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Analysis of 69 Cases of Adenocarcinoma of the Esophagogastric Junction (Siewert Type II/III): 10-Year Single Center Experience

Özofagogastrik Bileşke Adenekarsinomu (Siewert Type II/III) Bulunan 69 Hastanın Analizi: 10 Yıllık Tek Merkez Deneyimi

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Öz

Amaç: Bu çalışmada özofagogastrik bileşke adenekarsinomu (AEJ) bulunan 69 hastanın klinikopatoloji özellikleri ve genel sağ kalımı ile ilgili 10 yıllık deneyimimizi paylaşmaktır.
Hastalar ve Yöntem: AEJ tanısı konulan ve kliniğimizde opere edilen 69 ardışık hasta çalışmaya dahil edilmiştir. Hastaların demografik özellikleri; laboratuvar parametreleri, cerrahi rezeksiyon yaklaşımı; TNM evreleri; rezeksiyon kapsamı; alınan lenf nodu toplam sayısı; tümör lokalizasyonu; lenfatik, vasküler ve perinöral invazyon varlığı ile genel sağ kalım (OS) durumu kaydedilmiştir. Hastalar Siewert Type II ve Siewert Type III olmak üzere iki gruba ayrılmıştır.
Bulgular: Gruplar arasında yaş (p=0.696) ve cinsiyet (p=0.140) bakımından anlamlı fark yoktur. T evresi dağılımı gruplar arasında istatistiksel olarak anlamlı şekilde farklıdır (p=0.0026). R0 düzeyindeki hastalarda OS, R1 düzeyindeki hastalara kıyasla anlamlı olarak daha yüksektir. Lenfatik, vasküler ve perinöral invazyon bulunmayan hastalarda OS istatistiksel olarak anlamlı şekilde daha yüksektir. Bir yıllık OS %85.50, 3 yıllık OS %49.10 ve 5 yıllık OS %43.60 olarak belirlenmiştir. Mortalite riski perigastrik yağ infiltrasyonu varlığında 8.63 kat, vasküler invasyon durumunda 12.60 kat ve perinöral invazyon durumunda 13.45 kat artmıştır. Sağ kalım oranı Siewert Type II ve Type III hastalarda 10 yıllık medyan izlem süresinde sırasıyla %51 ve %41 olarak saptanmıştır.
Sonuç: Bu çalışma klinikopatolojik özellikleri ve genel sağ kalımı başarılı bir şekilde değerlendirmiş ve Siewert Type II tümörler ile Siewert Type III tümörlerin benzer sağ kalım sonuçlalarına sahip olduklarını göstermiştir. AEJ hastalarının sonuçları konusundaki mevcut bulgulara katkı sağlamak amacıyla daha geniş serili ve uzun dönem kapsamlı, çok merkezli ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Adenokarsinom, gastroözofageal bileşke, Siewert type II, lenf nodu metastazı, lenf nodu diseksiyonu

Abstract

Aim: In this study, we aimed to present our 10-year experience regarding clinicopathology characteristics and overall survival of 69 patients with adenocarcinomas of esophagogastric junction (AEJs).
Patients and Methods: A total of 69 consecutive patients diagnosed with AEJ and operated in our clinics were included in the study. Patients' demographic characteristics; laboratory parameters, surgical resection approach; TNM stages; resection extent; total number of removed lymph nodes; tumor localization; presence of lymphatic, vascular and perineural invasion and overall survival (OS) status were recorded. The patients were divided into two groups as Siewert Type II and Siewert Type III.
Results: There was no statistically significant difference between the groups in terms of age (p=0.696) and gender (p=0.140). Distribution of T stage was statistically significantly different between the groups (p=0.026). OS was found to be significantly higher in patients at R0 level compared to those at R1 level. OS was statistically significantly higher in patients without lymphatic, vascular and perineural invasion. 1-year OS was determined as 83.50%, 3-year OS as 49.10% and 5-year OS as 43.60%. The risk of mortality increased by 8.63 folds in the presence of perigastric fat infiltration, 12.60 folds in the case of vascular invasion and 13.45 folds in the case of perineural invasion. The survival rate was found as 51% and 41% in the Siewert Type II and Type 3 patients at median 10-year follow-up.
Conclusion: This study had successfully evaluated the clinicopathological characteristics and overall survival, and demonstrated that Siewert II tumors and Siewert III tumors had similar survival outcomes. Further comprehensive multicenter studies with larger series and long-term studies are needed to provide contribution to the existing evidence on outcomes of patients with AEJs.

Key words: Adenocarcinoma, gastroesophageal junction, Siewert type, lymph node metastasis, lymph node dissection

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INTRODUCTION

Because of the borderline location of adenocarcinoma of the distal esophagus (AEJ) between the esophagus and stomach, many differencies exist among the studies ragarding the cause and classification of these tumors. Based on purely topographic anatomical criteria, Siewert et al. classified these tumors in three types, including Type I: adenocarcinoma of the distal esopgahus, Type II: true carcinoma of the cardia and Type III: subcardial gastric carcinoma (1). Accordingly, a tumor can be defined as AEJ if it centers within 5 cm above and 5 cm below the anatomic esophagogastric junction. Siewert II/III tumors are the major subtypes in East Asian countries, whereas Siewert I tumor is the major subtype in the Western countries (2). Studies have reported that Siewert III tumors are typically larger with poorer survival outcomes compared to Siewert II tumors, and are seen in the majority of patients with advanced gastric cancer (3).

AEJ is a malignant tumor with early hematogenous and lymphatic dissemination. In recent years, although the incidence of gastric cancer decreased gradually, the incidence of AEJ has risen, particularly in Western countries. In the developed countries, the prevalence of AEJ is rising at an alarm level. Despite multimodality treatment, prognosis of these tumors is still poor with a 5-year survival rate of around 30% (4). Lymph node metastasis is another important predictor of survival, and studies have reported a decrease from 53% to 11% in 5-year OS with the presence of lymph node metastasis (5). The etiology of AEJs is still unclear. Increasing trends of obesity and gastroesophageal reflux disease (GERD) have been blamed (6). It has been reported that there is a strong link between obesity and the development of AEJs (7). Smoking and alcohol intake have also been associated with the development of AEJs (8).

Complete tumor resection is the primary therapeutic strategy for tumor of AEJ (9). In Siewert II tumors, distal esophagectomy and total gastrectomy are the preferred approaches. Whereas, surgical treatment of Siewert tumors includes total gastrectomy and D1 lymp node dissection (10). However, since currently there is no guideline for the treatment of AEJs, treatment of the disease is based on existing guidelines for gastric and esophageal cancers. Recent research has focused on lymph node metastasis, surgical approaches and surgical resection methods. Numerous studies have been performed on clinicopathology characteristics and overall survival of patients with AEJ. However, particularly long-term outcomes are still insufficient. In this study, we aimed to present our 10-year experience regarding clinicopathology characteristics and overall survival of 69 patients with AEJs.

PATIENTS AND METHODS

The study protocol was approved by the local ethics committee of our hospital with the 18.11.2020 dated and 2020-10/3 numbered decision. Patients' consent was not deemed necessary as the study was designed as retrospective. The necessary permission to use patient data was obtained from the hospital management. The study was executed following the ethical principles of the Declaration of Helsinki. A total of 69 consecutive patients aged 4-65 years, diagnosed with AEJ and operated in our clinics using either total or proximal gastrectomy were enrolled in the study. Patients with other gastric or esophageal tumors were excluded from the study. Data used in this study were obtained from the hospital information technologies system and hospital archives. Patients' demographic characteristics such as age and gender; laboratory parameters, including albumin, hemoglobin and lymphocytes; blood ABO group; surgical resection approach (total or proximal gastrectomy); simultaneous organ resection; TNM stages; Borman classes, Lauren classes; resection extent (R0 or R1); total number of removed lymph nodes; tumor localization; histological differentiation status; resected lymph nodes; presence of lymphatic, vascular and perineural invasion; chemotherapy and radiotherapy status; and survival status were recorded. The patients were divided into two groups as Siewert Type II and Siewert Type III and the data obtained were compared between these two groups.

Surgical Approach

A lesion centered between 1 cm oral and 2 cm aboral of the anatomic gastroesophageal junction (GEJ) was considered as Siewert Type II cancer, and a tumor centered more than 2 cm below the anatomic GEJ was considered as Siewert Type III cancer. The diagnostic evaluation included endoscopy with biopsy, barium swallow, abdominal ultrasonography and computed tomography (CT) of the chest and abdomen. No patient underwent preoperative chemotherapy or radiotherapy. The tumors were staged according to the International Union Against Cancer Cancer Staging (IUACC) 8th edition (11). The choice of surgical approach (total vs proximal resection) was based on the tumor type and the goal of achieving microscopic and macroscopic resection.

In patients with Siewert type II tumors, an attempt was made to obtain complete tumor resection by means of an extended gastrectomy with transhiatal resection of the distal esophagus. Whereas in patients with Siewert type III cancer, an extended total gastrectomy with transhiatal resection of the distal esophagus was performed. The removed lymph nodes were counted and identified according their locations. The lesions were further classified according to the Borman and Lauren classification. Overall survival (OS) was calculated from the time of diagnosis until death or the last follow-up contact. Follow-up assessments were made in the form of outpatient visits or telephone interviews.

Statistical Analysis

SPPS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) software was used for performing the statistical analysis. The Shapiro–Wilk test was used to assess whether the variables followed normal distribution. Variables were reported as mean ± SD and median (minimum:maximum) values. According to the normality test results, Mann-Whitney U test and independent samples t-test were used to compare type II siewert and type III siewert groups. Categorical variables were compared by Chi square test, Fisher's exact test and Fisher-Freeman-Halton test. To estimate survival times Kaplan-Meier method was performed and the log-rank test was used to compare survival times across groups. Cox regression analysis was performed to determine the factors affecting mortality. $p<0.05$ values were considered statistically significant.

RESULTS

A total of 69 consecutive patients with a mean age of 64.20±10.75 years were included in the study. The median follow-up duration for OS was 10 years. Female/male ratio was found as 6/31 in the Siewert type II group and 10/22 in the Sievert type III group. There was no statistically significant difference between the groups in terms of age (p=0.696) and gender (p=0.140). Among the studied parameters, only distribution of T stage was statistically significantly different between the groups (p=0.026). In the subgroup analysis, the rate of patients in T1/T2 stage was higher in the Siewert type III group (21.90% vs 5.40%), while the rate of patients in T3 stage was higher in the Siewert type II group (56.80% vs 28.10%). The rate of patients in T4 stage was not different between the groups. No statistically significant difference was found between the Siewert type II and type III groups in terms of the other studied parameters (Table 1). The rate of survival in both

Table 1. Clinicopathological characteristics of Siewert type II and type III groups

Baseline information	Siewert type II (n=37)	Siewert type III (n=32)	p value
Gender (F/M)	6/31	10/22	0.140[a]
Age (year)	64.70±9.54	63.69±11.96	0.696[b]
Albumin	36 (10:49)	35(23:48)	0.918[c]
Hemoglobin	10.90 (1.20:14.80)	11(7.70:15.40)	0.485[c]
Lymphocyte	1.60 (1:4.78)	1.60 (0.60:3.70)	0.833[c]
Blood Group			
A	17 (45.90%)	15 (46.90%)	
B	8 (21.60%)	6 (18.80%)	0.955[a]
0	12 (32.40%)	11 (34.40%)	
Surgical Resection Ways			
Total Gastrectomy (Open)	34 (91.90%)	31 (96.90%)	0.618[d]
Proximal Gastrectomy	3 (8.10%)	1 (3.10%)	
Simultaneous Organ Resection	10 (27%)	9 (28.10%)	0.919[a]
T Stage			
T1/T2	2 (5.40%)	7 (21.90%)	
T3	21 (56.80%)	9 (28.10%)	0.026[e]
T4	14 (37.80%)	16 (50%)	
N Stage			
N0	6 (16.20%)	7 (21.90%)	
N1	6 (16.20%)	4 (12.50%)	0.925[a]
N2	8 (21.60%)	7 (21.90%)	
N3	17 (45.90%)	14 (43.80%)	

Table 1. more

TNM Stage			
IA	1 (2.70%)	2 (6.30%)	
IB	0	3 (9.40%)	
IIA	4 (10.80%)	1 (3.10%)	0.406[e]
IIB	5 (13.50%)	4 (12.50%)	
IIIA	11 (29.70%)	7 (21.90%)	
IIIB	9 (24.30%)	6(18.80%)	
IIIC	7 (18.90%)	9 (28.10%)	
TNM Stage			
Stage I	1 (2.70%)	5 (15.60%)	
Stage II	9 (24.30%)	5 (15.60%)	0.167[e]
Stage III	27 (73%)	22 (68.80%)	
Borman Classification			
Type I	0	3 (9.40%)	
Type II	10 (27%)	8 (25%)	0.119[e]
Type III	23 (62.20%)	14 (43.80%)	
Type IV	4 (10.80%)	7 (21.90%)	
Lauren Classification			
Intestinal	28 (75.70%)	19 (59.40%)	
Diffuse	5 (13.50%)	5 (15.60%)	0.258[a]
Mix	4 (10.80%)	8 (25%)	
Grade			
Grade I	1 (2.70%)	4 (12.50%)	
Grade 2	12 (32.40%)	10 (31.30%)	0.324[e]
Grade 3	24 (64.90%)	18 (56.30%)	
Rezeksiyon			
R0	33(89.20%)	27 (84.40%)	0.723[d]
R1	4(10.80%)	5 (15.60%)	
Surgical Margin			
Negative	30 (81.10%)	24 (75%)	0.541[a]
Positive	7 (18.90%)	8 (25%)	
Totaol number of resected lymph nodes	25 (3:60)	19 (1:44)	0.081[c]
Number of metastatic lymph nodes	6 (0:26)	5 (0:35)	0.986[c]
Tumor diameter			
<5 cm	9 (24.30%)	8 (25%)	0.948[a]
≥5 cm	28 (75.70%)	24 (75%)	
Tumor localization			
Lesser curvature	17 (45.90%)	22 (68.80%)	
Greater curvature	7 (18.90%)	2 (6.30%)	0.143[e]
Bilateral involvement	13 (35.10%)	8 (25%)	
Histological Differentiation			
Differentiated	2 (5.40%)	4 (12.50%)	
Moderately differianted	10 (27%)	10 (31.30%)	0.491[e]
Slightly differianted	35 (67.60%)	18 (56.30%)	
Lymph node dissection			
D0 – D1	3 (8.10%)	6 (18.80%)	0.285[d]
D2 – D3	34 (91.90%)	26 (81.30%)	
Lymphatic invasion	30 (81.10%)	23 (71.90%)	0.366[a]
Vascular Invasion	24 (64.90%)	17 (53.10%)	0.322[a]
Perineural Invasion	25 (67.60%)	20(62.50%)	0.659[a]
Omental Implantation	1 (2.70%)	4 (12.50%)	0.175[d]
Perigastric Fat Infiltration	6 (16.20%)	3 (9.40%)	0.489[d]
Adjuvant Chemotherapy	30 (81.10%)	23 (71.90%)	0.366[a]
Adjuvant Radiotherapy	15 (40.50%)	12 (37.50%)	0.796[a]

Data were presented as median (minimum:maximum) and n (%).

groups is seen in Figure 1.

Overall survival (OS) was analyzed in both groups. OS was found to be significantly higher in patients at R0 level compared to those at R1 level (64.91 vs

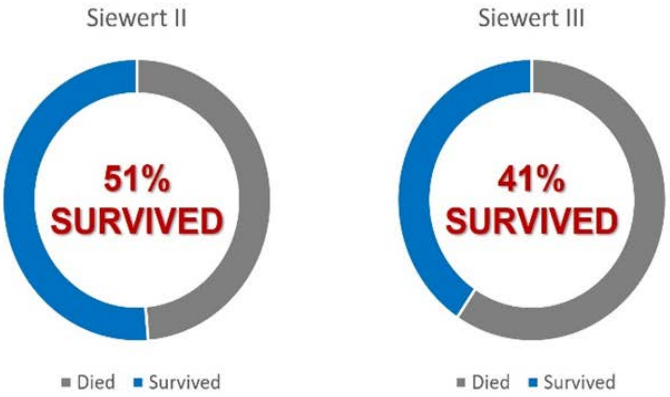

Figure 1. OS status of the patients in the Siewert type II and III groups.

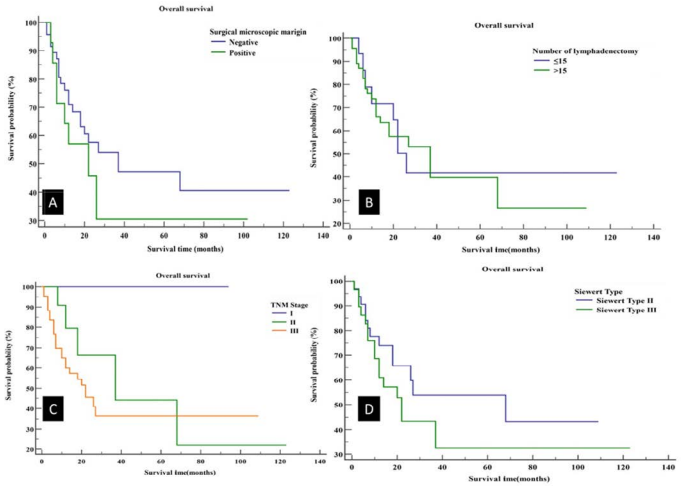

Figure 2. Kaplan-Meier curves based on surgical microscopic margin (A), number of lymphadentomy (B), TNM stage (C) and Siewert type (D).

Table 2. Kaplan-Meier analysis for 61 cases (Siewert type II/III)

n=61	Number of patients at risk (%)[ξ]	Number of Death (%)[ψ]	OS (months)	p-value[f]
Gender				
Female	14 (23%)	6 (42.90%)	58.52±12.98	0.763
Male	44 (77%)	23 (48.90%)	56.64±9.37	
ABO Blood Group				
A	29 (47.50%)	11 (37.90%)	69.85±12.44	
B	13 (21.30%)	8 (61.50%)	31.37±11.23	0.113
0	19 (31.20%)	10 (52.60%)	40.51±9.38	
Siewert type				
Type II	32 (52.50%)	13 (40.60%)	60.45±9.82	0.297
Type III	29 (47.50%)	16 (55.20%)	50.08±12.06	
Surgical Resection Approach				
Total Gst.	58 (95.10%)	27 (46.60%)	58.63±8.81	0.439
Proksimal Gst.	3 (100%)	2 (66.67%)	32±24.65	
Simultaneous Organ Resection				
Yes	16 (26.20%)	9 (56.30%)	35.82±12.76	0.294
No	45 (73.80%)	20 (44.40%)	65.24±9.33	
T Stage				
T1/T2	8 (13.10%)	1 (12.50%)	79.75±12.34	
T3	28 (45.90%)	15 (53.60%)	50.89±11.90	0.06
T4	25 (41%)	13 (52%)	53.21±10.21	
N Stage				
N0	12 (19.70%)	2 (16.70%)	78.06±10.11	
N1	8 (13.10%)	4 (50%)	62.09±21.27	0.06
N2	14 (23%)	7 (50%)	44.90±14.80	
N3	27 (44.30%)	11 (40.70%)	32±8.81	
TNM Stage				
IA	3 (4.90%)	0*	-	
IB	3 (4.90%)	0*	-	
IIA	5 (8.20%)	1 (20%)	24±8.49	0.577
IIB	7 (11.50%)	4 (57.10%)	56.34±18.25	
IIIA	16 (26.20%)	8 (50%)	58.64±12.61	
IIIB	13 (21.30%)	8 (61.50%)	16.69±2.89	
IIIC	14 (23%)	8 (57.10%)	36.14±11.17	

Table 2. more

TNM Stage				
Stage I	6 (9.80%)	0*	-	0.287
Stage II	12 (19.70%)	5 (41.70%)	54.86±16.97	
Stage III	43 (70.50%)	24 (55.80%)	47.35±8.16	
Grade				
Grade I	5 (8.20%)	1 (20%)	85.33±7.08	0.078
Gade 2	19 (31.10%)	7 (36.80%)	53.55±19.89	
Grade 3	37 (60.70%)	21 (56.80%)	46.17±8.72	
Resection				
R0	53(86.90%)	23 (43.40%)	64.01±9.05	0.034
R1	8(13.10%)	6 (75%)	14.38±3.62	
Surgical Margin				
Negative	47 (77%)	21 (44.70%)	62.28±9.59	0.32
Positive	14 (23%)	8 (57.10%)	40.49±13.48	
Total number of removed lymph nodes				
≤15	15 (24.60%)	8 (53.30%)	60.20±14.61	0.836
>15	46 (34.40%)	21 (45.70%)	47.69±9.87	
Tumor diameter				
<5 cm	16 (26.20%)	6 (37.50%)	66.67±13.50	0.592
≥5 cm	45 (73.80%)	23 (51.10%)	53.45±9.72	
Tumor localization				
Lesser Curvature	36 (59%)	16 (44.40%)	67.38±10.23	
Greater Curvature	8 (13.10%)	4 (50%)	22.01±2.60	0.989
Bilateral Involvement	17 (27.90%)	9 (52.90%)	47.06±11.19	
Histological Differentiation				
Differentiated	6 (9.80%)	2 (33.30%)	72.44±13.16	
Moderately Differentiated	17 (27.90%)	6 (35.30%)	55.78±21.44	0.214
Slightly Differentiated	38 (62.30%)	21 (55.30%)	47.51±8.60	
Lymph node dissection				
D0 – D1	8 (13.10%)	1(50%)	59.88±14.98	0.429
D2 – D3	53 (86.90%)	25(47.70%)	52.44±10.28	
Lymphatic invasion				
Yes	15 (24.60%)	4(26.70%)	82.74±15.78	0.021
No	46 (75.40%)	25(54.30%)	45.99±8.22	
Vascular Invasion				
Yes	26 (42.60%)	7(26.90%)	85.83±11.72	<0.001
No	35 (57.40%)	22(62.90%)	34.45±8.90	
Perineural Invasion				
Yes	21 (34.40%)	4 (19%)	72.67±9.34	0.001
No	40 (65.60%)	25 (62.50%)	44.14±9.19	
Omental Implantation				
Yes	57 (93.40%)	26 (45.60%)	61.15±8.78	0.465
No	4 (6.60%)	3 (75%)	18.50±2.51	
Perigastric Fat Infiltration				
Yes	55 (90.20%)	25 (45.50%)	62.03±8.84	0.117
No	6 (9.80%)	4 (66.70%)	14.50±3.83	
Adjuvant Chemoterapy				
Yes	53 (86.90%)	25 (47.20%)	57.42±9.08	0.948
No	8 (13.10%)	4 (50%)	51±15.34	
Radiotherapy				
Yes	27(44.30%)	13 (48.10%)	60.21±11.75	0.781
No	34 (55.70%)	16 (47.10%)	49.72±7.81	

[l]: n=69 kişi içerisindeki sayı ve oran olarak verilmiştir.
[J]: risk altındaki hasta sayısı içerisindeki sayı ve oran olarak verilmiştir.
*: The relevant category was excluded from the analysis due to the insufficient number of data.
Overall survival (OS) time was represented as median ± standart error or mean ± standart error, f: Log-rank Test

14.38; p=0.034). OS was statistically significantly higher in patients without lymphatic invasion (82.74 vs 45.99; p=0.021). Similarly, OS was significantly higher in patients without vascular invasion (85.83 vs 34.45; p<0.001). In addition, OS was significantly higher in patients without perineural invasion (72.67 vs 44.14; p=0.001). The other variables did not affect OS (Table 2). 1-year OS was determined as 83.50%, 3-year OS as 49.10% and 5-year OS as 43.60%.

In order to determine the factors affecting mortality, a cox regression analysis was performed and the results are presented in Table 3. Variables that provide p<0.25 condition in the univariate cox regression were included in the multivariate cox regression model and the obtained model was found to be significant (p=0.008). When the results of multivariate regression analysis were examined; it was found that resection at R1 level increased the hazard of mortality by 12.37 folds. A one-unit increase in the number of metastatic lymph nodes was found to increase the hazard of mortality 1.13 times. The hazard of mortality increased by 8.63 folds in the presence of perigastric fat infiltration, 12.60 folds in the case of vascular invasion and 13.45 folds in the

Table 3. Determination of the factors affecting mortality

	Univariate Cox Regression Model			Multivariate Cox Regression Model		
	Wald	HR(95%CI)	p	Wald	HR(95%CI)	p
Siewert (Type III)	1.05	1.47(0.71:3.05)	0.306			
Gender (Male)	0.09	1.15(0.47:2.82)	0.767			
Age	5.78	1.05(1.01:1.09)	0.016	1.05	1.05(0.98:1.12)	0.167
Blood Type	4.04	0.133	0.104			
B	3.95	2.55(1.01:6.40)	0.047	4.45	4.45(0.80:24.80)	0.088
0	1.32	1.66(0.70:3.91)	0.250	3.55	3.55(0.89:14.12)	0.072
Albumin	2.22	0.96(0.91:1.01)	0.137	0.96	0.96(0.88:1.04)	0.322
Hemoglobin	0.03	0.99(0.86:1.14)	0.868			
Lymphocyte	0.13	1.10(0.67:1.79)	0.716			
Surgical Resection Approach (Proksimal Gastrectomy)	0.57	1.75(0.41:7.49)	0.449			
Simultaneous organ resection (Yes)	1.06	1.51(0.69.3.33)	0.304			
Borrman Classification	9.93	2.55(1.43:4.57)	0.002	1.07	1.07(0.37:3.10)	0.900
Lauren Classification	2.21	1.39(0.91:2.14)	0.137	0.44	0.44(0.18:1.09)	0.077
Resection (R1)	4.04	2.56(1.02:6.42)	0.045	12.37	12.37(1.97:77.80)	0.007
Tumor diameter (>5 cm)	0.28	1.28(0.52:3.14)	0.597			
Tumor localization	0.022		0.989			
Greater curvature	0.01	1.04(0.34:3.14)	0.946			
Bilateral involvement	0.02	1.06(0.47:2.41)	0.885			
T Stage	4.10		0.129			0.088
T3	4.06	8.16(1.06:62.90)	0.044	16.48	16.48(0.07:3715.20)	0.311
T4	3.28	6.59(0.86:50.70)	0.070	6.39	6.39(1.23:33.33)	0.028
N Stage	6.22		0.102			0.453
N1	2.25	3.66(0.67:20.01)	0.134	0.33	0.33(0.01:8.10)	0.500
N2	2.05	3.18(0.65:15.49)	0.152	0.05	0.05(0.00:4.52)	0.187
N3	5.39	5.87(1.32:26.11)	0.020	0.03	0.03(0.00:2.98)	0.138
Lymph node dissection(D2-D3)	0.60	1.53(0.52:4.49)	0.438			
Number of lymphadenectomy(>15)	0.60	1.53(0.52:4.49)	0.438			
Number of metastatic lymph nodes	2.91	1.04(0.99:1.08)	0.088	1.13	1.13(1.00:1.28)	0.043
Omental Implantation (Present)	0.51	1.55(0.46:5.20)	0.475			
Perigastric Fat Infiltration (Present)	2.25	2.28(0.78:6.66)	0.134	8.63	8.63(1.18:63.15)	0.034
TNM STAGE	5.51	2.66(1.18:6.04)	0.019	22.43	22.43(0.70:719.36)	0.079
Vascular Invasion (Present)	1.66	4.76(1.94:11.64)	0.001	12.60	12.60(1.38:115.17)	0.025
Lymphatic Invasion (Present)	4.65	3.24(1.11:9.45)	0.031	0.16	0.16(0.02:1.46)	0.104
Perineural Invasion (Present)	8.45	4.87(1.68:14.14)	0.004	13.45	13.45(1.43:126.17)	0.023
Surgical Marigin (Positive)	0.95	1.50(0.66:3.41)	0.330			
Histological differentiation	0.285		0.241			0.239
Moderate	1.83	0.37(0.08:1.58)	0.177	3.59	3.59(0.07:197.63)	0.532
Differentiated	1.40	0.58(0.23:1.43)	0.237	15.10	15.10(0.54:419.10)	0.109
Grade	4.32		0.115			0.115
II	1.06	3.03(0.37:25.03)	0.302	0.02	0.02(0.00:22.95)	0.279
III	2.80	5.60(0.74:42.20)	0.094	0.57	0.57(0.00:228.56)	0.854
Radiotherapy (Yes)	0.08	0.90(0.43:1.89)	0.784	1.06	1.06(0.28:4.09)	0.932
Chemotherapy (Yes)	0.54	0.97(0.33:2.79)	0.948	1.36	1.36(0.22:8.50)	0.745

HR: Hazard Ratio, CI:Confidence Interval

case of perineural invasion. Figure 2 shows survival curves based on surgical microscopic margin, number of lymphadentomy, TNM stage and Siewert type.

DISCUSSION

In this study, clinicopathologic characteristics and overall survival were compared between Siewert type II and type III AEJs. No statistically significant difference was found between the two group in terms of demographic variables, including age and gender. Similarly, Yuasa et al. found no significantly different variables between Siewert type II and type III AEJs (12). In most countries, AEJ is twice to four times more frequent in men compared to women (13), which was supported in our study with a M:F ratio of 31/6 in the Siewert type II group and 22/10 in the Siewert type III group. Likewise, Siewert et al. was found a M:F of 5.4:1 and 2.1:1 in Siewert type II and III, respectively (1). In the present study, no significant difference was found between the two groups in terms of the studied parameters except for T stage (p=0.026). The T indicator is related to the extent of the tumor invasion. The T stage has a direct effect on patient's stage, the likelihood of metastatic nodal disease and outcome. In the subgroup analysis, the rate of patients in T1/T2 stage was higher in the Siewert type III group, while the rate of patients in T3 stage was higher in the Siewert type II group. Unlike our result, Zhang et al. found higher T1/T2 and T3 stages in type II compared to type II AEJ (2). Similarly, Yang et al. found higher rates of T1/T2 and T3 stages in type II AEJs (4). The differences might be resulted from patient selection and staging criteria.

The overall survival (OS) rate is poor in most patients with AEJ, because lymph node metastasis is often present at the time patients become symptomatic. A few patients are identified early in the disease upon screening for GERD and Barrett's esphagus. In our study, 51% of the patients in the Siewert type II group and %41 of the patients in the Siewert type III group survived. OS was reported as 27.5% and 24.5% by Bai et al. in the Siewert type II group and type III group, respectively (14). Zhang et al. reported 3-year OS as 59.1% for the Siewert type II group and 57.1% for the Siewert type III group. On the other hand, in the present study 1-year OS was determined as 83.50%, 3-year OS as 49.10% and 5-year OS as 43.60%. Cellini et al. followed their AEJ patients for median 45.4 months and reported 3-year OS as 58% and 5-year OS as 44% (15). As is seen, although different rates of OS were reported, in general the results are within a similar range. In majority of the studies no statistically significant difference was observed between Siewert type II and type III groups in terms of OS. R0 resection is the most important determinant of long-term survival in AEJs (16). The 5-year OS after R0 resection was reported as 43.2% (17). In our study, OS was higher in the patients with resection at R0 level (64.01 months). Siewert et al. reported 5- and 10-year survival rates as 38.7% and 28.3%, respectively, for patients with R0 resection, while this rate was 13.7% and 11.6% in patients with R1/R2 resection (1). Although results of the studies vary, most of these studies reported higher survival rates with R0 resection as in our study.

Lymphatic, vascular and perineural invasions are the factors affecting OS negatively. Junior et al. reported that lymphatic invasion is involved in the worsening survival prognosis (18). In addition, lymphatic invasion is associated with increased lymph node metastasis. The incidence of lymphovascular invasion of AEJ appears to be higher than that of esophageal and gastric cancers (19). However, the roll of vascular invasion has been yet to be clarified. In a study by Chen et al., multivariate regression analysis revealed perineural invasion was found to be an independent prognostic factor for overall survival (20). In our study, OS was significantly higher in patients without lymphatic (p=0.021), vascular (p<0.001) and perineural (p=0.001) invasions. From this point of view, our study is consistent with the literature. In our study, according to the results of multivariate analysis, resection at R1 level, number of metastatic lymph nodes >15, presence of perigastric fat infiltration, vascular invasion and perineural invasion were determined as the factors affecting mortality. In a study by Zheng et al., multivariate regression analysis revealed that neoplasms by histological type, lymphatic embolus and depth of perigastric fat infiltration were independent risk factors for lymph node metastasis in Siewert II/III AEJs (21). In a study by Ustaalioglu et al., according to the multivariate regression analysis, stage, grade, and recurrence were found as independent risk factors for OS, while grade, surgical margin, and preoperative chemoradiotherapy were independent risk factors for diseasse free survival (DFS) (22). Various parameters have been determined as independent risk factors of mortality, OS and DFS. Although the differences among the studies obtained from multivariate analysis are resulted from many factors ranging from patient selection criteria, surgical

approach, using adjuvant therapies preoperatively etc., yet these factors congregate at some points with mutual futures.

This study has some limitations. The study was designed as retrospective and executed in a single center with relatively small number of patients. On the other hand, this study had successfully evaluated the clinicopathological characteristics and overall survival, and demonstrated that Siewert II tumors and Siewert III tumors had similar survival outcomes. As a strength, long-term OS outcomes could be guiding for future comprehensive studies.

CONCLUSION

The findings of this study indicate that T1/T2 stage was higher in the Siewert type III group, while T3 stage was higher in the Siewert type II group. OS was higher in R0 resection. Lymphatic, vascular and perineural invasions affect OS negatively. Number of metastatic lymph nodes >15, presence of perigastric fat infiltration and were determined as the factors affecting mortality. Further comprehensive multicenter studies with larger series and long-term studies are needed to provide contribution to the existing evidence on outcomes of patients with AEJs.

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