Adrenocortical Carcinoma: Single Center Experience

Adrenokortikal Karsinom: Tek Merkez Deneyimi

Abdullah Sakin¹, Şaban Seçmeler², Orçun Can², Serdar Arıcı², Çağlayan Geredeli², Nurgul Yaşar², Cumhuriyet², Şener Cihan²

¹Yüzüncü Yıl University Faculty of Medicine, Department of Medical Oncology, Van, Turkey

²University of Health Sciences, Okmeydanı Training and Research Hospital, Department of Medical Oncology, Istanbul, Turkey

Abstract

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

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

Results: A total of 10 patients, 5(50%) men, and 5(50%) women, were included in the study. The mean age was 42.4 (range, 18-67) years. Six (60%) patients were in stage 3, and 4 (40%) patients were in stage 4. Eight (80%) patients underwent surgery. The release of glucocorticoid and/or androgen was detected in 6(60%) patients. Recurrence developed in 6(100%) patients, and 7 (70%) patients died during the follow-up. The median survival was 13 months in patients with stage 3 disease, and the median survival was 8 months in patients with stage 4 disease. There was no statistically significant survival difference between the stages (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 the overall survival (Log rank p: 0.01, Log rank p: 0.02).

Conclusion: We detected the statistically most significant factors for OS as the surgery and ECOG PS in our study. The increase of ECOG PS increased the mortality risk four folds.

Keywords: Adrenocortical Carcinoma, Overall survival, Metastasis, Glucocorticoids

INTRODUCTION

Adrenocortical carcinomas (ACC) are extremely rare. The annual incidence is 1-2/1000 000. The 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 before the age of 5, and in the 4th-5th decades. The prevalence is higher in women with the ratio of 1.5-2.5/1 compared with men (1).

Approximately 60% of the patients present with the symptoms of feminisation, virilisation, and hypokalemia due to the release of corticosteroid, androgen, estrogen, and mineralocorticoids.

Functional ACC is mostly detected in women and children, however nonfunctional ACC is mostly detected in the advanced age group. Nonfunctional 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 prognosis is poorer in adults compared with patients in the pediatric age group.

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

Address for Correspondence: Abdullah Sakin
Yüzüncü Yıl University Faculty of Medicine, Department of Medical Oncology, Van, Turkey
E-posta: drsakin@hotmail.com

©Copyright 2019 by the Health Sciences University, Okmeydanı Training and Research Hospital
European Archives of Medical Research published by Galenos Publishing House.

Received: 08.08.2018
Accepted: 23.02.2019

METHODS

The patients who were followed up, and treated in the oncology clinic Okmeydani Training and Research Hospital between 2006-2018 were retrospectively included in the study. The patients who were diagnosed with adrenocortical carcinoma in pathologic evaluation were included in the study. The data of age, sex, the Eastern cooperative oncology group performance status (ECOG PS), the stage, surgical status, surgical margin positivity (R0: complete resection, R1: Microscopic surgical margin positivity, R2: macroscopic surgical margin positivity), the use of adjuvant treatment, development of recurrence/metastasis, the location of the recurrence/metastasis, the location of metastasis at diagnosis, and the final condition(Exitus- alive) were obtained from the archive files. The staging of the patients were performed in accordance with the European network for the study of adrenal tumors (ENSAT). 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 were given 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 α value was regarded as $p < 0.05$. Ethics committee approval was obtained for the study.

RESULTS

A total of 10 patients, 5(50%) men, and 5(50%) women, were included in the study. The mean age was 42.4 (range, 18-67) years. The numbers of patients with ECOG PS 0,1-3 and 4 were 5 (50), 4 (40%) and 1 (10%), respectively. Six (60%) patients were in stage 3, and 4 (40%) patients were in stage 4. Eight (80%) patients underwent surgery and 3 of whom with R2 resection. The mean dimension of the tumor was 10.6 ± 4.3 cm. The release of glucocorticoid and/or androgen was detected in 6(60%) patients. 2 (20%) patients received adjuvant radiotherapy(RT), and 2(20%) patients received adjuvant mitotane. Recurrence developed in 6(100%) patients. Liver metastasis developed in 4 (66.7%) patients, and intraabdominal recurrence in 1(16.7%) patient, and bone metastasis in 1 (16.7%) patient. Liver metastasis was detected in 2(50%) patients, and lung+ liver metastasis was detected in 2(50%) patients at diagnosis. 7 (70%) patients died during the follow-up (Table-1).

The median survival was 13 months in patients with stage 3 disease, and the median survival was 8 months in patients with stage 4 disease. There was no statistically significant survival

difference between the stages (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 the overall survival (Log rank $p=0.01$, Log rank $p=0.02$)(Figure-1).

The median survival in all stages was calculated 12 months in patients who underwent surgery, however, the the median survival was 3 months in patients who were not performed surgery. The difference was statistically significant (Log rank $p=0.01$) (Figure-2).

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

Figure 1. The overall survival in accordance with the stage

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

Figure 3. The overall survival in accordance with the ECOG PS status. The ECOG PS was detected as the statistically most significant factors in the single variable analysis ($p=0.027$) (Table-2).

DISCUSSION

Complete surgical resection is the only potentially curative treatment for adrenocortical carcinoma. The first recommendation for the patients who were candidates for surgery with resectable stage I-III 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 the cortisol producing tumors is particularly important. Hypothalamic pituitary adrenal (HPA) axis suppression might have developed in these patients even in patients with mild hypercortisolism. To avoid postoperative adrenal insufficiency, glucocorticoid must be initiated in these patients (3). Surgery was performed for 8(80%) patients in our study, and complete resection(R0) could be performed only in 2(25%) patients. The tumors of 7(70%) patients were functional in our study, and 6 (60%) of them released glucocorticoid.

Although resection is technically possible in most of the patients with stage I –III disease, resection is not curative for most patients (4). Metastasis developed within 2 years in patients with stage I-III disease in a study conducted with 202 cases (5). Six (60%) patients in our study were in stage 3, and in all of stage 3 patients, recurrence or distant metastasis was detected, in the follow-up period.

Although some clinicians suggested that the maximal debulking surgery improved the survival even if the tumor is unresectable (4,6,7), some clinicians suggested that this strategy had no advantage for the survival (8,9). There is no adequate data to

Table 1. General demographic data

		n	%
Sex	Male	5	50
	Female	5	50
ECOG PS	0	5	50
	1	2	20
	3	2	20
	4	1	10
Stage	III	6	60
	IV	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
Localisation of the recurrence	Liver	4	66.7
	Intraabdominal	1	16.7
	Bone	1	16.7
The localisation 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)
Abbreviations: 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			

support the routinely surgery of the unresectable tumors. Debulking surgery in functional larger tumors may help to control the hormone hypersecretion, and to increase the efficacy of the other therapies (10). However, the prognosis is poorer in patients with unresectable disease than resectable. The overall survival is generally between 3-9 months (1,11). The overall survival was 3 months in patients who could not be performed surgery, and the OS was 12 months in patients who were performed surgery in

Table 2. Factors affecting the 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 (IV vs III)	3.000	0.567	15.883	0.186
Tumor size (cm)	1.078	0.847	1.372	0.540
Abbreviations: Cm: centimeter, ECOG PS: Eastern Cooperative Oncology Group Performance				

our study. Debulking surgery could only be performed in 2(20%) patients in the metastatic stage in our study.

The most important factors identifying the prognosis in ACC is the disease stage and the complete resection(12-13). In a series of 253 patients, The French Association of Endocrine Surgeons Study Group found the 5 years OS as 66%, 58%, 24%, and 0%, respectively for the stage I, II, III, and IV, respectively(12). However, numerous factors independent of the tumor stage affect the results. Inadequate resection is associated with the poor prognosis, independently of the disease stage. The effect of surgical margin on the prognosis was demonstrated in a study using with 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 performed to 2(25%) patients, and R1 resection to 3 (37.5%) patients, and R2 resection to 3 (37.5%) patients in our study and the median survival was calculated as 60, 10, and 8 months, in R0,R1 and R2 resection groups, respectively.

Adrenocortical carcinoma was suggested to be a radio-resistant tumor in the past. However, this may not be true closely for the modern RT techniques (14). There is no randomized study which 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 adjuvant RT were compared with 14 patients who were not treated adjuvant RT, and whose resection status, the use of adjuvant mitotane, disease stage, and tumor size matched in a study with the data of the German ACC registry. Local recurrence developed in 2 patients out of 14 who were treated with adjuvant RT, and local recurrence was detected in 11 patients out of 14 who received no radiotherapy. Despite this difference, the disease-free survival (DFS), and OS were not significantly better in patients who received radiotherapy (15). In a retrospective study from Michigan University, the results of 20 patients who were performed R0 R1 resection but

not received adjuvant RT was compared with 20 patients who received adjuvant RT and groups were very similar for stage, surgical margin, and the use of adjuvant mitotane. In a median 34 months follow-up, local recurrence was detected higher in patients who received no RT (60% versus %5%). However, this benefit had no effect on DFS, and OS (16). Only 2(20%) patients received adjuvant RT in our study.

Because of rarity of disease and lack of larger prospective randomised clinical studies, the benefit of the routine postoperative adjuvant therapy for ACCs is not clear. Although some uncontrolled non-randomised 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-III patients with macroscopic complete resection that were collected from 55 centers between 1985 and 2005 showed that adjuvant mitotane therapy was associated with significantly longer DFS in the 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 2(20%) patients were initiated adjuvant mitotane in our study.

Although our study involved 12 years, the number of the patients were inadequate. Multivariate analysis could not be performed due to the small number of patients. Although the tumor stage was no statistically significant due to the small number of the cases, it was clinically significant.

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

Funding Source: None

Conflict of Interest: The authors declare that they have no conflict of interest.

REFERENCES

1- Ng L, Libertino JM. Adrenocortical carcinoma: diagnosis, evaluation and treatment. J Urol. 2003;169(1):5.

2- Luton JP, Cerdas S, Billaud L. et al. Clinical features of adrenocortical carcinoma, prognostic factors, and the effect of mitotane therapy. N Engl J Med 1990; 322 (17): 1195-201.

3- Fassnacht M, Kroiss M, Allolio B. Update in adrenocortical carcinoma. J Clin Endocrinol Metab. 2013;98(12):4551.

4- Bertagna C, Orth DN. Clinical and laboratory findings and results of therapy in 58 patients with adrenocortical tumors admitted to a single medical center (1951 to 1978). Am J Med. 1981;71(5):855.

- 5- Abiven G, Coste J, Groussin L. et al. Clinical and biological features in the prognosis of adrenocortical cancer: poor outcome of cortisol-secreting tumors in a series of 202 consecutive patients. *J Clin Endocrinol Metab.* 2006;91(7):2650.
- 6- Luton JP, Cerdas S, Billaud L. et al. Clinical features of adrenocortical carcinoma, prognostic factors, and the effect of mitotane therapy. *N Engl J Med.* 1990;322(17):1195.
- 7- Gröndal S, Cedermark B, Eriksson B, et al. Adrenocortical carcinoma. A retrospective study of a rare tumor with a poor prognosis. *Eur J Surg Oncol.* 1990;16(6):500.
- 8- Hogan TF, Gilchrist KW, Westring DW, Citrin DL. clinical and pathological study of adrenocortical carcinoma: therapeutic implications. *Cancer.* 1980;45(11):2880.
- 9- Wajchenberg BL, Albergaria Pereira MA, Medonca BB, et al. Adrenocortical carcinoma: clinical and laboratory observations. *Cancer.* 2000;88(4):711.
- 10- Allolio B, Hahner S, Weismann D, Fassnacht M. Management of adrenocortical carcinoma. *Clin Endocrinol (Oxf).* 2004;60(3):273.
- 11- Macfarlane DA. Cancer of the adrenal cortex; the natural history, prognosis and treatment in a study of fifty-five cases. *Ann R Coll Surg Engl.* 1958;23(3):155.
- 12- Icard P, Goudet P, Charpenay C, et al. Adrenocortical carcinomas: surgical trends and results of a 253-patient series from the French Association of Endocrine Surgeons study group. *World J Surg.* 2001;25(7):891.
- 13- Bilimoria KY, Shen WT, Elaraj D, et al. Adrenocortical carcinoma in the United States: treatment utilization and prognostic factors. *Cancer.* 2008 Dec;113(11):3130-6.
- 14- Polat B, Fassnacht M, Pfreundner L, et al. Radiotherapy in adrenocortical carcinoma. *Cancer.* 2009;115(13):2816.
- 15- Fassnacht M, Hahner S, Polat B, Koschker AC, Kenn W, Flentje M, Allolio B. Efficacy of adjuvant radiotherapy of the tumor bed on local recurrence of adrenocortical carcinoma. *J Clin Endocrinol Metab.* 2006;91(11):4501.
- 16- Sabolch A, Else T, Griffith KA, et al. Radiation therapy improves local control after surgical resection in patients with localized adrenocortical carcinoma. *Int J Radiat Oncol Biol Phys.* 2015;92(2):252.
- 17- Schteingart DE, Doherty GM, Gauger PG, et al. Management of patients with adrenal cancer: recommendations of an international consensus conference. *Endocr Relat Cancer.* 2005;12(3):667.
- 18- Terzolo M, Angeli A, Fassnacht M, et al. Adjuvant mitotane treatment for adrenocortical carcinoma. *N Engl J Med.* 2007;356(23):2372.
- 19- Schteingart DE. Adjuvant mitotane therapy of adrenal cancer - use and controversy. *N Engl J Med.* 2007;356(23):2415.
- 20- Crucitti F, Bellantone R, Ferrante A, Boscherini M, Crucitti P. The Italian Registry for Adrenal Cortical Carcinoma: analysis of a multiinstitutional series of 129 patients. The ACC Italian Registry Study Group. *Surgery.* 1996;119(2):161.
- 21- Icard P, Goudet P, Charpenay C, et al. Adrenocortical carcinomas: surgical trends and results of a 253-patient series from the French Association of Endocrine Surgeons study group. *World J Surg.* 2001;25(7):891.