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Liver Resection and Ablation for Metastatic Adrenocortical Carcinoma

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Abstract

Background—Adrenocortical carcinoma (ACC) is a rare disease without effective chemotherapy treated most appropriately with resection. The aim of this study was to evaluate our experience with liver resection for metastatic ACC.

Methods—This study is a retrospective review of patients who underwent liver resection or radiofrequency ablation (RFA) for ACC from 1979 to 2009.

Results—A total of 27 patients were identified. Of the 27, 19 underwent liver resection. Of the 19, 10 had a single liver lesion, and 18 of 19 were rendered free of disease in the liver, although only 11 of 19 were rendered completely free of disease because of extrahepatic disease (EHD). Of the 19, 13 had synchronous EHD. Also, 6 of 17 remained disease free in the liver at a median follow-up of 6.2 years (status of 2 of 19 was unknown). Of the 27 patients, 8 underwent RFA, 7 of 8 became free of disease in the liver, and 5 of 7 had EHD. No patients responded to prior chemotherapy. Median overall survival and survival of patients who underwent liver resection or RFA were both 1.9 years (0.2–12 + years); 5-year actuarial survivals were 29% and 29%, respectively. Disease-free interval (DFI) greater than 9 months from primary resection was associated with longer survival (median 4.1 vs 0.9 years; $P = .013$).

Conclusions—This study is a tertiary institution series of liver resection and RFA for ACC. Given the lack of effective systemic treatment options and the safety of resection and ablation, liver resection or RFA may be considered in selected patients with ACC metastatic to the liver especially with a long DFI.

Adrenocortical carcinoma (ACC) is a rare malignancy with an annual incidence of 0.5–2 cases per million population and causes approximately 0.2% of all cancer deaths in the United States.^{1,2} The male-to-female ratio is 1:1.5.³ ACC presents with symptoms of an abdominal mass or of hormonal excess of Cushing's syndrome, virilization, feminization, or Conn's syndrome. The prognosis for ACC is poor with 5-year survival with complete

resection of 16%–50% and with almost no 5-year survivors among patients with incomplete resections.^{4–6}

Surgery remains the most effective treatment, and complete resection is the most consistently cited prognostic factor for long-term survival.^{7,8} However, despite complete resection, 70–85% of patients develop recurrences locally or distantly, which partially accounts for the poor 5-year survival.

Chemotherapy is commonly used despite minimal impact. Mitotane (o,p'DDD), an adrenolytic drug, is the most commonly used chemotherapeutic agent and had initially promising response rates; however, subsequent trials failed to confirm these observations with response rates of less than 20% (excluding minor responses) and with few complete responses.⁹ Mitotane in the adjuvant setting has had mixed results with no clear benefit.^{10–12}

A survival advantage has been suggested for patients undergoing resection of local recurrences and distant metastases. Similar to resection of primary disease, margin-negative, complete resection is associated with longer survival. Complete resection of metastatic disease is achieved more often than complete resection of local recurrences.⁷ The liver is the most common site of metastatic recurrence.^{4,8,13} Resection of liver metastases has been reported, but most series are small or combine resections of other distant sites.^{5,14,15}

The objective of this study was to review our experience with liver resection of metastatic ACC to the liver. We specifically evaluated prognostic factors to determine any factors associated with prolonged survival.

PATIENTS AND METHODS

Data Collection and Clinical Assessment

A retrospective review identified patients who underwent hepatic resection or RFA with a diagnosis of ACC at the National Cancer Institute (NCI, Bethesda, MD) from the year 1979 until 2009. Inclusion criteria included pathologically confirmed ACC from a resected liver lesion or from a biopsy prior to RFA. Exclusion criteria were embolization, needle biopsy, or resection to obtain margin-negative adrenalectomy. Patients who were enrolled on a protocol signed an institutional review board consent.

Complete staging was performed with history and physical examination, laboratory assessment, and computed tomography of the chest, abdomen, and pelvis.

Statistical Analysis

Overall survival (OS) was calculated from the date of hepatic resection until the date of the last encounter, or date of death, as appropriate. For the patients resected to no evidence of disease (NED), disease-free survival (DFS) was calculated as the time from hepatic resection until the first recurrence, or the last follow-up without a recurrence, as appropriate. Liver recurrence-free survival (RFS) was calculated from the date of liver procedure until the date of death, last follow-up, or date of first recurrence in the liver after the date of the liver procedure. For patients with residual disease after the operation, progression-free survival (PFS) was calculated from the date of liver resection until progression of disease at any site or the last follow-up without progression, as appropriate. The probabilities of survival, liver RFS, DFS, or PFS were calculated by the Kaplan–Meier method; the statistical significance of the difference between pairs of Kaplan–Meier curves was determined by the log-rank test for cases in which the distinguishing characteristic of the curve was known at the date of resection.

Clinicopathologic features including demographics, Lee stage, neoadjuvant and adjuvant chemotherapy for the initial operation, disease-free interval (DFI), neoadjuvant therapy for liver resection, number of hepatic metastases, extrahepatic disease (EHD), and resection were evaluated for their association with outcome by univariate methods described previously.

The DFI was defined as the time to first recurrence at any site from the date of the initial operation if the patient was initially resected to NED. A separate progression-free interval was also calculated in a similar manner, but restricted to those who had residual disease after the initial operation.

All *P* values are 2-tailed and are presented without adjustment for multiple comparisons.

RESULTS

Patient Characteristics

Of the 27 patients in this series (Table 1), 21 had the initial adrenalectomy prior to referral to the NCI. The majority of patients underwent hepatic procedures after the primary operation except for 2 with stage IV disease.

Operative Findings

A total of 19 patients underwent liver resection (Table 2), and all liver disease was resected in 18 of 19 patients (95%). Although the liver disease was resected in most patients with negative margins, only 11 of 19 (58%) were rendered NED because of EHD. Also, 10 of 19 (53%) had 1 lesion; the remainder had more than 1 lesion. Multiple hepatic resections were performed as listed in Table 2. Of 13 patients with EHD, 10 (77%) underwent resection of that disease, but only 5 were rendered NED. Also, 2 of the patients had pulmonary disease that was not approached during the liver operation, whereas 2 patients had a synchronous thoracotomy for pulmonary metastasectomy (Table 3). Of 27 patients, 8 (30%) underwent RFA (Table 2). Of 8 patients, 7 (88%) had all the liver disease ablated, but only 2 of 8 (25%) were NED after the procedure. Details are listed in Table 2.

When a single lesion was easily accessible for RFA, RFA was the procedure of choice. When the disease burden was determined to be the rate-limiting step for survival or when complex resections were required to render the patient NED, surgery was the procedure of choice. For example, 3 of 19 (16%) underwent segmentectomy of segments 1, 2, and 4 for 1 lesion each. The segment 4 resection included an en bloc resection of the duodenum and colon. Of 19 patients, 2 (10%) underwent trisectionectomies for single central lesions, and 1 of 19 (5%) underwent posterior sectionectomy and nonanatomic left liver resection for multiple lesions. None of these lesions were amenable to RFA.

No perioperative deaths occurred. Of 19 patients undergoing liver resection, 9 (47%) experienced morbidity (Table 2). Interestingly, 26% had clinically significant pulmonary emboli (PE) and/or deep venous thrombosis (DVT).

Clinical Outcomes and Prognostic Factors

For the 27 patients, the median overall survival and the 5-year actuarial survival were 1.9 years (0.22–12 + years) and 29%, respectively (Fig. 1a). There were 4 patients who survived longer than 5 years in the resection group. The median disease-free survival was 5 months. The median survival for those who received adjuvant chemotherapy or who did not was 2.0 and 1.2 years, respectively (*P* = .8). The median overall survivals for those who received

neoadjuvant chemotherapy (14 of 27, 52%) and those who did not (13 of 27, 48%) were 1.4 and 2.7 years, respectively ($P = .14$).

Similar to the overall group, for the 19 patients who underwent liver resection, the median overall survival and the 5-year actuarial survival were 1.9 years (0.2–12 + years) and 29%, respectively. The RFS and the PFS were both 6 months. The median overall survival for patients who received neoadjuvant chemotherapy (9 of 19, 47%) and those who did not (10 of 27, 53%) were 1.4 and 2.9 years, respectively ($P = .086$). Of 19 patients, 18 experienced recurrences. The patient who had not experienced recurrence had only 6 weeks of follow-up. Of 17 patients, 11 (65%) recurred in the liver and 6 of 17 (35%) never experienced liver recurrences with a median follow-up of 6.2 years. The 5-year actuarial liver RFS was 20% (Fig. 1b). For those who were resected and rendered NED in the liver, the median time to liver recurrence was 11 months (0.2–11 + years).

For the 8 patients undergoing RFA, the median overall survival had not been reached and the 2-year actuarial survival was 53%. The longest follow-up was 3 years. The median RFS was 5 months, and the median PFS was 3 months. All patients recurred distantly, and 50% recurred in the liver. The median time to liver recurrence was 14 months.

Prognostic factors were evaluated including synchronous and metachronous disease, adjuvant therapy after initial adrenalectomy, NED status at initial operation and at liver resection, liver NED status, number of hepatic lesions, presence of EHD, both neoadjuvant and adjuvant chemotherapy, and DFS. Of note, margin status was not evaluated as a prognostic factor given that all patients had a margin negative resection. DFI greater than 9 months after primary adrenalectomy was associated with longer survival (4.1 vs 0.9 years; $P = .013$; Fig. 2a) for the entire cohort. This factor remained significant when evaluated for the patients undergoing resection only ($P = .047$). No other factors reached significance, but the patients who received neoadjuvant therapy prior to liver procedure had a trend toward worse survival for both the entire cohort and the resected cohort ($P = .14$; $P = .086$, respectively; Fig. 2b).

DISCUSSION

The most effective treatment for adrenocortical carcinoma is surgical resection, but recurrences and metastatic disease are common, especially to the liver. Metastatic disease at initial presentation was reported to be 17.8%, 21.6%, and 39%.^{3,4,7} The liver disease was the most common site of metastases representing 57%, 10.9%, and 64%, respectively. Liver recurrences after initial curative resections occur frequently.^{4,8,13} Favia et al. reported that the liver was the most common site of recurrence among 9 patients.¹³ Crucitti et al. reported the liver as the second most common site after the lung (12 of 82).⁴ Of the 12 patients (12 of 27, 44%) in this series who presented with stage IV disease, 7 patients (7 of 12, 58%) had liver metastases. All patients ultimately had liver disease given that our intent is to evaluate resection or ablation of ACC to the liver.

Liver resection for ACC has been reported. Icard et al. reported that 19 patients underwent liver resection from the French Association of Endocrine Surgeons; 10 had right hepatectomies and 9 had segmentectomies.⁵ Owada et al. reported liver resection in 6 patients as 4 segmentectomies and 2 extended right hepatectomies.¹⁴ All had R0 resections. In our series, 27 patients with ACC metastatic to the liver underwent 19 liver resections and 8 RFA procedures (Table 2).

Prognostic factors revealed DFI greater than 9 months as the only positive predictive factor (Fig. 2a). Crucitti et al. reported DFI was higher among patients undergoing radical resection compared with palliative resection (16.5 vs 11.7 months; $P = .361$).⁴ Weitz et al.

reported outcomes of 141 patients after hepatectomy for noncolorectal, nonneuroendocrine carcinoma that included 15 patients with ACC.¹⁵ DFI greater than 24 months was a significant prognostic factor for both relapse-free survival and cancer-specific survival ($P = .02$; $P = .04$, respectively). The contribution of ACC (Weitz et al.) cannot be ascertained as it includes other histologies. Jensen et al. reported the initial series from 1965 until 1989 at the NCI that revealed DFI greater than 12 months predicted longer survival in 15 patients who had resection of metastatic disease (7 liver resections).¹⁶ With a 20-year update for patients with liver disease, DFI remained a significant predictor of survival. DFI was a significant prognostic factor for both the entire cohort and for patients undergoing liver resection (Fig. 2a). DFI as a predictor of longer survival indicates that the biology of ACC itself may be the major determinant of outcome rather than surgery itself. Dividing the patients based on a given DFI may be a selection criterion for patients with less malignant biology. However, since a prospective randomized trial to answer this question is not feasible because of the rarity of this disease, the question will remain open.

Reports regarding perioperative chemotherapy have revealed inconsistent conclusions.¹⁷ Several studies have evaluated adjuvant chemotherapy after initial adrenalectomy, but no studies have adequately evaluated neoadjuvant or adjuvant treatment in relationship to resection of metastatic ACC. Dickstein et al. reported a benefit for adjuvant mitotane after the primary adrenalectomy.¹⁰ Icard et al. reported that mitotane was of benefit only for patients undergoing palliative resection.⁵ Crucitti et al. also noted no benefit for adjuvant mitotane after the primary adrenalectomy.⁴ Grubbs et al. reported no benefit if R0 curative resection was performed.¹² In our study, adjuvant mitotane after the initial resection had no influence on the survival of patients after the liver resection. Also, neoadjuvant therapy prior to liver procedure was not associated with improved survival (Fig. 2b). Patients who received neoadjuvant therapy had a trend toward worse survival for the entire cohort and the resected cohort ($P = .14$; $P = .086$, respectively). Unfortunately, this study is underpowered to detect a difference if one exists, but given that chemotherapy minimally impacts this disease, metastatic ACC is more likely to progress while delaying an operation rather than to respond to chemotherapy. No patients in this series had an objective response to chemotherapy. To our knowledge, this study represents the most extensive evaluation of neoadjuvant therapy prior to metastatic resections for ACC even though it contains only 27 patients. In the absence of good data, findings in this study are consistent with reasonable clinical judgment, which is the only option to guide whether perioperative chemotherapy is appropriate. ACC is a rare disease and metastatic resections are infrequently performed; therefore, large well-designed studies are unlikely to ever be performed to adequately address this question. Based on these findings, we doubt that neoadjuvant therapy is beneficial and would recommend proceeding to surgery if resection is contemplated and technically feasible at the time of evaluation; however, given the small number of patients, strong recommendations cannot be made.

Other prognostic factors were evaluated. Benefit in terms of long-term survival after repeat resection has been reported.^{7,16,18} For patients who underwent resection of recurrences compared with those who did not, Crucitti et al. reported mean survivals of 41.5 and 15.6 months, respectively (5-year: 48.2% vs 7%; $P = .00012$).⁴ Schulick and Brennan noted that disease-specific survival after a second operation was much longer for patients who had complete resections compared with those who had incomplete resections (74 vs 16 months, respectively; $P < .001$). Liver resection was performed in 15 patients and lung in 29 patients. In our series, all patients underwent a liver procedure; therefore no comparative group exists to determine whether the procedure improved survival, but resection to NED was not a predictor of survival ($P = .69$). Although randomization may be required to state that patients benefitted, a cohort comparative group could lend support to a benefit, but most patients who were considered candidates underwent resection; therefore a matched cohort

was not possible. All patients but one had complete resection of the hepatic disease that was thought to be the life-limiting disease. Residual disease may not influence survival to the extent to which the liver disease did in this group of patients. Therefore, resection of EHD to NED should not be expected to create a difference in survival among this group of patients. Regardless, for patients deemed candidates for resection, complete resection should be obtainable for most patients.

Median overall survival and 5-year survivals after liver resection were 1.9 years and 29%, respectively. For the patients resected to NED in the liver (18 of 19, 95%), the median time to recurrence in the liver was 11 months with actuarial 5-year RFS of 20% (Fig. 1b). Despite complete resection of liver disease, all patients except 1 with short follow-up eventually recurred, but 35% of resected patients remained free of disease in the liver (Fig. 2b). These results suggest that although nearly 100% of patients experienced systemic recurrences, complete resection of hepatic ACC is attainable and hepatic control maintained for a reasonable amount of time.

The morbidity was 46% with 26% experiencing symptomatic DVT and PE. Other than 1 patient who had a PE in 2007, these events occurred earlier than 2001. With routine DVT prophylaxis with modern perioperative care, we suspect that the morbidity of liver resection would be comparable to modern series and lower than this study, which includes patients over a 30 year period. Another possibility is that hypercortisolism may have increased the incidence of venous thromboembolic disease, but this factor cannot be adequately addressed in this report.¹⁹

Several limitations of this study exist. This report is a retrospective review. Based on referral pattern and lengths of treatment, a selection bias may exist for patients who have a longer disease-specific survival, which may reflect a more favorable biology. Even though patients underwent an operation or an RFA, we cannot be certain that these interventions actually prolonged the patients' lives.

In conclusion, ACC portends a poor prognosis with no good systemic therapy. Despite complete adrenalectomy, most patients develop recurrences both locally and distantly. Resection of metastatic disease has been explored and is associated with longer survival if complete, margin-negative resections can be achieved. In this series, metastatic resection of liver lesions is technically feasible regardless of the number of hepatic lesions. Most patients will recur, but 35% may achieve long-term control of hepatic disease and median survival approaches 2 years after resection. Extra-hepatic disease is not a clear contraindication to resection. Currently, no role for neoadjuvant therapy exists, and we suggest proceeding with planned operations rather than attempting downstaging of resectable disease. Cure of ACC rarely if ever occurs, but given the lack of effective systemic agents and the association of complete resections with prolonged survival, liver resection or ablative therapies such as RFA are reasonable options for the treatment of liver metastases for patients with a DFI greater than 9 months.

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FIG. 1.

a Overall survival of the 27 patients who underwent liver resection ($n = 19$) or radiofrequency ablation ($n = 8$) for metastatic adrenocortical carcinoma. The 5-year actuarial survival was 29%. **b** Liver recurrence-free survival (RFS) for the patients who underwent liver resection to NED (18 of 19, 95%). The 5-year actuarial liver RFS was 20%

FIG. 2.

Prognostic factors. **a** For the cohort of 27 patients, disease-free interval longer than 9 months after the primary adrenalectomy was associated with longer survival (4.1 vs 0.9 years, $P = .013$). **b** For the cohort of 19 patients undergoing resection, patients who received neoadjuvant therapy prior to the liver resection had a trend toward decreased survival ($P = .086$).

TABLE 1

Demographics of 27 patients who underwent liver resection or radiofrequency ablation for metastatic ACC

Feature		
Age, years (range)		
At diagnosis		40 (6–73)
At liver procedure, years (range)		45 (8–73)
Sex, male/female		14/13
Lee staging classification, No. (%)		
II		4 (15)
III		11 (41)
IV		12 (44)
Hormonal status at initial presentation, No. (%)		
Nonfunctional		10 (37)
Functional		17 (63)
Hypercortisolism		9 (53)
Hyperaldosteronism		3 (18)
Virilization		3 (18)
Feminization		2 (12)
Disease status after initial operation, No. (%)		
No evidence of disease (NED)		22 (81)
Patient resected to NED (<i>n</i> = 22)		
Disease-free interval in months, median (range)		9.0 (1 month–21.5 + years)
Patients with residual disease (<i>n</i> = 5)		
Progression-free survival, months, median (range)		5.1 (0.9–17.3)
Systemic therapy for primary adrenalectomy, total No. (%) / mitotane No. (%)		
Neoadjuvant chemotherapy		2 (7) / 1 (4)
Adjuvant chemotherapy		8 (30) / 5 (18)

TABLE 2

Findings of liver resections and ablations

Operative findings of 19 liver resections	No. (%) ^a
Hepatic resection	
Right hepatectomy	7 (37)
Segmentectomy	3 (16)
Left lateral sectionectomy	3 (16)
Nonanatomic wedge resection	3 (16)
Trisectionectomy	2 (10)
Wedge of the left liver and posterior sectionectomy	1 (5)
No. of metastases	
1	10 (53)
2	3 (16)
3	1 (5)
4	3 (16)
Multiple	2 (10)
Synchronous extrahepatic metastases	
Extrahepatic disease present	13 (68)
Resection of EHD	10 (53)
Complete resection of EHD	5 (26)
Incomplete resection of EHD	5 (26)
Disease status after liver operation	
NED	11 (58)
NED in the liver	18 (95)
Margin status, negative	18 (95)
Remained NED in liver (2 unknown)	6 of 17 (35)
Time to liver recurrence (<i>n</i> = 11), months (range)	11.4 (1.9 months–11.5 + years)
Morbidity and mortality	
Mortality	0 (0%)
Morbidity	9 (47%)
Pulmonary embolus/DVT	5 (26%)
Intra-abdominal abscess	2 (11%)
Wound infection	1 (5%)
Renal failure and IVC thrombosis	1 (5%)
Bile leak (included as patient with DVT above)	1 (5%)
Systemic therapy for liver procedure	
Neoadjuvant chemotherapy	9 (47)
Adjuvant chemotherapy	13 (68)
Procedural findings for radiofrequency ablation	No. (%)
No. of metastases	
1	2 of 8 (25)

Operative findings of 19 liver resections	No. (%) ^a
2	3 of 8 (38)
4	1 of 8 (13)
Multiple	2 of 8 (25)
Synchronous extrahepatic metastases	
Extrahepatic disease present	6 of 8 (75)
Ablation of EHD	1 of 6 (17)
Disease status after liver operation	
NED	2 of 8 (25)
NED in the liver	7 of 8 (88)
Recurrence-free survival, months (range)	4.9 (4.9–5.0)
Progression-free survival, months (range)	3.4 (1–6.3)
Liver recurrence	4 of 8 (50)
Remained NED in liver	4 of 8 (50)
Time to liver recurrence, months (range)	14.0 (3.4–38.0)

DVT deep vein thrombosis, *IVC* inferior vena cava

^aExcept where noted

TABLE 3

Extrahepatic disease

Sites of EHD	NED (Y/N)	Sites of EHD resection
Spine, diaphragm, IVC	N	Diaphragm
Lung—15 nodules bilateral wedge resections	Y	Lungs
Adrenal bed, omentum, pelvis	N	Omentum, pelvis
Omentum, retroperitoneum, mesentery	Y	Omentum, retroperitoneum, mesentery
Lung	N	None
Lung, adrenal bed	N	Lung
Lung	N	None
Lung, portal vein	Y	Lung; portal vein
Lung, retroperitoneum	N	Retroperitoneum
Retroperitoneum, periportal LN	Y	Retroperitoneum, periportal LN
Diaphragmatic nodules	Y	Diaphragmatic nodules
Lung	N	None
Lung, adrenal bed	N	Adrenal bed
Sites of EHD	NED (Y/N)	Sites of EHD ablation
Lung, spine	N	None
Bilateral lung	N	None
Lung, retroperitoneum, adrenal bed	N	None
Lung	N	None
Lung, scapula	N	None
Adrenal bed	Y	Adrenal bed

IVC inferior vena cava, LN lymph node