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Combined Liver and Inferior Vena Cava Resection for Adrenocortical Carcinoma

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Abstract

Purpose. Adrenocortical carcinoma (ACC) is a rare malignancy, usually diagnosed at an advanced stage when it has invaded or adhered to adjacent organs. We report our experience of performing combined liver and inferior vena cava (IVC) resection for ACC.

Methods. Six patients with clinical stage III ($n = 4$) or IV ($n = 2$) ACC underwent combined resection of the liver and IVC. Two patients underwent extended right hepatectomy, and four underwent segmentectomy. In four patients, the IVC was resected segmentally: it was replaced with expanded polytetrafluoroethylene (ePTFE) in three of these patients, and not reconstructed in one. In two patients, the IVC was partially resected and closed directly.

Results. Perioperative mortality was zero, and morbidity was 33.3%, with temporary liver failure in two patients and renal failure in one patient. Recurrence was found within 8.1 months in three (50%) of the six patients. The mean recurrence-free survival period was 20.1 ± 7.7 months (95% confidence interval [CI]: 5.1–35.4), and the median survival time was 6.1 ± 9.8 months (95% CI: 00–25.3). The 5-year disease-free survival rate was 16.7%.

Conclusions. Patients with ACC involving both the liver and IVC are candidates for partial hepatectomy and segmental IVC resection. Resection affords the possibility of negative margins, acceptable perioperative morbidity and mortality, and prolonged survival in some patients.

Key words Adrenocortical carcinoma · Inferior vena cava replacement · Liver resection · Inferior vena cava resection

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Introduction

Adrenocortical carcinoma (ACC) is relatively rare and most cases are diagnosed at an advanced stage, with invasion of or adherence to the liver, kidney, and inferior vena cava (IVC).[1] Complete surgical resection is the treatment of choice for ACC,[2] and a margin-free resection (R0 resection) is a strong predictor of long-term survival.[3–5] Stage III and IV tumors defined by invasion of or adherence to adjacent organs often require en bloc resection of the liver, IVC, kidney, spleen, and pancreas to achieve R0 resection and prevent tumor spillage.[5] In the past, patients with ACC involvement of the IVC were considered poor candidates for surgery; however, the development of innovative surgical techniques for liver tumors involving the IVC[6–10] has resulted in a curative surgical approach for tumors involving both the liver and IVC. We report our experience of performing combined liver and IVC resection for stage III and IV ACC.

Patients and Methods

Clinical Evaluation and Staging

Six patients underwent resection of ACC between 1993 and 2005 at Gunma University Hospital and its affiliates, in Japan. There were three women and three men, with a median age of 56.3 years (range, 43–68 years). One (16.7%) woman had Cushing's syndrome and one (16.7%) woman had hypertension. Two patients had edema of the lower extremities. In four patients, the tumors were nonfunctioning and detected on screening computed tomography (CT) images done for other reasons. The right adrenal gland was involved in all patients. The mean tumor diameter was 14 cm [range, 7–20 cm; being <10 cm in two patients (40%) and >15 cm in four patients (60%)]. Locoregional invasion was

Table 1. Clinical characteristics of the six patients who underwent combined liver and inferior vena cava resection for stage III or IV adrenocortical carcinoma

Patient	Age (years)	Sex	Symptoms	Previous history	Tumor location	Elevated hormones	Cushing's syndrome	Clinical				
								Tumor size (cm)	T	N	M	Staging[a]
1	61	M	—	—	Right		No	8	T4	0	0	III
2	47	F	—	Myoma uteri	Right		No	18	T4	0	0	III
3	68	M	—	—	Right		No	16	T4	0	0	III
4	62	M	Weight loss Lower extremities edema	—	Right		No	20	T4	0	0	III
5	57	F	Hypertension	Cortical adenoma	Right	17-OHCS 17-KS	Preclinical	7	T4	0	Liver	IV
6	43	F	Moon face Lower extremities edema	—	Right	17-OHCS 17-KS DHEA	Clinical	15	T4	0	Lung Liver	IV

Patient # 6 had tumor thrombi in the inferior vena cava
17-OHCS, hydroxycorticosterone; 17-KS, ketosteroid; DHEA, dehydroepiandrosterone
[a] According to Lee et al.[11]

present in all six patients, and synchronous distant metastases were found at the time of presentation in two (33.3%) patients. Clinically, four (66.6%) patients had stage III disease and two (33.3%) had stage IV disease (Table 1).[11]

Surgery

The surgical procedure for liver and IVC resection is described elsewhere.[8] Briefly, the arteries supplying the tumor, including the adrenal, phrenic, lumbar, and renal arteries, were ligated and the para-aortic and hepatic hilar lymph nodes were resected. If the renal arteries or veins were involved, nephrectomy was required. Liver resection was performed anatomically, according to Couinaud's liver segments, after ligating the inflow arteries and portal branches to be resected. The liver parenchyma was divided using an ultrasonic surgical aspirator (CUSA EXcel Radionics, Burlington, MA, USA) and bipolar cautery with a saline irrigation system. Hemihepatic vascular occlusion or selective inflow occlusion was done to minimize blood loss during hepatic parenchymal resection. Occlusion was continued for 20 min, followed by release for 5 min, which was repeated until the liver parenchyma was resected. To expose the supra- to retrohepatic IVC, we used an anterior transhepatic approach, dividing the liver parenchyma first. The supra- or retrohepatic IVC just below the hepatic venous confluence was clamped to ensure that both the mean arterial and central venous pressures were maintained following intravenous hydration. Veno-venous bypass with a centrifugal pump was used for patients with a 30% drop in mean arterial pressure and those who we thought may require vascular exclusion for longer than 60 min. After en bloc resection of the tumor, bile leakage from the transected surface of the liver was tested, and an external drainage tube was inserted into the bile duct. An 18- to 22-mm expanded polytetrafluoroethylene (ePTFE) graft was used if IVC replacement was required. The ePTFE graft was overlapped using an omental pedicle. Patients who underwent ePTFE replacement received low-dose heparin postoperatively and then warfarin to give a prothrombin time/international normalized ratio (PT/INR) of around 2.3 for the first 3 months. Long-term anticoagulation was maintained with a single aspirin tablet daily thereafter.

Statistical Analysis

Statistical analyses were done using the program SPSS (SPSS, version 11.0J, Tokyo, Japan). Disease-free and overall survival curves were generated using the Kaplan-Meier method.

Results

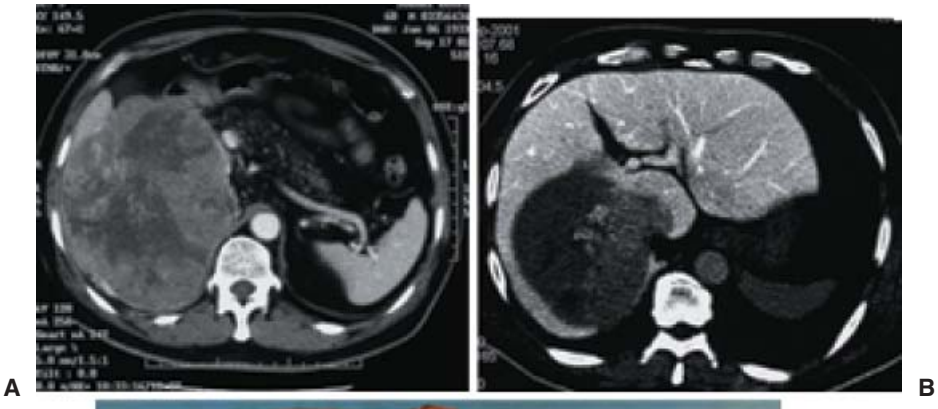
Surgical Results

We used a transabdominal approach in four patients, and a thoracoabdominal approach in two patients. Two patients underwent extended right hepatectomy, and four patients underwent segmentectomy of the posterior segment in three patients; and S4a, S5, and S6 in one patient. Two patients underwent right nephrectomy and

one patient underwent portal vein resection and reconstruction, extrahepatic bile duct resection, and hepaticojejunostomy. The IVC was resected segmentally in four patients and partially in two patients. After segmental IVC resection, the IVC was replaced with an ePTFE graft in three of the four patients and it was not reconstructed in the other one. Although ePTFE replacement was indicated in one of the other patients, the procedure was contraindicated because of the high risk of liver failure and expected hepaticojejunostomy leakage with extended hepatectomy, massive bleeding, and a low postoperative indocyanine green (ICG) K value.[12] The IVC was closed directly in the two patients undergoing partial IVC resection. An active venovenous bypass was done in one patient, and another patient required aortic cross-clamping below the superior mesenteric artery. We performed lymphadenectomy and R0 resection in all six patients. The average operating time was 10 h 35 min (range, 5 h 5 min to 20 h) and the average blood loss was 5187 ml (range, 779–17 483 ml). Two of the patients who underwent combined resection of the IVC and extended right hepatectomy suffered postoperative complications including hyperbilirubinemia, hepatic failure, acute renal failure, and lower extrimities edema (Table 2). There was no operative or hospital death. None of the IVC grafts became infected and they were still patent at the last follow-up. The typical CT findings of stage III ACC and the *en bloc* resected specimen from patient 4 are shown in Fig. 1.

Pathological Results

R0 resection was confirmed histopathologically in all six patients. We found extra-capsular invasion in all patients, which involved the IVC and liver in four patients each. Three patients had both liver and IVC invasion. The patient who underwent combined liver and IVC resection had no pathological extra-adrenal invasion and all but one patient had vascular invasion. One patient had a sarcoma-like component. The mitotic index ranged from 2 to 30/10 high power fields (HPF). The resection margins were microscopically clear of tumor cells in all patients. The clinical and pathological stages were the same (Table 3).



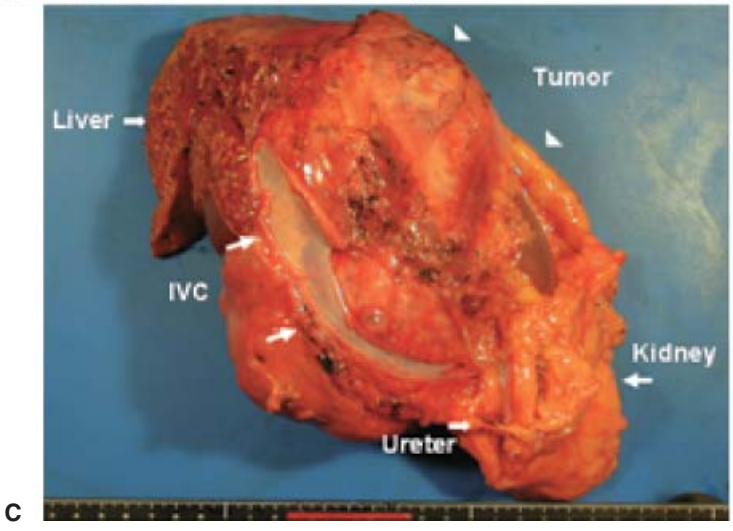


Fig. 1. A,B Abdominal computed tomography scan of patient no. 4, showing a huge mass invading the liver and inferior vena cava. **C** The resected en bloc specimen, showing the tumor with the liver, kidney, and longitudinally dissected inferior vena cava (*IVC*)

Table 2. Surgical procedures

Patient	Combined resection	Liver resection[a]	IVC resection/repair	Bypass	LN resection	Duration of operation (min)	Blood loss (ml)	Postop. K value	Morbidity
1	IVC	S6, S7	Direct closure	No	Yes	305	779	—	None
2	IVC	S6, S7	Direct closure	No	Yes	515	1250	0.142	None
3	IVC, Kidney	S6, S7	ePTFE	No	Yes	600	2510	0.180	None
4	IVC, Kidney Portal vein Bile duct	S4a, S5, S6 S7, S8	No reconstruction	No[b]	Yes	1200	17483	0.072	Hyperbilirubinemia Lower extremities edema Ascites Hepaticojejunostomy leakage Acute renal failure
5	IVC	S4a, S5, S6	ePTFE	No	Yes	650	3030	0.159	None
6	IVC	S4a,S5, S6 S7, S8	ePTFE	Biopump	Yes	540	6070	0.137	Hyperbilirubinemia Ascites

ePTFE, expanded polytetrafluoroethylene; IVC, inferior vena cava; LN, lymph node
[a] Couinaud segment
[b] Aortic half clamp

Fig. 2. Cumulative recurrence curve

Survival and Recurrence

None of the patients received adjuvant mitotane therapy or radiation therapy. The median follow-up period was 33.4 months (range, 11.4 to 57.6 months). The most frequent site of metastasis was the lung, seen in four patients. Liver and locoregional recurrences were also seen in one patient each. These metastases were unresectable because of bulky local recurrence or disseminated distant metastasis. Later, brain and bone metastasis occurred (Table 3). Recurrence developed within 8.1 months in three (50%) of the six patients. The cumulative recurrence curve is shown in Fig. 2. The mean recurrence-free survival time was 20.1 ± 7.7 months (95% confidence interval [CI]: 5.1–35.4), and the median survival time was 6.1 ± 9.8 months (95% CI: 00–25.3). The 5-year disease-free survival rate was 16.7%. Five patients were treated with mitotane (o,p′DDD; o,p′-dichlorodiphenyldichloroethane) with or without chemotherapy after tumor recurrence. Subsequently, cytotoxic agents were administered. The mean overall survival time for all patients was 33.5 ± 8.6 months (95% CI: 17.6–49.3), and the median survival time was 25.0 ± 11.1 months (95% CI: 3.2–46.8).

Discussion

We reported 20% mortality in a previous series of patients who underwent combined liver and IVC resection.[8] Conversely, there was no mortality in this series, although two patients who underwent extended right hepatectomy and IVC resection suffered postoperative liver failure. The reported perioperative mortality rate ranges from 11% to 25% in series of combined liver and IVC resection.[9,13] The operative mortality rate for ACC resection was 5.5% in one recent study,[5] and aggressive surgery for ACC with extension into the IVC was associated with a 10%–15% mortality rate[14] in another study. Both cortisol and androgen excess may be re-

Table 3. Pathologic results, recurrence, and outcome

Patient	Pathology			Site of recurrence	Time to recurrence (months)	Outcome (months)
	T	N	Staging			
1	T4	—	III	Lung	5.6	Died (34.2)
2	T4	0	III	No recurrence	—	Alive (48.9)
3	T3	0	III	Lung	36.5	Alive (50.5)
4	T4	0	III	Local	6.1	Alive (9.5)
5	T4	0	IV	Lung, Liver	3	Died (15.9)
6	T4	0	IV	Lung, Liver, Brain, Bone	21.7	Died (23.7)

sponsible for an increased risk of perioperative cardiovascular events. Furthermore, combined resection of the IVC and liver is a considerable operative challenge, with high mortality and morbidity rates. The keys to the success of such aggressive surgery are precise evaluation of the tumor extension and careful monitoring of the functions of the liver, kidneys, and adrenal hormone. When extensive liver resection is planned, even if the liver is normal, the remnant functional reserve is critical. We have found that perioperative real-time monitoring of ICG-K, measured using pulse spectrophotometry, is useful for evaluating the remnant liver functional reserve before, during, and after liver resection for hepatocellular carcinoma associated with cirrhosis.[12] We even use this measure to evaluate extensive liver resection of the normal liver.

In combined resection of the IVC and liver, all blood flowing to the tumor, IVC, and liver should be controlled as well as possible to obtain a bloodless field and minimize blood loss. We used an anterior approach to liver resection to expose the supra- to retrohepatic IVC.[8] One patient suffered a massive bleed from the right hepatic vein soon after parenchymal transection of the extended right hepatectomy, leaving the IVC, tumor, and a bare area connected. A possible explanation for this was that inflow from a feeding lumbar, adrenal, or phrenic artery had not been controlled completely, resulting in very rapid congestion of the liver, and the increased hepatic venous pressure caused the clamp to slip off. This situation required temporary half-clamping of the descending aorta. Clamping of the descending aorta[15] and the introduction of an occlusion balloon catheter (Baxter, Deerfield, IL, USA) near the diaphragm[16] are alternative methods for controlling massive bleeding from major vessels. The surgical approach should be flexible enough to adopt any of these variations and allow innovation in each patient.

There is no definite indication for reconstruction after resecting the retro- to suprahepatic IVC. The IVC can be repaired primarily if the resected segment is small. The suprarenal IVC may be ligated safely when the IVC collaterals, including the vertical vein systems, azygos, and hemi-azygos veins, are well developed. Acute renal failure occurred in one patient (No. 4) who did not undergo reconstruction of the IVC, as reported elsewhere.[17] Larger segmental resections of the IVC should be reconstructed with synthetic or autogenous grafts.[8,10] A ringed 18- to 20-mm ePTFE is currently our graft of choice. Although prosthetic material is associated with a risk of infection, there was no incidence of graft infection in this or our previous series [8], as reported elsewhere.[10,13]

We used an omental wrap for prosthetic caval grafts when performing combined liver resection and caval reconstructions, because the omentum has the capacity for absorption, adhesion formation, neovascularization, and infection defense.[13,18,19] We also inserted an external drainage tube in the bile duct through the cystic duct and sealed both the transected hepatic surface and the graft with fibrin glue, to protect the graft from bile leakage.[8] We used low-dose perioperative heparin, followed by warfarin, and then long-term maintenance aspirin. With this regimen, all grafts remained patent.

It remains unclear if surgical treatment should be attempted in patients with bulky T4 invading the liver and IVC, or stage IV metastatic disease and IVC extension. Complete tumor removal (R0 resection) offers by far the best chance for long-term survival, making surgery the treatment of choice for stage I–III ACC.[3–5,20–22] The reported 5-year survival rates for stages I, II, III, and IV are 66%, 58%, 24%, and 0%, respectively.[5] According to past reports, patients who underwent complete resection of the primary tumor had 5-year survival rates of 3%–55%, whereas those with incomplete resection had 5-year survival rates of 0%–9%.[20,21,23,24] The poorer survival of patients with stage III or IV disease is attributable to the incomplete resection of bulky T4 or metastatic disease.

Our small series showed that combined and complete resection of the liver, kidney, and IVC, aiming at complete resection, was feasible with acceptable morbidity. The 5-year disease-free survival rate was 16.7%, and the mean recurrence-free survival period was 20.1 ± 7.7 months. These survival rates are similar to those in a previous series, in which patients with stage III or IV disease had a median survival period of 15 months and

a 5-year survival rate of 10%.[21] Our two patients with stage IV ACC, who underwent resection of the primary tumor and metastases, survived for 16.1 months and 25.2 months, respectively, although mitotane was administered after recurrence. Conversely, patients who undergo debulking surgery and those who do not undergo surgery at all have a dismal outcome. According to previous reports, patients who did not undergo surgery died within 12 months,[21] and patients who underwent debulking or no surgery survived for only 8.6 ± 5.9 months.[25] Moreover, the 5-year survival rate of patients with stage IV disease was 0%–9%,[5,20,23,24] and the mean survival period was 7–8 months.[5,23] In comparing the survival in our series and those in these reports, we believe that the survival benefits justify complete resection for bulky T4 tumors, including the liver and IVC, and the resection of metastases. Furthermore, there are promising reports that aggressive surgery prolonged survival. Surgical resection of residual disease after etoposide, doxorubicin, and cisplatin (EDP) plus mitotane chemotherapy in patients who would not tolerate radical surgery has also achieved good results.[26] Considering that patients who underwent a complete second resection of locally recurrent or distant metastatic disease had a median survival time of 74 months and 5-year survival of 57%,[21] if surgery of the IVC allows complete resection of the primary tumor and its locoregional extension, involvement of the IVC should not be considered a contraindication for surgery.

Another concern is the operative mortality and morbidity of aggressive surgery. Although our series had 0% mortality and 33% (2/6) morbidity, the reported mortality is high, ranging from 10% to 15% for patients undergoing surgery for ACC with both metastatic disease and IVC extension, and from 11% to 25% for those undergoing combined liver and IVC resection.[9,13] Therefore, aggressive surgery should be restricted in patients with severe comorbidity or unresectable metastatic disease.

Recurrence was found within 8.1 months in three of our six patients and after a longer period in the other three. ACC may have two different types of tumor biology, leading to early or late recurrence after resection, and this might depend on the biological aggressiveness of the tumor. The presence of a stage III tumor, a tumor diameter greater than 12 cm, a high mitotic index, abnormal mitotic figures, and intratumor hemorrhage are all reported to be high-risk factors for recurrence.[27–29] We need to consider adjuvant therapy after surgical resection for high-risk patients and patients with bulky T4 invading the liver and IVC, or metastatic disease, although the effects of adjuvant therapy with mitotane alone have not been established.[5] Interestingly, the survival rate in a small series of patients with stage III ACC treated by postoperative radiotherapy was higher than expected.[30] Based on its response rate, EDP plus mitotane shows promise as combination therapy for high-risk patients with ACC in an adjuvant setting.

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