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Clinical Research Article

Prognostic Factors in Advanced Adrenocortical Carcinoma: Summary of a National Referral Center's 20 years of Experience

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Abstract

Context: Adrenocortical carcinoma (ACC) is a rare malignancy with poor prognosis for both locally advanced and metastatic disease. Standard treatment with combination etoposide–doxorubicin–cisplatin–mitotane (EDP-M) is highly toxic and some patients benefit from mitotane monotherapy. However, identification of these patients remains challenging.

Objective: We present a summary of the Israeli national referral center's 20 years of experience in treating advanced ACC, with the aim of identifying prognostic factors and assisting in treatment decision making.

Methods: We conducted a retrospective multivariate analysis of patients treated for metastatic or locally advanced ACC at Hadassah Medical Center between 2000 and 2020 to determine clinical, pathological, and treatment factors correlated with overall survival (OS).

Results: In our cohort of 37 patients, a combination of modified European Network for the study of Adrenal Tumors (mENSAT) staging with either grade and R status, or age and symptoms was validated to stratify prognosis ($P = .01$ and $P = .03$, respectively). Patients who underwent R0 resection followed by radiotherapy or metastasectomy for oligometastatic disease had longer OS than patients with residual disease: median OS of 55 months vs 14 months, respectively, hazard ratio 3.1 (CI 1.4-6.7, $P = .005$). Patients treated with mitotane monotherapy had a significantly better prognosis, yet this result was attenuated in a multivariate analysis controlling for mENSAT and R status. Of patients treated with EDP-M, 41.4% experienced grade 3 or higher adverse events.

Conclusion: Patients with advanced ACC achieving R0 status have a better prognosis and might benefit from mitotane monotherapy.

Key Words: adrenocortical carcinoma, mitotane monotherapy, GRAS, R status, mENSAT

Abbreviations: ACC, adrenocortical carcinoma; EDP-M, etoposide–doxorubicin–cisplatin–mitotane; GRAS, grade, HR, hazard ratio; R status, age, symptoms; mENSAT, modified European Network for the study of Adrenal Tumors; OS, overall survival; PFS, progression-free survival.

Adrenocortical carcinoma (ACC) is a rare malignancy with an approximate incidence of 1 per million new cases in the United States every year, with a bimodal age distribution in childhood and in the fourth and fifth decades of life [1]. Most patients with ACC present with symptoms resulting from either hyperfunctioning tumors or direct tumor mass extension, and about 15% are diagnosed because of incidental findings on imaging [2]. Cases of ACC are usually sporadic; however, several hereditary syndromes are associated with ACC including Li–Fraumeni, Lynch syndrome, Beckwith–Wiedemann, and multiple endocrine neoplasia type 1 (MEN1) [2, 3].

Metastatic or locally advanced disease (ie, lymph node involvement or locoregional spread to adjacent organs) similarly harbors poor prognosis [4]. Even with aggressive treatment with 1 of etoposide–doxorubicin–cisplatin–mitotane (EDP-M), these patients have a median progression-free survival (PFS) of 5 months and median overall survival (OS) of 14 to 16 months [5]. This combination therapy is highly toxic with more than half of the patients experiencing grade 3 to 4 adverse events [5]. Patients receiving mitotane monotherapy for advanced disease, especially those reaching therapeutic levels of mitotane (≥14 mg/L) and with a low-volume disease, have a similar OS of 18 months [6]. Since EDP-M treatment was compared in the phase III FIRM-ACT trial with a previously standard combination chemotherapy [5], it remains unclear which patients will benefit from combination therapy and which patients should be treated with single-agent mitotane monotherapy. This question remains a major challenge for clinicians treating patients with advanced ACC.

Several clinical and pathological factors have been correlated with prognosis and response to treatment, including resection status (R0, complete section; R1, residual micro; R2, residual macro; involved surgical margins; or nonresectable)

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[7], grade (according to mitotic index) [8], Ki 67 proliferation index [9], Weiss histopathological score [10], and the European Network for the Study of Adrenal Tumors (ENSAT) stage t diagnosis [11]. A recent study by Libé et al conducted on 444 patients with advanced ACC improved prognostic prediction by combining a modified ENSAT (mENSAT) staging system (stage IV was subdivided into 3 subgroups, IVa-IVc, according to the number of organs and regional lymph nodes involved), together with unfavorable GRAS (grade, R status, age, symptoms) parameters—histopathological grade (for this study Ki67 index >20 or Weiss >6), and R status (R1-R2, Rx), or age (>50), and hormone or tumor mass–related symptoms at diagnosis [12].

Over the last 20 years we have treated 47 patients with ACC, 40 of them with advanced or metastatic ACC, in our national referral center. Here we present a summary of our center's experience with the aim of identifying prognostic factors related to patients' characteristics and treatment and direct future treatment decision making.

Materials and Methods

Patients and Data Collection

We reviewed medical records of all consecutive patients, 18 years or older, treated for ACC at Hadassah University Hospital from January 2000 to December 2020. Inclusion criteria included patients with confirmed histological diagnosis of metastatic or locally advanced (lymph node or locoregional spread) mENSAT stage III-IVc ACC. Patients who were initially diagnosed with I- III stage disease without locoregional spread and suffered disease progression were also included. All patients received chemotherapy treatment within 2 months of diagnosis or resection and had available follow-up data for at least 2 years for surviving patients, or earlier in the case of death. All patients who had been treated with mitotane had recorded mitotane levels over at least 3 sperate measures. The study was approved by Hadassah Medical Organization institutional Helsinki committee 0368-21-HMO and all patients provided informed consent for review of their medical records.

Data collected included age of diagnosis; gender; ethnic origin; tumor side, TNM, capsular invasion, ENSAT at initial diagnosis, mENSAT and involved organs at diagnosis with locoregional or metastatic disease; R status; histological grade (according to mitotic rate as per novel 2022 WHO classification) [13]; Ki 67 proliferation index determined by manual immunohistochemistry using the same antibody (Cell Mark Ki 67; SPS, rabbit monoclonal antibody: RRID:AB 2892217); Weiss histopathological score; Lin–Weiss–Bisceglia for oncocytic subtype; symptoms at diagnosis; treatment type; maximal mitotane levels reached; treatment tolerability and adverse events; response to treatment and duration of response; time from diagnosis until death or last follow-up.

Statistical Analysis

Descriptive analyses were carried out using the median and SD or range for quantitative variables, while percentages were expressed or qualitative variables. The primary end point was OS, defined as the interval between the date of diagnosis (confirmed ACC pathology from resection or biopsy) with locally advanced or metastatic ACC and death due to any cause. Surviving patients were censored at the date of the last follow-up. The secondary end point was PFS, defined as the interval between the date of diagnosis with stage locally advanced or metastatic ACC and progression after first-line treatment. OS and PFS for patients initially diagnosed with local disease were calculated from progression to stage III-IVc according to mENSAT and until death or further progression. OS and PFS medians and rates were analyzed using the Kaplan–Meier method and compared between subgroups using the log-rank test. A univariate analysis was conducted to determine whether any single clinical, pathological parameter, or treatment type was significantly correlated ($P < .05$) with OS or PFS. A multivariate analysis was then conducted combining mENSAT together with GRAS parameters, incorporating mitotic index into grade (as per 2022 WHO classification), in correlation with OS and PFS, according to the previous model proposed by Libé et al [12]. A second multivariate analysis was then conducted combining treatment type, and mENSAT and GRAS parameters to determine if treatment type was independently correlated with OS or PFS. Hazard ratio (HR) and 95% CI were estimated using Cox's proportional hazards regression with the lowest risk group as the reference group. All tests were 2-sided. The statistical analysis was conducted using SPSS version 19.

Results

Population Characteristics

Between 2000 and 2020, we treated 47 patients with ACC, 40 of them with metastatic or locally advanced disease. Thirty-seven patients in whom sufficient pathological and clinical data were available for follow-up were included in this study. Twenty-four (64.9%) patients were female, and the median age of diagnosis was 47 years (range 24-76 years). Only 2 (5%) patients aged 27 and 35 were diagnosed as having hereditary syndromes, MEN1 and Lynch. Twenty-nine patients (78.4%) presented with symptomatic disease, of whom 22 (59.5%) had hyperfunctioning tumors, including 14 patients (37.9%) with Cushing's syndrome. In addition, 8 female patients (21.6%) presented with hirsutism, irregular menstruation, or skin changes (acne, seborrhea) due to hyperandrogenism, and in 6 of these patients elevated levels of testosterone, androstenedione, or dehydroepiandrosterone sulfate were found to be part of the ACC biochemical diagnosis.

Twelve patients (32.4%) who were initially diagnosed with stage II-III local disease, underwent total resection and received adjuvant mitotane, yet had disease progression with a median disease-free survival time of 18.3 (SD 5.9-30.7) months. Further patient characteristics, including histopathological grading, Ki 67 proliferation index, Weiss histopathological score, tumor size, and subdivision according mENSAT staging upon diagnosis with locally advanced or metastatic disease, are summarized in Table 1.

Treatment

Of 37 patients, 22 (59.5%) underwent complete resection during diagnosis with locally advanced or metastatic disease, of whom 15 (40.7%) achieved R0 status and including 10 (27.0 %) patients which had additional radiotherapy or metastasectomy for oligometastatic disease to achieve R0 status. Eight (21.6%) patients were initially treated with mitotane monotherapy, of them 6 patients achieving therapeutic blood levels (>14 mg/L) with good compliance and

Table 1. Clinical and pathological characteristics of 37 patients with locally advanced or metastatic adrenocortical carcinoma

Parameter	Number of patients (%)	Tumor size (cm), mean (range)
Gender		
Female	24 (64.9)	
Male	13 (35.1)	
Ethnic origin		
Ashkenazi-Jewish	28 (75.7)	
Born in former Soviet Union	13 (35.2)	
Born in Israel or Europe	15 (40.5)	
Non-Ashkenazi Jewish	6 (16.2)	
Arab-Muslim	3 (8.1)	
Age of onset		
<50	20 (54.1)	
≥50	17 (45.9)	
Modality of diagnosis		
Symptomatic disease	29 (78.4)	
Hormone-related symptoms—Cushing syndrome	14 (37.9)	
Hormone-related symptoms—hyperandrogenism	8 (21.6)	
Tumor mass–related symptoms	7 (18.9)	
Incidental imaging findings	8 (21.6)	
R status		
R0	15 (40.5)	8.6 (4-13)
R1-R2	7 (18.9)	10.6 (8-15)
Rx	15 (40.5)	9.6 (6-27)
Histopathological subtype		
Conventional	35 (94.6)	8 (4.5-27)
Sarcomatoid	1 (2.2)	(5)
Oncocytic	1 (2.2)	(8)
Grade		
Low grade: mitotic rate ≤20 per 10 mm^2	21 (56.8)	6.0 (4.5-13)
High grade: mitotic rate >20 per 10 mm^2	16 (43.2)	9.0 (5.7-27)
Additional histopathological grading		
High risk: Weiss >6 or Ki67 ≥20	17 (45.9)	7.1 (4-13)
Low risk: Weiss ≤6 and Ki67 <20	20 (54.1)	10.3 (4-27)
mENSAT stage		
III-IVa	23 (62.2)	8.1 (4-15)
IVb	5 (13.5)	9.2 (5.7-13)
IVc	9 (24.3)	12.6 (7-27)
Organs involved at diagnosis		
Lymph nodes	29 (78.4)	
Locoregional spread	24 (64.9)	
Distant metastasis	24 (64.9)	
Liver only	7 (18.9)	
Lung only	6 (16.2)	
Multi-organ metastasis	11 (29.7)	

tolerability. All patients who received mitotane monotherapy underwent initial primary resection with an R0 result, including 6 patients (75%) who had additional upfront lung or liver metastasectomy or radiotherapy. Four patients who initially received mitotane monotherapy were subsequently treated with EDP after disease progression.

The remaining 29 patients (78.4%) were treated with EDP chemotherapy for at least 2 cycles, 24 (64.8%) in combination with mitotane; of these, only 10 (34.4%) patients achieved therapeutic levels of mitotane. Twelve patients (41.4%) treated with EDP-based chemotherapy suffered from grade 3 or higher adverse events and required dose reduction, delay of treatment, or treatment cessation; 2 patients died due to febrile neutropenia and sepsis after EDP treatment. Twenty-four patients (64.8%) were treated with subsequent chemotherapy after disease progression including 12 (32.4%) treated with gemcitabine–fluorouracil–streptozocin. Treatment and outcomes including adverse events are detailed in Table 2.

Overall Survival and Progression-free Survival

Median OS was 20 months (CI 9.5-30.5) with a 5-year survival rate of 29.7% (11 patients) and 10-year survival rate of 8.1% (3 patients). Median PFS for first-line therapy was 10 months (CI 5.2-14.7). In the univariate analysis, no single demographic characteristic, including age of onset, ethnic origin, gender, or symptomatic disease at diagnosis, was found to be associated with OS or PFS.

Patients who were initially diagnosed with local disease and had disease progression had OS and PFS similar to patients who presented with metastatic or locally advanced disease. In the metastatic or locally advanced setting, patients who underwent total resection with an R0 result, together with radiotherapy or metastasectomy for oligometastatic disease, had significantly longer OS than patients with R1-R2 or Rx (unresected disease). A median OS of 55 months (CI 21.4-88.6) was observed in the R0 group compared with 14 months (CI 9.4-18.8) for the R1-R2, Rx group (HR 3.1, CI 1.4-6.7, $P = .005$).

mENSAT classification was significantly associated with OS, with a median OS of 46 months (CI 14.3-77.7) for stage III-IVa, 11 months (CI 8.1-18.7) for stage IVb, and 8 months (CI 2.0-13.9) for stage IVc; regarding PFS, a median PFS of 12 months (CI 10.2-13.7) was observed for stage III-IVa, followed by a median PFS of 3 months (CI 0.8-5.2) for stage IVb, and a median PFS of 3 months (CI 2.0-3.9) for stage IVc.

In the multivariate analysis mENSAT in combination with either grade (mitotic index of >20 per mm^2, Ki67 >20, or Weiss >6) and R status (R1-R2) or age (>50) and hormone or tumor-related symptoms (GRAS) was significantly correlated with OS (all $P = .01$ and $P = .03$ respectively), with each parameter except symptoms significantly correlated with OS. The multivariate analysis is detailed in Table 3. Of note, the cohort included 1 case of oncocytic ACC, which was evaluated by the Lin–Weiss–Bisceglia system [13] and was included in the high-risk grading group due to a mitotic rate of 27 per 10 mm^2 and a Ki 67 proliferation index of 70.

Patients who were treated with mitotane monotherapy had significantly longer OS than patients treated with EDP-M, with a median OS of 62 months (CI 44.3-79) in the mitotane group compared with 18 months (CI 8.4-27.6), in the EDP-M group (HR 0.35, CI 0.12-0.93, $P = .049$). However, this result was attenuated and was not significant in the multivariate analysis combining treatment type together with mENSAT and R status. PFS was similar in patients treated with first-line

Table 2. Treatment and outcomes of 37 patients with locally advanced or metastatic adrenocortical carcinoma

First-line treatment	Mitotane monotherapy	EDP (n = 29)	*P* value
Total patients	8	(n = 8)	
Upfront metastasectomy or radiotherapy for metastasis			
Yes	6 (75)	4 (13.8)	
Metastasectomy	5 (62.5)	2 (6.9)	
Radiotherapy	1 (12.5)	2 (6.9)	
None	2 (25)	25 (86.2)	
Mitotane levels			
≥14 mg/dL	6 (75)	10 (34.4)	.39
<14 mg/dL	2 (25)	14 (48.3)	
No mitotane	NA	5 (17.3)	
Adverse events			
All	0	12 (41.3)	.09
Grade 3	NA	7 (24.1)	
Grade 4		3 (10.3)	
Grade 5		2 (6.9)	
Second-line treatment			
No subsequent therapy	2 (25)	9 (31)	
Metastasectomy or radiotherapy	2 (25)	3 (10.3)	
	4 (50)	NA	
EDP	0	12 (41.3)	
Gemcitabine–fluorouracil–streptozocin			
Progression-free survival, months	12 (5.1-18.9)	9 (CI 4.8-13.2)	.27[a]
Overall survival, months	62 (44.3-79)	18 (8.4-27.6)	.049[a]

Data are presented a n (%) or median (95% CI).
Abbreviation: EDP, etoposide–doxorubicin–cisplatin.
[a]*P* value presented for univariate analysis. In the multivariate analysis controlling for mENSAT and R status resulted in a *P* value of 0.27 for progression-free survival and a *P* value of 0.40 for overall survival.

mitotane monotherapy compared with EDP-M, with a median PFS of 12 months (CI 5.1-18.9) and 9 months (CI 4.8-13.2) respectively (HR 1.64, CI 0.68-3.97, *P* = .27). The Kaplan–Meier survival estimates for OS and PFS according to treatment type are presented in Fig. 1.

Discussion

In the present study, we performed a detailed analysis of 37 consecutive patients with locally advanced or metastatic ACC treated in our center over the past 20 years. The median OS was 20 months (CI 9.5-30.5) and was significantly correlated with mENSAT and R status. This is similar to previous studies utilizing mENSAT and R status as prognostic factors [7, 10, 11, 14] and a recent larger cohort [15]. A considerable percentage (27%) of patients in our cohort underwent primary resection followed by upfront radiotherapy or metastasectomy for oligometastatic disease to achieve R0 status, emphasizing the importance of these treatments in locally advanced or oligometastatic disease to achieve a disease-free interval and improve prognosis [16, 17]. A recent retrospective analysis by Srougi et al, conducted on 339 patients with metastatic ACC and controlling for several prognostic factors such as mENSAT, found that patients who underwent cytoreductive surgery had significantly prolonged OS compared with patients who did not undergo surgical procedures. This included a considerable percentage of patients in the cytoreductive group who underwent metastasis treatment with radiotherapy or metastasectomy and is probably a reflection of the overall extent and control of the disease [18].

Patients receiving mitotane monotherapy had a significantly longer OS of 62 months (CI 44.3-79) than patients treated with first-line EDP-M. These results are similar to a study published by Megerle et al showing that patients with therapeutic mitotane levels, Ki67 <20%, and low-grade tumor burden had a median OS of more than 2 years [6]; several other studies have provided evidence supporting mitotane treatment for locally advanced resectable disease [19, 20]. While our study was limited by a relatively small sample size, mitotane monotherapy did not show any significant advantage in PFS or in the multivariate OS analysis. Hence, it may be assumed that the improved prognosis was confounded by the initial better disease status of the patients receiving mitotane monotherapy at diagnosis, including initial R0 status and radiotherapy or metastasectomy for oligometastatic disease. Similarly, a large retrospective analysis of 207 ACC cases conducted by Postlewait et al demonstrated improved OS for patients receiving mitotane (58.9 vs 31.7 months, *P* = .01), yet this association did not persist after excluding patients who received additional radiotherapy or in the multivariate analysis controlling for independently significant prognostic factors of R status, stage, and additional chemotherapy [21]. The improved OS observed in the mitotane monotherapy group might also be because only 34% of patients in the EDP group achieved therapeutic levels of mitotane; thus, we were not able to control for the relative added benefit of mitotane treatment in the latter group. The addition of mitotane treatment to

Table 3. Multivariate analysis of prognostic factors for 37 patients with locally advanced or metastatic adrenocortical carcinoma

	Model 1: mENSAT, grade, and R status. *P* value all = .01			Model 2: mENSAT, age, and symptomatic disease. *P* value all = .03		
Parameter	**Hazard ratio**	**CI 95%**	***P* value**	**Hazard ratio**	**CI 95%**	***P* value**
mENSAT						
III-IVa	1	1		1	1	
IVb	16.5	1.6-165.8	.02	10.5	1.1-98.9	.04
IVc	9.8	1.2-83.3	.04	8.0	1.0-683	.05
Histopathological grade						
Weiss ≤6, Ki 67 <20, and mitotic index ≤20 per 10 mm^2	1	1		NA	NA	NA
Weiss >6, Ki 67 ≥20, or mitotic rate >20 per 10 mm^2[a]	2.3	1.1-5.3	.05			
R status						
R0	1	1		NA	NA	NA
R1-R2, Rx	2.8	1.2-7.0	.02			
Age						
<50	NA	NA	NA	1	1	
≥50				2.4	1.1-5.5	.03
Symptomatic disease						
No	NA	NA	NA	1	1	
Yes				0.6	0.2 -1.7	.36

Model 1, modified European Network for the study of Adrenal Tumors (mENSAT) with grade and R status. Model 2, mENSAT with age and symptomatic disease at diagnosis.
[a]The cohort included 1 case of oncocytic ACC, which was evaluated by Lin–Weiss–Bisceglia system and was included in the high-risk grading group due to a mitotic rate of 27 per 10 mm^2 and a Ki 67 proliferation index of 70.

combination chemotherapy has not been previously tested in prospective randomized controlled trails. Nevertheless, only one-third of patients receiving combination therapy achieve therapeutic levels of mitotane; therefore, its benefit in combination therapy remains unclear [5].

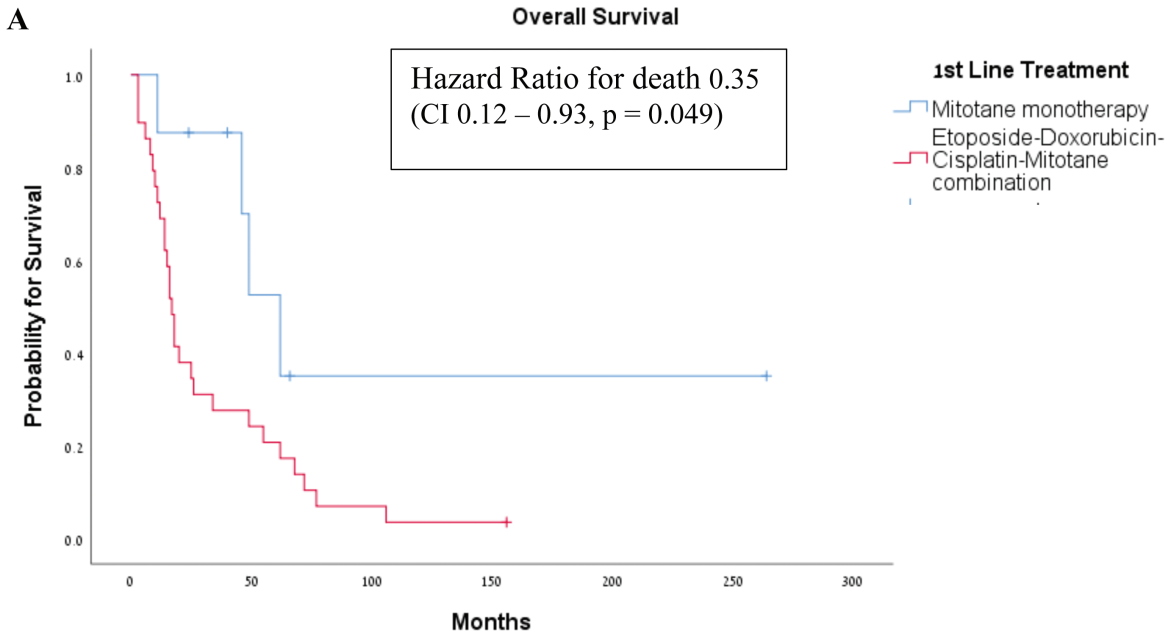
Similar to the FIRM-ACT trial [5], 41.4% of patients in our cohort who were treated with EDP-based chemotherapy suffered from grade 3 or higher adverse events and 2 patients died because of treatment toxicity. These results suggest that patients with low tumor burden and low grade who achieve R0, including radiotherapy or metastasectomy, might benefit from mitotane monotherapy, avoiding the toxicity of EDP. A prospective trial for a subgroup of patients with R0 oligometastatic disease comparing mitotane monotherapy with EDP-M will most probably give further insight into these findings. In addition, a better understanding of the molecular characterization of ACC may help guide therapy with mitotane, EDP, immunotherapy, or other targeted treatments [22]

The combination of mENSAT and GRAS parameters as a significant prognostic predictor tool [12] was validated in our cohort, apart from symptoms at diagnosis, probably owing to a small sample size and binomial design. Of note, 4 patients with low-grade tumors according to mitotic index were included in the high-risk histopathological grading group in the GRAS multivariate analysis, due to a Ki 67 proliferation index of more than 50 each and in accordance with the work of Libé et al [12]. Nevertheless, further omission of these patients from the high-risk histopathological grading group and reanalysis did not alter the significance of the multivariate analysis.

We did not find any demographic, pathological, or clinical parameters distinct to the longer surviving patients. Hence the explanation for improved prognosis in some patients is most likely found in an individual unique molecular pathology characterization. Indeed, a recent study further stratified prognosis by integrating ENSAT and GRAS with distinct molecular signatures including the Wnt/beta–catenin pathway and tumor suppressor pathways and high methylation patterns [23]. While these molecular changes are not routinely available on gene panels, a recent genetic analysis of 364 cases of ACC found a high prevalence of potentially actionable genomic alterations, including alterations in DNA mismatch repair pathways, pointing to future treatment options and perhaps improved prognosis for a subset of patients [24].

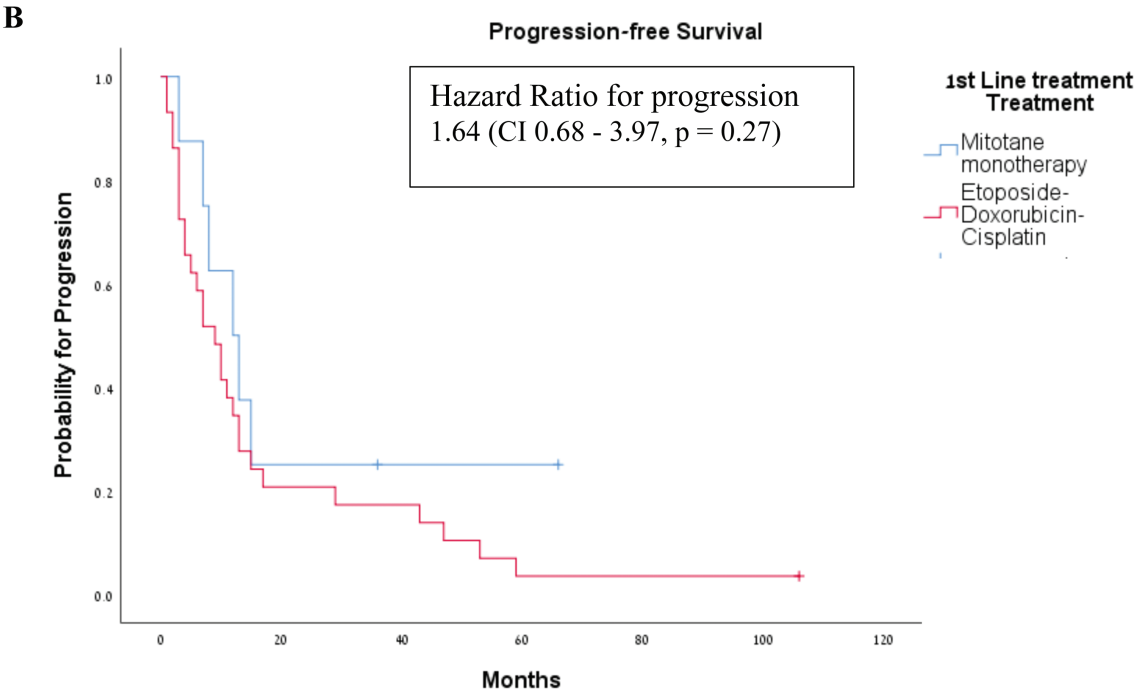
Of note, 8 of 24 female patients included in this study were diagnosed due to symptoms resulting from hyperandrogenism, and in 6 of these patients levels of testosterone, androstenedione, or dehydroepiandrosterone sulfate were found to be increased as part of the ACC biochemical diagnosis. This result emphasizes the importance of a thorough endocrine and imaging workup in cases of women presenting with irregular menstruation or hirsutism, as these cases might be misclassified as polycystic ovary syndrome when an underlying adrenal cancer is present.

A total of 13 (35.1%) of our patients were born in the former Soviet Union and immigrated to Israel at a later stage, which is 3 times greater than their proportion in the general Israeli population [25]. Our literature search (in English and in Russian languages) did not reveal any reported predisposition for an increased prevalence of ACC in the corresponding



No. at Risk

Mitotane monotherapy	8	6	3	1	1	1	1	1	1	1	1	0	0
Chemotherapy therapy	29	10	6	3	2	1	1	0	0	0	0	0	0



No. at Risk

Mitotane monotherapy	8	5	2	2	1	1	1	0	0	0	0	0	0
Chemotherapy therapy	29	14	7	6	6	3	1	1	1	1	1	0	0

Figure 1. Kaplan–Meier of overall survival (A) and progression-free survival (B) for 8 patients treated with mitotane monotherapy compared to 29 patients treated with etoposide-doxorubicin–cisplatin–mitotane chemotherapy (combination therapy) for advanced adrenocortical carcinoma.

countries. Among patients from the former Soviet Union in our cohort, only 2 patients had a history of smoking, and none had a history of other known exogenic exposures associated with ACC [26]. While only 4 patients in our study had known hereditary cancer syndromes or a family history of malignancy, we cannot rule out a possible founder effect, which may have led to an increase in ACC prevalence in patients born in the former Soviet Union. Some germline *TP53* mutations are known to cause attenuated Li–Fraumeni syndrome and may contribute to a relative increase in ACC prevalence in some populations, as can be seen in Brazil [27, 28]. However, most of these hereditary cases are of pediatric

patients and do not explain the high prevalence of adult ACC cases in patients from the former Soviet Union. Further somatic and germline genome analysis of these patients might reveal a mutual haplotype and perhaps a more unique founder mutation.

Conclusion

In our cohort of 37 patients with locally advanced and metastatic ACC, the combination of mENSAT and GRAS parameters was validated to significantly stratify the disease and treatment-related prognosis. Patients achieving R0 status after primary resection and radiotherapy or metastasectomy for oligometastatic disease had a better prognosis and might benefit from mitotane monotherapy due to its safety profile. A future prospective trial is needed for this subpopulation. ACC is a rare disease and, despite the relatively small size of our sample, we believe that long-term experience, such as ours, analyzing prognostic factors of disease- and treatment-related outcomes is important and relevant for future clinical decision making

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Disclosures

All authors have nothing do disclose.

Data Availability

Datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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