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Clinical Score Predicting Long-Term Survival after Repeat Resection for Recurrent Adrenocortical Carcinoma

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Abstract

BACKGROUND—Adrenocortical carcinoma (ACC) is an aggressive malignancy typically resistant to chemotherapy and radiation. Surgery, even in the setting of locally recurrent or metastatic disease, remains the only potentially curative option. However, the subset of patients who will benefit from repeat resection in this setting remains ill defined. The objective of this study was to propose a prognostic clinical score that facilitates selection of patients for repeat resection of recurrent ACC.

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STUDY DESIGN—Patients who underwent curative-intent repeat resection for recurrent ACC at 1 of 13 academic medical centers participating in the US ACC Study Group were identified. End points included morbidity, mortality, and overall survival.

RESULTS—Fifty-six patients underwent repeat curative-intent resection for recurrent ACC (representing 21% of 265 patients who underwent resection for primary ACC) from 1997 to 2014. Median age was 52 years. Sites of resected recurrence included locoregional only (54%), lung only (14%), liver only (12%), combined locoregional and lung (4%), combined liver and lung (4%), and other distant sites (12%). Thirty-day morbidity and mortality rates were 40% and 5.4%, respectively. Cox regression analysis revealed that the presence of multifocal recurrence, disease-free interval <12 months, and extrapulmonary distant metastases were independent predictors of poor survival. A clinical score consisting of 1-point each for the 3 variables demonstrated good discrimination in predicting survival after repeat resection (5-year: 72% for 0 points, 32% for 1 point, 0% for 2 or 3 points; $p = 0.0006$, area under the curve = 0.78).

CONCLUSIONS—Long-term survival after repeat resection for recurrent ACC is feasible when 2 of the following factors are present: solitary tumor, disease-free interval >12 months, and locoregional or pulmonary recurrence.

Adrenocortical carcinoma (ACC) is a rare malignancy with an incidence of approximately 1 per 1 million in the US.^{1,2} Progress on the management of ACC has been hampered by its rarity. Currently, the disease is typically refractory to standard chemotherapy and radiation modalities. Promising results with mitotane treatment were initially received with enthusiasm,³ however, additional studies have failed to replicate these findings consistently.^{4,5} Therefore, surgery remains the mainstay of treatment in patients with resectable primary ACC, with 5-year survival rates reaching 65% after margin-negative resection.⁶ However, even after curative resection of ACC, recurrence of disease is relatively common and can be detected in approximately two-thirds of patients after a median time to recurrence of 19 months.⁷ Surgeons are not infrequently asked to reevaluate patients with recurrent ACC for repeat surgery, given the lack of other effective treatment options. The benefit of repeat resection in patients with recurrent ACC remains a subject of debate, and very limited data exist to guide the clinician in this specific clinical scenario.

The primary objective of this study was to use a multi-institutional database of ACC patients who underwent surgical resection in US academic medical centers to evaluate perioperative and long-term outcomes after curative-intent repeat resection for recurrent ACC. The secondary objective was to generate a prognostic score that can be used by clinicians preoperatively to select patients with recurrent ACC who will benefit from surgical resection.

METHODS

Patient population and study design

Patients who underwent surgical resection for ACC between 1997 and 2014 were identified using a multi-institutional database of the following 13 academic institutions participating in the US Adrenocortical Carcinoma Study Group: Stanford University, Stanford, CA; John Hopkins Hospital, Baltimore, MD; Emory University, Atlanta, GA; Washington University,

St Louis, MO; Wake Forest University, Winston-Salem, NC; University of Wisconsin, Madison, WI; The Ohio State University, Columbus, OH; Medical College of Wisconsin, Milwaukee, WI; New York University, New York, NY; University of California at San Diego, San Diego, CA; University of California at San Francisco, San Francisco, CA; University of Texas Southwestern Medical Center, Dallas, TX; and Vanderbilt University Medical Center, Nashville, TN. Data were collected retrospectively within each participating institution after IRB approval.

The study cohort was defined as patients who underwent curative-intent repeat resection for recurrent ACC after previous primary resection. Only patients who underwent a macroscopically complete resection (R0 or R1) for locoregional recurrence, metachronous distant metastases, or both, were included in the study. Patients who underwent macroscopically incomplete (R2) resections in an attempt to debulk the tumor were excluded. Data on patient demographic characteristics, clinicopathologic characteristics, perioperative outcomes, and overall survival were collected. Postoperative morbidity was graded using the modified Clavien-Dindo classification of surgical complications.⁸ The seventh edition of the American Joint Commission on Cancer staging manual was used to determine stage.⁹ Disease-free interval (DFI) was defined as the interval between the first resection and diagnosis of recurrent disease, dichotomized by 2 groups, <12 months vs >12 months, as in previous studies.¹⁰

Statistical analysis

Continuous variables were presented as median with interquartile range and compared using ANOVA. Categorical variables were presented as frequency and percentage and compared using Fisher's exact test. Overall survival was calculated using the Kaplan-Meier method and compared using log-rank test. Univariate and multivariate survival analyses were performed using Cox proportional hazards model and expressed as hazard ratios (HR) with 95% CIs. Variables with $p < 0.05$ in univariate analysis were incorporated in the multivariate model. Independent predictors of survival were incorporated into a clinical score that assigned points to each factor based on their β -coefficients. The discriminatory ability of the clinical score was determined by evaluating the area under the curve (AUC) of the receiver operating characteristics curve obtained by the adjusted risk factor model. An AUC of 0.5 represents no discrimination and an AUC of 1 represents perfect discrimination. All statistical analyses were performed using the STATA statistical software package, version 13 (Stata Corp) and SPSS software, version 23.0 (IBM). Significance was set at $p < 0.05$ (2-tailed).

RESULTS

Of 265 patients with primary ACC in the US ACC Study Group database, 62 underwent repeat resection for recurrent disease between 1997 and 2014. Six patients who underwent R2 resection were excluded. Therefore, the study cohort was 56 patients who underwent curative-intent R0 or R1 repeat resection.

The sites of resected recurrence are shown in Table 1. The majority of repeat resections were performed for locoregional only recurrences (54%), followed by lung only (14%), and liver only metastases (12%).

The clinicopathologic and perioperative characteristics of the entire study population and the subgroups based on the site of recurrence resected are shown in Tables 2 (first resection) and 3 (repeat resection). Median age at diagnosis of recurrence was 52 years (interquartile range 42 to 61 years). Patients were predominantly females (58.9%), white (85.2%), and without hormonal excess (66.7%). Analyzing the characteristics of the initial resection (Table 2), patients who underwent repeat resection more commonly had primary tumors arising from the left adrenal gland (62.5%), with a median tumor size of 12 cm. Multivisceral resection at the time of the first operation was performed in 28.3% and IVC involvement was noted in 5.4%. Patients whose tumors were noted to have capsular and venous invasion pathologically at the first operation appeared to undergo repeat surgery more commonly for distant as opposed to locoregional recurrence; however, other Weiss criteria, margin status, or administration of any blood transfusion during the first operation did not appear to affect the type of subsequently resected recurrence. Adjuvant therapy was administered in the minority of patients after the initial operation: adjuvant mitotane in 31.9%, chemotherapy in 16.7%, and radiation in 11.1% of the cohort.

Table 3 details clinicopathologic and perioperative factors at the time of repeat resection based on site of ACC recurrence. Median DFI between the first resection and diagnosis of recurrence was 16.6 months. Neoadjuvant therapy for recurrence was more common than adjuvant therapy after initial resection (mitotane 40.8%, radiation 27.1%, chemotherapy 20.4%). Median recurrent tumor size was 4 cm and a quarter of patients underwent surgery for multifocal disease. Tumors recurring in the lung and other distant sites were smaller and were resected with lower blood loss and shorter operative time than those recurring locoregionally and in the liver, although these differences did not reach statistical significance. No significant differences in margin status were noted between the 3 groups and negative resection margins (R0) were achieved in 86.7% of patients undergoing repeat resection. The rate of any postoperative complication was 40% and the rate of serious complications was 18.6%. The distribution of complications was not different between the 3 groups. The 30-day and 90-day mortality rates were 5.4% and 8.9%, respectively. Median length of hospitalization was 6 days.

The actual 1-, 2-, and 3-year survival for the entire cohort were 76.5%, 51%, and 34%, respectively. Table 4 shows the results of univariate analysis of factors associated with actuarial survival after repeat resection for recurrent ACC. Factors associated with poor survival included the presence of multifocal tumors (5-year survival 0% vs 54%; $p = 0.004$), DFI < 12 months (20% vs 38.6%; $p = 0.048$), distant metastases other than pulmonary (12.1% vs 40.8%; $p = 0.023$), and IVC involvement (not reached vs 35%; $p = 0.026$). Age, sex, hormonal hypersecretion, resection of other adjacent organs, margin status (either of the primary or repeat resection), administration of mitotane or chemotherapy before the repeat resection, or any of the Weiss criteria studied, were not significantly associated with long-term survival after repeat resection on univariate analysis. Figure 1 illustrates the Kaplan-

Meier curves of the 4 prognostic factors found on univariate analysis to be associated with overall survival after repeat resection.

Multivariate survival analysis revealed 3 independent predictors of poor survival (Table 4): DFI < 12 months (adjusted HR = 2.617; 95% CI, 1.011–6.778; $p = 0.048$), multifocal disease (HR = 4.913; 95% CI, 1.962–12.305; $p = 0.001$), and distant metastasis other than pulmonary (HR = 2.511; 95% CI, 0.999–6.310; $p = 0.05$). All 3 variables had comparable β -coefficients and a clinical score consisting of 1 point for each predictor (with a maximum of 3 points) was created to predict long-term survival after repeat resection. Additional analysis revealed that this clinical risk score demonstrated good discrimination (AUC = 0.78) in predicting overall survival after repeat resection: 5-year survival 72% for 0 points, 32% for 1 point, and 0% for 2 or 3 points (Figure 2; $p = 0.0006$).

DISCUSSION

In this study, we identified several important determinants of poor survival after curative-intent resection of recurrent ACC, including distant metastases (except pulmonary), multifocal disease, and DFI < 12 months. Interestingly, microscopic margin status (R0 vs R1), hormonal hypersecretion, and recurrent tumor size did not have a significant prognostic impact on survival in patients undergoing repeat resection. Although a handful of studies have identified DFI^{11–13} and margin status^{12–14} as predictors of survival after repeat resection for recurrent ACC, our clinical score is the first prognostic tool that can be used to predict long-term outcomes in this situation, also incorporating multifocality as well as location of the recurrence as predictive factors. This study supports an aggressive surgical approach in carefully selected patients with 2 or more favorable criteria (ie DFI > 12 months, solitary recurrence, or locoregional or pulmonary recurrence).

A novel finding in our study, which has not been reported previously, is that the location of the ACC recurrence has major prognostic implications on the long-term outcomes after repeat resection. Locoregional and isolated pulmonary recurrences were found to represent favorable situations where surgical resection was associated with long-term survival. On the other hand, repeat surgery to resect other distant sites, such as liver metastases, was associated with inferior results. Previous studies examining this issue found no significant difference in outcomes by site of resected recurrence, likely because they only dichotomized recurrences generically as locoregional or distant.^{13,14} However, when we analyzed outcomes by the type of distant recurrence, we were able to find significant associations as described. Along the same lines, a US study analyzing 28 patients who underwent resection of ACC liver metastases reported a median DFS of 7 months and a median overall survival of 31 months. However, recurrent ACC eventually developed in all 28 patients, who died of disease during follow-up.¹⁵ On the contrary, results of pulmonary meta-stasectomy for ACC appear more encouraging, with a German study of 24 patients showing that complete resection of pulmonary metastases was associated with a considerable median survival of 50 months.¹⁶

The impact of margin status on survival after recurrent ACC resection remains a subject of debate. Our study did not find a significant difference in survival between R0 and R1

resections, however, R2 resections were a priori excluded from our analysis. Several previous studies have demonstrated the importance of margin status during resection for recurrent ACC; however, all of these studies included R2 resections in their analyses and lumped R2 and R1 resections together as “margin-positive” or “incomplete” resections.^{12–14} The poor outcomes of patients undergoing R2 resections likely dominated the outcomes of patients undergoing margin-positive (R1 and R2) resections in general. What remains clear from these studies is that incomplete resection for recurrent ACC is typically not associated with any survival benefit. However, we acknowledge that in highly selected cases, such cytoreductive procedures might be required to palliate symptoms associated with hormonal hypersecretion.¹²

The role of neoadjuvant or adjuvant chemotherapy in addition to surgery for ACC recurrence remains controversial. A study from the NIH evaluated the impact of chemotherapy before and after repeat resection and found no difference in outcomes.¹¹ Similarly, the efficacy of adjuvant mitotane remains unproven, even when current literature on its use after primary resection is applied on its use after resection of recurrent disease. A European study by Terzolo and colleagues³ contended that the use of mitotane after primary resection can reduce the risk of recurrence. However, subsequent studies in the US have questioned the efficacy of mitotane in the adjuvant setting.^{4,5} Although 20.4% of the patients received neoadjuvant chemotherapy before repeat resection and 40.8% received neoadjuvant mitotane, neither were associated with an improvement in survival after repeat resection on univariate analysis. This observation might be related to the lack of standardization of chemotherapy agents used, or the lack of consistency in achieving therapeutic levels of mitotane during the long period (17 years) of our multicenter study. Although there is no evidence to support the use of neoadjuvant systemic therapy before surgery for recurrent ACC, we acknowledge this approach might have several theoretical advantages, such as providing a way to test tumor biology as well as an *in vivo* assessment of chemosensitivity, so that the same agent might be used postoperatively.

There are several important limitations to the current study. Despite the multi-institutional nature of the study consisting of 13 major academic hospitals in the US, the sample size is still small; with each institution performing, on average, 1 repeat resection for recurrent ACC every 4 years. This underscores the extremely uncommon clinical scenario in which a patient with this rare malignancy can present with potentially resectable recurrent disease. Second, several of the Weiss pathologic criteria were not consistently recorded, and perhaps this is why these factors were not found to predict survival. Third, selection biases cannot be controlled for, given the retrospective nature of this study. Fourth, one can also imagine the difficulty in retrospectively discerning between liver metastases in the right posterior sector and locoregional recurrence in those who had a right-sided ACC primary. Lastly, the value of this clinical scoring system is limited due to the small sample size of the study, therefore, larger future studies are required to validate our proposed clinical score externally and confirm its predictive power. Nevertheless, this large multi-institutional collaborative study provides generalizable results for a rare malignancy, and a novel clinical scoring system that can be used to facilitate prognostication of patients with recurrent ACC for whom repeat surgical resection is considered.

CONCLUSIONS

Utilizing a multi-institutional database of patients who underwent surgical resection for ACC in 13 US academic medical centers, we found that repeat surgical resection for recurrent ACC can be justified in carefully selected patients with 2 or more favorable of these prognostic features: DFI >12 months, locoregional or lung recurrence, and a solitary lesion. R1 resection margins, hormonal hypersecretion, and large recurrent tumor size do not appear to preclude long-term survival after surgery in this setting. Patients with short DFI from primary resection to diagnosis of recurrence, multifocal disease, and nonpulmonary distant metastasis should be evaluated for repeat resection after careful selection and multidisciplinary discussion.

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Abbreviations and Acronyms

ACC	adrenocortical carcinoma
AUC	area under the curve
DFI	disease-free interval
HR	hazard ratio

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Figure 1.

Kaplan-Meier curves of overall survival after repeat resection for recurrent adrenocortical carcinoma based on (A) number of recurrent tumors, (B) disease-free interval, (C, D) site of recurrence, and (E, F) IVC involvement.

Figure 2. Kaplan-Meier survival stratified by our proposed clinical score (area under the curve 0.78).

Table 1

Site of Recurrence in 56 Patients with Recurrent Adrenocortical Carcinoma Who Underwent Repeat Surgical Resection

Site	Frequency	
	n	%
Locoregional only	30	53.6
Lung only	8	14.2
Liver only	7	12.5
Locoregional + lung	2	3.6
Liver + lung	2	3.6
Other distant *	7	12.5

* Brain, contralateral adrenal, soft tissue, and spleen.

Clinicopathologic and Perioperative Characteristics at First Resection Stratified by Site of Subsequent Recurrence

Table 2

Characteristic	Locoregional ($\pm$ lung) (n = 32)	Lung only (n = 8)	Liver ($\pm$ lung) (n = 9)	Other distant (n = 7)	Total (n = 56)	p Value*
Preoperative characteristics, n (%)						
Female sex	18 (56.3)	6 (75)	4 (44.4)	5 (71.4)	33 (58.9)	0.580
White race	27 (90)	7 (87.5)	7 (77.8)	5 (71.4)	46 (85.2)	0.467
American Society of Anesthesiologists class >3 (n = 43)	14 (60.9)	2 (40.0)	2 (25.0)	4 (57.1)	22 (51.2)	0.373
Hormonal hypersecretion (n = 51)	11 (39.3)	2 (25.0)	4 (50.0)	0 (0)	17 (33.3)	0.162
First operation						
Laparoscopic (vs open) (n = 52), n (%)	5 (17.9)	1 (12.5)	1 (11.1)	5 (71.4)	12 (23.1)	0.020
Other organs resected (n = 53), n (%)	7 (24.1)	3 (37.5)	3 (33.3)	2 (28.6)	15 (28.3)	0.877
IVC involvement, n (%)	1 (3.1)	1 (12.5)	0 (0)	1 (14.3)	3 (5.4)	0.236
Left-sided tumor, n (%)	24 (75.0)	4 (50.0)	5 (55.6)	2 (28.6)	35 (62.5)	0.093
Tumor size, cm, median (IQR)	11.4 (8.6–13.8)	13.4 (10.1–19.0)	14.5 (11.3–20.0)	7 (5–12)	12 (9–15)	0.789
T3/4 stage (n = 48), n (%)	16 (64)	5 (62.5)	4 (44.4)	2 (33.3)	27 (56.3)	0.483
N stage, n (%)						
N0	7 (21.9)	3 (37.5)	2 (22.2)	1 (14.3)	13 (23.2)	0.886
N1	2 (6.3)	0 (0)	1 (11.1)	0 (0)	3 (5.4)	
Nx	23 (71.9)	5 (62.5)	6 (66.7)	6 (85.7)	40 (85.7)	
M1 stage (n = 50), n (%)	1 (3.8)	0 (0)	3 (33.3)	0 (0)	4 (8.0)	0.066
Microvascular invasion (n = 31), n (%)	9 (47.4)	4 (100)	4 (66.7)	2 (100)	19 (61.3)	0.152
Lymphatic invasion (n = 30), n (%)	6 (31.6)	3 (60.0)	2 (50.0)	2 (100)	13 (43.3)	0.232
Margins, n (%)						
R0	15 (60)	8 (100)	6 (85.7)	5 (83.3)	34 (75.6)	0.174
R1	8 (32)	0 (0)	1 (14.3)	0 (0)	9 (20)	
R2	2 (8)	0 (0)	0 (0)	0 (0)	2 (4.4)	
Necrosis (n = 42), n (%)	24 (100)	7 (100)	100 (100)	5 (83.3)	41 (97.6)	0.262
Capsular invasion (n = 33), n (%)	10 (55.6)	3 (50.0)	0 (0)	5 (100)	18 (54.5)	0.025 [†]
Venous invasion (n = 17), n (%)	4 (30.8)	2 (100)	1 (100)	1 (100)	8 (47.1)	0.029 [†]

Characteristic	Locoregional (± lung) (n = 32)	Lung only (n = 8)	Liver (± lung) (n = 9)	Other distant (n = 7)	Total (n = 56)	p Value [*]
Atypical adrenocortical carcinoma (n = 36), n (%) [‡]	3 (3)	0 (0)	0 (0)	0 (0)	3 (8.3)	0.721
Any blood transfusion (n = 33), n (%)	7 (41.2)	2 (28.6)	2 (50)	2 (40)	13 (39.4)	0.907
Adjuvant chemotherapy (n = 54), n (%)	5 (16.7)	0 (0)	4 (44.4)	0 (0)	9 (16.7)	0.065
Adjuvant mitotane (n = 47), n (%)	9 (37.5)	3 (37.5)	2 (25.0)	1 (14.3)	15 (31.9)	0.758
Adjuvant radiation (n = 45), n (%)	2 (8.0)	2 (25.0)	0 (0)	1 (20.0)	5 (11.1)	0.252

^{*} p Values compare the observed distribution of clinical and pathologic characteristics across the different sites of recurrence.

[‡]Significant.

[‡]Atypical adrenocortical carcinoma defined as <3 Weiss criteria present in histologic analysis of surgical specimen.

IQR, interquartile range.

Table 3
Clinicopathologic and Operative Characteristics at Repeat Resection Stratified by Site of Recurrence

Second operation	Locoregional ($\pm$ lung) (n = 32)	Lung only (n = 8)	Liver ($\pm$ lung) (n = 9)	Other distant (n = 7)	Total (n = 56)	p Value
Age, y, median (IQR)	51 (38–63)	54 (47–56)	41 (26–63)	48 (46–63)	52 (42–61)	0.878
Disease-free interval, mo, median (IQR)	16 (9.1–31.5)	19.5 (4.6–57.1)	7.6 (2.9–32.8)	31.5 (9.1–40.4)	16.6 (6.9–34.0)	0.405
Neoadjuvant radiation (n = 49), n (%)	7 (25.0)	1 (16.7)	2 (25.0)	3 (50.0)	13 (27.1)	0.645
Neoadjuvant chemotherapy (n = 49), n (%)	5 (18.5)	1 (12.5)	3 (37.5)	1 (16.7)	10 (20.4)	0.687
Neoadjuvant mitotane (n = 49), n (%)	10 (37.0)	4 (50)	3 (37.5)	3 (50)	20 (40.8)	0.888
Recurrent tumor size, cm, median (IQR)	4.2 (2.7–5.0)	1.2 (0.7–1.5)	5.1 (3–8.5)	1.0 (1.0–1.8)	4.0 (2.4–6.5)	0.061
Multifocal disease (n = 55), n (%)	10 (31.3)	2 (25.0)	2 (22.2)	1 (16.7)	15 (27.3)	0.931
R1 margins (n = 45), n (%)	4 (16.0)	0 (0)	1 (11.1)	1 (33.3)	6 (13.3)	0.464
Operative time, min, median (IQR)	250 (140–310)	120 (55.5–162)	246 (213–424)	89 (31–233)	190 (120–305)	0.156
Estimated blood loss, mL, median (IQR)	62.5 (18.7–1,450)	37 (25–50)	500 (500–2,500)	100 (50–300)	450 (100–1,125)	0.153
Any blood transfusion (n = 44), n (%)	7 (29.2)	0 (0)	2 (28.6)	1 (20.0)	10 (22.7)	0.351
Any complication (n = 50), n (%)	12 (44.4)	2 (25.0)	4 (44.4)	2 (33.3)	20 (40.0)	0.824
Clavien grade >3 complication (n = 43), n (%)	5 (20.8)	1 (14.3)	2 (28.6)	0 (0)	8 (18.6)	0.775
Reoperation (n = 44), n (%)	1 (4.5)	0 (0)	0 (0)	0 (0)	0 (0)	1.000
Postoperative adrenal insufficiency (n = 47), n (%)	7 (28.0)	0 (0)	0 (0)	2 (40.0)	9 (19.1)	0.064
Respiratory failure requiring mechanical ventilation (n = 47), n (%)	2 (8.0)	0 (0)	0 (0)	0 (0)	2 (4.3)	1.000
Renal failure requiring dialysis (n = 47), n (%)	1 (4.0)	0 (0)	0 (0)	0 (0)	1 (2.1)	1.000
Deep vein thrombosis (n = 48), n (%)	0 (0)	0 (0)	0 (0)	1 (16.7)	1 (2.1)	0.125
Pulmonary embolism (n = 48), n (%)	0 (0)	0 (0)	0 (0)	1 (16.7)	1 (2.1)	0.125
Length of stay, d, median (IQR)	6 (5–8)	2 (2–3)	7 (7–8)	6 (4–8)	6 (4–8)	0.504
30-d mortality, n (%)	0 (0)	0 (0)	1 (11.1)	2 (28.6)	3 (5.4)	0.097
90-d mortality, n (%)	0 (0)	0 (0)	2 (22.2)	3 (42.9)	5 (8.9)	0.030*
Readmission in 90 d, n (%)	4 (16)	0 (0)	0 (0)	1 (25.0)	5 (11.1)	0.314

* Significant.

IQR, interquartile range.

Univariate and Multivariate Analysis of Factors Associated with Overall Survival after Repeat Resection for Recurrent Adrenocortical Carcinoma

Table 4

Factors	Univariate analysis			Multivariate analysis		
	5-y overall survival, %	HR (95% CI)	p Value	β	HR (95% CI)	p Value
Age (per y)	—	0.990 (0.966–1.014)	0.433			—
Sex						
Male	26	Ref				
Female	41	0.958 (0.428–2.144)	0.917			—
Hormonal hypersecretion						
None	40.9	Ref				
Cortisol	53	0.490 (0.110–2.188)	0.350			—
Other	27	1.099 (0.415–2.916)	0.849			—
Other organs resected (first operation)						
No	30.9	Ref				
Yes	48.1	1.274 (0.496–3.271)	0.615			—
Postoperative mitotane (after first resection)						
No	43	Ref				
Yes	0	2.793 (0.771–10.112)	0.118			—
Margin status (first operation)						
R0	38	Ref				
R1/R2	33.9	1.523 (0.535–4.334)	0.431			—
IVC involvement (first or second operation)						

Factors	Univariate analysis			Multivariate analysis		
	5-y overall survival, %	HR (95% CI)	p Value	β	HR (95% CI)	p Value
No	35.0	Ref		Ref	Ref	
Yes	—	4.400 (1.195–16.201)	0.026	0.99	2.699 (0.697–10.445)	0.150
Disease-free interval, mo						
>12	38.6	Ref		Ref	Ref	
<12	20.2	2.267 (1.007–5.104)	0.048	0.96	2.617 (1.011–6.778)	0.048
Recurrent tumors						
Single	54	Ref		Ref	Ref	
Multiple	0	3.419 (1.493–7.829)	0.004	1.59	4.913 (1.962–12.31)	0.001
Site of recurrence						
Local or lung	40.8	Ref		Ref	Ref	
Distant (except lung)	12.1	2.611 (1.144–5.960)	0.023	0.92	2.511 (0.999–6.310)	0.050
Margin status (repeat resection)						
R0	37.7	Ref				
R1	0	2.286 (0.809–6.459)	0.119		—	
Neoadjuvant mitotane (before repeat resection)						
No	28.2	Ref				
Yes	37.2	0.450 (0.179–1.127)	0.088		—	
Neoadjuvant chemotherapy (before repeat resection)						
No	41.5	Ref				
Yes	16.9	1.98 (0.760–5.778)	0.162		—	

Factors	Univariate analysis			Multivariate analysis		
	5-y overall survival, %	HR (95% CI)	p Value	β	HR (95% CI)	p Value
Capsular invasion						
No	25.4	Ref				
Yes	42.9	2.29 (0.687–7.689)	0.177			—
>10 mitoses high-power field						
No	0	Ref				
Yes	39.8	1.43 (0.279–7.312)	0.668			—
Atypical adrenocortical carcinoma*						
No	29.5	Ref				
Yes	0	1.98 (0.441–8.92)	0.372			—

* Atypical adrenocortical carcinoma defined as <3 Weiss criteria present in histologic analysis of surgical specimen.