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Factors Affecting Survival in Adrenocortical Cancers: Single-Center Experience

Adrenokortikal Kanserlerde Sağ Kalıma Etki Eden Faktörler: Tek Merkez Deneyimi

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Abstract

Objective: Adrenocortical cancer (ACC) is one of the rare endocrine system cancers that are aggressive. Despite surgical treatment, the mortality rate is quite high. This study aimed to examine prognostic factors affecting survival in patients with ACC, the role of dehydroepiandrosterone sulfate (DHEA-S), and the maximum standard uptake (SUV_{max}) values on predicting mortality through the single-center data. **Material and Methods:** A total of 21 patients who were diagnosed with adrenal cancer and followed from a single center were included in the study. Patients who survived follow-ups were included in the survived group (n=6), and those who died were included in the dead group (n=15). The demographic, anatomical, pathological, and clinical characteristics of the patients were analyzed. Positron emission tomography-computerized tomography imaging and SUV_{max} values of adrenal masses were compared. The effect of all these data on survival was examined. **Results:** The mortality rate among patients with ACC was 71%. According to the Kaplan-Meier survival analysis, the average life expectancy was 23.66±2.79 (95% CI=18.18-29.13) months. The mass size of the survived and dead groups was 9.2±3.82 cm and 10.84±4.74 cm, respectively. The production rate of adrenal hormone was higher in the dead group ($p<0.01$; 80%). Moreover, the DHEA-S level and SUV_{max} values were statistically significantly higher in the dead group ($p<0.001$; $p<0.05$, respectively). Although no metastases were observed in the survived group during follow-ups after the operation, distant metastases were observed in 8 people from the dead group (53%; $p<0.05$). **Conclusion:** The mortality rate was very high in ACC despite surgical and medical treatments. The higher DHEA-S and SUV_{max} values may indicate that the overall survival duration was low.

Keywords: Adrenocortical cancer; mortality; DHEA-S; positron emission tomography

Özet

Amaç: Adrenokortikal kanser [adrenocortical cancer (ACC)], agresif seyreden nadir görülen endokrin sistem kanserlerindendir. Cerrahi tedaviye rağmen mortalitesi oldukça yüksektir. Bu çalışmada, ACC hastalarda sağ kalıma etki eden prognostik faktörleri dehidroepiandrosteron sülfat (DHEA-S) ve maksimum standart uptake (SUV_{max}) değerlerinin mortaliteyi ön görmedeki rolünü, tek merkez verileri üzerinden araştırmayı amaçladık. **Gereç ve Yöntemler:** Adrenal kanser tanısı almış tek merkezden takipli 21 hasta çalışmaya alındı. Takiplerde hayatta olanlar sağ olan grup (n=6), ölenler ölü olan grup (n=15) olarak kabul edildi. Hastaların demografik, anatomik, patolojik ve klinik özelliklerine bakıldı. Adrenal kitlelerin, pozitron emisyon tomografi görüntülemesi ile SUV_{max} değerleri karşılaştırıldı.Tüm bu verilerin sağkalım üzerine etkileri araştırıldı. **Bulgular:** ACC'li hastalarda mortalite oranı %71 olarak bulundu. Kaplan-Meier yaşam analizine göre ortalama yaşam süresi 23,66±2,79 (%95 GA=18,18-29,13) ay olarak bulundu. Sırasıyla, sağ olan ve ölü olan grubun kitle boyutu 9,2±3,82 cm ve 10,84±4,74 cm olarak bulundu. Adrenal hormon üretimi, ölü olan grupta daha yüksek oranda izlendi ($p<0,01$; %80). Ayrıca DHEA-S seviyesi ve SUV_{max} değeri ölü olan grupta istatistiksel olarak yüksek bulundu (sırasıyla $p<0,001$; $p<0,05$). Operasyon sonrası takiplerde sağ olan grupta hiç metastaz yokken, ölü olan grupta 8 kişide uzak metastaz saptandı (%53; $p<0,05$). **Sonuç:** ACC'de mortalite oranı, cerrahi ve medikal tedavilere rağmen oldukça yüksektir. DHEA-S seviyesinin ve SUV_{max} değerinin yüksek olması, genel sağkalım süresinin düşük olduğunu öngörebilir.

Anahtar kelimeler: Adrenokortikal kanser; mortalite; DHEA-S; pozitron emisyon tomografi

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Introduction

Together with the widespread use of radiological imaging in clinics, the possibility of imaging an adrenal mass incidentally began to increase. Moreover, most of these adrenal masses are benign. Despite its rare occurrence, they are sometimes found to be adrenocortical cancer (ACC).

ACC, situated on the adrenal cortex, progresses aggressively with an average annual incidence of 1-2/1,000,000 (1). It is the second most aggressive malignant cancer of the endocrine system after anaplastic thyroid cancer (2). It can occur at any age, even in early childhood and the fourth and fifth decades of life.

ACC can be active or inactive hormonally. It can secrete corticosteroids, mineralocorticoids, or androgens from steroid hormones in 50%-70% of cases. More than half of the active hormone-producing ACCs lead to Cushing syndrome (3). A high level of dehydroepiandrosterone sulfate (DHEA-S), a marker of adrenal androgen release in the evaluation of the adrenal masses detected incidentally, suggests adrenocortical carcinoma (4). However, the DHEA-S level was lower in benign adrenal masses. Although the DHEA-S level is considered an indicator for ACC, its role in predicting the mortality rate has not yet been studied in the literature.

Computerized tomography (CT) and magnetic resonance imaging (MRI) detect changes in adrenal masses after the mass grows and becomes visible. Metabolic changes occur prior to canceration in the adrenal gland before the adrenal mass is formed. 18-Fluorodeoxyglucose (FDG) positron emission tomography (PET) shows these metabolic changes early and provide an early diagnosis (5).

As ACC is a rare endocrine tumor, researchers have not yet studied its clinical characteristics and prognostic factors affecting survival. This study aimed to examine demographic and clinical features of the ACC, factors affecting the prognosis, and the overall survival over single-center data.

Material and Methods

This retrospective study was approved by an institutional Ethics Committee of Dicle University Faculty of Medicine (Declaration No: 225, Approval Date: 04.07.2018). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study Protocol and Patients

A total of 21 patients who were histopathologically diagnosed with ACC during January 2005-May 2018 from the Dicle University Faculty of Medicine were included in this study. Patient data and medical follow-up were recorded retrospectively from the Dicle University Hospital Database System. The demographic characteristics of patients (age and gender), localization, size and volume of the tumor, whether the tumor was operated, tumor stage, hormonal activity (production of glucocorticoid, mineralocorticoid, androgen, and catecholamine), total Weiss scores of the pathology material of patients who were operated, preoperative DHEA-S level, maximal standardized uptake value (SUV_{max}) of adrenalin mass in pre-op PET-CT imaging, metastasis status, recurrence status, chemotherapy, and general follow-up period were all recorded. The status of patients survival and death was collected from the database system of public health directorate; the patients who died because of ACC were included in the study. Patients with ACC who died because of other reasons were excluded from the study. The overall survival time was calculated from the date of tissue diagnosis to the date of death or the last follow-up. Then, the patients were divided into two groups, including survival (n=6) and dead groups (n=15).

Calculation of the Size and Volume of the Adrenal Mass

The measurements of width, length, and depth were taken from the radiological imaging of the adrenal masses. The largest measurement of the mass was accepted as a dimension in centimeter. The volume of adrenalin masses was calculated in cubic centimeter using the prolate ellipse formula (widthxlengthxdepthxπ/6).

Evaluation of Hormonal Activity

a. Evaluation of glucocorticoid activity

1 mg dexamethasone suppression test

Preoperative basal adrenocorticotropic hormone (ACTH) and cortisol levels of patients

were recorded. Then, 1 mg dexamethasone tablets were administered to patients at 23:00, and the cortisol level was recorded the next morning. Patients with a cortisol value of less than 1.8 µg/dL after the intake of 1 mg dexamethasone were considered suppressed. Patients with a cortisol value of ≥1.8 µg/dL underwent the 2-day 2 mg dexamethasone test.

2-Day 2 mg dexamethasone suppression test

Patients who were not suppressed by 1 mg dexamethasone were given a 0.5 mg dexamethasone tablet every six hours for two days (with a total daily dose of 2 mg dexamethasone). The first dose was administered at 09:00 on the morning of the first day. After 6 h of administering the final dose at 03:00 on the second day, the blood was taken for the measurement of cortisol level. Patients with a cortisol value of <1.8 µg/dL were considered suppressed, and those with ≥1.8 µg/dL were considered not suppressed.

Free cortisol levels in 24-hour urine

In the morning, when the urine was collected, the residue urine in the bladder was emptied using micturition when a patient wakes up. All urine during the day and night was then collected in a container and stored in a cool place. When the patient wakes up again the next morning, the first urine was also collected and added, and all collected urine was examined.
If patients were not suppressed after administering 2-day 2 mg dexamethasone and had a higher level of 24-hour urine cortisol, the presence of hypercorticosomy was considered.

Evaluation of mineralocorticoid activity

Blood samples were collected from the patient at 08.00 in the morning for evaluating levels of aldosterone (ng/dL) and renin (ng/mL/hour). Patients with a rate of the plasma aldosterone level to plasma renin level ≥30 were considered positive.

Evaluation of androgen production

Patients with a high DHEA-S level because of the adrenal-induced androgen precursor or those with a high level of total testosterone were considered positive.

Evaluation of catecholamine production

Patients were provided with a diet deprived of food and beverages such as bananas, coffee, and vanilla-containing phenolic acid for three days. Later in the morning, after the first urine was ejected, all the urine urinated during the day, and overnight was collected in the same container. Urine was acidified with boric acid to a pH between 2 and 3. Urine samples collected for 24 h were kept in the dark and cool place. Urinary catecholamine levels were determined using high-performance liquid chromatography with electrochemical detection.

Analysis of Total Weiss Score

Pathologists evaluated the histologic changes according to the Weiss criteria (nuclear atypia; atypical mitoses; frequent mitoses; a small percentage of clear cells; diffuse architecture; necrosis; and the invasion of venous, sinusoidal, or capsular structures). Total Weiss scores were calculated on the basis of the number of positive results of these nine parameters.

Tumor Staging

Patients were staged on the basis of tumor node metastasis classification in the sample European Network for the Study of Adrenal Tumors (Ensat) in 2004 (6). Thus, the stage was classified as follows:
Stage 1: Tumor ≤5 cm
Stage 2: Tumor >5 cm
Stage 3: Lymph node involvement and/or tumor infiltration into surrounding tissue and/or a tumor thrombus in the vena cava and/or renal vein
Stage 4: Metastatic disease

Statistical Analysis

Data analyses were performed using the Statistical Package for Social Sciences (SPSS), Version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used for the normal distribution of data. The Mann-Whitney U test among non-parametric tests was used as the 24-hour free urine cortisol did not conform to the normal distribution among groups. Normally distributed variables were presented using means and standard deviations. The independent two-sample t-test was used to compare continuous variables between two

groups. The chi-square test was used to compare categorical data between groups. Pearson's correlation was used for the simple regression analysis. Kaplan-Meier survival curves and the log-rank test were used for determining the overall survival and specific probability of survival for each of the observed variables, respectively. A p-value of <0.05 was considered statistically significant for all analyses.

Results

Out of 21 patients, six were in the survived group and 15 in the dead group. The survived group included two men and four women; the dead group consisted of three men and 12 women. Overall, 76% of patients with ACC diagnosis were women. The average age of patients in the survived group was 54.67±13.36 years, and in the dead group was 42.07±18.07 years. The average age of the two groups was not statistically significant (p>0.05). Moreover, 14 adrenal masses were located on the right and seven on the left. The mass size was 9.2±3.82 mm, and 10.84±4.74 mm in the survived and dead groups, respectively; and the mass volume was 264.50±299.66 cm^3, and 493.61±679.51 cm^3 in the survived and dead groups, respectively (p>0.05). Demographic and anatomical data for the two groups are given below in Table 1.

Basal ACTH among patients examined was 13.31±8.16 pg/mL in the survived group and 11.93±11.99 pg/mL in the dead group. On the other hand, basal cortisol was 20.97±17.21 µg/dL, and 24.78±12.76 µg/dL in the survived and dead groups, respectively. Basal ACTH and basal cortisol levels in both groups were not significant (p>0.05). The results of 1 mg dexamethasone suppression test showed that three and nine patients from the survived and dead groups were not suppressed, respectively. The results of a two-day 2 mg dexamethasone suppression test showed that there was no cortisol suppression in one and seven patients from the survived and dead groups, respectively. As 24-hour urine cortisol values were not normally distributed, the Mann-Whitney U test among nonparametric tests was used. The median 24-hour urine cortisol in the survived and dead groups was 136 nm/day (min-max: 78-1106) and 148 nm/day (min-max: 80-2052), respectively. The 24-hour free urine cortisol values between the two groups were not significant, according to the Mann-Whitney U test (p>0.05). Moreover, one patient in the survived group and seven in the dead group had hypercortisolism. Considering the mineralocorticoid activity, hyperaldosteronism was detected in two patients in the dead group and no patient in the survived group. The 24-hour urine catecholamines were in the normal range in the survived group and higher in a patient in the dead group. Hyperandrogenemia was never observed in the survived group and was detected in six patients from the dead group. In general, the total adrenal endocrine hormone production was observed in one patient in the survived group and 12 patients from the dead group (p<0.01). Patient's status of secreting adrenal endocrine hormone is shown below in Table 2.

All patients in the survived group were operated, whereas five patients from the dead group were not operated because four of them had distant metastasis, and one had a low-performance status. According to the total Weiss scores calculated in the pathol-

Table 1. Demographic and anatomical data of groups.

Parameters	Survived group (n=6)	Dead group (n=15)	p
Male	2	3	>0.05
Female	4	12	>0.05
Age (years)	54.67±13.36	42.07±18.07	>0.05
Localization-right	3	11	>0.05
Localization-left	3	4	>0.05
Mass size (cm)	9.2±3.82	10.84±4.74	>0.05
Mass volume (cm^3)	264.50±299.66	493.61±679.51	>0.05

ogy for the patients operated, the average score was 5.33±1.21, and 5.3±1.94 in the survived and dead groups, respectively. Total Weiss scores were not significant between the two groups (p>0.05). DHEA-S levels measured when patients were diagnosed with the disease were 371.13±33.21 µg/dL in the survived group and 763.05±229.74 µg/dL in the dead group. A significant correlation was found between DHEA-S levels of the two groups (p<0.001). No significant elevation of the DHEA-S level was observed in the postoperative follow-up in the six patients who were operated in the survived group. In the dead group, ten patients who were operated survived for 5.15±1.65 months and had DHEA-S levels of 544±216.9 ug/dL when DHEA-S started to increase after the operation.

According to Pearson's correlation analysis, a negative-oriented relationship was observed between the DHEA-S level and the general survival rate (p<0.05; r=-0.45). The relationship between DHEA-S and general survival is shown below in Figure 1.

In the PET-CT scans taken before the patients were operated, the SUV_{max} value of the adrenal mass was 7.78±2.66 in the survived group and 14.26±5.67 in the dead group (p<0.05). According to Pearson's correlation analysis, a powerful negative-oriented relationship was observed between SUV_{max} values and general survival rate (p<0.001; r=-0.65). The relationship between SUV_{max} values and general survival is shown in Figure 2.

According to the ACC classification of ENSAT study group, five patients were at stage 2 and one at stage 3 in the survived group, whereas eight patients were at stage 2, three at stage 3, and four at stage 4 in the dead group. Metastasis was not observed in the survived group at the time of diagnosis, whereas four patients from the dead group had metastasis at the time of diagnosis. Moreover, metastasis was not developed in follow-ups after full resection of the tumor in the survived group; however, new metastasis developed in eight patients in the dead group (p<0.05). ACC-related metastases were most commonly observed in the lymph nodes, liver, lung, and bones. One patient from the survived group and seven patients from the dead group received chemotherapy. No recurrences were observed during the follow-ups of patients from the survived group; five patients who were operated had recurrences in the dead group (p>0.05). Appraisements related to groups are shown below in Table 3.

The average survival duration of patients according to the Kaplan-Meier survival analysis was 23.66±2.79 (95% CI=18.18-29.13) months, and the median survival duration was 19.1 (95% CI=13.01-25.18) months. The general survival chart of the patients is shown below in Figure 3.

Discussion

Information on ACC is limited as they are rarely observed. The incidence rate among women is 1.2 to 1.5 times more than men (7). ACC more frequently occurred between

Table 2. Adrenal endocrine hormone secretion status of the groups.

Parameters	Survived group (n=6)	Dead group (n=15)	p
Basal ACTH (pg/mL)	13.31±8.16	11.93±11.99	>0.05
Basal cortisol (µg/dL)	20.97±17.21	24.78±12.76	>0.05
1 mg DST non-suppression	3	9	>0.05
2 mg DST non-suppression	1	7	>0.05
Median 24-hour urine cortisol (nM/day)	136 (min-max: 78-1106)	148 (min-max: 80-2052)	>0.05
Hypercortisolism	1	7	>0.05
Hyperaldosteronism	0	2	>0.05
Hyperandrogenemia	0	6	>0.05
Elevation of 24-hour urine fractionated catecholamines	0	1	>0.05
Total adrenal endocrine hormone production	1 (%16)	12 (%80)	**<0.01**

* DST: Dexamethasone suppression test.

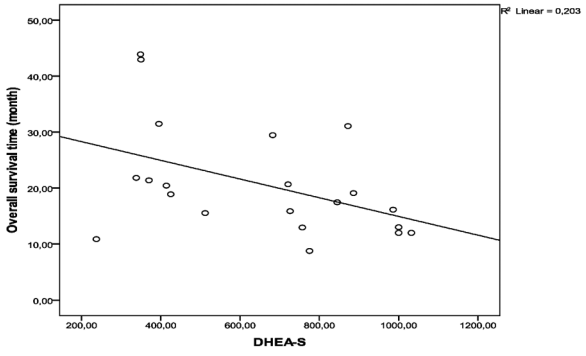


Figure 1: There was a negative correlation between dehydroepiandrosterone sulfate (DHEA-S), and overall survival time.

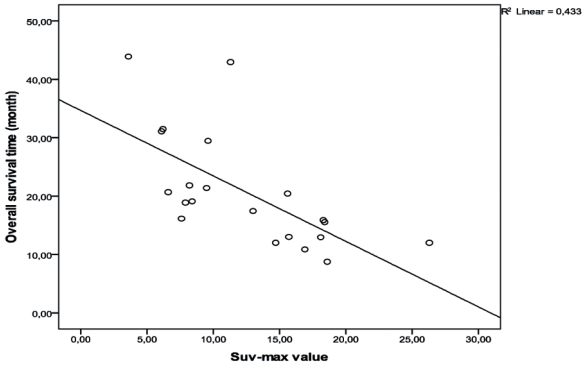


Figure 2: Negative-oriented relationship between standardized uptake value (SUV_{max}) values and overall survival time.

the fourth and sixth decades of life (8). Women's dominance was remarkable in this study, as 76% of ACC patients included were women. The average age of patients was between 40 and 50 years. More tumors were localized in the right adrenal gland.

When previous studies were analyzed, the diameter of the adrenal mass in patients with ACC was ≥10 cm (7,17). In this study, the average mass size was 10.37±4.47 cm (min-max=4.2-22 cm). The size of the adrenal mass among deceased patients was higher than those who survived. The survival rate of patients with a greater mass size was lower. However, it was not found statistically significant. In previous studies, tumor stage was found to be a strong prognostic factor in predicting mortality (6). As the staging was conducted on the basis of the mass size, the mass size affects the prognosis. However, the fact that the mass size was not statistically significant in this study may be because of the limited number of patients.

The most crucial stage in the treatment of ACC is complete resection of the tumor. The mortality rate was higher in patients who were not fully resected or who were inoperable because of being metastatic (8). In this study, only five deceased patients could not be operated because of the advanced stage. Steroid hormone production was observed among 50%-75% of patients with ACC. Mostly, cortisol was secreted. ACCs that are hormonally active have poor prognosis (9,16). The harmful effects of excessive steroid hormone production on the body and the increasing complications after the operation may be the reason for high mortality. In this study, eight of 21 (38%) patients

Table 3. Evaluations of the groups and comparison of over-all survival times.

Parameters	Survived group (n=6)	Dead group (n=15)	p
Operation	100%	66%	>0.05
Total Weiss score	5.33±1.21	5.3±1.94	>0.05
DHEA-S (µg/dL)	371.13±33.21	763.05±229.74	<0.001
SUV_{max} value	7.78±2.66	14.26±5.67	<0.05
Stage-1	0	0	>0.05
Stage-2	5	8	>0.05
Stage-3	1	3	>0.05
Stage-4	0	4	>0.05
Recurrence	0	5	>0.05
Metastasis in diagnosis	0	4	>0.05
Metastasis in follow-up	0	8	<0.05

DHEA-S: Dehydroepiandrosterone sulfate.

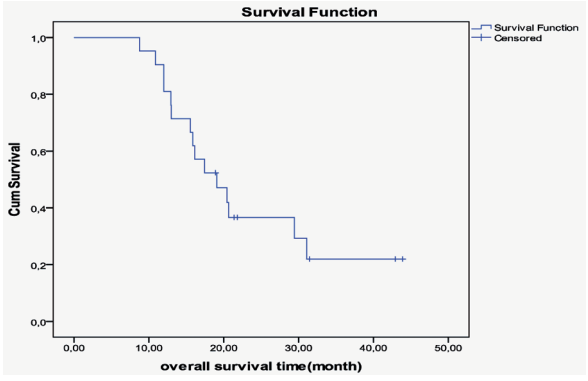


Figure 3: Kaplan-Meier survival curve for adrenocortical cancer.

showed extreme cortisol secretion. Seven of these patients were in the dead group. Moreover, two patients had hyperaldosteronism, and one had a high level of catecholamine. The fact that patients with hormone-producing ACC were dominant in the dead group and a statistically strong relationship was found may conclude that endocrine hormone secretion is an indicator of bad prognosis ($p<0.01$).

The adrenocortical adenoma and adrenocortical carcinomas can be histologically separated precisely using Weiss scoring. Patients with a total Weiss score of 3 or above were diagnosed with ACC. In previous studies, high Weiss scores were associated with recurrence and mortality (10-12). The Weiss scores in the patients operated in the study did not differ between the survived and the dead groups.

A higher level of DHEA-S may be observed in ACC than adrenocortical adenomas (13). Although the high level of DHEA-S was used as a parameter for diagnoses, it was not adequately examined by researchers in predicting mortality. The DHEA-S level was significantly higher in the dead group in this study ($p<0.001$). No correlation was observed between the size of the adrenal mass and the DHEA-S level. A negative-oriented correlation was observed between the DHEA-S level and the general survival, according to Pearson's correlation analysis. Considering this relationship, a high level of DHEA-S can be said to show poor prognosis. In this study, the low levels of DHEA-S noted in the patients after operation were markedly increased in the average clinical follow-up of 5.15±1.65 months. Therefore, it is crucial that clinicians follow these patients for the first six months postoperatively. The early diagnosis of this cancer that has high mortality can increase the survival of patients.

It is sometimes very difficult for clinicians to decide in favor of malignancy in adrenal masses. The F-18 FDG PET-CT plays a crucial role in the differentiation of the adrenal mass from benign, malignant types. The SUV_{max} value was higher in malignant adrenal masses (5,14). The relationship between the SUV_{max} value and mortality is not adequately studied. In this study, the SUV_{max} value was significantly higher in the dead group than the survived group ($p<0.05$). According to Pearson's correlation analysis, a strong negative-oriented relationship was observed between SUV_{max} values and the general survival rate. Thus, it is estimated that the mortality rate of patients with ACC with high SUV_{max} value is high.

In patients with ACC, lymph node invasion is typically observed at the time of diagnosis. It is most commonly observed in the lungs and liver as distal metastases (17). Metastasis in follow-ups, lymph node invasion was noted in three patients; lung and liver metastasis in three patients; lung and peritoneal metastasis in two patients. In follow-ups, ACC recurred at the operation site in five patients in the dead group. Relapse or metastasis development increased mortality (18). Despite surgical treatment, ACC relapse was noted frequently (23%).

Chemotherapy regimens are recommended in patients who are metastatic, progressive, or recurrent (18,19). The two most commonly used chemotherapy regimens are etoposide, doxorubicin, cisplatin, and mitotane (EDP-M) and streptozotocin and mitotane (Sz-M). In this study, nine patients were administered EDP-M in the dead group who were at an advanced stage and had a recurrence. However, despite surgery and chemotherapy regimens, ACC still had a high mortality rate (71%).

Bilimoria et al. found that the median survival was 32 months, and 5-year survival rate was 38% in patients with ACC (7). Tritos et al. reported a median survival of 17 months in patients with ACC (20). Tauchmanova et al. found that general survival

was 41 months in patients with ACC (3). Similar to the previous findings, this study showed that the median survival was 19.1 months, and the average survival was 23.66 months in patients with ACC.

Study Limitations

As this was a single-center study, a small number of patients were included. Thus, studies including large patient populations from multiple centers can help in better understanding ACC.

Conclusion

ACC still has high mortality rates despite surgical and medical treatments (71%). Moreover, it is observed 3.2 times more in women than men. The mass size and volume were not effective in mortality. The presence of adrenal steroid hormone production increased mortality. In follow-ups, the development of metastases was considered a poor prognostic factor. A high level of DHEA-S and SUV_{max} value at the time of diagnosis may predict lower overall survival. Closely following up with these patients is very important as relapses are common in the first six months postoperation.

Despite all the treatments in patients with ACC, the average survival was 23 months. Further large-scale studies are warranted to treat ACC, which has high mortality and is rarely seen.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Mehmet Güven; Design: Mehmet Güven; Control/Supervision: Alpaslan Kemal Tuzcu, Mehmet Güven; Data Collection and/or Processing: Mehmet Şimşek, Mehmet Güven; Analysis and/or Interpretation: Alpaslan Kemal Tuzcu, Mehmet Güven; Literature Review: Mehmet Şimşek; Writing the Article: Mehmet Güven; Critical Review: Mehmet Güven, Alpaslan Kemal Tuzcu.

References

1. Kerkhofs TMA, Verhoeven RHA, Van der Zwan JM, Dieleman J, Kerstens MN, Links TP, Van de Poll-Franse LV, Haak HR. Adrenocortical carcinoma: a population-based study on incidence and survival in the Netherlands since 1993. Eur J Cancer. 2013;49:2579-2586. [Crossref] [PubMed]
2. Schteingart DE, Doherty GM, Gauger PG, Giordano TJ, Hammer GD, Korobkin M, Worden FP. Management of patients with adrenal cancer: recommendations of an international consensus conference. Endocr Relat Cancer. 2005;12:667-680. [Crossref] [PubMed]
3. Tauchmanovà L, Colao A, Marzano LA, Sparano L, Camera L, Rossi A, Palmieri G, Marzano E, Salvatore M, Pettinato G, Lombardi G, Rossi R. Adrenocortical carcinomas: twelve-year prospective experience. World J Surg. 2004;28:896-903. [Crossref] [PubMed]
4. Osella G, Terzolo M, Borretta G, Magro G, Alí A, Piovesan A, Paccotti P, Angeli A. Endocrine evaluation of incidentally discovered adrenal masses (incidentalomas). J Clin Endocrinol Metab. 1994;79:1532-1539. [Crossref] [PubMed]
5. Elaini AB, Shetty SK, Chapman VM, Sahani DV, Boland GW, Sweeney AT, Maher MM, Slattery JT, Mueller PR, Blake MA. Improved detection and characterization of adrenal disease with PET-CT. Radiographics. 2007;27:755-767. [Crossref] [PubMed]
6. Fassnacht M, Johanssen S, Quinkler M, Bucsky P, Willenberg HS, Beuschlein F, Terzolo M, Mueller HH, Hahner S, Allolio B; German Adrenocortical Carcinoma Registry Group. Limited prognostic value of the 2004 International Union Against Cancer staging classification for adrenocortical carcinoma: proposal for a revised TNM classification. Cancer. 2009;115:243-250. [Crossref] [PubMed]
7. Bilimoria KY, Shen WT, Elaraj D, Bentrem DJ, Winchester DJ, Kebebew E, Sturgeon C. Adrenocortical carcinoma in the United States: treatment utilization and prognostic factors. Cancer. 2008;113:3130-3136. [Crossref] [PubMed] [PMC]
8. Icard P, Goudet P, Charpenay C, Andreassian B, Carnaille B, Chapuis Y, Cougard P, Henry JF, Proye C. Adrenocortical carcinomas: surgical trends and results of a 253-patient series from the French Association of Endocrine Surgeons study group. World J Surg. 2001;25:891-897. [Crossref] [PubMed]

9. Abiven G, Coste J, Groussin L, Anract P, Tissier F, Legmann P, Dousset B, Bertagna X, Bertherat J. 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;91:2650-2655. [Crossref] [PubMed]
10. Lucon AM, Pereira MA, Mendonça BB, Zerbini MC, Saldanha LB, Arap S. Adrenocortical tumors: results of treatment and study of Weiss's score as a prognostic factor. Rev Hosp Clin Fac Med Sao Paulo. 2002;57:251-256. [Crossref] [PubMed]
11. Weiss LM. Comparative histologic study of 43 metastasizing and nonmetastasizing adrenocortical tumors. Am J Surg Pathol. 1984;8:163-169. [Crossref] [PubMed]
12. Weiss LM, Medeiros LJ, Vickery Jr AL. Pathologic features of prognostic significance in adrenocortical carcinoma. Am J Surg Pathol. 1989;13:202-206. [Crossref] [PubMed]
13. Michalkiewicz E, Sandrini R, Figueiredo B, Miranda ECM, Caran E, Oliveira-Filho AG, Marques R, Pianovski MAD, Lacerda L, Cristofani LM, Jenkins J, Rodriguez-Galindo C, Ribeiro RC. Clinical and outcome characteristics of children with adrenocortical tumors: a report from the International Pediatric Adrenocortical Tumor Registry. J Clin Oncol. 2004;22:838-845. [Crossref] [PubMed]
14. Chong S, Lee KS, Kim HY, Kim YK, Kim BT, Chung MJ, Yi CA, Kwon GY. Integrated PET-CT for the characterization of adrenal gland lesions in cancer patients: diagnostic efficacy and interpretation pitfalls. Radiographics. 2006;26:1811-1824; discussion 1824-1826. [Crossref] [PubMed]
15. Margonis GA, Kim Y, Tran TB, Postlewait LM, Maithel SK, Wang TS, Glenn JA, Hatzaras I, Shenoy R, Phay JE, Keplinger K, Fields RC, Jin LX, Weber SM, Salem A, Sicklick JK, Gad S, Yopp AC, Mansour JC, Duh QY, Seiser N, Solorzano CC, Kiernan CM, Votanopoulos KI, Levine EA, Poultsides GA, Pawlik TM. Outcomes after resection of cortisol-secreting adrenocortical carcinoma. Am J Surg. 2016;211:1106-1113. [Crossref] [PubMed] [PMC]
16. Keskin S, Taş F, Vatansever S. Adrenocortical carcinoma: clinicopathological features, prognostic factors and outcome. Urol Int. 2013;90:435-438. [Crossref] [PubMed]
17. Dy BM, Strajina V, Cayo AK, Richards ML, Farley DR, Grant CS, Harmsen WS, Evans DB, Grubbs EG, Bible KC, Young WF, Perrier ND, Que FG, Nagorney DM, Lee JE, Thompson GB. Surgical resection of synchronously metastatic adrenocortical cancer. Ann Surg Oncol. 2015;22:146-151. [Crossref] [PubMed]
18. Berruti A, Baudin E, Gelderblom H, Haak HR, Porpiglia F, Fassnacht M, Pentheroudakis G; ESMO Guidelines Working Group. Adrenal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23:vii131-138. [Crossref] [PubMed]
19. Baudin E, Leboulleux S, Al Ghuzlan A, Chougnet C, Young J, Deandreis D, Dumont F, Dechamps F, Caramella C, Chanson P, Lanoy E, Borget I, Schlumberger M. Therapeutic management of advanced adrenocortical carcinoma: what do we know in 2011? Horm Cancer. 2011;2:363-371. [Crossref] [PubMed]
20. Tritos NA, Cushing GW, Heatley G, Libertino JA. Clinical features and prognostic factors associated with adrenocortical carcinoma: Lahey Clinic Medical Center experience. Am Surg. 2000;66:73-79. [PubMed]