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# Longitudinal patterns of recurrence in patients with adrenocortical carcinoma ☆



Jason A. Glenn, MD<sup>a,\*</sup>, Tobias Else, MD<sup>b</sup>, David T. Hughes, MD<sup>a</sup>, Mark S. Cohen, MD<sup>a</sup>,  
Shruti Jolly, MD<sup>c</sup>, Thomas J. Giordano, MD, PhD<sup>b,d</sup>, Francis P. Worden, MD<sup>e</sup>,  
Paul G. Gauger, MD<sup>a</sup>, Gary D. Hammer, MD, PhD<sup>b</sup>, Barbra S. Miller, MD<sup>a</sup>

<sup>a</sup> Division of Endocrine Surgery, Department of Surgery, Michigan Medicine, University of Michigan, Ann Arbor

<sup>b</sup> Division of Metabolism, Endocrinology and Diabetes, Department of Internal Medicine, Michigan Medicine, University of Michigan, Ann Arbor

<sup>c</sup> Department of Radiation Oncology, Michigan Medicine, University of Michigan, Ann Arbor

<sup>d</sup> Department of Pathology, Michigan Medicine, University of Michigan, Ann Arbor

<sup>e</sup> Division of Hematology and Oncology, Michigan Medicine, University of Michigan, Ann Arbor

## ARTICLE INFO

## Article history:

Accepted 23 April 2018

Available online 19 October 2018

## ABSTRACT

**Background:** Patterns and prognostic implications of recurrent adrenocortical carcinoma are poorly understood. In this study, we aim to describe temporal and spatial patterns of adrenocortical carcinoma recurrence.

**Methods:** This is a retrospective review of 576 patients with adrenocortical carcinoma evaluated at a single institution. Clinicopathologic and follow-up data were collected longitudinally.

**Results:** A total of 354 patients underwent resection of stage I-III adrenocortical carcinoma. We found that 249 (70%) patients developed disease recurrence. The median recurrence-free interval after primary resection was 11 months. The most common sites of initial recurrence were lung and tumor bed. The shortest time to recurrence was associated with lung or multiple site metastases. We found that 142 of 249 patients developed one or more additional sites of recurrence (median 5 months), most commonly involving the lungs. A total of 20 patients developed a third site of recurrence. We found that 100 patients underwent one or more reoperations or metastasectomies and 79 recurred again after reoperation. Same organ or site recurrence was common after reoperation (67%). Although lung metastases occurred early, recurrences to the peritoneal cavity or to multiple sites were associated with worse survival. Metastasectomy beyond three total operations did not improve overall survival.

**Conclusion:** Survival varies according to site of recurrence and other clinicopathologic factors. Knowledge of patterns of recurrence may assist in anticipating disease course and lead to better informed selection of treatment.

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## Introduction

Surgical resection remains the primary treatment modality to achieve cure in patients with adrenocortical carcinoma (ACC). Although recurrences are common and prognosis remains poor, progress is being made because of the improved understanding of

this rare disease and an increased utilization of multimodal therapies.<sup>1–7</sup> Throughout the past decade, with better patient selection and more uniform treatment with mitotane and chemotherapy, metastasectomy has been increasingly performed.<sup>8–10</sup> Current data suggest tumor biology, volume of disease, adherence to oncologic principles of resection, recurrence-free interval (RFI) after primary resection, and response to various nonsurgical treatments are key factors when deciding whether surgery is prudent in patients with recurrent ACC.<sup>1–7</sup>

Optimal patient selection for primary surgical resection and concurrent metastasectomy (in those presenting with stage IV disease) or for reoperative metastasectomy is crucial to optimize outcomes.<sup>11,12</sup> However, the few available studies exploring patient selection are limited by patient volume and various biases, attributable to the rare nature of this disease process, variability in

**Abbreviations:** RFI, recurrence-free interval; EDP, Etoposide/Adriamycin/Cisplatin; NED, no evidence of disease; SBRT, single beam radiation therapy; RFA, radio-frequency ablation; MWA, microwave ablation; XRT, external beam radiation therapy; HIPEC, hyperthermic intraperitoneal chemotherapy.

☆ Presented at the 2018 annual meeting of the American Association of Endocrine Surgeons.

\* Corresponding author: 2920H Taubman Center, 1500 E. Medical Center Drive, Ann Arbor, MI 48109.

E-mail address: [gjason@med.umich.edu](mailto:gjason@med.umich.edu) (J.A. Glenn).

<https://doi.org/10.1016/j.surg.2018.04.068>

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treatment, and duration of follow-up.<sup>13–19</sup> Importantly, the temporal and spatial patterns of disease recurrence in individual patients have neither been well studied nor well integrated into overall treatment plans. By understanding where, when, and in what order ACC recurs, selection of available treatments may be better informed to positively impact survival and quality of life.

In this study we aim to describe the patterns of disease recurrence in patients with ACC. We will explore the temporal nature of recurrences by anatomic site and the interval between recurrences (both with and without surgical intervention) to provide insight into the overall disease course and how these factors may impact treatment selection and patient survival.

## Methods

Patients with a diagnosis of ACC were identified through the Institutional Review Board–approved Michigan Endocrine Oncology Repository and the University of Michigan Endocrine Disease Outcomes data set. The medical records of 576 patients, diagnosed with ACC between June 1983 and July 2017 and evaluated or treated at our institution (Michigan Medicine, University of Michigan, Ann Arbor), were retrospectively reviewed. The follow-up accrual end date was February 2018. Those identified as having metastatic (stage IV) disease at the time of initial diagnosis, those not physically examined or treated at our institution (eg, remote consults), those who underwent palliative or debulking primary resection without curative intent, and pediatric patients (age < 18 years) were censored from analysis ( $n=222$ ). The remaining 354 patients, all of whom underwent primary resection with curative intent for stage I–III ACC, were included.

Patient charts were individually reviewed for longitudinal data related to demographics, diagnosis, hormone secretion, operative findings, tumor characteristics, adjuvant therapy, recurrence, reoperations, follow-up, and death. Date of death was queried using the medical record, Social Security Death Index, online searches, and phone calls to the patient's primary care physician or oncologist. Computed tomography, magnetic resonance imaging, or positron emission tomography images were reviewed in longitudinal fashion for each patient. The date and site of each recurrence was catalogued by anatomic location. Surveillance imaging was most often obtained every 3 months for 2 years, every 6 months for 3 years, and then annually if there was no evidence of disease. If disease were present, imaging was obtained every 3 months (or sooner), depending on treatment undertaken or patient condition. RFI was defined as either the time from operation to subsequent recurrence based on radiologic findings or pathology results or the time from recurrence to subsequent recurrence in a different organ or site if no reoperation was performed. Overall survival was the time from diagnosis to either time of last follow-up or death.

Stage was determined according to the European Network for the Study of Adrenal Tumors staging system.<sup>20</sup> Tumor grade was based on mitotic activity and/or Ki-67 proliferation index using immunohistochemistry, with high-grade tumors exhibiting  $\geq 20$  mitoses per 50 high-power fields or  $> 30\%$  by Ki-67. Adrenal hormone excess was defined by documentation of diagnostic biochemical testing or overt physical examination findings noted in the examining physician's documentation.<sup>21,22</sup> Sites of recurrence with low overall frequency (eg, brain, axial skeleton, chest or abdominal wall) were grouped together as "other single site" for the purposes of analysis. The intent of each reoperation was categorized as either curative by surgery alone, curative by multimodal treatment of multiple site recurrent disease, or debulking for symptoms or anatomic preservation. Radiation therapy (XRT) to the tumor bed was considered adjuvant if it was initiated after primary R0 or R1 surgical resection but before initial recurrence.

Continuous variables were evaluated for significant differences using Student *t* test. Categorical variables were analyzed with  $\chi^2$  tests as appropriate. Log-rank and Fisher exact tests, Poisson regression models, binomial logistic regression models, and Kaplan-Meier curves were used to evaluate associations between clinicopathologic variables, recurrence patterns, and survival data. Associations between variables and primary outcome measures are reported as risk ratios (RR) with 95% confidence intervals (CI). Multivariable models were designated in a backward fashion, using the following clinicopathologic variables: age, sex, date of diagnosis, operative approach, tumor laterality, hormone production, tumor dimension, stage, tumor grade, extra-adrenal extension, margin status, lymphovascular invasion, tumor necrosis, tumor thrombus, adjuvant XRT, sites of recurrence, RFI, and reoperative status. All analyses were performed with Stata v 13.0 (StataCorp, College Station, TX).

## Results

Data from 354 patients who underwent primary resection with curative intent for stage I–III ACC were analyzed. Demographics, initial presentation data, and pathology are described in [Table 1](#). The median number of imaging studies reviewed per patient was 6 (range 1–17).

### Timing and sites of recurrence

More than two-thirds of patients ( $n=249$ , 70%) experienced disease recurrence during follow-up. RFI after primary resection was associated with initial recurrence sites in the following order (from shortest to longest): lung, multiple sites (different organs or areas), liver, other single site, peritoneal cavity, tumor bed ([Fig. 1, A](#)). Data for initial and subsequent recurrences and reoperative data, including site-specific risk factors, are outlined in [Tables 2, 3](#), and online Supplemental Fig A. Median RFI after primary resection was 11 months (range 1–200), and factors associated with disease recurrence and RFI are outlined in [Table 4](#). Primary resection performed via laparoscopic approach (versus open resection) was associated with an increased risk of positive margins (29% versus 21%, RR 1.4, CI 1.2–1.6,  $P=.045$ ) and an increased risk of initial peritoneal cavity recurrence (31% vs 16%, RR 1.8, CI 1.3–2.5,  $P=.002$ ). Adjuvant XRT to the tumor bed was associated with a lower risk of subsequent tumor-bed recurrence. Of the 114 patients who received adjuvant XRT, only 15 (13%) recurred in the tumor bed; whereas, of the 241 patients who did not receive adjuvant XRT, 86 (35%) recurred in the tumor bed (RR 0.4, CI 0.2–0.6,  $P < .001$ ).

### Sites of recurrence in those undergoing no reoperation

Of the 242 patients who developed recurrent disease during the study period, 142 patients did not undergo reoperation. Within this nonoperative group, median RFI after primary resection was 8 months. RFI decreased as stage at presentation increased. Initial recurrences in this group were most often to the lungs or multiple sites ([Table 3](#)). Nonsurgical treatments (ie, mitotane, chemotherapy, XRT, or localized interventions) or palliative therapies were employed in these patients. Almost one-third of these patients developed a subsequent recurrence: multiple sites (10), tumor bed (9), liver (8), lung (7), other single site (6), peritoneal (4). Median RFI until second recurrence was 5 months (range 0.4–51). We found that 20 patients then developed a third recurrence, most of which were to the peritoneal cavity (7). A total of 3 patients later developed additional sites of recurrence.

**Table 1**  
Demographic and clinicopathologic data\*.

Patients	354
Male	130 (37%)
Female	224 (63%)
Presentation	
Date of diagnosis	
Before 2000	28 (8%)
2000–2010	171 (48%)
After 2010	155 (44%)
Median age at diagnosis, years (range)	47 (18–83)
Stage at diagnosis	
I	14 (4%)
II	177 (50%)
III	163 (46%)
Hormone secretion	173 (49%)
Surgery	
Primary resection performed at U-M	45 (13%)
Before 2000	7 (15%)
2000–2010	24 (53%)
After 2010	14 (32%)
Open	260 (73%)
Laparoscopic	92 (26%)
Robotic	2 (1%)
Right	159 (44%)
Left	195 (55%)
Tumor thrombus (renal vein, vena cava)	44 (12%)
Reoperations performed at U-M (up to three)	46 (31%)
Pathology	
Tumor size (cm), median (range)	11 (3–30)
High grade	141 (40%)
Positive margins	82 (23%)
Open	55/260 (21%)
Laparoscopic/robotic	27/94 (29%)
Extra-adrenal extension	161 (45%)
MPLI	190 (54%)
Tumor necrosis	241 (68%)
Adjuvant therapy	
Mitotane	168 (47%)
Stage I	29%
Stage II	44%
Stage III	53%
Radiation to tumor bed	114 (32%)
Stage I	21%
Stage II	28%
Stage III	38%
Other systemic chemotherapy	14 (4%)

\* Mitotane therapy duration, dosage, and serum levels were not specifically captured because frequent discontinuation of treatment or a lack of appropriate monitoring of serum mitotane levels (in patients who received most of their treatment elsewhere) precluded such analysis. U-M, University of Michigan; MPLI, microscopic peritumoral lymphovascular invasion.

#### Sites of recurrence in those undergoing reoperations

A second operation (first reoperation or metastasectomy) was performed for initial recurrence in 100 (41%) patients, with the operative intent being curative with surgery alone in 80% (Table 3). Median RFI after primary resection was 17 months (range 0.8–179). Additional recurrence was observed in 79 patients after undergoing a second operation (median RFI 6 months, range 0.2–191), 63 of which had their disease burden previously cleared to no evidence of disease (NED) at reoperation. RFI after second operation was associated with sites of recurrence in the following order (from shortest to longest): lung, peritoneal cavity, multiple sites, other single site, liver, tumor bed (Fig. 1, B). Adjuvant XRT and initial diagnosis after 2010 were associated with a decreased risk of recurrence after second operation (Table 4). Initial tumor-bed or peritoneal cavity recurrences were associated with higher likelihood of subsequent recurrence, although tumor bed recurrence was also a predictor of RFI > 12 months after second operation; however, selection bias likely plays a role in this prolonged RFI. Second recurrence in the same organ or area as the initial recurrence was observed in 67% of cases (tumor bed 25% [median RFI 5.5 months,

range 0.7–115], liver 10% [median RFI 22.0 months, 3.9–108], lung 10% [median RFI 4.2 months, 0.2–11], peritoneal 18% [median RFI 3.4 months, 0.8–38], other single site 4% [median RFI 2.6 months, 1.3–4]), but there were no predictors of same site recurrence in this group.

A third operation (second reoperation or metastasectomy) was performed in 37 (47%) patients. Recurrence after third operation was observed in 29 (78%) patients at a rate of 1 recurrence per 0.9 person-months. Median RFI after third operation was 8 months (range 0.3–90), and RFI was associated with sites of recurrence in the following order (from shortest to longest): liver, peritoneal cavity, multiple sites, lung, other single site, tumor bed. There were no factors associated with prolongation of RFI after a third operation. Third recurrence in the same organ or area as the initial or second recurrence was observed in 72% of cases (tumor bed 21%, liver 10%, lung 24%, peritoneal 14%, other single site 3%), and again there were no predictors of same site recurrence. A fourth operation was performed in 12 (41%) patients. Additional recurrences were observed in 10 (83%) patients, and 3 of these patients went on to have additional surgery.

Of the 354 patients included in the current study, 29% did not develop any recurrence during follow-up (median follow-up 28 months, range 0–180), 34% developed only 1 episode of recurrence, 19% developed 2 episodes of recurrence, 16% developed 3 or more episodes of recurrence, and 2% had recurrences in which the dates or sites were not designated. In patients with initial recurrence to either the lung or peritoneal cavity who then underwent reoperation, all second recurrences occurred within 23 months of reoperation (Fig. 1, B).

Median length of follow-up was 35 months (range 0.2–295); 16% of patients had follow-up of less than 12 months (many visited for single consultations only). There were 160 (45%) deaths verified during the follow-up period at a rate of 1 death per 116 person-months from the time of diagnosis. At the time of last follow-up, 120 (34%) patients had NED and 74 (21%) were alive with disease (AWD). Some patients considered as AWD at last follow-up continued their care at other institutions, of which at least 2 had plans to undergo further surgery elsewhere, 54 (15%) patients were verified to be alive within 3 years of follow-up accrual end date, and the vital status of the remaining 20 (6%) could not be verified.

For those who died during the study period, median overall survival from diagnosis was 80 months (range 1–160) and 53 months (range 1–145) from date of initial recurrence. Duration of overall survival was associated with initial recurrence sites in the following order (from shortest to longest): multiple sites, peritoneal, liver, lung, other single site, tumor bed (Fig. 2). Factors, such as high tumor grade, extra-adrenal extension, initial multiple site recurrence, and RFI < 12 months were strongly associated with decreased overall survival (Table 5). Microscopic peritumoral lymphovascular invasion was an additional factor associated with increased risk of recurrence and decreased survival. Patients who underwent either a second or third operation experienced prolonged survival; whereas additional operations after 3 total surgeries were not associated with significantly improved outcomes (Fig. 3). On multivariable analyses, recurrence patterns were associated with primary tumor biology, date of diagnosis, and adjuvant therapy. In addition, survival was associated with initial recurrence site (Table 6).

#### Discussion

With the aim of describing patterns of disease recurrence in patients with ACC, the key findings of this study are as follows: (1) Most patients with ACC will experience a recurrence of their disease (70% in the current study), although tempo of disease progression will vary by patient and site of initial recurrence, whose cancer recurs will continue to experience additional recurrences even

**Table 2**  
Recurrence by anatomic site.

Episode/Site	n (%)	Recurrence-free interval Median months (range)	Most frequent sites of next recurrence
Initial recurrence	249/354 (70%)		
Tumor bed	40 (11%)	11.1 (1.8–106.6)	Tumor bed
Liver	21 (6%)	11.2 (0.4–96.1)	Tumor bed
Lung	53 (15%)	10.9 (0.5–200.1)	Tumor bed
Peritoneal	21 (6%)	10.2 (1.5–72.1)	Peritoneal
Other single site	9 (3%)	11.1 (0.8–179.4)	Liver, lung
Multiple sites	98 (28%)	10.5 (0.6–99.4)	Multiple sites
(Tumor bed 61, liver 57, lung 49, peritoneal 50, other 11)			
Unknown site	7 (3%)		
Second recurrence	123/242 (51%)		
Tumor bed	25 (20%)	10.3 (0.9–116.1)	Lung
Liver	18 (15%)	7.8 (0.4–52.2)	Lung
Lung	21 (17%)	3.8 (0.7–22.1)	Peritoneal
Peritoneal	21 (17%)	10.1 (0.6–191.1)	Lung, liver
Other single site	9 (7%)	6.0 (0.9–45.7)	Other single site
Multiple sites	29 (24%)	7.1 (0.4–107.6)	Peritoneal, other single site
(Tumor bed 16, liver 11, lung 14, peritoneal 14, other 10)			
Third recurrence	57/123 (46%)		
Tumor bed	7 (12%)	16.6 (11.4–32.1)	Other single site
Liver	6 (11%)	4.6 (0.8–24.0)	Other single site
Lung	10 (18%)	8.3 (0.6–64.2)	Lung
Peritoneal	11 (19%)	7.1 (0.9–26.9)	Peritoneal
Other single site	9 (16%)	5.1 (1.9–23.0)	Multiple sites
Multiple sites	14 (25%)	10.0 (0.5–93.4)	Lung, multiple sites
(Tumor bed 3, liver 9, lung 10, peritoneal 6, other 5)			
Additional recurrences	20/57 (35%)		

**Table 3**  
Reoperations by recurrence site.

Episode/Site	n (%)	Recurrence-free interval median months (range)	Survival after (re)operation median months (range)
Patients with recurrent disease	249/354 (70%)		
Unknown reoperative status	7		
No reoperation	142	7.9 (0.5 - 200)	27.4 (3.6–216)
Tumor bed	10 (7%)	14.4 (1.8–80)	31.5 (5.8–135)
Liver	12 (9%)	8.4 (0.4–54)	35.5 (8.4–138)
Lung	35 (25%)	6.0 (0.5–200)	33.3 (5.7–216)
Peritoneal	10 (7%)	7.2 (0.3–22)	23.4 (6.9–53)
Other single site	3 (2%)	12.3 (11–43)	104 (18.4–105)
Multiple sites	72 (51%)	7.8 (0.6–92)	24.7 (3.6–133)
Second operation	100	16.5 (0.8–179)	29 (0.4–198)
Tumor bed	29 (29%)	17.6 (2.1–107)	74.2 (0.4–198)
Liver	9 (9%)	45.0 (3.5–96)	55.7 (2.6–179)
Lung	18 (18%)	9.8 (1.0–28)	26.9 (2.5–137)
Peritoneal	12 (12%)	27.3 (2.5–52)	16.8 (0.7–121)
Other single site	6 (6%)	15.3 (0.8–179)	25.5 (4.3–151)
Multiple sites	26 (26%)	17.0 (2.9–99)	16.7 (0.4–157)
Curative, surgery alone	80 (80%)		
Curative, MTM	10 (10%)		
Debulking	10 (10%)		
Performed at U-M	33 (33%)		
Third operation	37	6.0 (0.2–191)	36.1 (0.3–165)
Tumor bed	6 (16%)	5.9 (1.8–115)	51.8 (12.5–110)
Liver	8 (22%)	14.6 (2.6–49)	41.0 (0.3–82)
Lung	7 (19%)	5.4 (0.2–21)	51.8 (27.4–165)
Peritoneal	8 (22%)	6.5 (0.8–191)	43.6 (6.4–119)
Other single site	2 (5%)	11.0 (3.9–18)	57.4 (18.6–96)
Multiple sites	6 (16%)	5.1 (0.7–108)	20.1 (5.1–54)
Curative, surgery alone	31 (84%)		
Curative, MTM	1 (3%)		
Debulking	5 (14%)		
Performed at U-M	9 (24%)		
Fourth operation	12	8.5 (0.3–90)	29.2 (0.6–86)
Tumor bed	3 (25%)	17.9 (11.4–32)	15.0 (1.5–53)
Liver	0 (0%)	N/A	N/A
Lung	2 (17%)	5.9 (0.6–64)	33.2 (0.6–67)
Peritoneal	4 (33%)	6.7 (0.3–8)	29.2 (13.5–86)
Other single site	1 (8%)	15.3	18.3
Multiple sites	2 (17%)	15.3 (2.5–90)	53.7 (42.5–65)
Curative, surgery alone	7 (58%)		
Curative, MTM	1 (8%)		
Debulking	4 (33%)		
Performed at U-M	4 (33%)		
Additional operations	4		

MTM, multimodal treatment of multiple site recurrent disease; U-M, University of Michigan.

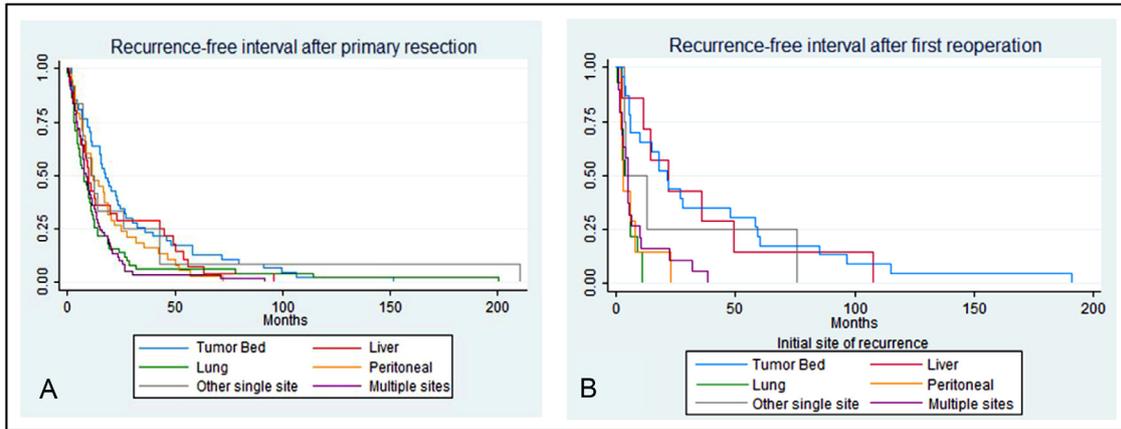


Fig. 1. Kaplan-Meier plots of recurrence-free interval by sites of initial recurrence, after (A) primary resection ( $n=242$ ), and (B) second operation ( $n=72$ ).

**Table 4**  
Factors associated with recurrence (unadjusted)\*.

	Risk Ratio	95% Confidence Interval	P value
Recurrence after primary resection ( $n=249$ )			
Diagnosis after 2010	0.7	0.6–0.8	< .001
Tumor size > 12cm	1.2	1.0–1.3	.034
High grade	1.3	1.1–1.5	< .001
Extra-adrenal extension	1.2	1.0–1.4	.010
MPLI	1.3	1.1–1.5	.033
Adjuvant radiation	0.6	0.5–0.7	< .001
Site of initial recurrence ( $n=242$ )			
Tumor bed			
Diagnosis after 2010	0.6	0.4–0.8	.003
High grade	1.5	1.0–2.1	.030
Adjuvant radiation	0.4	0.2–0.6	< .001
Liver			
Tumor size > 10cm	2.0	1.3–3.1	.003
Lung			
Tumor size > 14cm	1.9	1.4–2.6	< .001
Extra-adrenal extension	2.0	1.4–2.8	< .001
High grade	1.7	1.2–2.4	.003
Tumor thrombus	1.7	1.0–2.8	.048
Peritoneal			
Laparoscopic resection	1.9	1.3–2.9	.002
High grade	1.7	1.1–2.7	.016
Multiple sites			
High grade	1.6	1.1–2.4	.008
Positive margins	1.4	1.1–1.8	.005
RFI < 12 months after primary resection ( $n=134$ , 38%)			
High grade	2.2	1.7–3.0	< .001
Extra-adrenal extension	1.7	1.3–2.3	< .001
Positive margins	1.2	1.0–1.5	.048
MPLI	1.4	1.0–2.1	.043
Tumor necrosis	4.1	1.4–12.2	.010
Lung recurrence, initial	2.5	2.0–3.3	< .001
Multiple site recurrence, initial	1.9	1.5–2.5	< .001
Second recurrence ( $n=123$ )			
Diagnosis after 2010	0.5	0.3–0.6	< .001
Adjuvant radiation	0.5	0.4–0.8	.001
Tumor bed recurrence, initial	1.9	1.4–2.5	< .001
Peritoneal recurrence, initial	1.4	1.0–1.9	.031
RFI < 12 months after second operation ( $n=51$ , 51%)			
Tumor bed recurrence, initial	0.7	0.5–0.9	.033
Lung recurrence, initial	1.2	1.0–2.1	.041
Peritoneal recurrence, initial	1.5	1.1–1.9	.009
Third recurrence ( $n=57$ )			
Diagnosis after 2010	0.3	0.1–0.5	< .001
Adjuvant radiation	0.5	0.3–0.9	.017
Tumor bed recurrence, initial	2.0	1.2–3.1	.005
RFI < 12 months after third operation ( $n=14$ , 38%)			
None			

\* Clinicopathologic variables listed in the Methods section of this report were assessed, and only significant associations are presented here (based on a  $P$  value < .05).  
RFI, recurrence-free interval; MPLI, microscopic peri-tumoral lymphovascular invasion.

**Table 5**  
Factors associated with survival (unadjusted)\*.

	Risk ratio	95% Confidence interval	P value
Death (n = 160, 45%)			
Survival > 2 years (n = 226, 64%)			
High grade	0.7	0.6–0.9	.001
Extra-adrenal extension	0.8	0.7–0.9	.006
Positive margins	0.8	0.7–1.0	.037
RFI < 12 months after primary resection	0.6	0.5–0.8	< .001
Survival > 5 years (n = 110, 31%)			
High grade	0.5	0.3–0.7	< .001
Extra-adrenal extension	0.6	0.4–0.8	.003
Positive margins	0.7	0.5–0.9	.018
Peritoneal recurrence, initial	0.6	0.4–0.9	.032
Multiple site recurrence, initial	0.4	0.3–0.7	.001
RFI < 12 months after primary resection	0.3	0.2–0.5	< .001
Survival > 10 years (n = 34, 10%)			
High grade	0.3	0.1–0.8	.015
Extra-adrenal extension	0.4	0.2–0.9	.024
Length of overall survival			
High grade	0.6	0.5–0.8	< .001
Extra-adrenal extension	0.7	0.6–0.8	< .001
Positive margins	0.8	0.7–0.9	.004
MPLI	0.8	0.6–1.0	.048
Tumor bed recurrence, initial	1.2	1.0–1.6	.049
Peritoneal recurrence, initial	0.8	0.6–0.9	.020
Multiple site recurrence, initial	0.7	0.6–0.8	<.001
RFI < 12 months after primary resection	0.5	0.4–0.6	<.001

\* Clinicopathologic variables presented in the Methods section of this report were assessed, and only significant associations are listed in this Table (based on a P value < .05). RFI, recurrence-free interval; MPLI, microscopic peri-tumoral lymphovascular invasion.

**Table 6**  
Multivariable analyses of recurrence and death\*.

	Risk Ratio	95% Confidence Interval	P value
Initial recurrence (P < .001, R <sup>2</sup> = 0.233, obs. 289)			
Diagnosis after 2010	0.5	0.3–0.7	.005
Tumor size > 12 cm	2.1	1.3–3.8	.002
High grade	2.8	1.4–4.3	<.001
Extra-adrenal extension	1.8	1.2–3.6	.001
MPLI	1.2	1.1–1.4	.041
Adjuvant radiation	0.4	0.3–0.5	.009
Second recurrence (P < .001, R <sup>2</sup> = 0.034, obs 328)			
Adjuvant radiation	0.6	0.4–0.8	<.001
Third recurrence (P < .001, R <sup>2</sup> = 0.066, obs 354)			
Diagnosis after 2010	0.4	0.3–0.5	<.001
Death during study period (P < .001, R <sup>2</sup> = 0.254, obs 324)			
Diagnosis after 2010	0.5	0.2–0.7	<.001
High grade	2.2	1.4–3.0	<.001
Liver recurrence (initial)	2.8	1.3–4.1	<.001
Lung recurrence (initial)	2.1	1.5–2.9	.003
Peritoneal recurrence (initial)	3.1	1.7–5.4	<.001

\* Multivariable models were designated in a backward fashion, using the clinicopathologic variables presented in the Methods section of this report. MPLI, microscopic peri-tumoral lymphovascular invasion; obs, observations

after reoperations clear disease burden to NED (79%). (2) Although metastatic disease to the lung may occur early, recurrences in multiple sites or in the peritoneal cavity are associated with worse survival. (3) Recurrence in the same organ or site after reoperation is common; however, adjuvant XRT appears to limit tumor-bed recurrence. (4) With time, recurrences are found in more distant (other single sites) or multiple sites, limiting options for surgical or other locally directed therapy. Armed with these findings regarding patterns of recurrence, in conjunction with knowledge of tumor biology and primary resection characteristics (R0 resection, lack of tumor spillage, open resection, adherence to oncologic principles, etc), clinicians may be able to make more informed decisions as they develop overall treatment plans for patients (Fig. 4).

The current study has several strengths, most notably the high volume of patients evaluated or treated at a single institution. In addition, we have sought to track disease course longitudinally in a

detailed fashion, as opposed to reporting recurrences without consideration of time or ongoing treatment. To our knowledge, this is the first time data for ACC recurrence has been reported in this manner. Pathologic evidence of microscopic peritumoral lymphovascular invasion (as opposed to gross evidence of large vessel invasion) is now documented as an additional factor associated with increased recurrence and decreased survival (Tables 4 and 5). This factor, in combination with others, may contribute to the early recurrences observed in the lung and liver. The significance of initial recurrence in the peritoneal cavity having the shortest survival of any single site once again brings conduct of the initial resection to the forefront of a continuing debate. Those undergoing open resection (as opposed to laparoscopic resection) continue to fare better in this expanded data set in terms of minimizing peritoneal recurrence.<sup>23–25</sup> Despite laparoscopic primary resection being associated with a higher rate of positive margins, operative approach

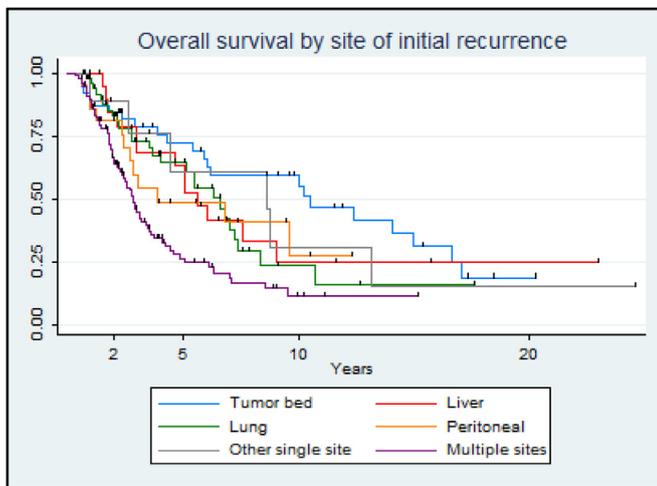


Fig. 2. Kaplan-Meier plot of overall survival by sites of initial recurrence ( $n=354$ ). Censored patients (hash marks).

was not associated with an increase in tumor-bed recurrence in this current study; however, this finding is likely influenced by the increased recommendation for XRT to the tumor bed by our group during the past decade. Last, serial resections of recurrences over time may be feasible in some patients, but pursuit beyond three total operations should be carefully considered on an individual patient basis because there is a decreasing impact on survival with an increasing number of operations and RFI shortens between each reoperation (Fig. 3).

Several studies have previously evaluated the feasibility, safety, and impact of surgery in patients with recurrent ACC. Some have reported sites of recurrent disease but not in a sequential fashion as in the current study. In a study using data from the German ACC registry, improved survival was noted to occur in patients undergoing surgery for recurrent disease, but 94% again recurred.<sup>14</sup> The Mayo Clinic group reported a 3.5-year median survival and symptomatic improvement in 80% of ACC patients with hormone excess.<sup>13</sup> Improvement in survival persisted over those receiving best medical or supportive therapy, including those having R1 resections. In another study evaluating reoperative surgery for ACC, survival was improved if recurrent disease was solitary, occurred locoregionally, or occurred in the lungs; however, morbidity and mortality rates were found to be considerable and should be considered in the decision-making process.<sup>16</sup> The 30-day morbidity in the 56 patients undergoing reoperation was 40%, with mortality of 5.4%. Operations for locoregional and liver resections had the highest morbidity (20% and 28%, respectively).

Given this information, coupled with our finding that repeated recurrence in the same site is likely, future recommendations for formal surgical resection may change in some instances to selection of other localized, non-anatomic resections or less invasive treatments. These alternative therapies, such as stereotactic beam radiation, radiofrequency ablation, microwave ablation, or cryoablation, often result in preservation of greater amounts of normal tissue (eg, lung and liver), may limit procedure-related morbidity, shorten recovery time, and may allow for better quality of life during the treatment phase. Diligent surveillance of patients is warranted, given the likelihood of repeated recurrence. The longest initial RFI in the current study was 16 years. In a separate study, recurrence was noted in 7 of 12 patients after 10 years.<sup>15</sup> Going forward, we suggest long-term surveillance strategies for patients with ACC, extending further into the future, with anticipation of development of additional (and more distant) recurrences.

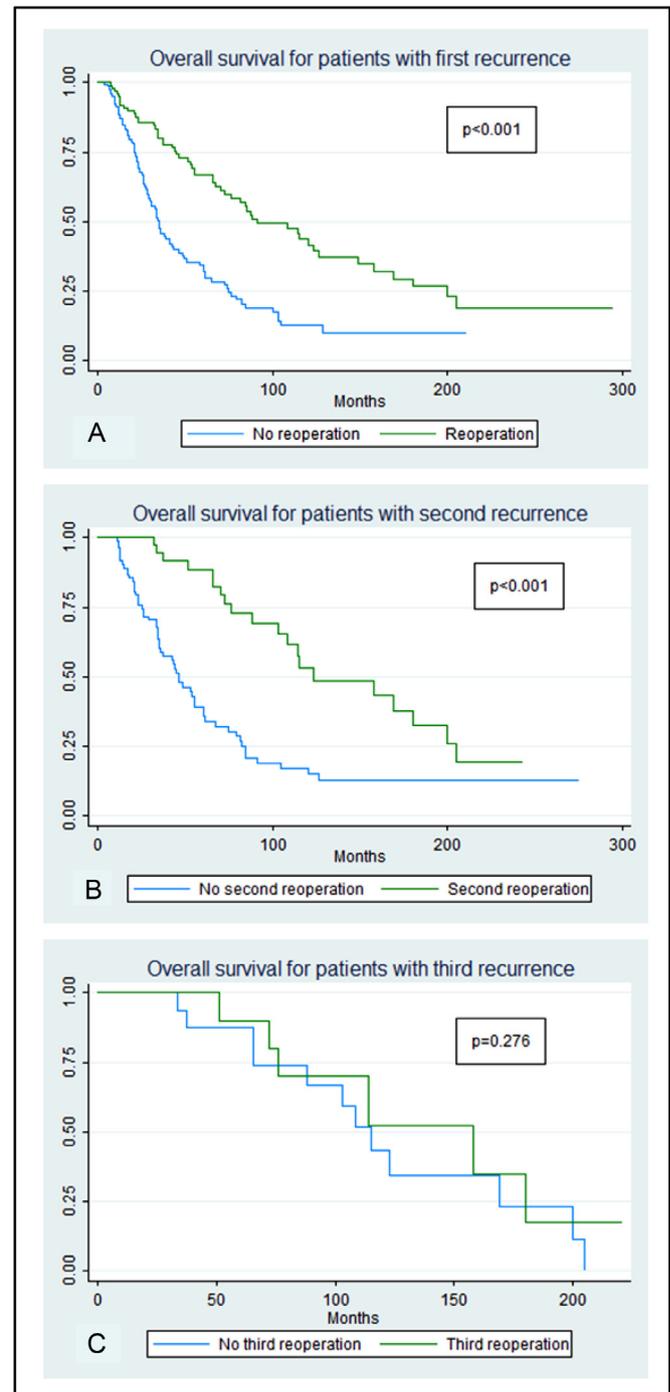


Fig. 3. Kaplan-Meier plots of overall survival for patients who underwent reoperation versus no reoperation after (A) first recurrence, (B) second recurrence, and (C) third recurrence.

The findings of the current study should be considered in the context of its limitations, some of which are inherent to retrospective studies, rare diseases, and quaternary referral centers. This study group represents a heterogeneous population, and the data set is influenced by referral and indication bias. Patients are evaluated at different time points in their disease course. Some are primarily treated at our institution, and others seek only our opinion and receive most of their care elsewhere. Variations in medical and surgical treatment between institutions, as well as other factors affecting recurrence and the decision to reoperate, cannot be accounted for in this data set. Likewise, enhanced diag-

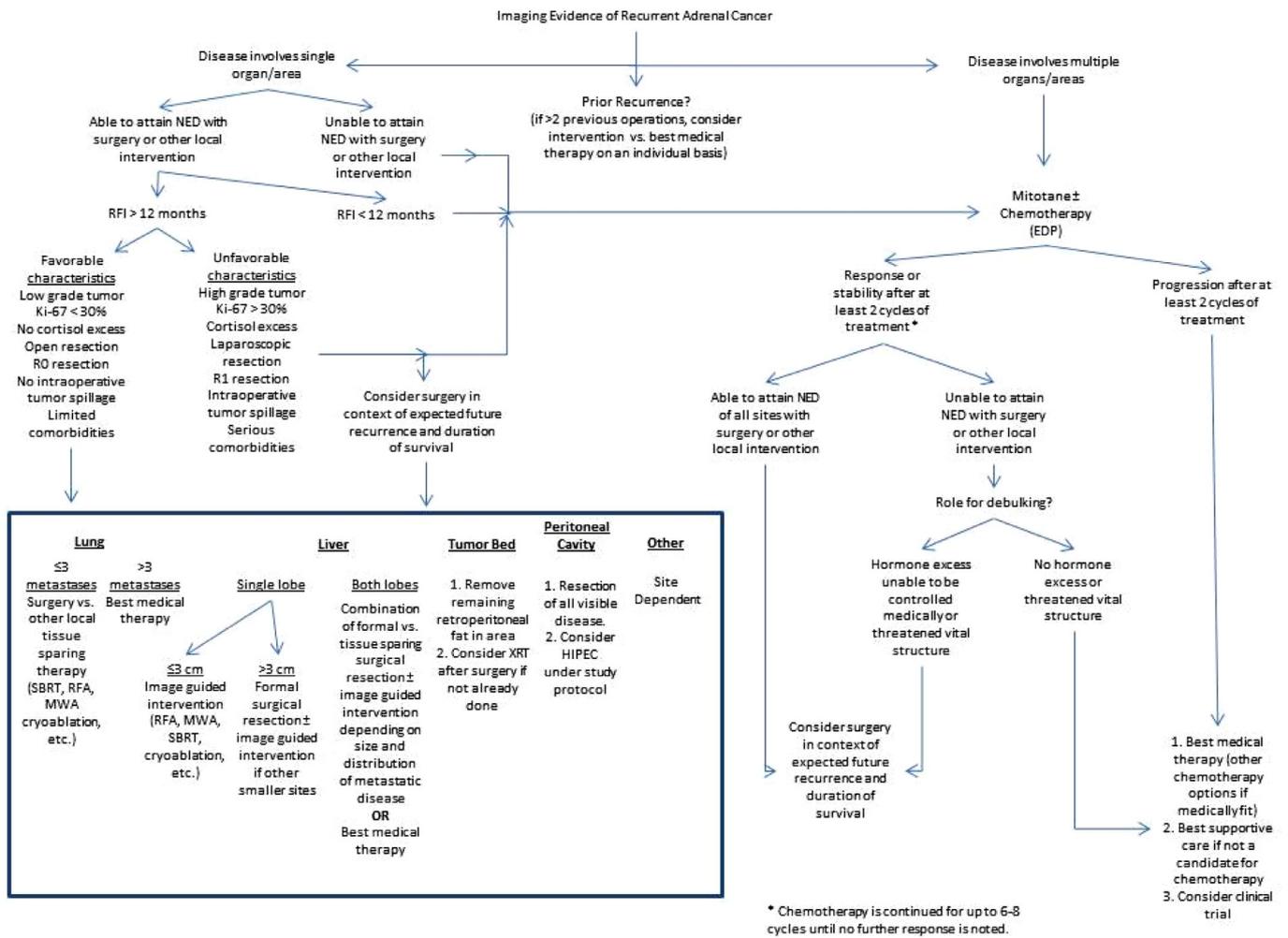


Fig. 4. University of Michigan treatment algorithm for patients with recurrent metastatic disease after primary resection of adrenocortical carcinoma with curative intent.

nostic technologies, improved surgical techniques, and changes in adjuvant therapy regimens have likely influenced the management and outcomes of recurrences throughout the course of this study.

Based on the data presented in the current study and taking earlier studies into consideration, we have developed the algorithm presented in Fig. 4. This represents the general approach (and does not encompass all potential decision points or options) taken by our Multidisciplinary Endocrine Oncology Group when considering the care of patients with recurrent ACC. Deviation from this algorithm may occur depending on the situation because care is individually tailored to the patient. As an overarching theme, we remember that the quest for increased duration of survival must be balanced with the patient's quality of life, values, and expectations.

In conclusion, a majority of patients with ACC experience disease recurrence. Survival appears to vary based on site of recurrence and other clinicopathologic factors, all of which should be considered when contemplating treatment of patients with recurrent ACC. In the future, general knowledge of temporal and spatial patterns of recurrence may assist in anticipating disease course and lead to more informed treatment selection for patients with recurrent ACC.

**Conflicts of interest**

Gary Hammer, MD, PhD, is a Founder and Advisor for Millendo and an Advisor for Orphagen.

**Supplementary materials**

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.surg.2018.04.068.

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## Discussion

**Dr Richard A Prinz** (Evanston, IL): Very nice presentation on a problem that continues to vex us. You mentioned that there was a difference in the frequency of recurrence after 2010. Is that related to the size of the tumors that you are seeing? Perhaps screening with CT and so forth is giving us a different type of disease in recent years?

Second, I know that this was not the focus of the study, but do you have any thoughts on how this information is changing your approach to the tumor bed, where hopefully we can limit the local recurrence?

**Dr Jason Glenn:** Thank you for your questions.

I think that the difference we see after 2010, at least at our institution, may be that we are picking up more of these on imaging, potentially earlier, which may translate to more operations. But really the protective effect after 2010, I think, is more due to the standardization of care. Around that time is when we formed our multidisciplinary endocrinology group. Hopefully, we are seeing some improvements in surgical techniques and adjuvant therapies over time as well.

As far as changing our approach, I can't really say at this point. We have developed a management algorithm for patients based on our experience, but any data related to operative conduct and outcomes specifically is still forthcoming.

**Dr Janice Pasioka** (Calgary, AB, Canada): Jason, very nicely presented. I may have missed it, but was function of the tumors part of your analysis, since about 60% seem to be functioning?

The other question is whether you have any data on the histologic type? Oncocytic adrenocortical carcinomas we think may behave a little bit differently, and I am wondering what your analysis would show if you looked at those separately.

**Dr Jason Glenn:** As this is a heterogeneous group, we are seeing patients as referrals from a number of different institutions over a long period of time. The beginning of the study period was 1983 and it ended in 2017. So there's obviously some variability in reporting of hormonal status and standardization between institutions.

We did not characterize each hormone (cortisol versus aldosterone versus sex hormones) separately. We did look at the group as a whole, and it was not found to be significant.

As far as the histologic type, the limitations were similar. Again, we are looking at a wide range of time and institutions.

Our pathologist did look at all of the slides and cell blocks that we were able to obtain from these other institutions, but we did not specifically look at each individual histologic type as a variable.

**Dr Scott Wilhelm** (Cleveland, OH): I was curious if you looked specifically at the amount of time to recurrence? Obviously, the most common type is tumor-bed recurrence. For the time-to-bed recurrence, did that impact what percentage of patients on whom you went back and did that re-resection? I think you said your average was 14 months to your third recurrence for tumor-bed resections, but did that vary with the amount of time for the first occurrence or not? I think that is important for us to know in selecting patients for going back for re-resections.

**Dr Jason Glenn:** We didn't look at it specifically. Definitely, those who had an initial recurrence rate interval longer than 12 months were more likely to undergo reoperation.

I was surprised to find that once they went down that reoperative arm, the recurrence-free interval became less important in the decision to reoperate after that.

**Dr Peter Mazzaglia** (Providence, RI): Congratulations on this large series of patients.

Correct me if I am wrong, but I think you managed to talk about over 300 ACC patients without mentioning mitotane. I may be opening Pandora's box—but you talked about local radiation and its effect, and I'm just curious why you chose not to look at mitotane. Did it complicate the picture too much? Do you plan to look at it in the future?

**Dr Jason Glenn:** Excellent question. We looked at radiation therapy because it was much easier to standardize between institutions whether or not they got radiation therapy. For patients who are on mitotane at one point or another, it is very difficult to tell whether or not they were at therapeutic levels, if levels were even drawn, how much they were on, or if they had any interruptions



in therapy. We looked at whether or not they were on it at any point, and it didn't come out to be significant.

**Dr Amanda Laird** (New Brunswick, NJ): I think that your data certainly show the importance of keeping databases on your patients because it is quite a large series of patients with adrenocortical cancer.

I think we all expect patients with ACC to recur, and the question for me at least has been not exactly where, but when, and is it surgically resectable? So how is it that knowing where and how it might recur impacts or influences your treatment?

**Dr Jason Glenn:** Again, we clearly saw that a recurrence interval less than 12 months was a negative predictor of survival, so in many instances we use recurrence-free interval as a decision point.

We found that certain sites showed up at shorter intervals versus longer intervals. If it's treated adequately, survival and prognosis can still be quite good. But again, it's very site and procedure specific.