

# Prognostic factors of recurrence-free and overall survival in 52 patients with adrenocortical carcinoma

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## Background

Adrenocortical carcinoma (ACC) is a rare and very aggressive tumor with poor prognosis. Its prevalence is estimated on 0.5-2 cases per million population per year[1]. The overall 5-year survival is generally between 16-44%[2]. Prognosis is dependent on stage at presentation. The 5-year overall survival rate was 80% for stage I, 61% for stage II, 50% for stage III and 13% for stage IV disease[3]. The median overall survival is 32-34 months[1,4]. The median recurrence free survival was 42 months[5]. There are several features that may be useful in outcome prediction such as margin status, distant metastasis, tumor invasion of vessels, tumor capsule or adjacent organs, tumor necrosis and mitotic rate >5/50 high power fields(HPF)[4]. Older age and cortisol-secreting ACCs was also reported to be associated with poor survival [6]. According to European Society for Medical Oncology „low-risk” patients with complete resection R0, stage I-II and Ki67 <10% have lower risk of disease recurrence compared to patients with R0 together with stage III disease or Ki67>10% (“high-risk”)[7].

## Objectives

The present study has two main objectives:

- 1) to assess overall survival (OS) and recurrence-free survival (RFS)
- 2) to identify prognostic factors of OS and predictive features of RFS

## Methods

52 patients were diagnosed with ACC between 2002 – 2015. 50 of them had primary tumors. Two females suffered from recurrent disease and were excluded from the further analysis (both had survival of 142 and 165 months). We investigated a number of clinical and histological factors such as: age, sex, stage, hormonal activity, tumor size, margin status, thrombus in vena cava, tumor necrosis, tumor invasion of vessels, neighboring structure or adjacent organs, tumor infiltration of capsule with crossing its border, mitotic rate >20/50HPF, Ki67 score, high-risk patients. Survival curves were calculated using Kaplan-Meier method and the difference between groups or factors were compared using the log-rank test. The univariate and multivariate Cox proportional hazard regression model was performed. Patients with stage I and II were analyzed together (only 3 patients had stage I). Recurrent disease was defined as a new lesion confirmed in imaging.

## Results

Characteristic of patients	Total	5-year OS	2-year RFS
<b>Total</b>	<b>50</b>		
<b>Sex</b>			
Female (F)	34 (68%)	44.5%	72%
Male (M)	16 (32%)	24.8%	25%
<b>Age (yr)</b>			
< 50 years	24(48%)	60%	71.6%
≥50 years	26(52%)	14%	44%
<b>Tumor size (cm)</b>			
Range (Median)	2.2-25(11.8)		
<10 cm	16 (32%)	35%	69%
≥ 10 cm	28 (56%)	42%	54%
<b>Stage I (ENSAT)</b>	3 (6%)	66.7%	100%
<b>Stage II</b>	18 (36%)	60%	77%
<b>Stage III</b>	20 (40%)	25%	46%
<b>Stage IV</b>	9 (18%)	0%	18%
<b>Hormonal activity</b>	27 (54%)	34%	50%
<b>Hormonally inactive</b>	12 (24%)	46%	62%
<b>Resection status - R0</b>	37 (74%)	44%	64%
R1	3 (6%)	66%	67%
R2	5 (10%)	0%	30%
<b>Inoperable</b>	5 (10%)	0%	--
<b>Tumor necrosis (n=45)</b>			
Present	29(64%)	40%	56%
Absent	6 (13%)	75%	100%
<b>Invasion in vessels (n=45)</b>			
Present	21(47%)	24%	47%
Absent	7(15.5%)	71%	86%
<b>Capsular invasion (n=45)</b>			
Present	19 (42%)	35%	45%
Absent	22 (49%)	45%	70%
<b>Invasion in neighboring structure (n=45)</b>			
Present	18 (40%)	22%	33%
Absent	27 (60%)	52%	78%
<b>Invasion in adjacent organs (n=45)</b>			
Present	13 (29%)	8%	12.5%
Absent	30 (67%)	56%	78%
<b>Mitotic rate (n=45)</b>			
<20/50HPF	12 (27%)	70%	92%
≥20/HPF	12 (27%)	30%	24%
<b>Ki67% (n=45) &lt;10%</b>	9 (18%)	52%	76%
≥10%	9 (18%)	--	53%
<b>High-risk</b>	16 (14%)	39%	61%
<b>Low-risk</b>	7 (14%)	75%	83%
<b>Thrombus in vena cava (n=45)</b>			
Present	5 (11%)	27%	75%
Absent	38 (84%)	43%	62%

Table 1. Patient's characteristics and difference between groups in 5-year overall survival (OS) rates. High-risk and low-risk patients definition in text.

## Results

Patients baseline characteristics is provided in table 1. Results are presented in Table2. The study included 36 females and 16 males of median age 47.5 (22-73) and 57 years (33-77) respectively. 64% of tumors were hormonally active mainly with overproduction of cortisol (88%). 44 patients received adjuvant mitotane. 27 patients suffered from recurrent disease. The median of recurrence-free survival was 20.7 months (1.57-132.8) and 25.9 months (2.4-133.4) for overall survival. The median of RFS without stage IV disease was 27 months (2-132.8). Patients ≥50years had more stage III and IV disease.

### Prognostic factors associated with decreased OS:

- in univariate analysis: male sex, age≥50years disease stage, tumor invasion in vessels, neighboring structure or adjacent organs and mitotic rate>20/50HPF.

- in multivariate analysis with age as covariate: stage, mitotic rate>20/50HPF and invasion of neighboring structure or adjacent organs.

### Predictive features associated with decreased RFS:

- in univariate analysis: male sex, age≥50years, stage IV, tumor invasion in vessels, infiltration in neighboring structure adjacent organs and mitotic rate>20/50HPF.

- in multivariate analysis with age as covariate: stage IV, mitotic rate>20/50HPF and invasion of neighboring structure or adjacent organs.

- interestingly, there was no difference between stage I+II vs stage III (p=0.124)

- When the analysis was performed without stage IV disease margin status (R2vsR0) was associated with decreased RFS (p=0.01)

Resection status R0vsR2, „high-risk” factor and tumor necrosis despite the noticeable difference in 5-year OS and 2-year RFS did not reach a statistical significance in Cox model probably due to a small number of events.

Hormonal activity, tumor size, thrombus in vena cava, Ki67 score, tumor infiltration of capsule had no influence on neither OS nor RFS.

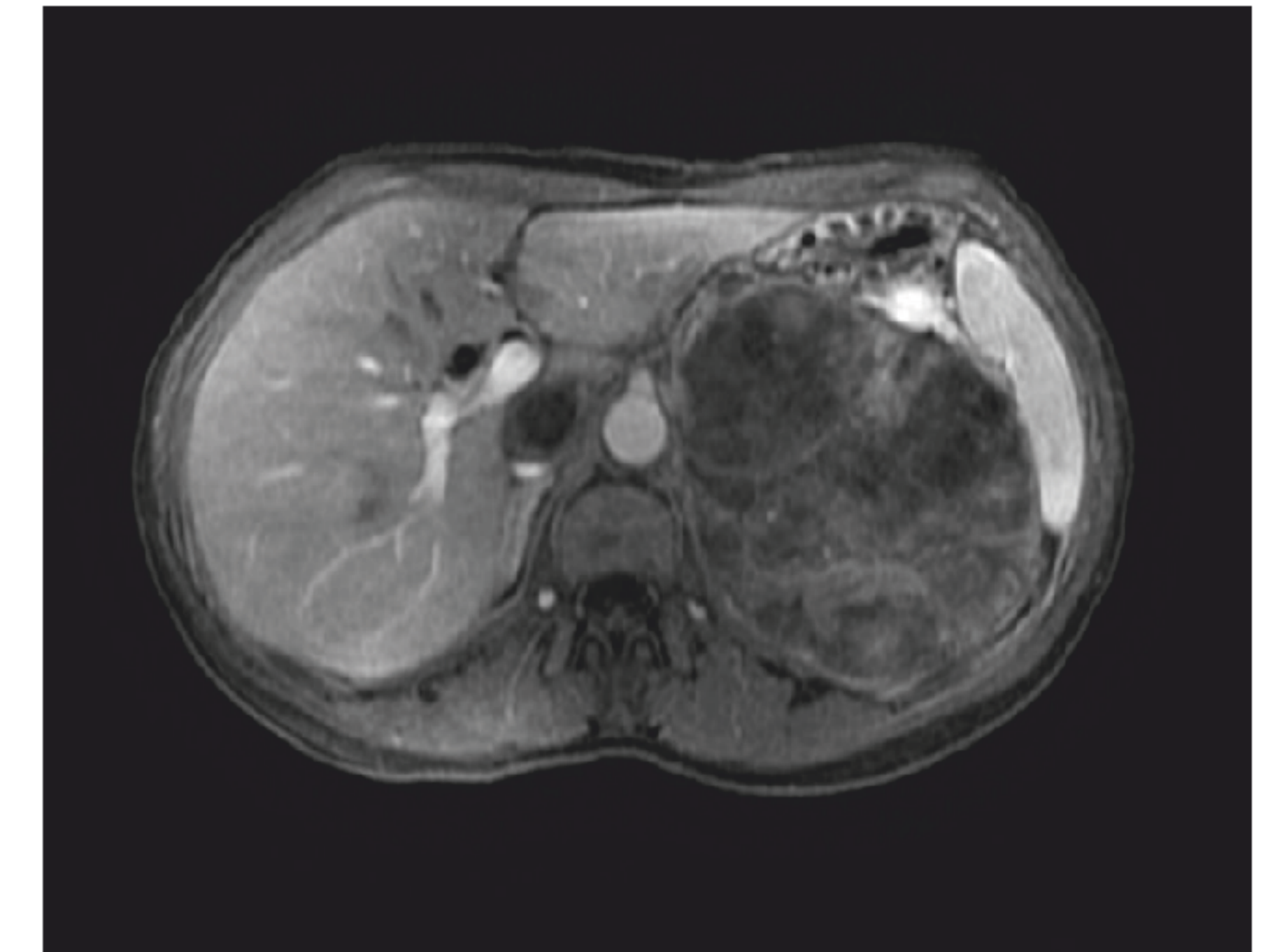


Fig1. Adrenocortical carcinoma

## Conclusions

Our study indicates a major role of prognostic factors on survival in patients with ACC. The 5-year survival, median of RFS and OS were worse than previously reported. We identified a number of features associated with decreased with both OS and RFS such as: male sex, age≥50years, stage, tumor invasion in vessels, neighboring structure or adjacent organs and mitotic rate>20/50HPF. Margin status and tumor necrosis did not reach a significance probably due to a small number of events despite the differences in survival rates. There was no difference in RFS between stage I+II vs stage III disease. Due to the aggressive behavior of ACC and high percentage of relapse it is crucial to conduct more studies in order to help improving survival.

## References

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Variable	Univariate (OS)			Univariate (RFS)		
	HR	95% CI	Pvalue	HR	95% CI	Pvalue
<b>Age ≥ 50yrs</b>	1.03	1.0-1.04	0.001	1.02	1.0-1.03	0.017
<b>Sex**</b>	2.57	1.21-5.45	0.013	2.69	1.21-5.99	0.015
<b>Tumor stage</b>						
I+II	1			1		
III	2.53	1.11-5.77	0.026	1.93	0.83-4.49	0.124
IV	5.11	1.83-14.3	0.002	3.7	1.2-11.27	0.021
<b>Invasion in vessels</b>	4.79	1.07-21.3	0.04	5.4	1.21-24.5	0.027
<b>Invasion in neighboring structure</b>	2.26	1.06-4.8	0.033	2.16	0.98-4.7	0.055
<b>Infiltration in adjacent organs</b>	3.72	1.66-8.35	0.001	3.78	1.55-9.2	0.003
<b>Mitotic rate &gt;20/50 HPF</b>	6.35	1.62-24.8	0.008	5.68	1.4-21.9	0.012

Table 2. Prognostic factors for overall survival. \*\*female sex was a reference category

