ORIGINAL ARTICLE

Prognostic factors in adrenocortical carcinoma: data from a large Polish series

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KEY WORDS

adrenocortical carcinoma, Ki67, mitotane, prognostic factors

ABSTRACT

INTRODUCTION Adrenocortical carcinoma (ACC) is a rare malignancy, associated with poor outcome and few therapeutic options. Despite increasing attention, the knowledge about the clinical course and treatment of these tumors is limited.

OBJECTIVES Survival rates in ACC are still low and the percentage of relapse is high. Thus, it is crucial to identify the prognostic factors of overall survival (OS) and recurrence-free survival (RFS).

PATIENTS AND METHODS This was a retrospective analysis of 66 patients diagnosed with ACC between 2002 and 2015.

RESULTS The median OS was 43.5 months, 78.19 months for stage I + II, 22.95 months for stage III, and 19.54 months for stage IV ACC. Older age, stage IV ACC, margin status R2, and no mitotane treatment were associated with poor OS. Low Ki67 and mitotic indices were related to improved OS in a univariate analysis. The median RFS was 101.1 months. Disease recurrence after potentially curative surgery was reported in 1 patient (25%) with stage I, 12 patients (46%) with stage II, and 9 patients (45%) with stage III ACC. Male sex and no mitotane treatment were associated with a reduced RFS in a multivariate analysis and higher Ki67 and mitotic indices in the univariate analysis.

CONCLUSIONS Ki67 and mitotic indices should be considered as prognostic factors when planning the adjuvant treatment of ACC. Mitotane treatment may be independently associated with better outcomes regardless of the tumor stage.

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INTRODUCTION Adrenocortical carcinoma (ACC) is a malignant tumor, associated with poor prognosis. Although this type of cancer is generally rare (0.5–2 cases/million/year),[1] it was the most common finding after surgery (25.2%) in a series of 139 cases of adrenal tumors greater than 5 cm in size.[2] The 5-year survival rates in this aggressive cancer range between 16% and 44%,[3] while the median overall survival (OS) varies from 32 to 77 months.[1,4-7] Due to poor long-term outcome in patients with ACC, numerous retrospective studies have been conducted to identify prognostic factors.

Prognosis of ACC is dependent on the tumor stage at presentation. Although the survival rates in advanced disease are still low, more recent studies suggest that prognosis in early stages is improving.[3,5] The European Network for the Study of Adrenal Tumors (ENSAT) staging system has a better prognostic stratification than the International Union Against Cancer classification; thus, it is widely used in contemporary studies.[8] Stage I is defined as a tumor size of 5 cm or lower; stage II, as a tumor size of more than 5 cm; stage III, any tumor size plus one of the following: tumor infiltration into surrounding organs, such as the kidney, pancreas, spleen, and liver or large blood vessels (renal vein or vena cava); and, finally, stage IV is defined as distant metastases.[8]

TABLE 1 Baseline characteristics of the study group (n = 66)

Parameter		Nonmissing observations	Value
Age, y, mean (SD)		66	51.4 (14)
Sex, female/male, n		66	43/23
Hormonal activity, n (%)		56	33 (58.9)
Tumor size, mm, mean (SD)		63	114.25 (50.66)
ENSAT stage, n (%)	I	4	4 (6.1)
	II	26	26 (39.4)
	III	25	25 (37.9)
	IV	11	11 (16.7)
Capsular invasion with crossing its border, n (%)		62	26 (41.9)
Capsular invasion without crossing its border, n (%)		62	17 (27.4)
Invasion in capsular vessels, n (%)		62	28 (45.2)
Tumor infiltration into surrounding tissue, n (%)		62	22 (35.5)
Tumor invasion in adjacent organ, n (%)		62	16 (25.8)
Presence of necrosis, n (%)		50	40 (80.0)
Necrosis, %, mean (SD)		26	43 (19.55)
Necrosis ≥50%, n (%)		26	13 (50.0)
Venous tumor thrombus in vena or renal vein, n (%)		61	8 (13.1)
Ki67 index, %, mean (SD)		56	23.55 (21.5)
Ki67 index ≥10%, n (%)		56	38 (67.9)
Mitotic index per 50 HPF, mean (SD)		38	37.25 (40.16)
Mitotic index per 50 HPF ≥20, n (%)		38	19 (50.0)
Mitotane treatment, n (%)		64	57 (89.1)
Duration of mitotane treatment, mo, mean (SD)		49	31.2 (24)
Margin status R0, n (%)		50	50 (76.9)
Margin status R1, n (%)		3	3 (4.6)
Margin status R2, n (%)		7	7 (10.8)
Death, n (%)		66	34 (51.5)
Recurrent disease, n (%)		41	20 (48.8)

Abbreviations: ENSAT, European Network for the Study of Adrenal Tumors; R0, uninvolved; HPF, high power field; R1, microscopically involved; R2, macroscopically involved

In a study by Ayala-Ramirez et al[6] and Fassnacht et al,[8] the 5-year OS rates were 66% and 80%, respectively, for stage I; 58% and 61%, respectively, for stage II; 24% and 50%, respectively, for stage III; and 0% and 13%, respectively, for stage IV disease. The median OS was 289.2, 73, 41.6, and 10.7 months for stages I, II, III and IV, respectively.[6]

The 5-year survival after surgery was reported to be 46%, 21%, and 10% for uninvolved (R0), microscopically involved (R1), and macroscopically involved (R2) margins, respectively.[9]

The Ki67 proliferation index was found to play a major role in predicting recurrence in patients with stages I to III after complete resection (R0).[10] Ki67 was also found to be a prognostic factor of OS in patients with stage IV disease.[11]

Data on the association between hormonal activity and poorer prognosis are inconsistent. One of the studies did not identify it as a prognostic factor,[12] while other authors reported that patients with cortisol-secreting tumors had shorter recurrence-free survival (RFS),[13] OS,[14] or both disease-free survival and OS.[15] Another factor associated with poor survival is older age.[7,14]

The adjuvant mitotane treatment may improve survival in stages I to III of ACC;[12] nevertheless, such treatment is not always recommended in early stages.[16] Due to the toxicity of mitotane, discussions are ongoing which patients will benefit from this treatment. The clinical practice guidelines of the European Society for Medical Oncology (ESMO) stratify a risk for recurrence as "low risk" in patients with complete resection (R0), stages I and II, and Ki67 of less than 10%.[16] Patients are defined as "high-risk" in the case of uninvolved margins (R0) after surgery, together with stage III disease or Ki67 of 10% or higher. Although according to the ESMO the mitotane treatment is not mandatory in low-risk patients, they can suffer from recurrence,[17] and even in stages I and II of the disease, the percentage of relapse is high and reaches 27% and 46%, respectively.[14]

"High-grade ACC", defined as a mitotic count of at least 20/50 high-power fields (HPF), was associated with poorer prognosis than "low-grade ACC" (<20/50 HPF).[18] In another study, together with the mitotic rate of more than 5/50 HPF, several features were reported to be useful in outcome prediction, namely, distant metastasis at initial presentation,[5,19] tumor invasion of the vessels, tumor capsule, or adjacent organs, and tumor necrosis.[19] Disease-free survival was different for patients with 1 to 2, 3 to 4, and more than 4 features (84%, 37%, and 9%, respectively). Only the mitotic rate exceeding 5/50 HPF was found to be a prognostic factor in a multivariate analysis in patients without distant metastasis at diagnosis.[19]

Since the recurrence of the disease is still very common even after complete resection and in the lower stages of the disease, there is a need to identify prognostic factors that would help identify patients requiring a more aggressive treatment. Therefore, the aim of the study was to identify the prognostic factors of RFS and OS in Polish patients with ACC. The second objective was to verify treatment results in the studied population.

PATIENTS AND METHODS

We included a total of 66 adult patients enrolled retrospectively from the Polish Registry of Adrenocortical Carcinoma. The patients were diagnosed with ACC between 2002 and 2015 in 1 of the 3 participating endocrinology departments in Warsaw, Poland. The baseline characteristics of the patients are presented in TABLE 1. Of the 66 patients, 61 underwent an open adrenalectomy in 1 of the 2 surgical departments. The margin status was evaluated based on surgical and pathological reports. Five patients with stage III disease had an inoperable tumor due to its local invasion into surrounding vital organs. The functional status of ACC was evaluated with standard hormonal tests. Recurrent disease was defined as a new lesion confirmed by imaging tests. The RFS was determined as time from surgery to the date of first

evidence of relapse on imaging tests and was calculated only for patients with stages I to III after complete resection (R0) (intention to cure). The follow-up lasted until June 2016. To identify the prognostic factors of OS and RFS, a number of clinical and histological features were investigated: age, sex, ENSAT stage,[10] hormonal activity, tumor size, margin status, mitotic index, and Ki67 index. The study was approved by the ethics committee of the Centre of Postgraduate Medical Education in Warsaw.

Statistical analysis Percentages and means with SD were used to describe the data. The Kaplan–Meier test was used to estimate the probability of OS and RFS. Survival curves were compared with a log-rank test. Univariate and multivariate proportional-hazard Cox regression models were used to determine the hazard ratios (HRs) and 95% confidence intervals (CIs). To ensure the estimability of point estimates in the multivariate analysis of OS, only variables with more than 50 nonmissing observations and a *P* value of less than 0.1 in the univariate analysis were included. In the analysis of RFS, the minimum required number of nonmissing observations was set at 30. Forward stepwise selection at a significance level of 0.1 was used for variable selection in the multivariate models. A *P* value of less than 0.05 was considered significant. All tests were 2-sided. The analyses were performed with Stata software, version 13.1 (Stata Corporation, College Station, Texas, United States).

RESULTS The study included 43 women and 23 men at a mean (SD) age of 49 (14.2) years and 55.4 (12.4) years, respectively. Patients aged 50 years or older more often had stages III and IV disease. Of all tumors, 58.9% were hormonally active, mainly with overproduction of cortisol (93%). Only 2 patients had hyperandrogenism alone. One woman and one man had hyperestrogenism coexisting with excessive cortisol levels. Mitotane was administered in 53 patients after surgery as an adjuvant treatment; 4 patients with an inoperable tumor received mitotane as a palliative treatment; 7 patients (3 with stage II and 4 with stage III ACC) did not receive mitotane treatment or any other therapy (1 patient in this group had an inoperable tumor). For the 2 remaining patients (out of 66), data were missing. The mean (SD) time of mitotane treatment was 31.2 (24) months. No patient received radiotherapy; 4 patients who received mitotane after surgery (3 patients with stage IV and 1 patient with stage III) were also treated with chemotherapy.

Overall survival The median OS was 78.19 months for stages I + II, 22.95 months for stage III, 19.54 months for stage IV, and 43.5 months for all the ENSAT stages. The overall 5-year survival was 75%, 73%, 27%, and 0% for stages I, II, III, and IV, respectively. The 5-year survival rate for stage III reached 32% when only operable tumors were included. The 2-year and 5-year OS for all stages was 66% and 46%, respectively. Death was reported for 85.7% of the patients who did not receive mitotane and 49.1% of the patients who received mitotane; the 5-year survival rate was 28.6% and 48.2%, respectively.

The results of the univariate and multivariate analyses of prognostic factors of OS are presented in TABLE 2. In the univariate analysis, older age, advanced stage (FIGURE 1), higher Ki67 index (FIGURE 2), higher mitotic index, and margin status R2 were associated with a decreased OS. Age as a continuous variable was independently associated with OS in the multivariate analysis (HR, 1.09; $P = 0.001$). Patients aged 50 years or older had a higher risk of death. The 5-year survival rate for patients younger than 50 years old was 66.9% (95% CI, 44.2–82.1), compared with 29.3% (95% CI, 14.1–46.3) for patients aged 50 years or older ($P = 0.004$). In the multivariate analysis (of >50 nonmissing observations), other factors remained independently associated with poorer prognosis, such as stage IV (HR, 6.65; $P = 0.01$) and margin status R2 (HR, 4.3; $P = 0.03$). Patients treated with mitotane had improved OS both in the univariate (HR, 0.46; $P = 0.09$) and multivariate analyses (HR, 0.29; $P = 0.04$). These results were observed even after excluding 4 patients who received both mitotane treatment and chemotherapy. Interestingly, there was no difference in OS between stages I + II and stage III (HR, 1.62; $P = 0.4$) in the multivariate analysis.

In the univariate analysis, HR for death was 1.03 per 1% increase in the Ki67 index ($P = 0.003$) and 3.19 for the Ki67 index of 10% or higher ($P = 0.01$). The 5-year survival of patients with a Ki67 index of less than 10% differed from that in patients with a Ki67 index of 10% or higher (66.8% vs 36.2%, respectively, $P = 0.01$). Although, the Ki67 index was significant in the univariate analysis, in the forward stepwise analysis for variable selection in the multivariate model it did not reach the 0.1-significance level, thus it was not included.

In the univariate analysis, HR for death was 7.91 ($P = 0.002$) for a mitotic index of 20/50 HPF or higher. The 5-year survival rate was 79.8% for a mitotic index of 20/50 HPF or higher compared with 36.3% for a mitotic index of less than 20/50 HPF ($P < 0.001$). However, because the multivariate analysis was performed for more than 50 nonmissing observations, this prognostic factor was not included.

Recurrence-free survival Twenty patients suffered from disease recurrence after potentially curative surgery (R0): 1 patient (25%) with stage I, 12 patients (46%) with stage II, and 9 patients (45%) with stage III ACC. The median probability of RFS was 101.1 months.

The results of the univariate and multivariate analyses of the prognostic factors of RFS after curative surgery are presented in TABLE 3. In the univariate analysis, male sex, higher Ki67 index as

TABLE 2 Results of univariate and multivariate analyses (Cox regression) of overall survival

Variable	N = 66	N+	Univariate analysis			Multivariate analysis		
			HR	95% CI	*P* value	HR	95% CI	*P* value
Age, y[a]	66		1.06	1.03–1.09	<0.001	1.09	1.03–1.15	0.001
Male sex	66	23	1.83	0.91–3.68	0.09			
Hormonal activity	56	33	1.85	0.82–4.18	0.14			
Tumor size[a]	63		1.01	1.00–1.01	0.12			
Tumor size ≥10 cm	63	37	1.25	0.61–2.57	0.54			
ENSAT stage	66							
ENSAT stage I + II		30	1.00			1.00		
ENSAT stage III		25	3.99	1.78–8.94	0.001	1.62	0.53–4.99	0.40
ENSAT stage IV		11	7.31	2.60–0.52	<0.001	6.65	1.45–30.1	0.01
Ki67 index[a]	56		1.03	1.01–1.04	0.003			
Ki67 index ≥10%	56	38	3.19	1.28–7.97	0.01			
Mitotic index per 50 HPF[a]	38		1.02	1.01–1.03	<0.001			
Mitotic index per 50 HPF ≥20	38	19	7.91	2.15–9.11	0.002			
Margin status R0		50	1.00			1.00		
Margin status R1		3	0.88	0.20–3.79	0.86	2.08	0.39–10.9	0.39
Margin status R2		7	4.26	1.65–1.01	0.003	4.30	1.16–15.9	0.03
Mitotane treatment	56	5	0.46	0.19–1.12	0.09	0.29	0.09–0.92	0.04
Inoperable tumor		5	40.88	10.1–165	<0.001			

a Continuous variable

Only variables with >50 nonmissing observations and $P < 0.1$ in the univariate analysis were included in the multivariate analysis. Forward stepwise selection at 0.1 significance level was used for variable selection in the multivariate model. "Inoperable tumor" was not included in the multivariate analysis as it may overlap with stage.

Abbreviations: CI, confidence interval; HR, hazard ratio; N+, number of patients who met the given criteria; others, see TABLE 1

a continuous variable, higher mitotic index, and no mitotane treatment were associated with decreased RFS. In the multivariate analysis (of >30 nonmissing observations), only male sex was associated with reduced RFS (HR, 4.44; $P = 0.03$), while mitotane treatment was associated with prolonged RFS (HR, 0.15; $P = 0.01$). HR for disease recurrence after curative surgery was 1.03 per 1% increase in the Ki67 index, but it did not reach significance. The Ki67 index as a categorized variable was not associated with longer RFS (FIGURE 3), probably due to the small number of events. Interestingly, patients with stage III ACC had the same risk for recurrence as patients with stage I or II (HR, 1.62; $P = 0.30$).

Patients defined as "high-risk" according to the ESMO[16] were not found to be at higher risk of disease relapse (HR, 2.02; $P = 0.39$).

DISCUSSION The present study is the largest analysis of a cohort of Polish patients with ACC, in which numerous clinical and histopathologic prognostic factors as well as treatment results were analyzed. The Ki67 index was associated with reduced OS (as a continuous and categorized variable) and RFS (as a continuous variable) in the univariate analysis. These results confirm recently published data showing that Ki67 is the major prognostic factor of OS and RFS.[10] In our series the Ki67 index was not included in the multivariate model of OS, as it did not reach the 0.1 significance level in the forward stepwise selection. As for the multivariate analysis of RFS, Ki67 did not reach significance (HR, 1.03; $P = 0.1$), probably due to the small number of events. There was a marked difference in the 5-year survival rates: 66.8% for Ki67 <10% vs 36.2% for Ki67 ≥10% ($P = 0.01$). The mitotic index was also reported to be useful in outcome prediction.[19] In our series the index was identified as a prognostic factor of OS in the univariate analysis, and there was a notable difference in the 5-year survival rates (79.8% for the mitotic index <20/50 HPF vs 36.3% for the mitotic index ≥20/50 HPF, $P = 0.001$). However, too many missing observations and too small a number of events made it impossible to include this factor in the multivariate analysis. The higher mitotic index was strongly associated with decreased RFS in the univariate analysis (TABLE 3), and the HR for death reached 4.79 ($P = 0.03$) for the mitotic index of 20/50 HPF or higher. There was significant difference in 2-year RFS rates: 93.3% and 66.7% for the mitotic index of less than 20/50 HPF and of 20/50 HPF or higher ($P = 0.02$), respectively. However, due to more than 30 missing observations this factor was not included in the multivariate analysis. As in the case of the lower Ki67, there was a clear tendency for improved OS and RFS in the case of the lower mitotic index. Both the Ki67 and

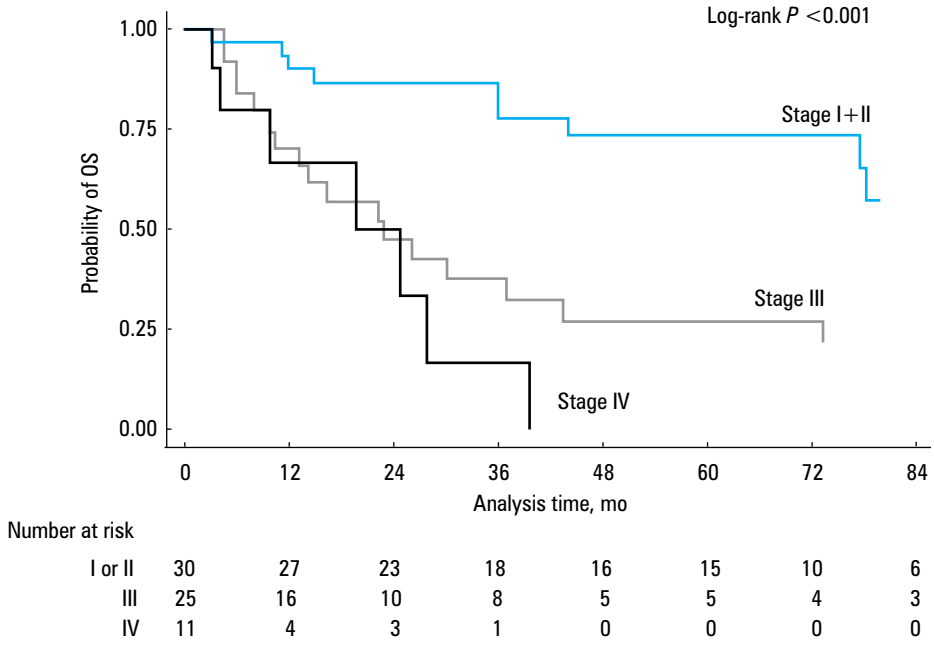

FIGURE 1 Survival curves showing the effect of the European Network for the Study of Adrenal Tumors stage on overall survival (OS)

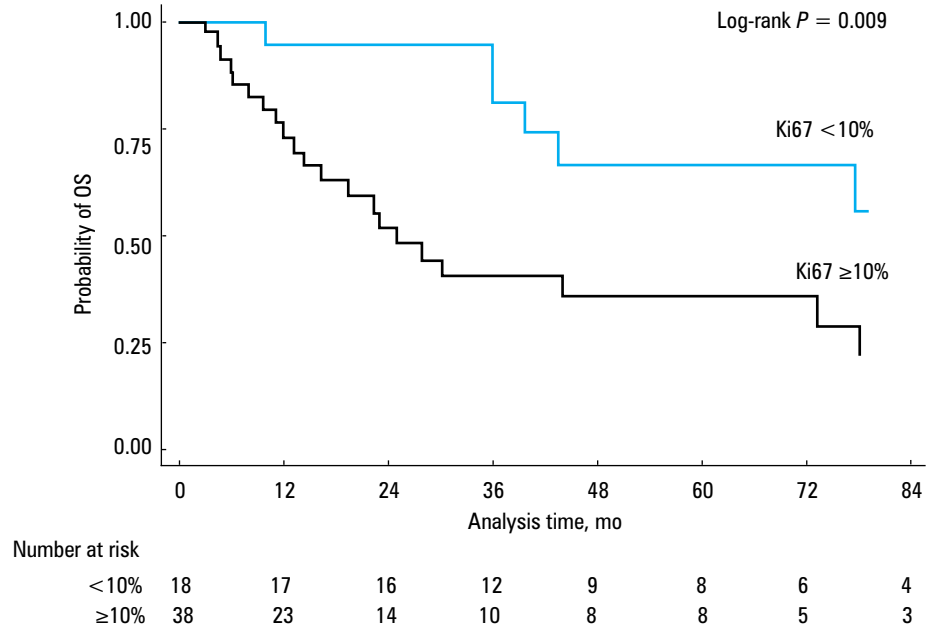

FIGURE 2 Survival curves showing the effect of the Ki67 index on overall survival (OS)

mitotic indices should be an obligatory part of every histopathologic report of ACC as they may have strong prognostic value.

In the present study, the median probability of OS was 43.5 months and the 5-year OS was 46%, which is comparable to other reports.[1,3,4,6,7] However, the authors of one of the latest studies showed that the 5-year survival rate can reach over 90% when patients with stage II are treated with mitotane and followed prospectively by specialized centers.[3] In our cohort, 5-year OS for stage II ACC reached 73%, which is better than in previous series that reported a range from 58% to 61%.[6,8] Interestingly, despite the noticeable difference in the 5-year survival rates between stages I + II and stage III (73.2% vs 27%, respectively, P <0.001), stage III was not associated with worse OS in the multivariate analysis (HR 0.73, P = 0.68) probably due to the small size of our cohort. Only for stage IV (metastasis at initial presentation), OS was significantly decreased. As for RFS, there was no significant difference in the 2-year survival rate between stages I + II and III (58% and 84.7%, respectively, P = 0.30), and the ENSAT stage was not found to be a prognostic factor of RFS in the univariate analysis. These results, again, may be related to the small size of our cohort or the fact that other factors may have a greater influence on OS and RFS than stage (eg, Ki67 or mitotane treatment). Such a good outcome in stage II in our cohort (5-year survival rate of 73%) may be related to the fact that 88% of patients with stage II received adjuvant mitotane treatment after a potentially curative surgery (R0). The results of the present study show that mitotane treatment may be associated with

TABLE 3 Results of univariate and multivariate analyses (Cox regression) of recurrence-free survival

Variable	N = 41	N+	Univariate analysis		Multivariate analysis			
			HR	95% CI		95% CI	HR	95% CI
Age, y	41		1.03	0.99–1.07	0.12			
Male sex	41	13	4.03	1.48–11	0.01	4.44	1.12–7.54	0.03
Hormonal activity	34	16	1.53	0.52–4.55	0.44			
Tumor size[a]	39		1.00	0.99–1.01	0.51			
Tumor size ≥100 mm	39	18	1.27	0.46–3.48	0.64			
ENSAT stage	41							
ENSAT stage I or II		28	1.00					
ENSAT stage III		13	1.62	0.65–4.08	0.30			
Ki67 index[a]	c		1.03	1.00–1.06	0.03	1.03	1.00–1.06	0.1
Ki67 index ≥10%	34	20	2.09	0.64–6.83	0.22			
Mitotic index per 50 HPF[a]	26		1.05	1.01–1.09	0.01			
Mitotic index per 50 HPF ≥20	26	9	4.79	1.13–20.38	0.03			
Mitotane treatment	41	36	0.34	0.12–0.96	0.04	0.15	0.04–0.56	0.01

a Continuous variable

Only variables with >30 nonmissing observations and P <0.1 in the univariate analysis were included in the multivariate analysis. Forward stepwise selection at 0.1 significance level was used for variable selection in the multivariate model.

Abbreviations: see TABLES 1 and 2

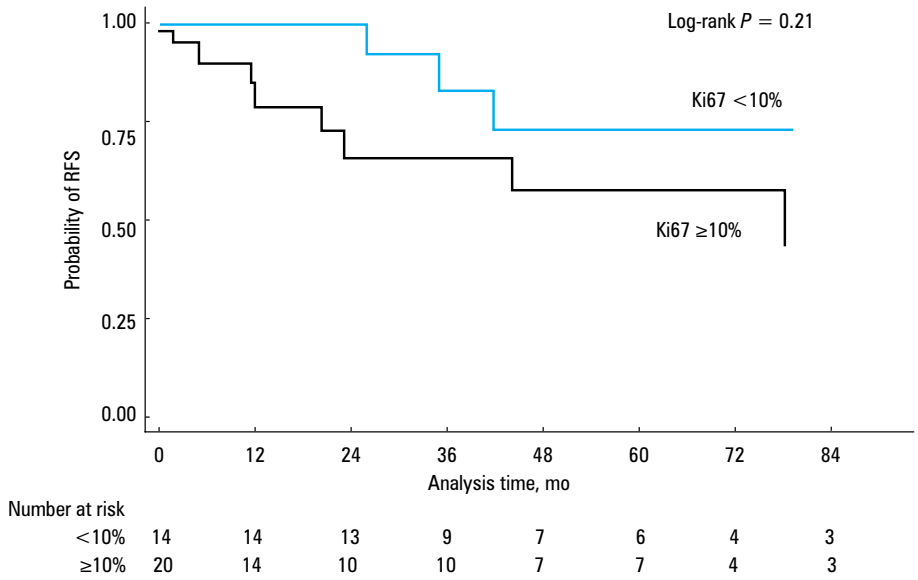

FIGURE 3 Survival curves showing the effect of Ki67 index on recurrence-free survival (RFS)

prolonged OS and RFS in patients with ACC, regardless of the tumor stage. These findings are consistent with previous reports.[13,20-22] However, in our study, after potentially curative surgery only 6 patients were not treated with mitotane (vs 53 patients who received this treatment). Despite the fact that the percentage of relapse is high (27% and 46% for stage I and II, respectively),[14] and numerous reports show that mitotane may improve outcome in stages I and II,[3,13] this treatment is not mandatory in early stages of ACC.[16] This is probably because those results have not been confirmed in randomized trials. There has been only one report recently suggesting that mitotane treatment is associated with decreased OS and RFS in the univariate analysis (Cox proportional hazards analysis), but these results were no longer observed in the multivariate analysis.[23] However, this was a retrospective analysis, which used the TNM staging[24] instead of the ENSAT staging system and the patient selection for treatment was biased. In patients who received mitotane, the authors reported more advanced stage, more hormonally active tumors, more adjuvant chemotherapy and/or radiotherapy (factors which are per se associated with worse prognosis), compared with patients not receiving mitotane treatment.[23] Hopefully,

data from the first randomized trial (ADIUVO) on evaluating mitotane in the treatment of stages I to III ACC will soon be published, and mitotane may finally find its way to routine clinical practice. Based on our long experience in the management of ACC,[17,20,25-27] we recommend mitotane in every patient with ACC who is tolerant to this type of treatment.

In line with our findings, other studies also described older age[7,14] as a prognostic factor of worse survival. A recent report proposed a modification of the ENSAT staging system that would include patient age (>55 years of age).[28] In our study, patients aged 50 years or older had more advanced stage of the disease, which may indicate a delayed diagnosis in older patients not related to the functional status of ACC (there was no difference between both age groups in tumor hormonal activity, $P = 0.17$). Another important prognostic factor is the margin status after surgery. It was previously shown that 5-year survival rates are lower for patients with microscopically (21%) and macroscopically (10%) involved margins, compared with uninvolved margins (46%).[9] In the present study, margin status R2 was related to poorer OS in the multivariate analysis, but margin status R1 did not reach significance, probably due to the small number of events (only 3 patients).

Similarly to a previous study,[19] tumor size was not associated with reduced OS or RFS. Except one report,[12] most authors claimed that patients with cortisol-secreting tumors had poorer prognosis.[13-15] In the present study, hormonal activity was not related to shorter OS or RFS.

The strength of the present study is follow-up duration from 2002 to 2015, which allowed us to obtain reliable data. On the other hand, the major limitation is a relatively small number of participants, and as this is a retrospective study, some of the medical data are incomplete. Moreover, patients were recruited from different centers, so methods of follow-up were inconsistent. Unfortunately, we do not have information on mitotane concentrations as they were not provided. For further research, it is crucial to standardize the monitoring process. It is also necessary that the mitotane treatment is fully controlled with plasma levels within the therapeutic range to ensure that the therapy is adequate and safe. However, ACC is extremely rare and most of the relevant information about the course of the disease and treatment results come from retrospective analyses of national registries.[3,5,6,8,10]

In conclusion, we identified prognostic factors of survival in patients with ACC: older age, stage IV ACC, margin status R2, no mitotane treatment, and higher Ki67 and mitotic indices. These factors should be considered when planning the management after surgery. Mitotane treatment may be associated with better outcomes in patients with ACC regardless of the tumor stage. Due to the aggressive behavior of ACC and high percentage of relapse, more studies are needed to help improve survival.

CONTRIBUTION STATEMENT KMN and LP designed the study. KMN, RS, AC, AŁ-Sz, UA, LK, MO, KR-P, WZ, and LP were involved in data collection. KMN analyzed the data. All authors edited and approved the final version of the manuscript.

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