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An outcome comparison of adenocarcinoma of the esophagus to squamous cell carcinoma after transthoracic esophagectomy

Adenokarsinom ve skuamöz hücreli karsinomlu distal özofagus kanserinde transtorasik özofajektomi sonuçlarının karşılaştırılması

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Background: In this study, we assessed the results of adenocarcinoma (ADC) and squamous cell carcinoma (SCC) cases of distal esophagus, who underwent transthoracic esophagectomy.

Methods: Between January 1999 and July 2010, 22 ADC (12 females, 10 males; mean age 61.5±11.2 years; range 40 to 79 years) and 48 SCC cases of distal esophagus (28 females, 20 males; mean age 56.8±12.1 years; range 28 to 83 years), who underwent transthoracic esophagectomy were retrospectively analyzed.

Results: The most commonly encountered symptoms of ADC and SCC were dysphagia and weight loss (90.9%, 40.9% and 93.8%, 37.5%, respectively). Six cases (27.3%) with ADC and 18 cases with SCC (37.5%) had smoking history. Four cases with ADC (18.2%) and 21 cases with SCC (43.8%) developed postoperative complications (p=0.033). No intraoperative mortality is observed in ADC cases, while three SCC cases (6.3%) died intraoperatively. Median survival was 34.3 months in ADC and 30.5 months in SCC. Five-year survival was 33.3% in ADC and 17.1% in SCC cases (p=0.55).

Conclusion: In this study, it was observed that postoperative complication rate was significantly higher in SCC compared to patients with ADC; however, there was no statistically significant difference in the long-term survival. Transthoracic esophagectomy appears to be a safe treatment modality in distally located esophagus cancer cases.

Key words: Esophageal cancer; histology; transthoracic esophagectomy.

Amaç: Bu çalışmada transtorasik özofajektomi uygulanan distal özofagus yerleşimli adenokarsinom (ADK) ve skuamöz hücreli karsinomlu (SHK) olguların sonuçları değerlendirildi.

Çalışma planı: Ocak 1999 ve Temmuz 2010 tarihleri arasında transtorasik özofajektomi uygulanan distal özofagus yerleşimli 22 ADK (12 kadın, 10 erkek; ort. yaş 61.5±11.2 yıl; dağılım 40-79 yıl) ve 48 SHK olgusu (28 kadın, 20 erkek; ort. yaş 56.8±12.1 yıl; dağılım 28-83 yıl) retrospektif olarak incelendi.

Bulgular: Adenokarsinom ve SHK'de en sık görülen semptomlar disfaji ve kilo kaybı (sırasıyla %90.9, %40.9 ve %93.8, 37.5%) idi. Adenokarsinomlu altı olguda (%27.3), SHK'li 18 olguda (%37.5) sigara içme öyküsü vardı. Ameliyat sonrası komplikasyon ADK'li dört olguda (%18.2) ve SHK'li 21 olguda (%43.8) gelişti (p=0.033). Ameliyat sırası ölüm ADK'li olgularda gözlenmez iken, SHK'li üç olgu (%6.3) ameliyat sırasında hayatını kaybetti. Medyan sağkalım ADK'de 34.3 ay, SHK'de 30.5 ay idi. Beş yıllık sağkalım ADK'de %33.3, SHK'de %17.1 idi (p=0.55).

Sonuç: Bu çalışmada ameliyat sonrası komplikasyon oranının SHK'de ADK'lı olgulara göre anlamlı derecede daha yüksek olduğu, ancak uzun dönem sağkalımda istatistiksel olarak anlamlı bir fark olmadığı görüldü. Distalde yerleşmiş özofagus kanserli olgularda transtorasik özofajektomi güvenli bir tedavi yöntemi olarak görülmektedir.

Anahtar sözcükler: Özofagus kanseri; histoloji; transtorasik özofajektomi.

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Esophageal cancer consists 5-7% of all gastrointestinal cancers.[1] It progresses rapidly and is difficult to treat, with surgery being the only curative option. Significant levels of morbidity and mortality are encountered after an esophagectomy; however, the five-year survival rate is still low at nearly 20%.[2-11]

Adenocarcinoma (ADC) and squamous cell carcinoma (SCC) are the two most common histological types of esophageal cancer. While ADC is nearly always located at the distal esophagus, SCC can be encountered at any segment. Although there have been many studies related to the general treatment results of these two types of cancer, there are few in which results from the same location have been evaluated. In this study, we aimed to compare the results of patients with ADC and SCC located at the distal part of the esophagus for whom a transthoracic esophagectomy was performed.

PATIENTS AND METHODS

Between January 1999 and July 2010, we retrospectively reviewed 22 patients of ADC (12 females, 10 males; mean age 61.5±11.2 years; range 40 to 79 years) and 48 of SCC (28 females, 20 males; mean age 56.8±12.1 years; range 28 to 83 years) in which a transthoracic esophogectomy was performed on the cancer located in the distal esophagus. Hospital records were used to evaluate the patients, who were selected sequentially. Patients were excluded from the study if they had undergone an esophagectomy for palliative reasons, been treated with neoadjuvant chemotherapy, undergone another surgical procedure in conjunction with an Ivor-Lewis esophagectomy, or undergone reconstructions with tissue from other areas besides the stomach.

A median laparotomy was performed on all patients. The stomach was mobilized, and the abdomen was closed after the dilatation of the esophageal hiatus. The surgeon entered the thoracic cage through a right thoracotomy at the fifth intercostal space and dissected the esophagus. Proximal and distal tumor negative margins of 7-8 cm in length were excised, and reconstruction was performed via stapling. Two-field lymph node dissection was then performed. Following the placement of a nasogastric tube and two thoracic tubes, the surgery was completed.

In addition to the hospital records, outpatient clinic visit notes along with endoscopic, surgical, and pathological examination reports were also used to gather patient information. They were then were classified according to age, gender, concomitant diseases, pathological type of tumor, tumor stage, length of hospital stay, morbidity and mortality rates, and survey results. Our patients' results were then compared with those in the literature.

Statistical analysis

Statistical analysis was performed using the SPSS (SPSS Inc., Chicago, Illinois, USA) for Windows version 10.0 software program, and the data was presented as the mean ± standard deviation (SD) and standard error (SE). Statistical differences between groups were determined by Student's t-test, a chi-square test, or Fisher's exact test where appropriate. Survival rates were calculated with the Kaplan-Meier method, and the differences were compared via a log-rank test. A value of $p<0.05$ was considered to be statistically significant.

RESULTS

Comorbidities were seen in eight patients (36.4%) with ADC [hypertension in 8; diabetes mellitus (DM) in 2; hyperthyroidism in 2; congestive heart failure in 1; chronic obstructive pulmonary disease (COPD) in 1; coronary artery disease (CAD) in 1 patients] while 17 patients with SCC (35.4%) had comorbidities (hypertension in 8; hyperthyroidism in 5; peptic ulcer in 3; DM in 2; epilepsy in 1; CAD in 1 patients). Some of the patients in each group had more than one comorbidity. In addition, six subjects in the ADC group (27.3%) and 18 in the SCC group (37.5%) had a history of smoking.

The most commonly encountered symptoms in both the ADC and SCC groups, were dysphagia (90.9%, 40.9%, respectively) and weight loss (93.8%, 37.5%, respectively).

In 2010, according to the seventh edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system, four of the ADC patients in our study (18.2%) were in stage 1, seven (31.8%) were in stage 2, and 11 (50%) were in stage 3. For the SCC patients, 11 (22.9%) were in stage 1, 18 (37.5%) were in stage 2, and 19 (39.6%) were in stage 3.

Complications were encountered postoperatively in four of the ADC patients (18.2%), but the numbers were higher in the SCC group with 21 reporting problems (43.8%) ($p=0.033$). While perioperative mortality was not observed in the ADC group, mortality occurred in three of the SCC patients (6.3%) [two via anastomosis leakage and one via adult respiratory distress syndrome (ARDS)] (Table 1).

The median survival rates were 34.3 months in the ADC group and 30.5 months in the SCC group, and the five-year survival was 33.3% and 17.1% in the ADC and SCC groups, respectively ($p=0.55$) (Figure 1).

Table 1. Patient characteristics

	Adenocarcinoma			Squamous cell carcinoma			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Number of patients	22			48			
Median age (range)			61.5±11.2			56.8±12.1	
Gender							
Female	12			28			0.88
Male	10			20			
Major symptoms							
Dysphagia	20	90.9		45	93.8		
Weight loss	9	40.9		18	37.5		
Smoking	6	27.3		18	37.5		0.7
Comorbidities	8	36.4		17	35.4		
Postoperative complications	4	18.2		21	43.8		
Anastomotic leaks	1	4.6		3	6.3		
Recurrences	1	4.6		8	16.6		
Contralateral hydrothorax	2	9.0		4	8.3		
Empyemas				2	4.1		0.033
Anastomotic strictures				2	4.1		
Atrial fibrillation				1	2.1		
Myocardial infarction				1	2.1		
Pyloric stenosis				1	2.1		
ARDS				1	2.1		
Postoperative death rate (2 from anastomotic leaks, 1 from ARDS)	No			3	6.3		0.316
Staging							
Stage 1A	2	9.1		3	6.3		
Stage 1B	2	9.1		8	16.6		
Stage 2A	1	4.5		13	27.1		
Stage 2B	6	27.3		5	10.4		0.165
Stage 3A	4	18.2		11	22.9		
Stage 3B	4	18.2		5	10.4		
Stage 3C	3	13.6		3	6.3		
Adjuvant concomitant chemotherapy	7	31.8		13	27.1		
Hospital stay (days)			15±13.9			12.0±3.9	
Survival rate (years)	1	81.8		1	85.4		
	3	50.0		3	27.5		0.36
	5	33.3		5	17.1		

SD: Standard deviation; ARDS: Acute respiratory distress syndrome.

DISCUSSION

Adenocarcinoma and SCC are two histological types that consists nearly all of esophageal malignancies. In the last couple of decades, the incidence of ADC has increased dramatically due to gastroesophageal reflux and Barrett's esophagus in Western populations.[12] However, in Oriental populations, such as our study, SCC at the distal part of the esophagus is the most common histopathological type.

There is no consensus regarding the natural progression or the treatment results of these two types of cancer. Although the presentations of ADC and SCC are similar, the epidemiology, etiology, tumor biology, treatment strategies, and results are quite different. In actuality, they are really two different diseases encountered in the same organ. While SCC is generally found in patients ranging from 60-70 years old, ADC is more frequently observed in those between the ages of 50 and 60. There have been more male patients in both histologies. Furthermore, while SCC is observed in low socioeconomic groups, ADC is more commonly found in moderate and high socioeconomic groups. Another dissimilarity is that SCC is related to head

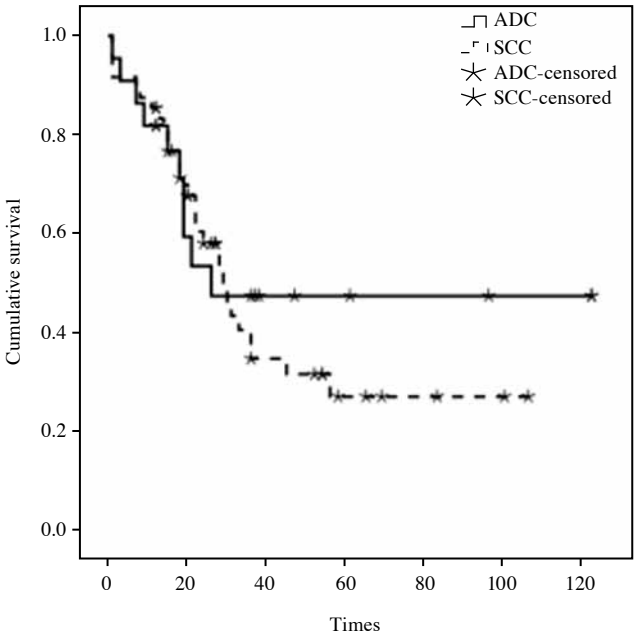

Figure 1. Survival rate in patients with adenocarcinoma and squamous cell carcinoma. ADC: Adenocarcinoma; SCC: Squamous cell carcinoma.

and neck cancer, smoking and alcohol consumption, radiation exposure, achalasia, bad nutritional status, human papilloma virus infection, corrosive substance intake, tylosis palmaris, and Plummer-Vinson syndrome, whereas ADC is associated with Barrett's esophagus, gastroesophageal reflux, hiatal hernias, obesity, scleroderma, and family history. However, their symptoms are similar, with dysphagia being the most frequently seen.[13,14] When gender distribution was examined in our study, both histological types were more commonly observed in females. The female-to-male ratio in the SCC group was 7:5 while it was 6:5 in the ADC group. The mean age was higher in the ADC group (61.5 versus 56.8 years), but this was not statistically significant. In addition, the smoking percentage was higher in the SCC group (37.5%) than in the ADC group (27.3%), but this was also not statistically significant. Alcohol consumption was very rare in our study, as only two of the SCC patients were consuming alcohol.

The biological behavior of these two tumors is still not clear. In previous studies, it was demonstrated that cardiopulmonary morbidity rates were significantly higher in SCC patients after resection, but there was no difference in the long-term prognosis.[12,15] Additionally, SCC in the upper and middle third of the esophagus was also included in the majority of the reported studies. Therefore, comparing tumor and lymph node behaviors and surgical complications with regard to their localization might not permit a clear evaluation of the results among these two cellular types. In some studies, surgical treatment, which is performed by avoiding a thoracotomy due to its proximity to the cardia, was shown to hinder the ability to accurately compare ADC and SCC. In fact, there are only a few studies[12-15] that have used the same method to compare treatment results regarding tumors located in the same region of the esophagus.

In these studies,[12,13] the surgical resection rates were similar for both ADC and SCC, and this procedure was suggested in some cases in order to provide low morbidity and mortality rates as well as good palliation. These studies also found that in 22% of ADC cases in which resection was performed, the patient was classified as having stage 4 disease. The bypass rate in SCC was higher than that of ADC in patients with unresectable tumors for whom explorative surgery was performed.[12] Moreover, since patient follow-up programs in Oriental countries are not optimal when compared to those in the West, both SCC and ADC are diagnosed when they have become symptomatic, so the prognosis is equally dismal.[12]

In various studies[15,16] that have focused on esophageal cancer, it has been reported that the T and N classification, number of lymph nodes that tested positive for cancer, histopathological cellular types, histological staging, cancer localization, and different cancer characteristics between Oriental and Western populations affected the survival rates.[16]

Mathisen et al.[17] published a five-year survival rate of 33.2% with ADC and 7.7% with SCC, and Griffith and Davis[18] reported a better survival rate with SCC than in was reported in ADC. Moreover, these investigators reported that squamous cell tumors in the middle esophagus had a worse prognosis than distal malignant tumors.

In a large scale study conducted in China involving patients with tumors in the esophagus and cardia for whom resection was performed, the five-year survival rates were compared, and the authors reported rates of 47% with esophageal tumors and 24% with cardia tumors.[19] However, this study provided no information regarding histological cell types. The authors rationally assumed that the majority of the tumors in the esophagus were SCC and that the tumors in the cardia were ADC.

Better survival results in SCC have been recently reported.[17-24] However, higher survival rates have only been reported in a few studies regarding patients with ADC versus those with SCC. For example, Giuli

and Gignoux[25] in a multi-center retrospective study involving 2,400 patients reported that the five-year survival rate was 27% for ADC and 16% for SCC.

Tachimori et al.[26] reported no differences in the comprehensive survival rate between SCC and ADC located in the lower esophagus and cardia with lymph node involvement. However, the prognosis was worse for the patients with ADC.

Mariette et al.[13] compared 624 patients with SCC and 118 with ADC who underwent a radical esophagectomy between 1982 and 2002 and found that the five-year survival rates after complete resection were 46% for SCC and 45% for ADC. Knowing the survival rates for pT_1, pN_0, and stage 1 tumors is critical for determining the independent prognostic factors connected with ADC. In our study, the tumor cellular type did not serve as an independent prognostic factor in the multivariate analyses. However, complete resection and pN in both tumor types were independent prognostic factors that affected survival. In addition, secondary primary tumor response and histological neoadjuvant response were specific prognostic factors for SCC, whereas the pT category and pretherapeutic dysphagia were specific prognostic factors for ADC.[13]

In another multi-center retrospective study, ADC and SCC were evaluated in 2,400 cases, and the five-year survival rates were 27% and 16%, respectively.[25] We also discovered that cellular type was not an independent prognostic factor in various other multivariate analyses.[13,17,20]

Altorki et al.[27] published the results of 80 patients (48 with ADC and 32 with SCC) in which three regional lymphadenectomies were performed. The authors determined that the comprehensive survival rates were 46% for ADC and 65% for SCC and discovered that disease stage was an important marker for survival. However, there was no significant difference in survival between the lymph node-positive patients who were receiving chemotherapy and those who were not.

Siewert et al.[28] reported the results of 1,059 esophageal carcinoma cases in which the patients underwent curative resections at a single center and found that the survival rates were better for those with ADC after resection. The authors also noted that histological type was an independent prognostic factor for these patients. In our study, although the five-year survival rate was 33.3% for ADC and 17.1% for SCC, the histological type was not statistically significant as an independent prognostic factor.

Alexandrou et al.[12] compared the clinical features and prognosis of patients with ADC and SCC located at the distal esophagus and cardia. Cardiac and major respiratory complications were observed more frequently with SCC, and they were statistically significant. The hospital mortality rates were 7.6% in the patients with ADC and 11.4% in those with SCC. In our study, the complication rate for the SCC group was much higher than for the ADC group (43.8% versus 18.2%, respectively; p=0.033). While mortality was not observed in the ADC group, the rate was 6.3% for the patients with SCC.

In conclusion, the clinical presentations of ADC and SCC located in the distal esophagus were similar in our study. The postoperative complication rates of the regional tumors in the patients with SCC who underwent a transthoracic esophagectomy were significantly higher than for those with ADC, but no statistically significant difference was seen in the comprehensive survival rate. According to the results of our study, a transthoracic esophagectomy is a safe treatment method for distally-located esophageal cancer patients who have ADC and SCC.

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