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Stage and disease-free interval help select patients for surgical management of locally recurrent and metastatic adrenocortical carcinoma

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Abstract

Background and Objectives: Chemotherapeutic options for patients with recurrent/metastatic adrenocortical carcinoma (ACC) are limited, leading to consideration for surgical management. We sought to determine characteristics associated with an unequivocal survival benefit amongst patients undergoing re-resection or metastasectomy.

Methods: Patients who underwent surgery for recurrent/metastatic ACC were identified and stratified into two groups: those with postoperative survival comparable with what has been reported with chemotherapy alone (<12 months) and those surviving twice that duration (>24 months). Those who survived between 12 and 24 months were excluded, as the objective was to characterize patients who most distinctly benefited from resection. Clinicopathologic and treatment variables were evaluated for associations with survival.

Results: Forty-three patients survived more than 24 months and 15 patients died less than 12 months after reoperation. Tumor stage (odds ratio [OR], 0.66; 95% confidence interval [CI], 0.45–0.96) and disease-free interval (DFI; OR, 3.23; 95% CI, 1.68–6.22) were associated with prolonged survival. Tumor size, hormonal status, resection margin, and treatment with chemotherapy, radiation, and mitotane were not associated with prolonged survival. Patients who survived more than 24 months underwent more procedures for subsequent recurrences (median 4 vs 2; $P < .001$).

Conclusion: Stage and DFI can help select optimal candidates for resection of recurrent/metastatic ACC. Patients selected for surgical management should be informed of the likelihood of requiring multiple interventions.

Keywords

adrenocortical carcinoma; metastasectomy; reoperation

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

1 | INTRODUCTION

Adrenocortical carcinoma (ACC) is an aggressive disease with a dismal prognosis. Patients are frequently diagnosed at an advanced stage and 5-year overall survival (OS) for patients with stage IV disease is estimated to be less than 13% to 17%.[1,2] Even after complete resection, recurrence is common and median survival is only 23 months.[3] There is no globally accepted standard for the management of oligometastatic disease, though current recommendations encourage multidisciplinary discussion and use of mitotane, multimodal chemotherapy, surgery, and radioablative procedures in highly selected patients.[4,5] European guidelines recommend surgery for locally recurrent disease and oligometastatic disease when R0 resection is achievable, in low-risk patients (ie, delayed recurrence, low Ki-67 status), and when the operation can be performed with low morbidity and mortality rates.[5]

Radical resection for the oligometastatic or locally recurrent disease has previously been described.[6–11] Patients who have been selected to undergo radical resection for metastatic disease experience longer survival than patients who undergo debulking procedures or medical management alone.[8,9] While early studies reported moderately high rates of complications and some mortalities,[6] recent studies have demonstrated that pulmonary and hepatic metastasectomy can be performed with no mortalities and acceptable perioperative morbidities.[7–11] Despite radical resection; however, up to 94% of patients develop disease progression in some series.[10] The current challenge is how to prospectively discern which patients may experience long-term survival compared with those in whom resection is futile.

The aim of this study was to describe the characteristics of patients who survived at least 2 years after their first resection for disease recurrence and to identify predictors associated with prolonged survival after surgical intervention.

2 | MATERIALS AND METHODS

A single-institution, retrospective review was performed to identify patients diagnosed with ACC who had undergone surgical resection for metastatic or locally recurrent disease (which we will refer to as metastasectomy) at our institution. The patient data used for this study were deidentified before evaluation by the authors and were exempt for review from our Institutional Review Board. We chose to group patients with the locally recurrent and distant diseases together given the limited number of patients and the fact that both are potentially managed operatively. Patients were divided into two groups based on the survival of less than 12 months or more than 24 months after the first metastasectomy. Those who survived between 12 and 24 months after metastasectomy were excluded, as the aim was to characterize patients who most clearly benefited from resection. Patients who had less than 12 months follow-up after the first metastasectomy were also excluded (Figure 1). Patients were surveilled with imaging and laboratory evaluation every 3 to 6 months for 5 years after metastasectomy and annually thereafter. Patient and tumor-specific data were collected and included tumor size at diagnosis, AJCC/ENSAT stage, functional status, the extent of resection, receipt of chemotherapy, receipt of radiotherapy, time to recurrence(s), and management of recurrence(s). Disease recurrence was defined as local and/or metastatic

disease and was determined by radiographic and/or clinical documentation. Disease-free interval (DFI) was defined as the time from index adrenalectomy to the time recurrent/metastatic disease was diagnosed. For patients who underwent metastasectomy at the time of index adrenalectomy (ie, those who presented with stage IV disease), a DFI of 0 months was assigned. Patients who did not undergo an R0 resection at initial adrenalectomy were also assigned a DFI value of 0 months.

Initially, univariate statistical methods were used to identify which factors may be associated with long (>24 months) vs short (<12 months) survival after metastasectomy. Factors were compared between these two groups of patients using an exact Wilcoxon rank-sum test for continuous parameters, a Fisher's exact test for two-group parameters, Mehta's modification to Fisher's exact test for unordered categorical parameters, and a Cochran-Armitage trend test for ordered categorical parameters. After univariate analysis to determine eligibility for inclusion in a multivariable model ($P < .10$), a multiple logistic regression was performed to identify factors that associated with patient survival less than 12 months or ≥24 months from metastasectomy. Factors found to be significant were further used to construct a classification model to predict survival after metastasectomy. All P values were two-tailed and reported without adjustment for multiple comparisons. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

3 | RESULTS

3.1 | Patients

Eighty-three patients underwent resection for metastatic or locally recurrent ACC at our institution between 1988 and 2016. Median follow-up for the cohort was 103 months (range, 0–206 months). Twenty-five patients were excluded, either due to survival between 12 and 24 months (n = 11), or follow-up of less than 12 months from first metastasectomy (n = 14). Of the 58 patients meeting our selection criteria, 43 (74%) survived at least 24 months after the first metastasectomy and 15 (26%) died within 12 months (Table 1). Median age at diagnosis did not differ significantly between groups (42 vs 45; $P = .405$). Metastasectomy procedures were predominantly pulmonary and hepatic resections, with a minority of patients undergoing ablations (radiofrequency, microwave, and cryoablation procedures) and laparotomies for peritoneal or retroperitoneal recurrent disease.

The majority of patients who survived less than 12 months were diagnosed with stage IV disease (n = 8; 53.3%). Their median tumor size was 10.3 cm and 53.3% (n = 8) had functional tumors. None of these patients received neoadjuvant systemic therapy. Of patients whose records commented on surgical margin at index adrenalectomy, half did not have an R0 resection (n = 6). Ten patients received adjuvant mitotane, and nine patients were given some form of platinum-based chemotherapy. Four patients underwent adjuvant radiation or an ablative procedure after initial adrenalectomy. Median DFI was 3.4 months.

A smaller proportion of patients who survived ≥24 months were diagnosed with stage IV disease (n = 7; 16.3%). The median tumor size amongst these patients was 10.8 cm. Forty-nine percent of patients (n = 21) had functional tumors. Two patients received neoadjuvant therapy. In contrast to the shorter survival cohort, most patients (n = 26; 60.5%) had an

R0 resection. Most patients (n = 38; 88.4%) received adjuvant mitotane though only 25 (58.1%) received adjuvant platinum-based chemotherapy. Twenty-one patients underwent some form of adjuvant radiation or postoperative ablative procedure. Median DFI in this cohort was 16.0 months. Further, patients who survived at least 24 months after the first metastasectomy underwent more subsequent operations and ablative procedures for metastatic disease (median number of procedures 4 vs 2; $P < .001$; Table 1; Figure 2).

3.2 | Predictors of survival

Patients who died within 12 months of initial metastasectomy were more likely to present with stage IV disease (53.3% vs 16.3%; $P = .010$) (Table 1). However, there was no significant difference in the proportion of functional tumors, receipt of neoadjuvant chemotherapy, the extent of primary tumor resection, or treatment with adjuvant mitotane, etoposide/doxorubicin/cisplatin (EDP), or radiation. Survival ≥24 months from index metastasectomy was associated with a significantly longer DFI between initial adrenalectomy and first recurrence of disease (median 16.0 vs 3.4 months; $P < .007$) (Table 1, Figure 2).

After univariate determination of factors differing between survival groups, a multiple logistic regression analysis was used to identify factors that were independently associated with survival. The extent of primary tumor resection was excluded from the multiple logistic regression because adrenalectomy margin data was only available in 43 of 58 patients. Additional procedures were also excluded from the multivariable model because it is not a factor that would be known before metastasectomy. The multiple logistic regression demonstrated that both stage at diagnosis (odds ratio [OR], 0.657; 95% confidence interval [CI], 0.449–0.961) and DFI (OR, 3.234; 95% CI, 1.682–6.219) were independently associated with survival. A classification model using these parameters was able to correctly predict 71.4% of patients who died within 1 year and 70.3% of patients who survived at least 2 years from metastasectomy (Figure S1).

4 | DISCUSSION

ACC is an aggressive malignancy with a proclivity for metastasis and recurrence. Multiple consensus statements and clinical guidelines recommend surgical management of locally recurrent or oligometastatic ACC if complete resection is feasible.[5,12,13] However, the optimal candidates for these potentially morbid operations remain a matter of uncertainty. In this study, we sought to identify characteristics associated with an unambiguous survival benefit after re-resection or metastasectomy for recurrent/metastatic ACC. We found that a higher stage at initial diagnosis and a prolonged DFI were predictive of prolonged survival after these procedures.

The limitations of systemic chemotherapy for recurrent/metastatic ACC highlight the importance of selecting patients for surgical management. Mitotane has long been the mainstay of systemic therapy for ACC despite very modest response rates and a narrow therapeutic window.[14–16] The only treatment regimen for ACC to be studied in a randomized trial is mitotane plus etoposide, doxorubicin, and cisplatin (EDP-M). In comparing this to mitotane monotherapy, the authors demonstrate superior objective response rates with

EDP-M (23% vs 9%; $P < .001$), but comparably poor rates of OS in both treatment arms approximating 1 year.[17] Although systemic therapy may benefit patients with inoperable disease, resection remains the only potentially curative treatment for ACC.

Surgery has previously been evaluated for the management of recurrent ACC. Multiple studies have demonstrated the safety and efficacy of pulmonary metastasectomy[18,19] and hepatic metastasectomy.[7,8] However, there is little consensus as to the tumor- and patient-specific factors that indicate better candidates for aggressive surgical resection. DFI has been previously reported as an important prognostic factor for survival in ACC. A prior study by Ripley et al[8] found that DFI more than 9 months was predictive of longer survival after hepatic metastasectomy or ablation for metastatic ACC. Similarly, Erdogan et al[10] and Tran et al[20] found that DFI less than 12 months was independently predictive of poor survival after repeat resection of recurrent ACC. On the other hand, a recent study by the German Adrenocortical Carcinoma Study Group found that prolonged DFI was not associated with survival in their multivariable analysis ($P = .116$).[11] Our finding of DFI as a predictor of longer survival after the first metastasectomy validates DFI as an important prognostic factor for patients with metastatic or recurrent ACC that should be considered when contemplating a major resection.

Previous reports have not demonstrated the tumor stage to be significant in stratifying patients with recurrent/metastatic ACC.[21,22] One problem that may contribute to the limited prognostic value of stage is the inherent nature of the ENSAT/AJCC staging system for ACC, which relies on lymph node status in the overall staging schema. Previous studies by the US Adrenocortical Carcinoma Study Group suggest that the majority of patients undergoing adrenalectomy for ACC do not have a lymphadenectomy.[20,23] It is therefore possible that the many patients with ACC are understaged at the time of their index adrenalectomy. In our cohort, the stage was found to be predictive of prolonged survival after metastasectomy. However, it should be noted that nearly one in five of the patients with prolonged survival had stage IV disease at the time of diagnosis. This suggests that stage alone is insufficient to determine which patients will benefit the resection of metastatic/recurrent ACC.

Surgical margin status was not associated with survival in our patient cohort. This differs from what has been previously reported. In a multi-institution study evaluating margin status on recurrence-free survival, margin status was an independent predictor of worse OS (hazard ratio, 2.22; 95% CI, 1.03–4.77; $P = .04$) and recurrence-free survival.[24] In a separate National Cancer Database analysis evaluating adrenalectomy for ACC between 1998 and 2012, margin status was a significant predictor of survival with microscopically and macroscopically positive margin status associated with compromised survival.[25] The discrepancy between our findings and those observed in larger studies could potentially be attributed to the unavailability of margin data from primary adrenalectomy in our cohort. Most of the patients in our dataset were referred for subsequent metastasectomy and data on the index surgery was available for only 68.6% (35 of 51) subjects. Thus, our observation is limited by the incomplete reporting available from index adrenalectomy in our dataset.

In addition to DFI and stage predicting survival, our findings also suggest that patients exhibiting longer survivorship underwent a higher number of subsequent procedures for metastatic disease. This has previously been described by the US Study Group, which characterized the differences between patients with early (<2 years) vs long (10 years) survival following operative intervention for primary disease. Seven of the twelve 10-year survivors characterized in this report experienced recurrent disease. Of those seven patients, 71% underwent subsequent resections for metastatic disease, suggesting there is a role for serial interventions in this patient population.[23] It is certainly possible that the increased number of interventions observed amongst prolonged survivors is simply a function of these patients living long enough to undergo additional operations. Furthermore, the need for future operations is not something that would be knowable at the time of metastasectomy, and therefore cannot be used to select patients for these procedures.

The results of this study bolster previous reports of DFI being useful for predicting longer survival and add stage at diagnosis as another predictive factor. However, our conclusions are not without significant limitations. First, our study is limited by the retrospective nature of this examination as well as the heterogeneity of patients in the studied cohort. The patients examined were accrued over a long observation period and underwent a broad variety of treatment regimens. Since the FIRM-ACT trial,[17] EDP-M has become commonly accepted for advanced disease. Many of the patients in our study were included in the FIRM-ACT trial and while all patients received mitotane, not all received EDP-M. However, EDP-M is associated with prolongation of PFS, but not OS and should not have affected patient stratification into short- and long-survivor cohorts. Hence, we believe that the heterogeneity of treatment strategy does not limit the generalizability of our findings. Second, our study was limited by sample size. The rarity of ACC and the even greater rarity of patients able to undergo metastasectomy or re-resection for ACC makes it difficult to obtain a substantial patient cohort, even at the busiest of tertiary centers. Finally, this study reflects the characteristics of patients who were historically considered to have the adequately indolent and limited disease to merit surgical therapy and cannot comment on the outcomes for patients who were treated with medical management alone or who were not surgical candidates.

5 | CONCLUSIONS

In this retrospective study, we describe characteristics associated with long-term survival after resection of recurrent/metastatic ACC. Lower tumor stage at diagnosis and longer DFI after index adrenalectomy were independently associated with a survival benefit. These findings will be helpful in identifying optimal candidates for surgical management and for and counseling patients with recurrent or metastatic ACC. Furthermore, our findings suggest that multiple interventions are likely necessary for patients selected for metastasectomy, which should be included as part of the management discussion with patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical reasons.

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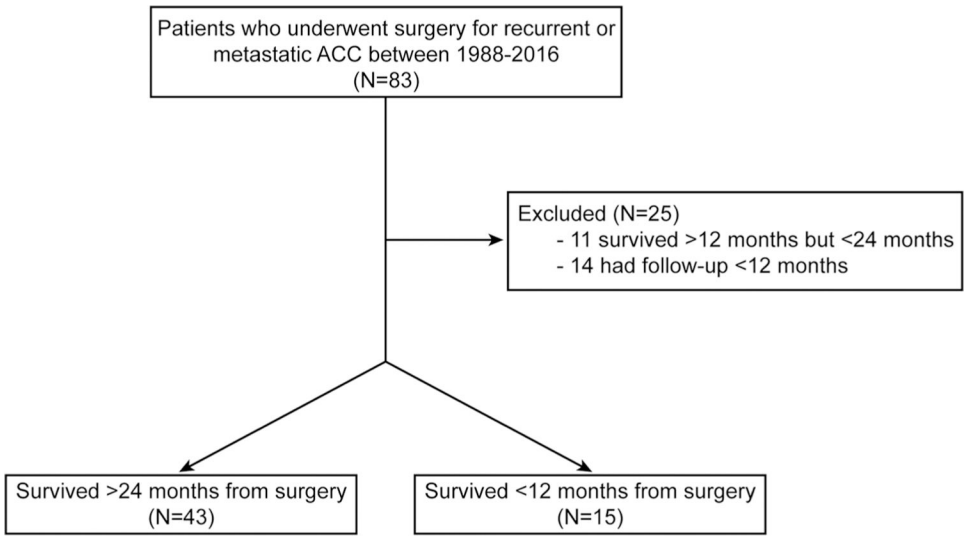

FIGURE 1.
Consort diagram showing patient cohort selection. ACC, adrenocortical carcinoma

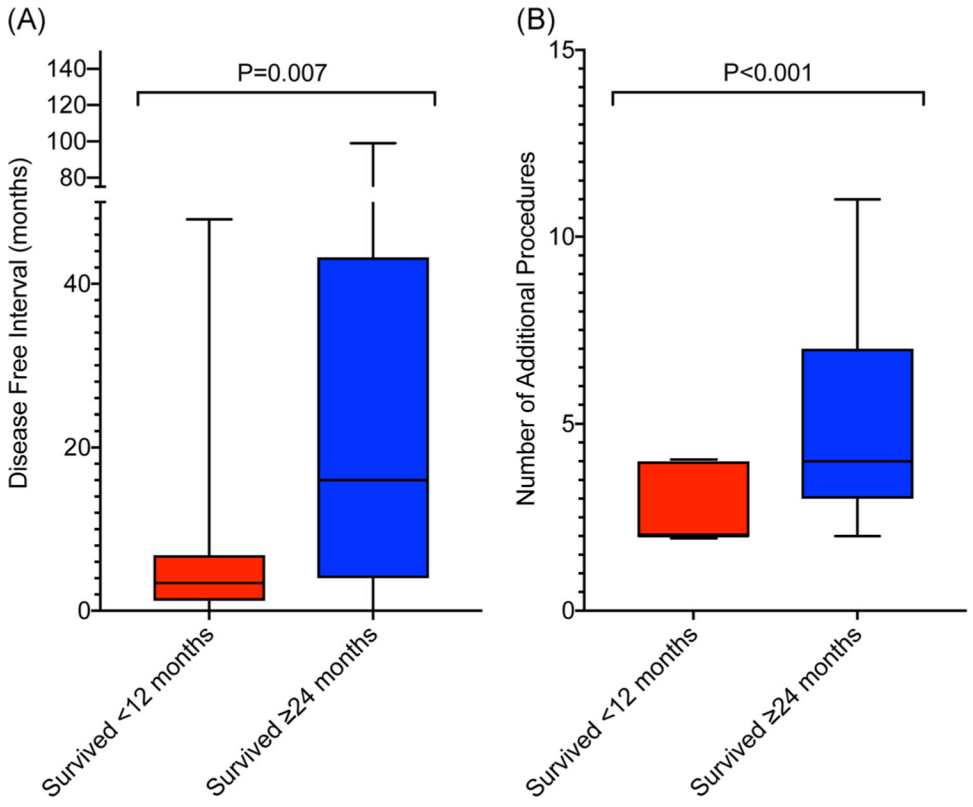

FIGURE 2.

Extended survival after metastasectomy was associated with a longer disease-free interval (A) and increased number of additional procedures (B) for recurrent disease [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1

Patient demographics, clinicopathologic, and treatment characteristics

	Surived <12 mo (N = 15)	Survived ≥24 mo (N = 43)	*P* value
Age, y	42 (25–50)	45 (33–53)	.405
Stage at diagnosis			.010
I	0 (0.0%)	4 (9.3%)	
II	5 (33.3%)	22 (51.2%)	
III	1 (6.7%)	6 (13.9%)	
IV	8 (53.3%)	7 (16.3%)	
Tumor size, cm	10.3 (7.2–15.5)	10.8 (8.0–13.9)	.120
Tumor functional status			1.000
Nonfunctional	7 (46.7%)	20 (46.5%)	
Functional	8 (53.3%)	21 (48.8%)	
Receipt of neoadjuvant therapy			1.000
No	15 (100.0%)	41 (95.3%)	
Yes	0 (0.0%)	2 (4.6%)	
Extent of primary tumor resection			
R0	6 (40.0%)	26 (60.5%)	.056
R1	2 (13.3%)	1 (2.3%)	
R2	4 (26.7%)	4 (9.3%)	
Adjuvant mitotane			.337
No	3 (20.0%)	4 (9.3%)	
Yes	10 (66.7%)	38 (88.4%)	
Adjuvant EDP			.484
No	6 (40.0%)	18 (41.9%)	
Yes	6 (40.0%)	11 (25.6%)	
Other regimen	3 (20.0%)	14 (32.6%)	
Adjuvant radiation			.356
No	11 (73.3%)	22 (51.2%)	
Yes	2 (13.3)	13 (30.2%)	
Ablative procedure	2 (13.3)	8 (18.6%)	
Disease-free interval, mo	3.4 (1.2–6.8)	16.0 (4.0–43.2)	.007
Number of additional procedures	2 (2–4)	4 (3–7)	<.001

Continuous variables expressed as median (25th–75th percentile). Missing values were not included.

Abbreviation: EDP, etoposide/doxorubicin/cisplatin.