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

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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.

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. (J Am Coll Surg 2016;223:794–803.

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

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 re-evaluate 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).