Original Article

Running Title: Overall Survival in Esophageal Cancer
Received: December 31, 2020; Accepted: May 01, 2021

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

Zahra Sadin[*], MD, Abdolazim Sedighi Pashaki[**], PhD, Elham Khanlarzadeh[***], PhD, Mohammad Hadi Gholami[****], PhD, Safoora Nikzad[*****♦], PhD

[*]*Faculty of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran*
[**]*Departement of Radiooncology, Faculty of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran*
[***]*Department of Community Medicine, Faculty of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran*
[****]*Mahdieh Radiotherapy and Brachytherapy Charitable Center, Hamadan, Iran*
[*****]*Department of Medical Physics, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran*

♦Corresponding Author
Safoora Nikzad, PhD
Department of Medical Physics, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran
Tel: 08138380572
Fax: 08138380208
Email: s.nikzad@umsha.ac.ir

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 definitediagnoses 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 obrained 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

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 esophageal cancer. 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 our 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. Table1 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 distant metastasis. 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 to 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 to 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 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*-value =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 wide spread study investigated demographic parameters, signs, and 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.

Our 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.

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 to 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.

Distant metastasis 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 to those with SCC.[4] Another study suggested a relation between the site of distant metastases 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.

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.

Funding

This study was supported by the Student Research Committee contract number 9710186016 under the ethical number IR.UMSHA.REC.1397.648 of Hamadan University of Medical Sciences, Hamadan, Iran.

Acknowledgments

The authors would like to thank Hamadan University of Medical Sciences research center.

Conflict of Interest

None declared

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. *CA Cancer J Clin*. 2011;61(2):69-90. doi: 10.3322/caac.20107.
2. Yarhoseini A, Shrifzadeh L, Sayehmir, Kourosh , Mortazavi- Tabatabae SAR. Survival rates for esophageal carcinoms in Iran: a systematic review and meta-analysis. *Iran J Cancer Prev.* 2014;7(2):61-5.
3. Zhang Z, Chen Y, Chen Y, Jeter M, Hofstetter WL, Ajani J, et al. Outcomes with esophageal cancer radiation therapy. *J Thorac Oncol*. 2009;4: 880-8. doi: 10.1097/JTO.0b013e3181a6f204
4. Wu SG, Zhang WW, Sun JY, Li FY, Lin Q, He ZY. Patterns of distant metastasis between histological types in esophageal cancer. *Front Oncol.* 2018;8. doi: 10.3389/fonc.2018.00302.

5. Kim KH, Chang JS, Cha JH, Lee IJ, Kim DJ, Cho BC, et al. Optimal adjuvant treatment for curatively resected thoracic esophageal squamous cell carcinoma: A radiotherapy perspective. *Cancer Res Treat.* 2017;49(1):168-77. doi: 10.4143/crt.2016.142.
6. Herrmann E, Mertineit N, De Bari B, Hoeng L, Caparrotti F, Jumeau R, et al. Outcome of proximal esophageal cancer after definitive combined chemoradiation: A multicenter retrospective study. *Radiat Oncol.* 2017; 12, 97. doi:10.1186/s13014-017-0834-8.
7. Carstens H, Albertsson M, Friesland S, Adell G, Frykholm G, Wagenius G, et al. A randomized trial of chemoradiotherapy versus surgery alone in patients with resectable esophageal cancer. *Journal of Clinical Oncology.* 2007;25(18_suppl):4530. doi: 10.1200/jco.2007.25.18_suppl.4530
8. Bashash M, Shah A, Hislop G, Brooks-Wilson A, Le N, Bajdik C. Incidence and survival for gastric and esophageal cancer diagnosed in British Columbia, 1990 to 1999. *Can J Gastroenterol*. 2008;22:143-48. doi: 10.1155/2008/645107.
9. Eloubeidi MA, Desmond R, Arguedas M R, Reed CE, Wilcox CM. Prognostic factors for the survival of patients with esophageal carcinoma in the U.S.: the importance of tumor length and lymph node status. *Cancer*. 2002; 95(7):1434-43. doi:10.1002/cncr.10868.
10. Li H, Zhang Q, Xu L, Chen Y, Wei Y, Zhou G. Factors predictive of prognosis after esophagectomy for squamous cell cancer. *J Thorac Cardiovasc Surg*. 2009;137(1):55-9. doi: 10.1016/j.jtcvs.2008.05.024.
11. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst*. 2005;97:142-6. doi: 10.1093/jnci/dji024.
12. Brown LM, Devesa SS, Chow WH. Incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, and age. *J Natl Cancer Inst*. 2008;100:1184-7. doi: 10.1093/jnci/djn211.
13. Bosch A, Frias Z, Caldwell WL, Jaeschke WH. Autopsy findings in carcinoma of the esophagus. *Acta Radiol Oncol Radiat Phys Biol*. 1979;18(2):103-12. doi: 10.3109/02841867909128196.
14. Chen MQ, Xu BH, Zhang YY. Analysis of prognostic factors for esophageal squamous cell carcinoma with distant organ metastasis at initial diagnosis. *J Chin Med Assoc*. 2014;77(11):562-6. doi: 10.1016/j.jcma.2014.05.014.
15. Tustumi F, Kimura CM, Takeda FR, Sallum RA, Ribeiro-Junior U, Cecconello I. Evaluation of lymphatic spread, visceral metastasis and tumoral local invasion in esophageal carcinomas. *Arq Bras Cir Dig*. 2016;29(4):215-7. doi: 10.1590/0102-672020160004000.
16. Samadi F, Babaei M, Yazdanbod A, Fallah M, Nouraie M, Nasrollahzadeh D, et al. Survival rate of gastric and esophageal cancers in Ardabil province, North-West of Iran. *Arch Iran Med*. 2007;10:32-7.
17. Ghadimi MR, Mahmoodi M, Mohammad K, Rasouli M, Zeraati H, Fotouhi A. Factors affecting survival of patients with oesophageal cancer: a study using inverse Gaussian frailty models. *Singapore Med J.* 2012;53:336-43.
18. Ravikanth R. Esophageal carcinoma causing cystic metastases of liver. *Digital Medicine.* 2017;3(3):145-6. doi: 10.4103/2226-8561.220129.
19. Kesler KA, Hammoud ZT, Helft PR, Rieger KM, Pritz MB, Brown JW. Long-term survival after excision of a solitary esophageal cancer brain

metastasis. *J Thorac Cardiovasc Surg.* 2006;131(2):497-8. doi: 10.1016/j.jtcvs.2005.09.041.
20. Wu SG, Zhang WW, He ZY, Sun JY, Chen YX, Guo L. Sites of metastasis and overall survival in esophageal cancer: a population-based study. *Cancer Manag Res.* 2017;9:781-8. doi: 10.2147/CMAR.S150350.
21. Amin RN, Parikh SJ, Gangireddy VG, Kanneganti P, Talla S, Daram S. Early esophageal cancer specific survival is unaffected by anatomical location of tumor: A population-based study. *Can J Gastroenterol Hepatol.* 2016;2016:6132640. doi: 10.1155/2016/6132640.
22. Nassri A, Zhu H, Muftah M, Ramzan Z. Epidemiology and survival of esophageal cancer patients in an American cohort. *Cureus*. 2018;10(4). doi:10.7759/cureus.2507.
23. Jung HK, Tae CH, Lee HA, Lee H, Don Choi K, Park JC, et al. Treatment pattern and overall survival in esophageal cancer during a 13-year period: A nationwide cohort study of 6,354 Korean patients. *PLoS One*. 2020;15(4):e0231456. doi: 10.1371/journal.pone.0231456.
24. Delpisheh A, Veisani Y, Sayehmiri K, Rahimi E. Esophageal carcinoma: long-term survival in consecutive series of patients through a retrospective cohort study. *J Gastroenterol Hepatol*. 2014;7(2):101-7.
25. Azami A, Yazdanbod A, Abbasgholizadeh N, Sadeghi Y. Esophagus cancer risk factors in relation with different anatomical sites of esophagus in Aras GI clinical, Ardabil. [In Persian] *J Ardabil Univ Med Sci.* 2005;6(2): 126-31.
26. Brown LM, Devesa SS. Epidemiologic trends in esophageal and gastric cancer in the United States. *Surg Oncol Clin N Am*. 2002;11:235-56. doi: 10.1016/s1055-3207(02)00002-9.
27. Moghimi Dehkordi B, Rajaiifard A, Safaii A, Tabatabai H, Zeighami B, Tabei SZ. Application of life chart in estimating life expectancy and its effective factors in esophageal cancer. [In Persian] *J Adv Med Biomed Res.* 2008;16(63):67-74.
28. Bashash M, Yavari P, Hislop TG, Shah A, Sajadi A, Babaei M, et. al. Comparison of two diverse populations, British Columbia, Canada, and Ardabil, Iran, indicates several variables associated with gastric and esophageal cancer survival. *J Gastrointest Canc*. 2011;42:40-5. doi: 10.1007/s12029-010-9228-y.
29. Tanaka T, Fujita H, Matono S, Nagano T, Nishimura K, Murata K, et. al. Outcomes of multimodality therapy for stage IVB esophageal cancer with distant organ metastasis. *Dis Esophagus*. 2010;23(8):646-51. doi: 10.1111/j.1442-2050.2010.01069.x.
30. Blank S, Lordick F, Dobritz M, M Burian, R Langer, W Roth, et al. A reliable risk score for stage IV esophagogastric cancer. *Eur J Surg Oncol*. 2013;39(8):823-30. doi: 10.1016/j.ejso.2013.01.005.

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 & Regurgitation	2	0.7
	Weight Loss	2	0.7
	Dysphagia & 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 & 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	105	34.5
	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: Adeno carcinoma

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

Factor		Interval (months)	Beg. Total	Death	Lost	Survival	Std. Error	(95% conf. Int.)	
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	5	15	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	Haz.Ratio		Std.Err.		z	p>|z|	(95% conf. Int.)	
	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% conf. Int.)	
	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

Survival based on metastasis	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	Haz.Ratio			Std.Err.		z	p>|z|	(95% conf. Interval)	
	Metastasis-hx	0.9686			0.1819		-0.17	0.865	0.6703	1.3997
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	Haz. Ratio			Std. Err.		z	p>|z|	(95% conf. Interval)	
	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
conf. Int.: Confidence interval
Haz.Ratio: hazard ratio
Std.Err. : Standard error

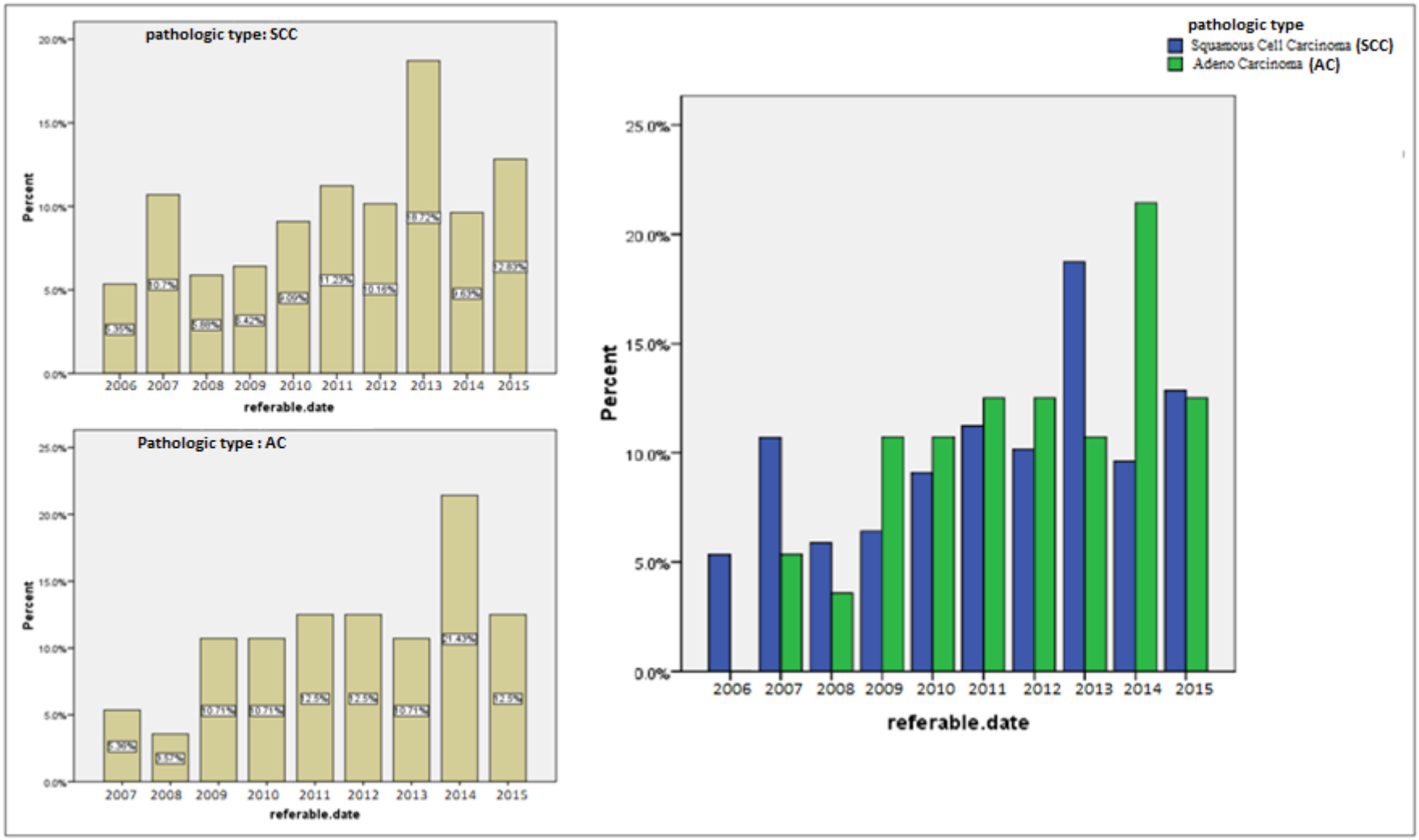

Figure 1. The incidence of Adeno carcinoma (AC) compared to squamous cell carcinoma (SCC) type from 2006 to 2015, the incidence rate (percent) of AC increased compared to SCC as time went by.

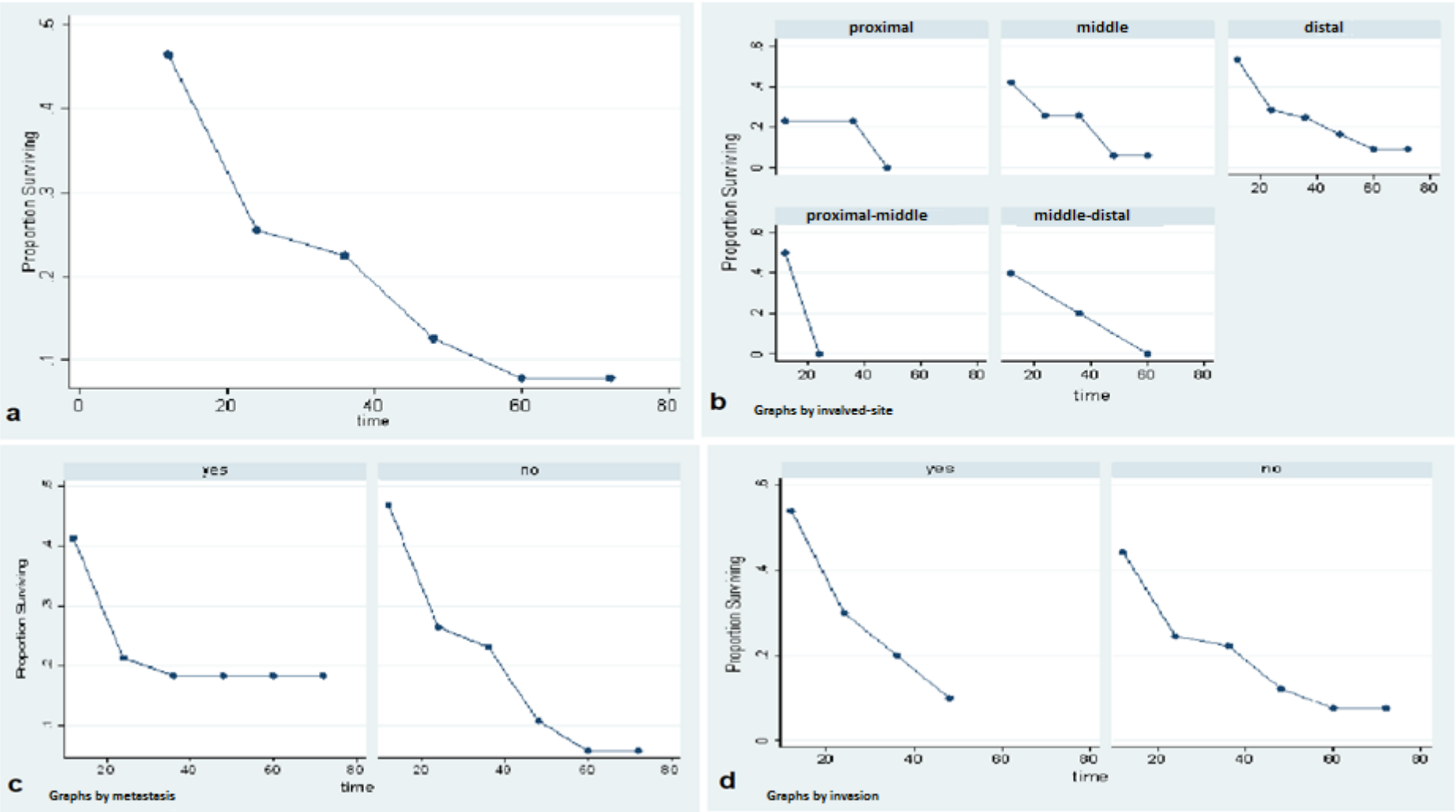

Figure 2. Rate of survival of the patients (proportion surviving) by the use of COX regression. Graph **a.** shows that survival declined as time went by, graph **b.** represents the rate of survival based on the anatomical site of tumor (proximal, middle, distal, proximal+middle, and distal+middle),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

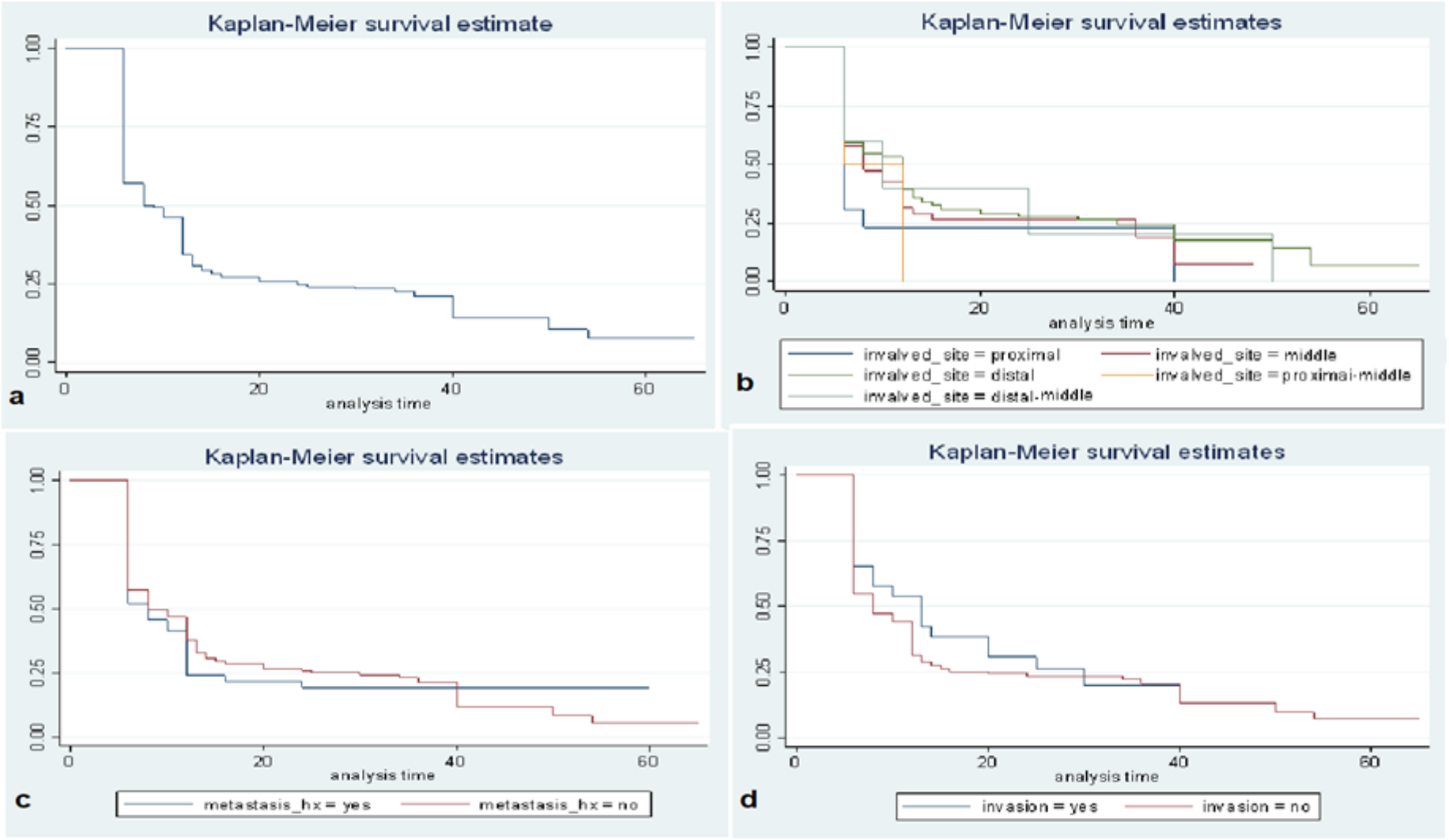

Figure 3. Rate of survival of the patients (proportion surviving) by the use of Kaplan Meier analysis. Graph **a.** presents that survival declined as time went by, graph **b.** shows the rate of survival based on the anatomical site of tumor (proximal, middle, distal, proximal+middle, and distal+middle),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