ORIGINAL RESEARCH

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Clinicopathological Features, Treatment Outcomes, and Prognostic Factors in Adrenocortical Carcinoma: A Single-Center Experience

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ABSTRACT Objective: The study aimed to analyze clinicopathological features, treatment outcomes, and prognostic factors of patients with adrenocortical carcinoma (ACC). **Material and Methods:** The records of 25 patients with confirmed ACC were retrospectively examined who were followed up in our clinic. The clinical and pathological data were recorded. The prognosis was estimated using the Kaplan-Meier method, and prognostic variables were determined using Cox regression models. **Results:** The study included 21 patients, 19 (90.5%) of whom initially had Stage III or IV disease, and 18 (85.7%) had surgery for the primary tumor. In the subgroup with non-metastatic disease and primary tumor resection, patients who received adjuvant mitotane had significantly longer median disease-free survival than patients who had not (22.7 vs. 2.5 months, p=0.02). Five-year overall survival (OS) was 36%. De novo metastatic disease, primary tumor resection, and tumor functional status were the factors affecting OS significantly or having a trend in univariate analysis. Primary tumor resection was the only independent prognostic factor for OS after adjusting for other factors (hazard ratio=0.06, p=0.04). **Conclusion:** In our study population, adjuvant mitotane conferred a significant improvement in disease-free survival of patients with ACC who were operated on for localized disease. Primary tumor resection persisted in being a significant prognostic factor for OS.

Keywords: Adrenocortical carcinoma; prognosis; survival

The most common primary tumor of the adrenal gland is adrenocortical carcinoma (ACC). ACC is a highly rare malignancy, with an incidence of 0.7-2 per million population.[1] Although a diagnosis can be made at any age, ACC more frequently affects women, and its incidence peaks in the fourth to fifth decades of life.[2] ACCs are generally sporadic; however, they are occasionally observed as a component of hereditary syndromes like Li-Fraumeni or Beck-with-Wiedemann syndrome.[3] Approximately 60% of patients present with symptoms owing to adrenal hormone secretion, where cortisol excess (Cushing syndrome) is the leading manifestation followed by secretion of sex hormones (primarily androgen).[1,4] Non-functional ACCs cause symptoms owing to tumor burden, particularly abdominal pain and weight loss. Most ACC cases are diagnosed at an advanced stage, and 5-year survival remains below 50%.[5]

Primary treatment of localized ACC is the tumor resection with or without removal of regional lymph nodes. Adjuvant therapy with an oral adrenolytic agent, mitotane, for a minimum of 2 years is recommended in patients with no macroscopic residual disease if a high risk of recurrence (large tumor size, Ki67>10% or R1 resection) persists.[1] Radiotherapy

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(RT) to the tumor bed is recommended for cases with R1 resection or Stage III disease.[1] Metastatic ACC is generally treated using mitotane and/or combinations of cytotoxic agents, including platinum compounds, etoposide, and doxorubicin. In particular, a four-drug regimen comprising cisplatin, etoposide, doxorubicin, and mitotane (EDP-M) improved response rate and reduced risk of progression compared to mitotane plus streptozocin in a randomized Phase III trial enrolling patients with advanced ACC.[6]

In this study, we aimed to investigate clinicopathological features, treatment outcomes, and prognostic factors of patients with ACC at our institute.

MATERIAL AND METHODS

STUDY DESIGN

This was a retrospective descriptive study. The records of patients with histologically verified ACC who were diagnosed between 2007 and 2020 and followed up at our clinic until March 2021 were reviewed. Age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities, familial history of cancer, initial symptom(s), functional status of the tumor, date of diagnosis, initial stage according to American Joint Committee on Cancer TNM Staging System 8th Edition, and history and date of primary surgery for ACC were recorded. In operated cases, the following pathological parameters were noted: Tumor size, nuclear (Fuhrman) grade, mitosis per 50 high-power fields (HPF), Ki67 level, surgical margins, tumor capsule rupture, and lymph node status. Patients were categorized regarding mitotic count (20/50 HPF as cut-off) and Ki67 (10% as cut-off).[1,7]

In initially non-metastatic patients who had undergone resection of the primary tumor, histories of adjuvant mitotane and RT, initiation date and dose, as well as discontinuation date of mitotane were recorded. Cases experiencing relapse were also determined, and relapse date and metastatic sites were noted. Information regarding treatments in a metastatic setting was obtained. Response to treatment was evaluated using the Response Evaluation Criteria in Solid Tumors Version 1.1. Dates of the last visit and death were also recorded. The Ethics Committee of Marmara University School of Medicine approved this study in compliance with the Helsinki Declaration (Number: 09.2021.363, Date: 05.03.2021).

STATISTICAL ANALYSES

Descriptive data were given as frequencies and percentages. Continuous variables were expressed as mean or median values depending on the distribution. For patients without metastatic disease at presentation, disease-free survival (DFS) was accepted as the time interval between the date of surgery and the date of relapse, death, or last visit (in months). Overall survival (OS) was accepted as the time interval between the date of diagnosis and death or last visit (in months). Survival was estimated using the Kaplan-Meier method and compared with the log-rank test between groups. Prognostic factors for OS were evaluated with Cox regression models; significant or close to significant variables in univariate analysis ($p<0.1$) were processed in multivariate analysis. The confidence interval (CI) was set as 95%, and a p-value of <0.05 was accepted as statistically significant. All data were analyzed using the software SPSS Version 22 (SPSS Inc., USA).

RESULTS

PATIENT CHARACTERISTICS

Twenty-one patients were included in the study, and their baseline characteristics are shown in Table 1, after excluding four patients with missing clinical data. There were more men than women, and the median age at the time of diagnosis was 49 (38-57) years. Nine patients (42.9%) had a familial history of cancer, and nine had hypertension. Pain was the most common presenting symptom (61.9%). Three patients had hormone-secreting tumors; one of them had presented with hirsutism and amenorrhea due to androgen excess, and another one with hypertension due to cortisol excess. Eleven (52.4%) cases had Stage III, and 8 (38.1%) cases had Stage IV disease at the time of diagnosis. The liver was the most common site of distant metastasis (38.1%) at diagnosis or during the follow-up period.

The primary tumor was resected in 18 (85.7%) patients, 5 of whom had de novo metastatic disease. Regional lymph node dissection was not done in the

TABLE 1: Baseline patient characteristics.

Characteristics	Patient number	Percentage
Sex		
Male	12	57.1
Female	9	42.9
Age at diagnosis		
<50 years	11	52.4
≥50 years	10	47.6
ECOG-PS		
0	16	76.2
1	3	14.3
2	1	4.8
3	1	4.8
Initial symptom(s)		
Pain	13	61.9
Constitutional	2	9.5
Hirsutism+amenorrhea	1	4.8
Hypertension	1	4.8
Non-specific	2	9.5
Unknown	2	9.5
Tumor functional status		
Hormone-secreting	3	14.3
Non-functional	18	85.7
TNM stage at diagnosis		
II	2	9.5
III	11	52.4
IV	8	38.1
Resection of the primary tumor		
Yes	18	85.7
No	3	14.3
Sites of distant metastasis*		
Liver	8	38.1
Lung	4	19
Lymph nodes	4	19
Bones	3	14.3
Local recurrence	4	19
Unknown	1	4.8

*At any time during follow-up; ECOG-PS: Eastern Cooperative Oncology Group performance status.

majority (77.8%). The median primary tumor size was 15.7 (9.5-27) cm. Seven (38.9%) patients had a Fuhrman grade of 3 or 4. Mitotic count was greater than 20/50 HPF in four (22.2%) patients and Ki67 greater than 10% in six (33.3%) patients. Two (11.1%) patients had tumor capsule rupture, and 2 had positive surgical margins. Table 2 summarizes the patient characteristics who had surgery for the primary tumor.

TREATMENT OUTCOMES AND PROGNOSTIC FACTORS

In the patient subgroup without initial distant metastases and had undergone surgery for the primary tumor, nine cases received adjuvant mitotane treatment. Mitotane was initiated 3 g/day except for one patient who received a starting dose of 2 g/day. The mean duration of adjuvant mitotane treatment was 7.5±4.7 months. In the final analysis of the non-metastatic surgery cohort, seven (53.8%) patients ex-

TABLE 2: Characteristics of 18 patients who had undergone resection of the primary tumor.

Characteristics	Mean (minimum-maximum)	SD
Tumor size (cm)	15.7 (9.5-27)	5.7
Characteristic	**Patient number**	**Percentage**
Fuhrman grade		
2	1	5.6
3	4	22.2
4	3	16.7
Not specified	10	55.6
Mitotic count (per 50 HPF)		
≤20	7	38.9
>20	4	22.2
Not specified	7	38.9
Ki67		
≤10%	7	38.9
>10%	6	33.3
Not specified	5	27.8
Rupture of tumor capsule		
Yes	2	11.1
No	14	77.8
Not specified	2	11.1
Surgical margins		
Negative	11	61.1
Positive	2	11.1
Not specified	5	27.8
Lymph node status		
Negative	3	16.7
Positive	1	5.6
Unknown (Nx)	14	77.8
Adjuvant mitotane*		
Yes	9	69.2
No	4	30.8
Adjuvant RT*		
Yes	0	0
No	13	100

*Includes only patients without metastatic disease initially; SD: Standard deviation; HPF: High power field; RT: Radiotherapy. .

perienced relapse, and median DFS was 22.7 (95% CI, 14-31.4) months. The median DFS of patients who had received adjuvant mitotane was significantly longer than those who had not (22.7 vs. 2.5 months, p=0.02) (Figure 1).

Fifteen patients had either de novo or metachronous relapsed or metastatic disease. First-line treatment for these patients included systemic therapy in 12 cases, stereotactic radiosurgery for local recurrence in one patient, surgery plus RT for local recurrence in 1 patient, and best supportive care in 1 patient. Systemic therapy regimens were mitotane in 6 patients, cisplatin-etoposide-mitotane in 4 patients, EDP-M, and cisplatin-doxorubicin in one patient. Nine (60%) patients with relapsed or progressive metastatic disease proceeded to second-line systemic treatment, which included cisplatin- or carboplatin-etoposide, cisplatin-etoposide-mitotane or -doxorubicin, gemcitabine-docetaxel-mitotane, paclitaxel-vincristine-mitotane, and oral etoposide.

The median duration of follow-up was 24.9 (10.6-59.9) months. At the data cut-off date, 12 (57.1%) patients had died, and the median OS was 28.3 (95% CI, 12.8-44) months. The 5-year OS rate was 36%. The factors significantly affecting OS or having a trend in univariate analysis were de novo metastatic disease, history of primary tumor resection, and functional tumor status (Table 3). In multivariate analysis, only history of primary tumor resection was detected to be an independent predictor of OS [hazard ratio (HR)=0.06, p=0.04] (Figure 2).

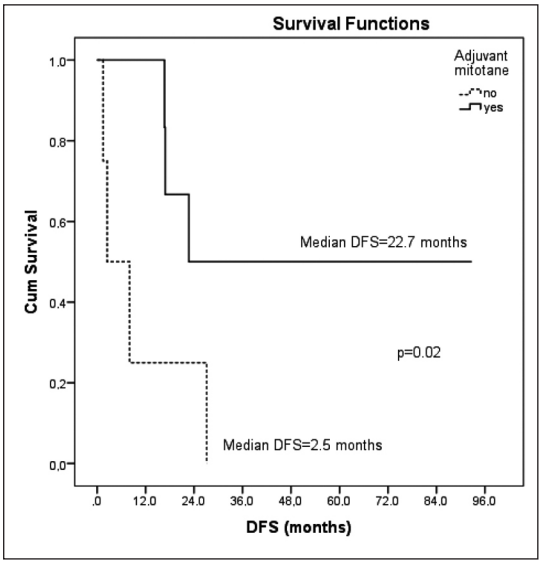

FIGURE 1: DFS plots by adjuvant mitotane treatment.
DFS: Disease-free survival.

DISCUSSION

This study aimed to evaluate clinical outcomes and prognostic factors of patients with ACC followed up at a tertiary oncology clinic. Our cohort reflects the disease aggressiveness, with approximately 38% of patients having Stage IV disease at the time of diagnosis, which is similar to the literature.[8] The 5-year survival of 36% is also concordant with previous reports in the field.[9,10] Two remarkable outcomes in our study were improved DFS with adjuvant mitotane treatment and primary tumor resection being a significant prognostic factor.

Owing to the rare occurrence of ACC, there is a lack of randomized prospective trials investigating

TABLE 3: Analysis of prognostic factors for overall survival.

	Univariate analysis		Multivariate analysis	
Factor	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
Age	1.29 (0.41-4.09)	0.66		
Sex	1.02 (0.32-3.19)	0.98		
ECOG-PS	2.35 (0.70-7.92)	0.17		
De novo metastatic disease	3.22 (0.99-10.45)	0.05	2.21 (0.58-8.40)	0.24
Surgery for primary tumor	0.20 (0.05-0.92)	0.04	0.06 (0.00-0.91)	0.04
Tumor functional status	6.73 (0.92-49.19)	0.06	3.30 (0.29-37.96)	0.34

HR: Hazard ratio; CI: Confidence interval; ECOG-PS: Eastern Cooperative Oncology Group performance status.

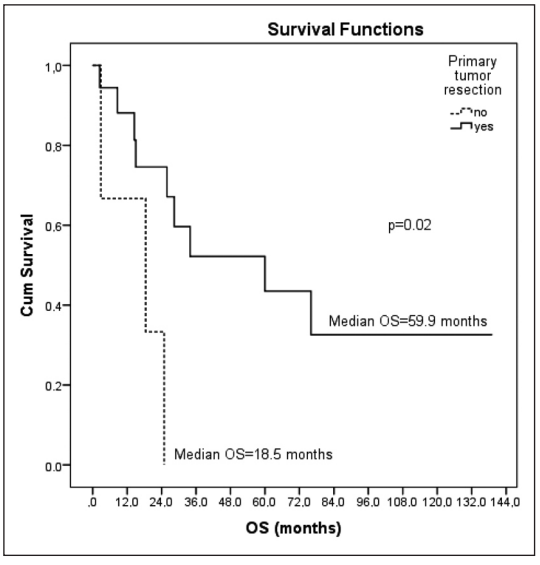

FIGURE 2: OS plots by primary tumor resection.
OS: Overall survival.

adjuvant therapy, and recommendations were extrapolated primarily from retrospective series and meta-analyses. In a study, including 152 ACC patients with complete resection, Calabrese et al. demonstrated a significant improvement in median recurrence-free survival (RFS) of patients who received postoperative mitotane treatment (36.8 vs. 21 months, p<0.001), OS was longer in patients with higher Ki67 levels (>10%) and Stage III disease.[11] The benefits of adjuvant mitotane were also demonstrated in a comprehensive meta-analysis, including 1,249 patients with ACC.[12] Moreover, mitotane significantly prolonged median RFS and OS (HR=0.62 and 0.69, respectively). In our study, the patients' subgroup with initially non-metastatic disease and primary tumor resection comprised 13 cases. Moreover, all of these had a minimum of one risk factor for recurrence (large tumor size, Ki67>10%, mitotic count >20/50 HPF, or R1 resection). Although median DFS in our study is lower than the other retrospective series (possibly elucidated by the heterogeneity between study populations), a significant difference in median DFS emphasizes the benefit of adjuvant mitotane in patients with high recurrence risk. Two ongoing randomized Phase III trials are assessing the efficacy of adjuvant mitotane in low- or intermediate-risk ACC (ADIUVO, NCT00777244) and effects of adjuvant mitotane alone or combined with cisplatin-etoposide in high-risk ACC (ADIUVO II, NCT03583710).

The primary tumor resection is the treatment of choice for localized ACC. Moreover, it also confers survival benefits in synchronous metastatic disease.[13,14] Our results highlight the importance of this procedure as well, with a 41.5 months improvement in OS for patients who had undergone surgery, and this corresponded to more than 90% reduction in death risk. OS was also affected by other factors with a trend toward significance in univariate analysis, namely, de novo metastatic disease and tumors' functional status; however, these were not independent factors in the multivariate model. The tumor stage is a well-established prognostic factor in ACC; however, our sample size and particularly the underrepresented early-stage patients may have precluded an accurate analysis.[15] Prognostic value of functional status in ACC is controversial. To date, cortisol secretion has been reported as a predictor of cancer-specific death.[1,16] In our study, the rate of functional tumors was lower than reported in the literature, probably as patients were referred at an advanced stage and symptoms related to tumor burden were predominant. Furthermore, the benefit of early diagnosis in hormone-secreting ACCs is possibly neutralized by the increased morbidity associated with excess hormone.

However, our study had some limitations. There was a selection bias due to the retrospective design of the study. Moreover, some of the pathological data were missing as they were reported inconsistently. Therefore, regression analysis for DFS could not be performed. Definitive conclusions could not be achieved owing to the relatively small sample size. Nevertheless, outcomes compatible with the literature on this rare malignancy were revealed.

CONCLUSION

ACC is an aggressive tumor that has a poor prognosis. In non-metastatic cases with resected primary tumors and harboring a high recurrence risk, adjuvant mitotane appears to provide the benefit of DFS. As suggested by our results, surgery for primary tumors can reduce the risk of death in ACC. Further studies with larger sample sizes are required to confirm these findings.

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: *Nazım Can Demircan, Özlem Ercelep, Perran Fulden Yumuk;* ***Design:*** *Nazım Can Demircan, Tuğba Akın Telli;* ***Control/Supervision:*** *Faysal Dane, Perran Fulden Yumuk;* ***Data Collection and/or Processing:*** *Nazım Can Demircan, Tuğba Akın Telli, Tuğba Başoğlu, Rukiye Arıkan, Alper Yaşar, Abdussamet Çelebi, Özkan Alan, Selver Işık;* ***Analysis and/or Interpretation:*** *Nazım Can Demircan, Tuğba Akın Telli, Özlem Ercelep;* ***Literature Review:*** *Nazım Can Demircan;* ***Writing the Article:*** *Nazım Can Demircan, Faysal Dane, Perran Fulden Yumuk;* ***Critical Review:*** *Faysal Dane, Perran Fulden Yumuk;* ***References and Fundings:*** *Nazım Can Demircan,* ***Materials:*** *Nazım Can Demircan.*

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