ORIGINAL ARTICLE

DOI: 10.4274/eamr.galenos.2019.25744
Eur Arch Med Res 2020; 36 (1):52-6

Adrenocortical Carcinoma: Single Center Experience

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Abstract

Objective: The prevalence of adrenocortical carcinoma (ACC) is approximately 0.02% of all cancers, and the annual incidence is approximately 1-2 per million population. ACC is more aggressive, and the prognosis of ACC is poorer in adults than that in pediatric patients. We aimed to investigate the clinicopathological characteristics and factors affecting overall survival (OS) in patients with ACC who were followed-up and treated in our hospital.

Methods: The patients, who were treated and followed up in the oncology clinic between 2006 and 2018, were included in the study. The patients who were diagnosed with ACC in the pathologic evaluation were included.

Results: A total of 10 patients, five men (50%) and five women (50%), were included in the study. The mean age was 42.4 years (range=18-67). Six patients (60%) were stage 3, and four patients (40%) were stage 4. Eight patients (80%) underwent surgery. The release of glucocorticoid and/or androgen was detected in six patients (60%). Recurrence developed in six patients (100%), and seven patients (70%) died during the follow-up. The median OS was 13 months in patients with stage 3 disease, and the median OS was eight months in patients with stage IV disease (Log-rank p=0.177). The eastern cooperative oncology group performance status (ECOG PS) and performing of surgery were detected as the most significant factors affecting OS (Log-rank p=0.01, Log-rank p=0.02).

Conclusion: The significant factors for OS were found to be surgery and ECOG PS in our study.

Keywords: Adrenocortical carcinoma, overall survival, metastasis, glucocorticoids

INTRODUCTION

Adrenocortical carcinomas (ACC) are extremely rare. The annual incidence is 1-2/1000 000. Its prevalence among all cancers is approximately 0.02%. Although ACC may be detected in all ages, there is a bimodal distribution for age. The disease is most frequently detected under the age of five years and in the 4th-5th decades. The prevalence is higher in women with a ratio of 1.5-2.5/1 compared with men (1).

Approximately 60% of the patients present with the symptoms of feminization, virilization, and hypokalemia due to the release of corticosteroid, androgen, estrogen, and mineralocorticoids. Functional ACC is mostly detected in women and children; however, non-functional ACC is mostly detected in the advanced ages. Non-functional ACC symptoms are detected in the late period due to the pressure of the mass, organ invasion, and distant metastasis (2). Generally, ACC is more aggressive, and the prognosis is worse in adults compared with patients in the pediatric patients.

In the present study, we aimed to investigate the clinicopathological characteristics and factors affecting overall survival (OS) in patients with ACC who were followed-up and treated in our hospital.

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Received: 08.08.2018
Accepted: 23.02.2019

Cite this article as: Sakin A, Seçmeler Ş, Can O, Arıcı S, Geredeli Ç, Yaşar N, Demir C, Sakin A, Cihan Ş. Adrenocortical Carcinoma: Single Center Experience. Eur Arch Med Res 2020; 36 (1):52-6

METHODS

The patients who were followed up and treated in the oncology clinic of Okmeydanı Training and Research Hospital between 2006 and 2018 were included. The patients who were diagnosed with ACC via pathologic evaluation were included in the study. The data including age, gender, the eastern cooperative oncology group performance status (ECOG PS), stage, surgical status, surgical margin status (R0=Complete resection, R1=Microscopic surgical margin positivity, R2=Macroscopic surgical margin positivity), adjuvant treatment, recurrence, the site of the recurrence, the site of metastasis at diagnosis, and the final status (Exitus-alive) were obtained from the archive files. The staging was performed in accordance with the European network for the study of adrenal tumors.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) 22.0 for Windows program was used in the statistical analysis. The descriptive statistics were given as mean, standard deviation, minimum, and maximum for the numerical variables, and number and percentage for the categorical variables. The survival analyses were performed using the Kaplan Meier analysis. The predictive factors were investigated using the Cox Regression analysis. The statistical significance was regarded as $p<0.05$.

Ethics committee approval was obtained for the study (48670771-514.10).

RESULTS

A total of 10 patients, five men (50%) and five women (50%), were included in the study. The mean age was 42.4 years (range=18-67). The numbers of patients with ECOG PS 0, 1-3, and 4 were five (50%), four (40%), and one (10%), respectively. Six patients (60%) were stage 3, and four patients (40%) were stage 4. Eight patients (80%) underwent surgery, with three of whom having R2 resection. The mean dimension of the tumor was 10.6±4.3 cm. The release of glucocorticoid and/or androgen was detected in six patients (60%). Two patients (20%) received adjuvant radiotherapy (RT), and two patients (20%) received adjuvant mitotane. Recurrence developed in six patients (100%). Liver metastasis developed in four patients (66.7%), intra-abdominal recurrence in one patient (16.7%), and bone metastasis in one patient (16.7%). Liver metastasis was detected in two patients (50%), and lung/liver metastasis was detected in two patients (50%) at diagnosis. Seven patients (70%) died during the follow-up (Table 1).

The median OS was 13 months in patients with stage 3 disease, and the median OS was eight months in patients with stage 4 disease (Log-rank p=0.177) (Figure 1).

The median OS in all stages was calculated as 12 months in patients who underwent surgery; however, the median OS was three months in patients who did not undergo surgery. The difference was statistically significant (Log-rank p=0.01) (Figure 2).

A statistically significant difference was detected in OS in accordance with the ECOG PS (Log-rank p=0.02) (Figure 3).

Table 1. Demographic and clinical data of the patients

		n	%
Gender	Male	5	50
	Female	5	50
ECOG PS	0	5	50
	1	2	20
	3	2	20
	4	1	10
Stage	3	6	60
	4	4	40
Surgery	No	2	20
	Yes	8	80
Margin	R0	2	25
	R1	3	37.5
	R2	3	37.5
Tumor status	Glucocorticoid ± androgen	6	60
	Androgen	1	10
	Not evaluated	3	30
Adjuvant treatment	Mitotane	2	20
	RT	2	20
Recurrence - metastasis	Yes	6	100
Localizations of the recurrence	Liver	4	66.7
	Intraabdominal	1	16.7
	Bone	1	16.7
The localization of metastasis at diagnosis	Liver	2	50.0
	Liver + Lung	2	50.0
Status	Exitus	7	70
	Alive	3	30
Age (Years)	Mean ± SD (min-max)	10	42.4±14.5 (18-67)
Tumor size (cm)	Mean ± SD (min-max)	9	10.6±4.3 (5-18)

Cm: Centimeter, ECOG PS: Eastern cooperative oncology group performance status, R0: Complete resection, R1: Microscopic surgical margin positivity, R2: Macroscopic surgical margin positivity RT: Radiotherapy, SD: Standard deviation, Min: Minimum, Max: Maximum

The ECOG PS was detected as the most significant factor in the univariate analysis (p=0.027) (Table 2).

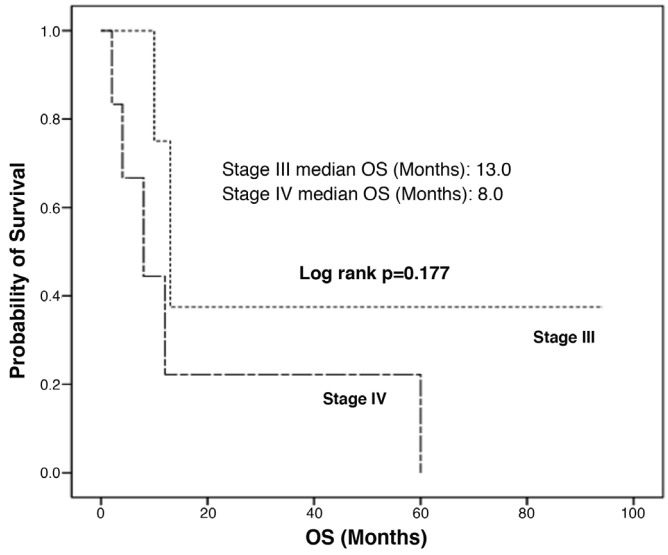

Figure 1. The overall survival in accordance with the stage
OS: Overall survival

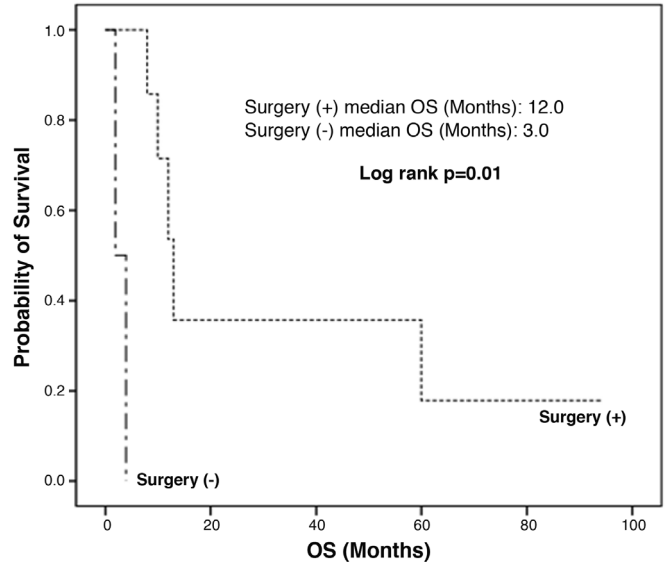

Figure 2. The overall survival in accordance with the surgical status
OS: Overall survival

Table 2. Univariate analysis for overall survival				
	HR	**95% CI**		**p**
Sex (Female vs male)	1.221	0.243	6.122	0.809
Age at diagnosis (Years)	1.018	0.972	1.066	0.451
ECOG PS	4.145	1.173	14.650	**0.027**
Stage (4 vs 3)	3.000	0.567	15.883	0.186
Tumor size (cm)	1.078	0.847	1.372	0.540
Cm: Centimeter, ECOG PS: Eastern cooperative oncology group performance, HR: Hazard ratio, CI: Confidence interval				

DISCUSSION

Complete surgical resection is the only potentially curative treatment for ACC. The first recommendation for the patients, who were candidates for surgery with resectable stage 1 to 3 disease, is the complete surgical resection. Before the surgery, the hormonal evaluation of all patients must be conducted to identify the secretory activity of the tumor. The identification of cortisol-producing tumors is particularly essential. The suppression of the Hypothalamic pituitary adrenal axis might have been developed in these patients, even in patients with mild hypercortisolism. To avoid postoperative adrenal insufficiency, glucocorticoid therapy must be initiated in these patients (3). Surgery was performed in eight patients (80%) in our study, and complete resection (R0) could be achieved only in two patients (25%). The tumors of seven patients (70%) were functional in our study, and six (60%) of them released glucocorticoid.

Although resection is technically possible in most patients with stage 1 to 3 disease, resection is not curative for most patients (4). Metastasis developed within two years in patients with stage I to 3 disease in a study, including 202 cases (5). Recurrence developed in all stage 3 patients in our study.

Although some clinicians suggested that the maximal debulking surgery improved survival, even if the tumor is unresectable (4,6,7), other clinicians suggested that this strategy had no advantage for survival (8,9). There are no adequate data to support the routine surgery for unresectable tumors. Debulking surgery in functional larger tumors may help control the hormone hypersecretion and increase the efficacy of the other

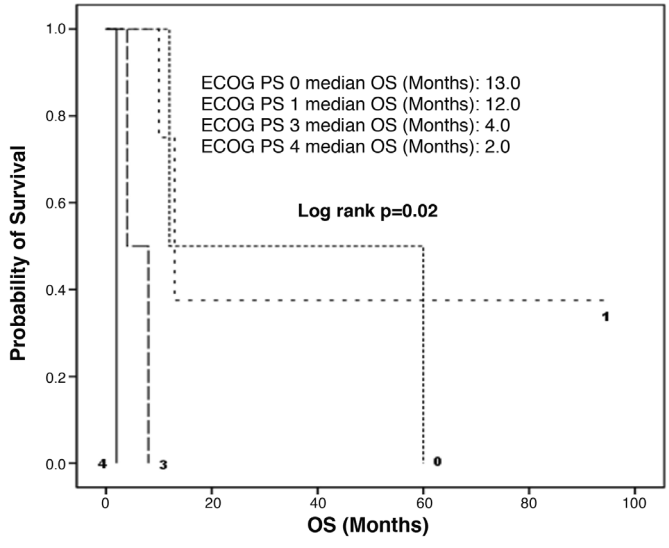

Figure 3. The overall survival in accordance with the ECOG PS status
ECOG PS: Eastern cooperative oncology group performance, OS: Overall survival

therapies (10). However, the prognosis is worse in patients with an unresectable disease than in those resectable counterparts. The OS generally ranges between three and nine months (1,11). The OS was three months in patients who could not undergo surgery, and the OS was 12 months in patients who underwent surgery in our study. Debulking surgery could be performed in only two patients (20%) in the metastatic stage in our study.

The most important factors identifying the prognosis in ACC are the disease stage and complete resection (12,13). In a series of 253 patients, The French Association of Endocrine Surgeons Study group found the five years OS as 66%, 58%, 24%, and 0% for stage I, II, III, and IV disease, respectively (12). Inadequate resection is associated with a poor prognosis, independently of the stage. The effect of surgical margin on the prognosis was demonstrated in a study using the national cancer database. The 5- years OS rates were found as 46%, 21%, and 10% for R0, R1, and R2 resection, respectively, in this study (13). R0 resection could be achieved in two patients (25%), R1 resection in three patients (37.5%) and R2 resection in three patients (37.5%) in our study and the median survival was calculated as 60, 10, and 8 months, in R0-, R1- and R2-resected groups, respectively.

ACC was suggested to be a radio-resistant tumor in the past. However, this may not be true for modern RT techniques (14). There is no randomized study that demonstrated the efficacy of adjuvant RT in resected-ACC patients. Some studies supported the benefit of RT in patients who had a high risk of local recurrence (14-16).

The results of 14 patients (stage I, II, and III) with no macroscopic residual disease who were treated with adjuvant RT were compared to 14 patients not receiving adjuvant RT, in terms of resection status, the use of adjuvant mitotane, disease stage, and tumor size. Local recurrence developed in two patients out of 14 who were treated with adjuvant RT compared to 11 patients out of 14 who received no RT. Despite this difference, the disease-free survival (DFS) and OS were not significantly better in patients who received RT (15). In a retrospective study from Michigan University, the results of 20 patients with R0 or R1 resection without adjuvant RT was compared to 20 patients who received adjuvant RT, and the results for both groups were similar for the stage, surgical margin, and the use of adjuvant mitotane. In a median 34 months of follow-up time, local recurrence was detected higher in patients without RT (60% vs %5%). However, this benefit did not affect DFS and OS (16). Only two patients (20%) received adjuvant RT in our study.

Because of the rarity of the disease and lack of larger prospective randomized clinical studies, the benefit of the routine postoperative adjuvant therapy for ACC is not clear. Although some uncontrolled non-randomized studies suggested that the adjuvant mitotane might delay or prevent the recurrence in non-metastatic disease (17-19), the other studies suggested that there was no benefit for DFS or OS (20,21).

The retrospective analysis of 177 stage I to III patients with complete macroscopic resection, which were collected from 55 centers between 1985 and 2005, showed that adjuvant mitotane therapy was associated with significantly longer DFS in comparison with the control group (42 months vs 10-25 months). Less number of patients died in the mitotane-receiving group compared with the control group (55% vs 25-41%) (18). Only two patients (20%) were initiated adjuvant mitotane in our study.

Although our study involved a follow-up time of 12 years, the number of patients was inadequate. The multivariate analysis could not be performed due to the small number of patients. Although the tumor stage was not statistically significant due to the small number of cases, it was clinically significant.

CONCLUSION

In conclusion, the most significant factors, which affected the survival, were detected as performing surgery and ECOG PS. The increase in ECOG PS increased the mortality risk by four-folds.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the Istanbul Okmeydanı Training and Research Hospital (approval no: 48670771-514.10).

Informed Consent: Patients were not required to give informed consent, because the study was retrospective and anonymous data were used, which were obtained after each patient agreed to treatment by written consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.S., Ş.S., Ç.G., Ş.S., Concept: S.A., Ç.G., Ay.S., Ş.C., Design: A.S., S.A., C.D., Ş.C., Data Collection or Processing: Ş.S., O.C., N.Y., C.D., Analysis or Interpretation: A.S., O.C., Ş.C., Literature Search: Ş.S., O.C., S.A., Ç.G., Writing: A.S., S.A., Ay.S., Ş.C. .

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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