→SUR→RT were considered as the most effective modality therapy for treatment of GEJAD in Iranian patients.

## ACKNOWLEDGMENT

We would like to thank all staffs at Reza radiotherapy and oncology center that participated for data collecting in this study.

## FUNDING/SUPPORT

There has been no financial support for this work.

## AUTHORS CONTRIBUTION

Marjaneh Mirsadraei designed the study, contributed to the data entry and analyzed the data. Hojjat Khalili-Hezarjaribi analyzed data and wrote the paper. All authors read and approved the final manuscript.

## CONFLICT OF INTEREST

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this paper.

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