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Overall Survival in Esophageal Cancer Based on Type, Anatomical Location, and Site of Metastasis

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Abstract

Background: The current study aimed to determine the trends in esophageal cancer (EC) patients and examine the impact of the type and anatomical location of the tumor and the site of metastasis on their survival.

Method: In this retrospective cohort study, we investigated 305 patients with a definite diagnoses of EC, who had been hospitalized at the Mahdie Hospital of Hamadan, Iran, during ten years from 2005-2015. EC-related survival considering different types and locations of the tumor, as well as the sites of metastasis, was evaluated. Survival was calculated using Kaplan-Meier curves and a multivariable Cox regression analysis (MVA) was performed.

Results: Squamous cell carcinoma was found in 76.6% of the patients and 23.4% had adenocarcinoma (AC). There was a significant relationship between the location and pathological type of tumor; 87% of ACs happened in the lower part of the esophagus ($P = 0.015$). The 1- to 5-year relative survival of the patients was 46%, 25%, 22%, 12%, and 7%, respectively. The rate of death in liver, lung, brain, pancreas, abdomen, and lymph nodes metastasis were respectively 42.9%, 21.4%, 14.3%, 7.1%, 7.1%, and 7.1%. No significant relationships were observed between the tumor type and metastasis ($P = 0.14$) or between the tumor type and the location of metastasis ($P = 0.7$).

Conclusion: Similar to other reports, the rate of survival was higher in AC type, yet the rate of total survival in Iran was much lower than that in developed countries. There were no differences in the survival rate concerning the location of the tumor. The obtained results did not show any relationships among the tumor type, the location of metastasis, and the total survival.

Keywords: Esophageal neplasms, Survival, Adenocarcinoma, Carcinoma, Squamous cell, Metastasis

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Introduction

Esophageal cancer (EC) is one of the most aggressive malignancies globaly.[1, 2] Based on previous reports, the rate of five-year survival in EC patients has been estimated to be about 32.2%, 17.5%, 37.6%, 52%, and 37%, in the USA, China, Korea, Swizerland, and Sweden, respectively.[3-7] Histologically, ECs are divided into two types according to the sort of the involved cells. Squamous cell carcinoma (SCC) grows in the inside layer of the lining of the esophagus and adenocarcinoma (AC) starts in gland cells.[8] Anatomically, ECs have been divided into three types of upper, middle, and lower cancers. Anatomical location is defined as upper-third (20-25 cm from the incisors), middle-third (25-30 cm), and lower-third cancer (>30 cm) based on the epicenter of the tumor. Certain studies have indicated that the tumor location affects the survival rates of ECs.[9, 10]

It is not exactly clear what causes EC. According to reports, the leading causes of SCC are the usage of tobacco, excessive alcohol consumption, a diet without fresh fruits and vegetables, and low socioeconomic status. SCC occurs most frequently in the upper and middle portions of the esophagus. AC is more likely to be due to genetics, reflux, obesity, and infection with Helicobacter pylori. This type mostly occurs in the lower portion of the esophagus. Most esophageal cancers are of the SCC type.[2]

Based on reports, over the past decades, rapid changes have been observed in cancer incidence and mortality and histologic subtype has shifted from SCC to AC, such that the majority of new diagnosed ECs are AC of the lower esophagus.[11, 12]

EC is highly lethal and approximately 50% of the patients present with EC most commonly spread to the liver, lung, bone, and brain.[13-16] Having information about distant metastasis (DM) and the correlation between the location of metastasis and survival is useful for improving patient treatment and follow-up.

Most previous survival studies on esophageal cancer have indicated the importance of gender, age, and risk factors.[16, 17] Few studies have investigated the correlation between the type of tumor, location of metastasis, and survival.[18-20] Therefore, the primary objective of this study was to determine whether the type and anatomical location of the tumor affect the overall outcomes in patients with EC. The next purpose was to assess the site-specific patterns of DM and survival outcomes of metastatic EC.

Materials and Methods

Patient selection

This study was a retrospective cohort study. The data were obtained from the patients with primary esophageal tumors localized in the upper, middle, and lower esophagus, who referred to Mahdieh Radiotherapy center from 2005 to 2015. The inclusion criteria comprised the patients with a definite diagnosis of EC. Demographic data including age, sex, marital status, occupation, place of residence, habits like smoking, drug or alcohol usage, disease profile, including location of tumor, type of cancer, and disease outcomes like recovery, recurrence, and metastasis were extracted from the medical records of the patients. Vital status and date of death were determined with official death certificates. Survival time was calculated using the date of diagnosis up to the date of death or last follow-up. The exclusion criteria included incomplete data recorded or lack of access to treatment-related records.

Statistical analysis

The Kaplan-Meier estimate determined the survival rate. COX regression was used to evaluate the factors influencing survival and the log-rank test was utilized to different survival rates in different groups. To compare the outcome of the disease in terms of nominal and qualitative variables, the chi-square test (or Fisher's exact test) was used. The t-test (or Mann-Whitney) was employed to compare the low variables. We used the life chart to examine the survival of the subjects. All the statistical analyses were performed with SPSS16.0 (*P*-value less than 0.05).

Results

General characteristics

A total number of 305 patients were identified.

Table 1 summarizes the demographic, initial clinical symptoms, and pathological characteristics of the patients on top of the distribution of different distant metastasis sites.

According to the obtained statistics, the highest rate of EC incidence happened in 2014 with 53 patients (17.4%) and the lowest rate happened in 2007 with 10 patients (3.3%). Mean age ± standard deviation (SD) was 66.9 ± 12.8 years with a range of 30 to 92 years. Among all the cases, 54.4% were male, 45.6% female, and 99.3% were married. The most common complaint at presentation was dysphagia (76.6%) and symptoms such as dysphagia and regurgitation, weight loss, obstruction, and neck mass were the least frequent symptoms (0.7%). Based on the histological type of tumor, SCC was found in 76.6% of the patients and 23.4% had AC. The largest proportion of tumors was located in the lower third part (57.7%), followed by middle third (19.3%) of the esophagus. Table 1 also shows the distribution of different sites of DM. Liver was found to be the most commonly affected site (28.6%), followed by bones (22.4%), lung (18.4%), and brain (12.2%). Most of the cancers were diagnosed once the tumor was in stage 4 (39%) or 3 (34.5%). 36 patients were suspected of having stomach invasion, two patients were pathologically confirmed with have tumor invasion into aortia, and one patient had aortia and cardia invasion.

Based on figure 1, the rate of incidence of AC increased compared with SCC, as time went by.

There was a significant relationship between the location and pathological type of tumor; 87% of ACs happened in the lower part of esophagus ($P = 0.015$).

Table 2 illustrates the 1 to 5-year survival of the subjects. A total of 198 patients initially fulfilled the inclusion criteria.

The 1- to 5-year relative survival of the patients was 46%, 25%, 22%, 12%, and 7%, respectively. The 1- to 5-year survival based on the type of tumor was respectively 43%, 25%, 22%, 11% and 5% in SCC type and 54%, 20%, 17%, 11%, and 11% in AC type. Based on table 2, the rate of survival in the patients with tumors localized to upper esophagus was 23%. 1 to 3 years of

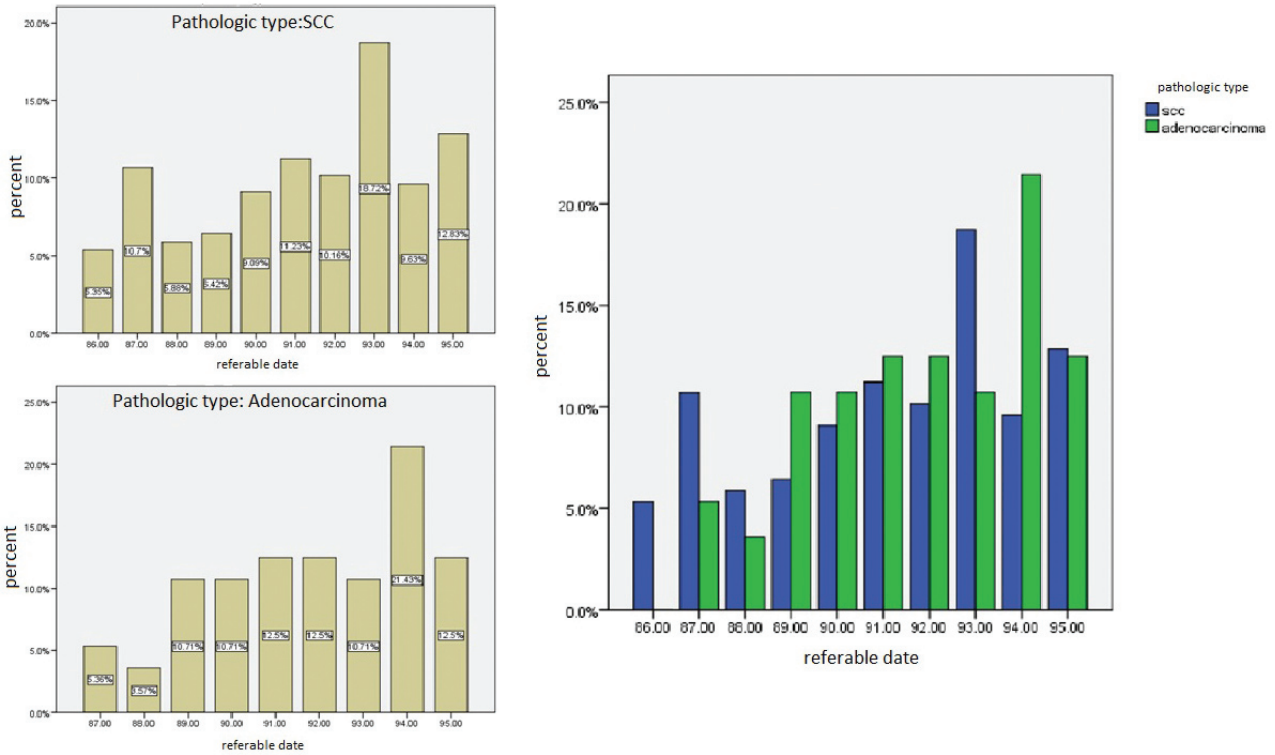

Figure 1. The incidence of adenocarcinoma (AC) compared to squamous cell carcinoma (SCC) type from 2006 to 2015, the incidence rate (percent) of AC increased compared to SCC as time went by.

Table 1. Demographic and Clinicopathological characteristics of the patients

Factor	Abundance	Percentage
Age (year), Average ± SD	12.8 ± 66.9	30-92
Gender		
Male	166	54.4
Female	139	45.6
Marital status		
Married	303	99.3
Single	2	0.7
Occupation		
Farmer	31	10.2
Housewife	109	35.7
Labor	3	1
Employee	12	3.9
Self-employment	150	49.3
Residence		
Urban	195	63.9
Rural	110	36.1
Drugs	33	10.8
Cigarette	56	18.5
Alcohol	5	1.6
Clinical signs		
Dysphagia	234	6.6
Spasm	17	5.5
Cachexia	27	9
Dysphagia and Regurgitation	2	0.7
Weight Loss	2	0.7
Dysphagia and Weight Loss	15	4.8
Obstruction	2	0.7
Neck mass	2	0.7
Hysteria	4	1.4
Total	305	100
Histological type		
SCC	234	76.6
AC	71	23.4
Location		
Upper	22	7.2
Middle	59	19.3
Lower	176	57.7
Upper and Middle	10	3.3
Middle and Lower	38	12.5
Metastasis		
Yes	49	16.1
No	256	83.9
Site of metastasis		
Liver	14	28.6
Bone	11	22.4
Lungs	9	18.4
Brain	6	12.2
Adrenal, lymphatic group, liver, and stomach	2	4.1
Lung and liver, peritoneum, pancreas	1	2
Stage at diagnosis		
0	5	1.6
1	11	3.6
2	65	21.3
3	34.5	105
4	119	39
Invasion		
Yes	39	12.8
No	276	87.2
Location of invasion		
Stomach	36	92.1
Aorta	2	5.3
Aorta and cardia	1	2.6

SD: Standar deviation; SCC: Squamous cell carcinoma; AC: Adenocarcinoma

survival in the patients with tumors in the middle part was 42%, 25%, and 25%, respectively and for those with lower part tumors was 53%, 28%, and 24%, respectively. 1-year survival in the patients with tumors in the upper-middle part was 50% and 1- to 2-year survival in those with middle-lower part tumors was 40% and 20%, respectively. 1- to 3-year survival of the subjects with metastasis was 53%, 29%, 19%, respectively.

Figure 2 represents the survival rate based on the type, location, metastasis, and invasion by the use of COX regression.

Figure 3 depicts these correlations based on Kaplan Meier analysis.

The rate of death in the patients who did not have metastasis was 0.96 based on COX regression. The trends of survival based on invasion showed that 1- to 5-year survival of those with invasion was 41%, 21%, 18%, 18%, and 18%, respectively. The rate of death in these patients was 1.13 based on COX regression. There was a significant relationship between metastasis and cancer death; the rate of death in liver, lung, brain and pancreas, abdominoplasty, and lymph nodes were 42.9%, 21.4%, 14.3%, 7.1%, 7.1%, and 7.1%. There were no significant relationships between the tumor type and metastasis ($P = 0.14$) and between tumor and the location of metastasis ($P = 0.7$). Liver metastasis was the most prevalent in both types of tumors.

Discussion

Based on our investigations, most previous studies in Iran and other countries have focused on the importance of gender, age, and the risk factors on the survival of patients with ECs. Few studies have investigated the trends of variations of the tumor type during the years. Furthermore, few researches have studied the correlation between the type of tumor, location of metastasis, and survival. The present widespread study investigated demographic parameters, signs, and

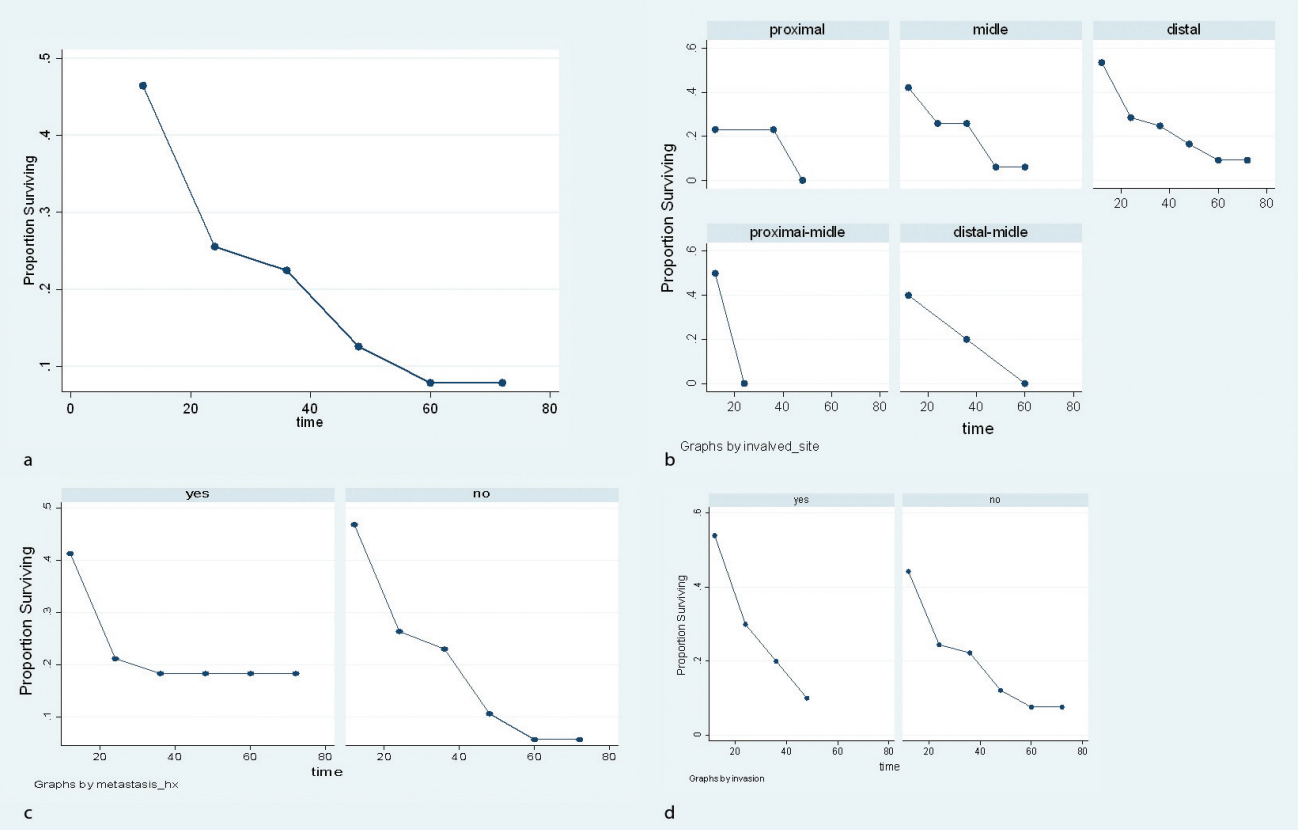

Figure 2. Rate of survival of the patients (proportion surviving) by the use of COX regression. Graph a. shows that survival declined as time went by; graph b. represents the rate of survival based on the anatomical site of tumor (proximal, middle, distal, proximal+middle, and distal+middle; graph c. shows the trend of survival based on metastasis; and graph d. depicts the trend of survival based on invasion.

trends of occurrence and variations during a period of ten years and determined whether the type and anatomical location or sites of metastasis of the tumor affect the overall outcomes in patients with EC. All the findings herein were compared to the results of other similar studies in each field.

Results revealed that the mean age of incidence was 66.9 years in Iran, which was similar to that reported in the USA, China, Korea, and Switzerland.[21, 22, 4, 23, 6] The information gathered from the patients' medical history showed that the most prevalent symptoms among our patients were dysphagia (76.6%) and symptoms such as weight loss and neck mass were the least common symptoms (0.7%). However, based on a recent study conducted in the USA, weight loss (55.7%) followed by dysphagia to solids (40.2%) were the most common symptoms among patients.[22]

Histological assessments indicated that most tumors among Iranian patients are of SCC type (76.6%), which is in agreement with the findings in other cities of the country.[3, 6, 24-28] Additionally, some researches have reported that similar to Iran, SCC is the most common type of ECs in Korea and Switzerland.[23, 6] However, based on certain articles, most ECs were of AC type in the U.S.[22] and China.[20, 4]

The results of a study conducted by Zhang et al. in the USA[3] showed that the abundance of occurrence has varied over the years. Before 2000, most ECs were of SCC type. After that, they were mostly of AC type. Our analysis also implied that the proportion of the patients diagnosed with AC increased slightly over the study period, whereas SCC diagnoses decreased proportionally.

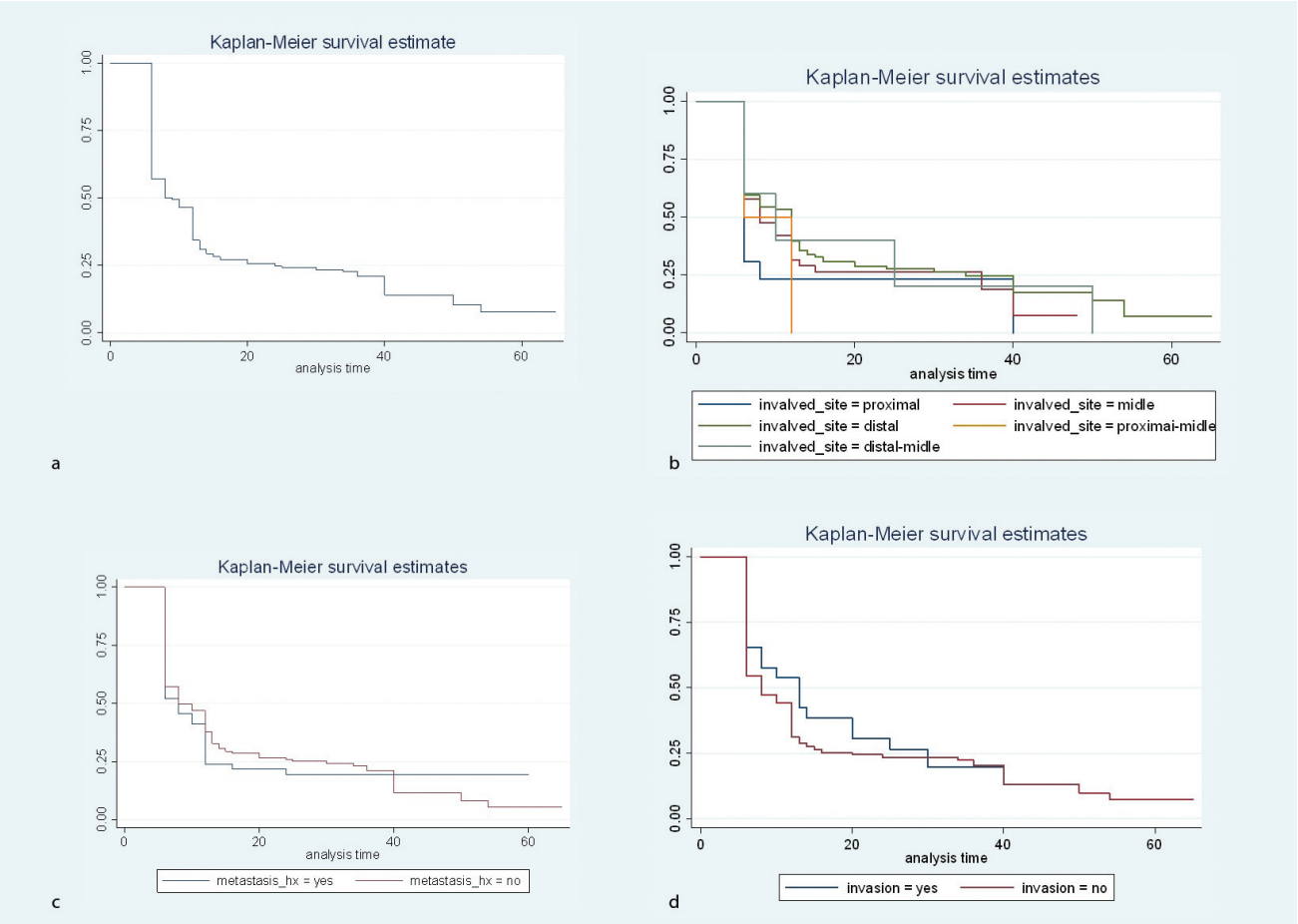

Figure 3. Rate of survival of the patients (proportion surviving) by the use of Kaplan Meier analysis. Graph a. presents that survival declined as time went by; graph b. shows the rate of survival based on the anatomical site of tumor (proximal, middle, distal, proximal+middle, and distal+middle); graph c. illustrates the trend of survival based on metastasis; and graph d. shows the trend of survival based on invasion.

Table 2. 1- to 5-year survival based on location, type of tumor, invasion, and metastasis (Continued)

Factor	Interval (months)		Beg. Total	Death	Lost	Survival	Std. Error	(95% CI)	
Total survival									
	0	12	198	106	0	0.4646	0.0354	0.3939	0.5322
	12	24	92	41	2	0.2553	0.0311	0.1967	0.3178
	24	36	49	51	5	0.2245	0.0302	0.1682	0.2860
	36	48	29	11	8	0.1257	0.0280	0.0774	0.1864
	48	60	10	3	4	0.0786	0.0277	0.0355	0.1440
	60	72	3	0	3	0.0786	0.0277	0.0355	0.1440
Survival based on the type of tumor									
SCC	0	12	125	71	0	0.4320	0.0443	0.3442	0.5166
	12	24	54	22	0	0.2560	0.0390	0.1833	0.3348
	24	36	32	3	9	0.2281	0.0380	0.1583	0.3056
	36	48	20	9	3	0.1171	0.0329	0.0625	0.1903
	48	60	8	3	4	0.0586	0.0290	0.0184	0.1333
	60	72	1	0	1	0.0586	0.0290	0.0184	0.1333
AC	0	12	37	17	0	0.5405	0.0189	0.3690	0.6842
	12	24	20	12	1	0.2079	0.0674	0.0950	0.3505
	24	36	7	1	2	0.1733	0.0644	0.0702	0.3146
	36	48	4	1	2	0.1155	0.0638	0.0283	0.2706
	48	60	1	0	1	0.1155	0.0638	0.0283	0.2706
Survival based on the location of tumor									
Proximal	0	12	13	10	0	0.2308	0.1169	0.0558	0.4746
	12	24	3	0	1	0.2308	0.1169	0.0558	0.4746
	24	36	2	2	0	0.0000...			
Middle	0	12	36	22	0	0.4211	0.0801	0.2642	0.5700
	12	24	16	6	1	0.2581	0.0716	0.1322	0.4038
	24	36	9	0	2	0.2581	0.0716	0.1322	0.4038
	36	48	7	5	1	0.0596	0.0457	0.0082	0.1912
	48	60	1	0	1	0.0596	0.0457	0.0082	0.1912
Distal	0	12	101	47	0	0.5347	0.0496	0.4329	0.6261
	12	24	54	25	1	0.2848	0.0450	0.2004	0.3749
	24	36	28	3	11	0.2468	0.0441	0.1659	0.3364
	36	48	14	4	4	0.1646	0.0446	0.0887	0.2608
	48	60	6	2	3	0.0914	0.0458	0.0271	0.2046
	60	72	1	0	1	0.0914	0.0458	0.0271	0.2046
Proximal-middle	0	12	2	1	0	0.5000	0.3536	0.0060	0.9104
	12	24	1	1	0	0.0000...			
Distal-middle	0	12	5	3	0	0.4000	0.2119	0.0520	0.7528
	12	24	2	1	0	0.2000	0.1789	0.0084	0.5819
	24	36	1	1	0	0.0000	-	-	-
-t	HR			Std.Err.		z	p>|z|	(95% CI)	
Middle	0.8191			0.2766		-0.59	0.555	0.4225	1.5880
Distal	0.6900			0.2146		-.1.19	0.233	0.3700	1.2697
Proximal-middle	1.1741			0.8990		0.21	0.834	0.2618	5.2657
Distal-middle	0.8023			0.4296		-0.41	0.681	0.2808	2.2919
Factor	**Interval (year)**		**Beg. Total**	**Death**	**Lost**	**Survival**	**Std. Error**	**(95% CI)**	
Survival based on metastasis									
Yes	0	12	26	12	0	0.5384	0.0978	0.3329	0.7058
	12	24	14	6	1	0.2991	0.0908	0.1386	0.4786
	24	36	7	2	2	0.1994	0.0836	0.0683	0.3795
	36	48	3	1	2	0.0997	0.0820	0.0097	0.3178
No	0	12	163	91	0	0.4417	0.0389	0.3645	0.5161
	12	24	72	32	1	0.2440	0.0337	0.1811	0.3122
	24	36	39	3	12	0.2218	0.0330	0.1608	0.2892
	36	48	24	10	4	0.1210	0.0296	0.0706	0.1859
	48	60	10	3	4	0.0756	0.0278	0.0330	0.1418
	60	72	3	0	3	0.0278	0.0278	0.0330	0.1418
-t	HR			Std.Err.		z	p>|z|	(95% CI)	
Metastasis-hx	0.9686			0.1819		-0.17	0.865	0.6703	1.3997

Table 2. 1- to 5-year survival based on location, type of tumor, invasion, and metastasis (Continued)

Factor	Interval (months)		Beg. Total	Death	Lost	Survival	Std. Error	(95% CI)	
Survival based on Invasion									
Yes	0	12	46	27	0	0.4130	0.0726	0.2711	0.5494
	12	24	19	9	1	0.2121	0.0608	0.1078	0.3398
	24	36	9	1	3	0.1838	0.0589	0.0860	0.3106
	36	48	5	0	3	0.1838	0.0589	0.0860	0.3106
	48	60	2	0	1	0.1838	0.0589	0.0860	0.3106
	60	72	1	0	1	0.1838	0.0589	0.0860	0.3106
No	0	12	143	76	0	0.4685	0.0417	0.3850	0.5476
	12	24	67	29	1	0.2642	0.0370	0.1949	0.3385
	24	36	37	4	11	0.2307	0.0359	0.1644	0.3037
	36	48	22	11	3	0.1069	0.0304	0.0568	0.1750
	48	60	8	3	3	0.0576	0.0265	0.0199	0.1249
	60	72	2	0	2	0.0576	0.0265	0.0199	0.1249
-t	HR			Std.Err.		z	p>|z|	(95% CI)	
Invasion	1.1389			0.2675		0.55	0.580	0.7187	1.8048

Beg. Total: Numbers of patients at the start of each stage (year); -t : Analysis time; SCC: Squamous cell carcinoma; AC: Adenocarcinoma; Std: Standard; CI: Confidence interval; HR: Hazard ratio; Std.Err. : Standard error

It has been mentioned in previous reports that SCCs are closely associated with tobacco and alcohol use, a diet without fresh fruits and vegetables, and lower socioeconomic status.[26] AC has strong associations with obesity, gastroesophageal reflux disease, and Barrett esophagus.[2, 12] Comparing the results of this study with other papers, we observed that the usage of drugs, cigarettes, and alcohol are much lower in Iran than in other countries, such as the U.S.A.[22] These findings revealed a clear association between socioeconomic status and SCC histology.

Global reports have indicated that SCC occurs most frequently in the upper and middle portions of the esophagus and AC occurs in the lower part.[21] Meanwhile, the obtained results herein showed that although most of the tumors among our patients were of SCC type, the majority of the cancers happened in the lower esophagus.

The 1- to 5-year relative survival results of this study agree with the findings of other studies in other cities of Iran.[2, 27, 28] Histology of the patients with AC had longer 1- and 5-year survival (54% and 11%) than the histology of those with SCC (43% and 5%). Based on reports, 1-year survival in the USA for ECs was 90% and 94% for SCC and AC, and 5-year survival was 68% and 83%, respectively. Even though similar to our results, the rate of survival is higher in AC type, the rate of total survival in Iran is much lower than that in the USA.[26]

The results showed that tumors located in the lower third had better 1- to 5-year survival compared with those located in the middle and upper third. The results of another study in the USA,[21] have also shown a similar trend. However, another study has been done by Delpishe et al. indicating that 1- to 5-year survival was higher in the middle and upper parts.[24] In all these studies, the differences were not significant after the first year. Therefore, there were no survival differences concerning the location of the tumor.

DM is the major cause of death in ECs; therefore, we investigated the distant metastasis patterns in this study.

Similar to other studies,[20, 4] liver was found to be the most frequently affected site of metastasis. Other locations of metastasis in this study were bone, lung, brain, adrenal, lymph nodes, and pancreas, while in other studies,[13-15, 20, 4] they were lymph nodes, lung, bone, and brain. The rate of incidence was higher in other studies for all the sites. Moreover, certain studies have claimed that there is a relationship between the tumor type and the location of metastasis. Wu et al. showed that patients with esophageal AC were more likely to develop brain and liver and less likely to develop lung metastasis compared with those with SCC.[4] Another study suggested a relation between the site of DM and the survival

of patients and reported that survival was the worst for bone metastases and greatest for distant lymph node metastases. However, in accordance with our results, Chen et al.,[14] Taken et al.,[29] and Blank et al.[30] did not show any relationships between these variables.

Conclusion

In conclusion, our findings revealed that most tumors among Iranian patients are of SCC type although the proportion of the patients diagnosed with AC increased slightly over the study period. Meanwhile, SCC diagnoses decreased proportionally. Furthermore, the majority of cancers were found to happen in the lower esophagus. Despite the high rate of survival in AC type, the rate of total survival in Iran is much lower than that in other countries. No survival differences were observed concerning the location of the tumor and site of metastasis. Therefore, it seems that more patients should be investigated and the role of other treatment procedures, such as radiotherapy and chemotherapy, should be considered to determine the relationship between survival and site of metastases.

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Conflict of Interest

None declared

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