

## Surgical Outcomes of Adrenocortical Carcinoma; 20 Years of Experience in a Single Institution

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**Purpose:** Adrenocortical carcinoma (ACC) is a rare malignant tumor. Early detection is difficult and prognosis is poor. We report on 20 years of ACC surgical experience at our institution.

**Methods:** This study included 32 ACC patients who underwent surgical resection at the Department of Surgery of the Yonsei University Health System in South Korea between January 1990 and February 2012. We reviewed these 32 patients and retrospectively analyzed long-term clinical outcomes and prognosis after radical surgery for ACC.

**Results:** The median age of the 32 patients at diagnosis was 42.25 years (range 3~81 years). There were 16 (50%) female and 16 (50%) male patients. Mean tumor size was 12.36 cm (range 1.8~20 cm). Twenty-five patients (78.12%) had nonfunctioning tumors while the other seven patients (21.87%) had functioning tumors. Seventeen patients (53.12%) were classified as stage II, two (6.25%) as stage III, and 13 (40.62%) as stage IV. Fourteen patients underwent radical surgical resection, while 14 patients received adjuvant chemotherapy, two received adjuvant radiotherapy, and two received adjuvant chemoradiation. Four patients were lost to follow-up. Among the remaining 28 patients, 15 patients survived. The 5- and 10-year overall survival was 60.6% and 37.8%, respectively (median survival=85±24.3 months). Seventeen patients (53%) experienced disease recurrence. Five- and 10-year recurrence-free survival was 41.5% and 29.7%, respectively (median survival=18±5.5 months).

**Conclusion:** Early stage at diagnosis and surgical resection were the most important prognostic factors associated with prolonged survival. The role of additional therapy remains controversial and new agents should continually be evaluated for efficacy.

**Key Words:** Adrenocortical carcinoma, Surgical resection, Survival

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## INTRODUCTION

Adrenocortical carcinoma (ACC) is a rare malignant tumor. Its incidence is approximately 0.7 to 2 per million every year, and it accounts for 0.05 to 0.2% of all carcinoma worldwide.<sup>(1-4)</sup> Early detection is difficult because ACC tumors are located in the retroperitoneal space, and 40~50% of ACC cases have local invasion or distant metastases at diagnosis. This location also makes it more difficult to

achieve complete resection.<sup>(1,5)</sup> Adrenocortical tumors are classified as either functional or nonfunctional according to hormone secretion. In functioning tumors, patients can develop symptoms due to excessive amounts of steroid, androgen, estrogen, or mineralocorticoid. Although many tumors show abnormal serum hormone levels, clinical features are sometimes not prominent. In nonfunctional tumors, symptoms are often unremarkable or a nonspecific clinical manifestation such as abdominal pain may develop.<sup>(6,7)</sup>

Complete surgical resection is the treatment of choice, and is the only curative therapy for ACC. Early detection and complete resection are strong predictors of long-term survival.<sup>(8)</sup> Mitotane is a cornerstone of medical treatment for ACC, and the adjuvant use of mitotane after radical resection shows beneficial effects on outcome in patients with ACC.<sup>(9–11)</sup> Another treatment option is adjuvant chemoradiation, but its survival efficacy is questionable. So far there is no common protocol yet defined. ACC has a very poor prognosis, with a median survival of 3 months without any treatment<sup>(6)</sup> and 5-year survival of 16 to 35% after complete resection.<sup>(12,13)</sup>

Herein, we report on 20 years of ACC experience at the Department of Surgery of the Yonsei University Health System, South Korea. This includes the clinical characteristics, treatment outcomes, and prognosis of 32 patients who received radical adrenalectomy with ACC.

## METHODS

The medical records of patients diagnosed with ACC between 1<sup>st</sup> January 1990 and 29<sup>th</sup> February 2012 were reviewed retrospectively. A total of 62 patients were diagnosed with ACC. Thirty two patients underwent radical surgical resection, 2 patients refused any treatment, and 3 patients visited other hospitals for further evaluation. Twenty-five patients were confirmed by biopsy, but had multiple distant metastases and advanced cancer lesions at diagnosis that were considered unresectable. These patients underwent other treatment options, such as systemic chemotherapy or chemoradiation without any surgery. Information on age, gender, tumor size, tumor laterality, clinical presentations, stage at diagnosis, laboratory findings, imaging studies, pathology, and treatment details for the 32 patients who underwent surgical resection were collected. Among these 32 patients, 4 patients were lost completely to follow-up. All tumors were pathologically confirmed as ACC.

An overnight 1-mg dexamethasone suppression test was performed to rule out Cushing syndrome, and a 24-hour urine collection for 17-ketosteroids was done if a functioning adrenal tumor was suspected. A 24-hour urine collection to measure catecholamine and metanephrine

concentrations was also done to exclude pheochromocytoma. Imaging studies included computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). ACC was strongly suspected on CT findings if readings had irregular shape, inhomogeneous density of central tumor necrosis, tumor calcification, diameter greater than 4 cm, or unilateral location. ACC stage was determined according to the European Network for the study of Adrenal Tumors (ENSAT) staging system.<sup>(14,15)</sup>

The pathologic diagnosis of ACC is based on the recognition of several morphologic parameters, none of which is pathognomonic of malignancy, per se. To assess malignancy potential, the histo-pathologic grade of ACC was calculated in some patients by referring to the Weiss criteria.<sup>(16,17)</sup> This is not a definitive criteria for diagnosing ACC, but it is the most efficient and reliable method for assessing malignancy. If an adrenal tumor met 3 or more of the criteria, it was assumed to be malignant. The Weiss criteria includes the following nine points: Nuclear grade III or IV, 5 or more mitotic figures/50HPF, atypical mitotic figure, clear or vacuolated cells less than 25%, diffuse architecture, and invasion of veins, sinusoids, and capsules.

We retrospectively analyzed long-term clinical outcomes and prognosis after radical surgery for ACC with overall survival (OS) and recurrence-free survival (RFS) as the primary endpoint. OS was defined as the time from first resection to last follow-up or time of death. Recurrence-free interval (RFI) was defined as the time from resection of ACC to detection of first recurrence on imaging. All statistical analyses were performed with SPSS software (version 20.0; SPSS, Chicago, IL). Rates and proportions were calculated for categorical data while medians and ranges were calculated for continuous data. Survival curves were computed according to the Kaplan-Meier method and were compared by the log-rank test. P values of less than 0.05 were considered to indicate statistical significance.

## RESULTS

### 1) Patient characteristics

The median age of 32 patients at diagnosis was 42.25 years (range 3~81 years). Of these patients, 16 (50%) were female and 16 (50%) were male. ACC showed the same prevalence rate in males and females. Mean tumor size was 12.36 cm (range 1.8~20 cm). ACC was on the right side in 11 patients (34.37%), the left side in 19 patients (59.37%), and both sides in 2 patients (6.25%). The tumor appeared more frequently on the left side than the right. Regarding clinical features, 14 patients (43.75%) presented with flank pain and a palpable mass. Seven patients (21.87%) had endocrine symptoms: 4 patients (12.5%) had generalized edema and weight gain, 3 patients (9%) had virilizing features,. On the other hand, disease in 6 patients was detected accidentally (e.g., via routine medical examination or evaluation for another disease). Regarding hormonal laboratory findings, 25 patients (78.12%) had nonfunctioning tumors, and 7 patients (21.87%) had functioning tumors. Of the functioning tumors, 5 patients (15.62%) had Cushing features and 2 patients (6.25%) had primary aldosteronism. Nonfunctioning tumors were more prevalent than functioning tumors. Cushing features were the most common symptom in functioning tumors (Table 1).

**Table 1.** Clinical features of 32 patients who received adrenalectomy with adrenocortical carcinoma

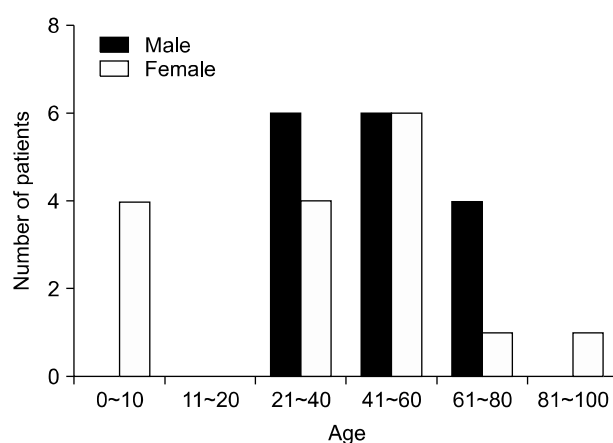
	Total (N=32)
Gender (male : female)	16 : 16
Age (years)	42.25±20.4 (3~81)
Mean tumor size±SD (cm)	12.36±4.4 (1.8~20)
Mean tumor weight±SD (gm)	560.2 (47~2,500)
Site (left : right : both)	19 : 11 : 2
Symptoms and signs	
Abdominal pain, tenderness	14
Virilization	3
General edema, weight gain	4
General weakness	4
Non-specific symptom (detected by chance)	6
Hormone-secreting	
Non-functioning	25
Functioning	
Cushing	5
Primary aldosteronism	2

Regarding age distribution, 4 patients were 1 to 10 years old (male 0, female 4), 10 patients were 21 to 40 years old (male 6, female 4), 12 patients were 41 to 60 years old (male 6, female 6), 5 patients were 61 to 80 years old (male 4, female 1), and 1 female patient was above 81 years old. The age range of 41 to 60 years was the most prevalent (37.5%), corresponding with previous studies. Furthermore, there was high incidence in the age range of 21 to 40 years (31.25%). Incidence for ages below 10 years was 12.5% (Fig. 1).

### 2) Stages and treatment modalities

According to the ENSAT staging system,<sup>(14,15)</sup> 17 patients (53.12%) were classified as stage II, 2 (6.25%) as stage III, and 13 (40.62%) as stage IV. No patients were classified as stage I. Patients with stage IV at diagnosis had distant metastases in the following organs: 8 lung metastases, 6 liver metastases, 2 bone metastases, 1 pancreatic metastasis, 1 ovarian metastasis, and 1 opposite adrenal gland metastasis. There were multiple metastases in 5 patients. Stage II was predominant, with 53.12%. Stage IV comprised 40.62% (Table 2).

Among 32 patients, 14 patients underwent radical surgical resection only and 18 received postoperative adjuvant chemotherapy. For the surgical approach, 28 patients underwent conventional open adrenalectomy, and 4 patients received laparoscopic adrenalectomy. Mitotane was used for 10 patients in combination with other chemotherapy regimens. Seven patients received



**Fig. 1.** Age distributions of 32 adrenalectomy patients with adrenocortical carcinoma.

cisplatin and etoposide (EP). Other regimens included combination 5-FU, doxorubicin, and carboplatin in 1 patient, capecitabine in 1 patient, and paclitaxel with vincristine in 1 patient. All patients received at least 6 months of chemotherapy. To prevent disease progression during follow-up, various regimens were used for 6 patients. For 2 patients, radiotherapy was performed at previous adrenalectomy sites with a total dose of 3,600 Gray (Gy) for 1 month and 5,580 Gy for 2 months. Two other patients received chemoradiation with similar regimens and doses (Table 3).

Among 13 patients with stage IV disease, 10 patients had resectable adrenal tumors; therefore, surgical resection was performed to reduce tumor burden. Three patients among these 10 underwent combined resection of metastatic sites, with 1 liver lobectomy, 1 pancreatectomy, and

1 oophorectomy. The other 3 patients who suffered from severe hypercortisolism received adrenalectomy for palliative care.

### 3) Outcomes and prognosis

The mean follow-up period was 28.5 months, and 4 patients were lost to follow-up. Among 28 patients, 16 patients survived. The 5- and 10-year overall survival was 60.6% and 37.8%, respectively. Seventeen patients (53%) experienced disease recurrence, and the 5- and 10-year recurrence-free survival was 41.5% and 29.7%, respectively (Fig. 2).

Among 15 survivors, 10 patients with stage II ACC and 2 patients with stage III ACC underwent radical surgery. There were 3 patients with stage IV ACC and, among them, 3 patients underwent surgery with palliative goals. After surgery, 6 patients received postoperative adjuvant chemotherapy. Of these, 4 patients had mitotane regimens and 2 had EP (etoposide and cisplatin) regimens. Three patients received radiotherapy. During follow-up, 5 patients experienced disease recurrence: 2 patients had liver and lung metastases, 1 patient had kidney, lymph node, and

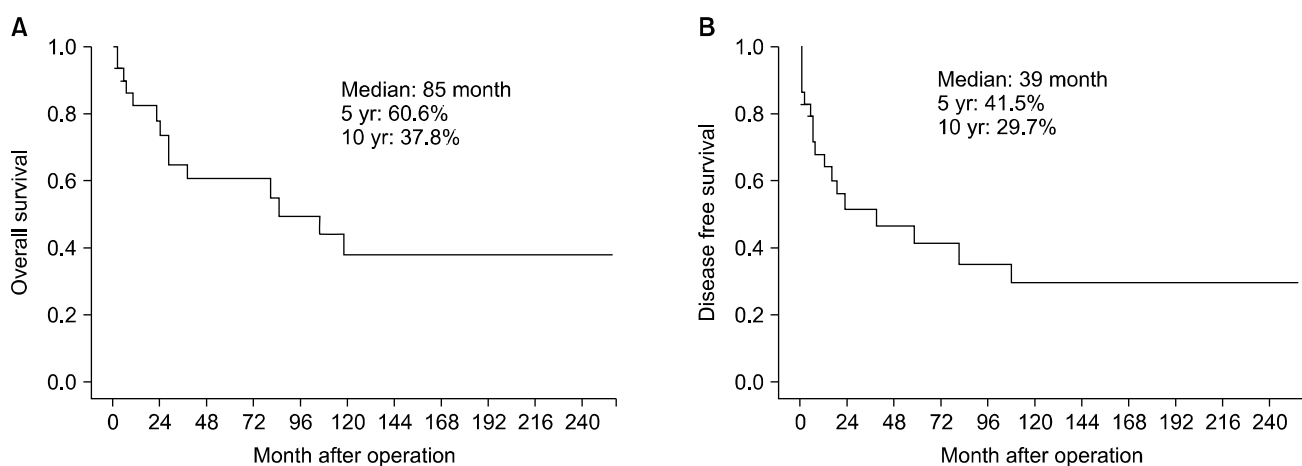
**Table 2.** Stages of 32 adrenalectomy patients with adrenocortical carcinoma

	Total (N=32)
Stage (ENSAT)	
I	0 (0%)
II	17 (53.1%)
III	2 (6.3%)
IV	13 (40.6%)
Distant metastases by organ	
Lung	8
Liver	6
Bone	2
Pancreas	1
Ovary	1
Opposite adrenal gland	1

ENSAT = European Network for the study of Adrenal Tumors.

**Table 3.** Treatment modalities in 32 adrenalectomy patients with adrenocortical carcinoma

Treatment modality	Total (N=32)
Operation only	14
Operation + Chemotherapy	14
Operation + Radiotherapy	2
Operation + Chemotherapy + Radiotherapy	2



**Fig. 2.** Kaplan-Meier estimates of overall survival and recurrence-free survival. (A) Overall survival. (B) Recurrence-free survival.

bone metastases, and 1 had metastatic nodules. One patient had lung and liver metastases and another with nodular metastasis is undergoing additional chemotherapy with mitotane and EP regimens. The other patient with liver and lung metastases underwent lung wedge resection, transarterial chemo-embolization (TACE) and radiofrequency ablation (RFA) for liver metastasis, and systemic chemotherapy. A patient with kidney, lymph node, and bone metastases received partial nephrectomy and additional chemoradiation. A mitotane and EP regimen was used for chemotherapy, and a total dose of 3,000 Gy radiation was given for pelvic bone metastasis. The 1 remaining patient with lung metastases refused any further

treatment (Tables 4, 5).

Survival was compared by stage and treatment modality. There were significant differences in overall survival and disease-free survival by stage (Fig. 3). An early stage at diagnosis had beneficial effects on survival. However, there were no significant differences in survival due to treatment modality. The most important prognostic factor in treatment modality was found to be complete resection, while other treatment options didn't affect clinical survival (Fig. 4).

## DISCUSSION

ACC is a rare and aggressive malignant tumor with a worldwide incidence of approximately 0.7 to 2 per million per year, accounting for 0.05 to 0.2% of all carcinomas.<sup>(1-4)</sup> The age distribution is bimodal with a peak in childhood and a higher second peak in the 4th to 5th decade.<sup>(6)</sup> ACC is reported to be 1.5 times more prevalent in females than in males.<sup>(1)</sup> Tumors appear more frequently on the left side (52.8%) than on the right. Tumors appear on both sides 2.4% of the time.<sup>(1)</sup> The majority are functioning tumors (59.3%).<sup>(3)</sup> Hypercortisolism resulting in Cushing features is the most common endocrine symptom, while primary

**Table 4.** Clinical course and treatment modalities of 15 survivors with adrenalectomy

Survivors	Total (N=15)
Alive without recurrence	10
Alive with recurrence	5
Additional Systemic Chemotherapy	2
Additional Surgery+Chemoradiation	1
Additional Surgery+TACE and RFA+Chemotherapy	1
Additional Treatment rejection	1

TACE = transarterial chemoembolization; RFA = radiofrequency ablation.

**Table 5.** Clinical features of 15 survivors with adrenalectomy (median follow-up: 28.5 months)

	Stage (ENSAT)	Adjuvant chemotherapy	Adjuvant radiotherapy	Recurrence	Additional treatment
Case 1	II	None	None	None	None
Case 2	II	None	None	None	None
Case 3	II	Mitotane, etoposide, doxorubicin	None	None	None
Case 4	II	None	None	None	None
Case 5	II	Gemcitabine, cisplatin	None	None	None
Case 6	II	None	3,600 Gy	Lymph node	Etoposide
Case 7	II	Cisplatin, etoposide	None	None	None
Case 8	II	None	None	None	None
Case 9	II	None	None	None	None
Case 10	II	None	None	None	None
Case 11	III	Mitotane	None	Liver, Lung	Mitotane, cisplatin, etoposide, doxorubicin
Case 12	III	None	5,580 Gy	None	None
Case 13	IV	None	None	Lung	None
Case 14	IV	Mitotane	None	Lung, Liver	Surgery/TACE, RFA/mitotane, etoposide, paclitaxel, carboplatin
Case 15	IV	Cisplatin, etoposide	5,040 Gy	Kidney, Bone, Lymph node	Surgery/3,000 Gy/ cisplatin, doxorubicin, vincristine, etoposide, cyclophosphamide

ENSAT = European Network for the study of Adrenal Tumors; TACE = transarterial chemoembolization; RFA = radiofrequency ablation; Gy = gray.

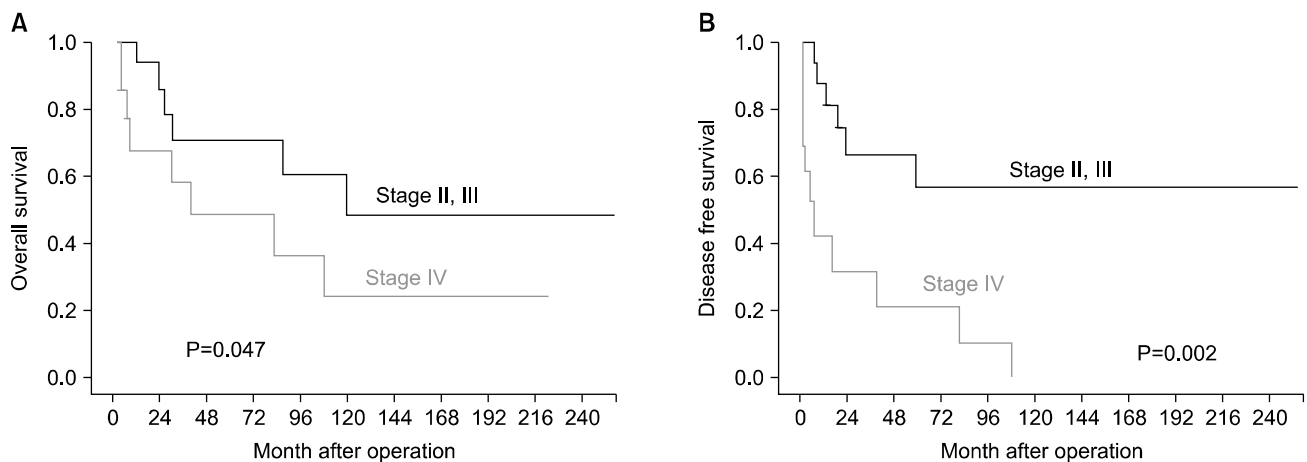


Fig. 3. Kaplan-Meier estimates of overall survival and recurrence-free survival according to stage. (A) Overall survival. (B) Recurrence-free survival.

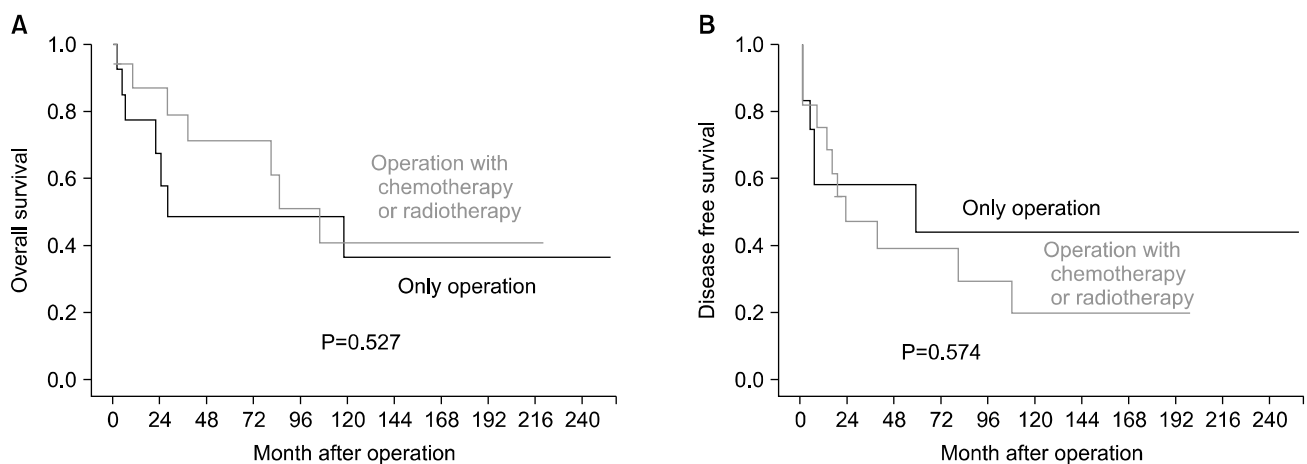


Fig. 4. Kaplan-Meier estimates of overall survival and recurrence-free survival according to treatment modality. (A) Overall survival. (B) Recurrence-free survival.

aldosteronism and adrenogenital syndrome are also possible. With nonfunctioning tumors, most patients present with abdominal pain and a palpable mass.<sup>(1)</sup> Incidental findings on imaging studies with no clinical symptoms are rather common.<sup>(1)</sup> ACC might be associated with a relatively high incidence of advanced stage at diagnosis. Stage I ACC accounts for 21%, stage II accounts for 20%, stage III accounts for 20%, and stage IV accounts for 39% of all ACC cases. ACC commonly metastasizes to lung, liver, lymph node, and bone.<sup>(1)</sup>

The vast majority of ACCs are sporadic (not inherited), but some, particularly in children, are caused by a genetic defect. Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, and Multiple Endocrine Neoplasia type 1 (MEN1) are known to result from defects in *TP53*, *IGF-2*,

and *MEN-1* genes, respectively.<sup>(18,19)</sup> Sporadic ACCs are presumed to be associated with similar gene defects, according to recent studies.<sup>(20)</sup>

A hormonal evaluation is necessary in all patients with suspected ACC. Cortisol hypersecretion is the most common hormone excess in ACC, so evaluation for adrenal corticosteroids is essential. This includes an overnight dexamethasone suppression test, 24-hour urinary free cortisol excretion, and determination of plasma ACTH. Elevated serum dehydroepiandrosterone sulphate (DHEAS) levels strongly suggest ACCs, as benign adrenocortical tumors often exhibit low DHEAS concentrations.<sup>(7)</sup> Imaging evaluation is useful in diagnosing ACC, and CT or MRI are commonly used. CT is the most diagnostic imaging tool, while MRI, PET, and adrenal angiography are

complementary.(1)

Since adrenal adenomas and cancers can look similar microscopically, a biopsy may not definitively determine whether an adrenal tumor is cancerous or not. In addition, needle biopsy of an ACC can actually spread tumor cells. If a suspected adrenal tumor turns out to be another tumor, such as a pheochromocytoma, biopsy may cause massive bleeding and hypertensive crisis. For these reasons, a biopsy is generally not performed if the adrenal tumor's size or other features suggest malignancy. Blood tests for hormone secretion and imaging studies are more useful than biopsies in diagnosing ACC.(7)

The pathological diagnosis of ACC is challenging due to its rarity and difficulty in performing biopsies. The only definitive diagnostic criteria for ACC are local invasion and distant metastasis. The Weiss histopathologic system is the most common method used to assess the malignancy of adrenocortical tumors because of its simplicity and reliability.(16) The original Weiss system, established in 1984, was based on 9 microscopic criteria, and 3 or more criteria are required for malignancy. The lack of reliability for some Weiss criteria led to a statistically modified system based on the most reliable criteria (2 x mitotic figures (> 5/50 HPF)+2 x cytoplasm (clear cells<25%)+abnormal mitoses+necrosis+capsular invasion).(16,17)

Complete surgical resection is the treatment of choice for ACC, as it is the only curative treatment. Invasion by or adherence of carcinoma into adjacent organs often requires en bloc organ resections. In addition, lymphadenectomy is often included.(21) The benefit of routine lymphadenectomy during adrenalectomy was suggested in a report from the German ACC Study Group of 283 patients with completely resected ACC.(22) They reported a significantly reduced the risk of tumor recurrence (hazard ratio: 0.65; 95% confidence interval: 0.43~0.98; P=0.042) and disease-related death (hazard ratio: 0.54; 95% confidence interval: 0.29~0.99; P=0.049) in patients who underwent lymphadenectomy versus those who did not.

In stage IV ACCs, the ability to perform complete resection is a critical issue. Even if the tumor cannot be entirely removed, some clinicians insist on maximal debulking to improve survival,(6,23,24) although others

disagree with the survival benefits of this strategy.(25,26) There is agreement that incomplete resection of primary tumors or metastatic disease is associated with a poor prognosis. So far, there is minimal data to support routine debulking of nonresectable tumors. Thus, the treatment modalities for stage IV ACC are determined and individualized by the histologic grade, underlying tumor biology, and aggressiveness of tumors. A surgical approach is considered for functioning tumors with hormone hypersecretion. Patient desire is another important factor for surgery.

ACC is found at an advanced stage in many cases, making complete resection difficult. If tumors are not amenable to surgical resections, cytotoxic chemotherapy has been considered. Mitotane (1,1 dichloro-2(o-chlorophenyl)-2-(p-chloro-phenyl) ethane) is an isomer of the insecticide p,p'-DDD and a chemical congener of the insecticide DDT. It is known to function as an adrenolytic agent with specific cytotoxic effects on the adrenal cortex.(27) Due to high rates of locoregional or metastatic recurrence after resection, adjuvant treatment options are needed. Terzolo et al.(28) reported that adjuvant treatment with mitotane can be administered in ACC with beneficial effects on outcome. A comparison of 47 patients treated with adjuvant mitotane and 130 patients without showed significantly longer RFS of 42 months (hazard ratio of recurrence: 2.91; 95% confidence interval: 1.77~4.78; P<0.001) with adjuvant treatment compared to 10 months without (hazard ratio of recurrence: 1.97; 95% confidence interval: 1.21~3.20; P=0.005). They also reported that mitotane concentrations above 14 mg/L predict effective responses to adjuvant treatment associated with prolonged RFS (hazard ratio of recurrence: 0.418; 95% confidence interval: 0.22~0.79; P=0.007). This suggests that monitored adjuvant mitotane treatment may benefit patients after radical ACC removal.(29)

Regarding chemotherapy for ACC, there is no standard regimen or dose that results in favorable clinical outcomes. Several cytotoxic agents have been used as single drugs or in combination for advanced ACCs, including cisplatin, etoposide, doxorubicin, vincristine, 5-fluorouracil, and streptozocin. Among variable results, the highest response

rate was demonstrated in a phase II multicenter trial with the 'EDP' combination regimen of etoposide (100 mg/m<sup>2</sup>/day on days 5~7), doxorubicin (20 mg/m<sup>2</sup>/day on days 1 and 8), and cisplatin (40 mg/m<sup>2</sup>/day on days 1 and 9) every 4 weeks (3~8 cycles) given together with continuous mitotane (planned dose 4 g/day). The overall response rate was reported as 53.5% (2 complete and 13 partial responses in 28 patients) (95% confidence interval, 35~72%).<sup>(30)</sup> Another combination of etoposide, vincristine, and cisplatin with mitotane showed a 22% overall response rate, but the response was questionable without mitotane.<sup>(31)</sup>

Radiation therapy is not often used as a main treatment for ACC. The role of radiotherapy in ACC has not been well defined and is usually regarded as offering limited benefits. Radiation may be used after surgery to kill remaining cancer cells. Radiation may also be used for palliative purposes if metastasis to bone or brain has occurred.<sup>(32)</sup>

ACC has a dismal prognosis, with a median survival of 3 months without any treatment.<sup>(6)</sup> The overall 5-year survival is 16 to 35% after complete resection.<sup>(12,13)</sup> According to the European Network for the Study of Adrenal Tumors (ENSAT) staging system, the 5-year survival of stage I ACC is 73.9%, stage II is 63.8%, stage III is 44.1%, and stage IV is 6.9%.<sup>(33)</sup>

According to the current survival analysis, early stage at diagnosis had significant survival benefits, and surgical resection was the only curative treatment with better survival (Figs. 3 and 4). These results support that surgical resection of ACC is important. This study showed better overall survival rates than other studies, with overall survival of 50% at stages II and III, and 24% at stage IV. RFS was 58% at stages II and III, and 10% at stage IV. It is possible that more early stage II patients were included in our study (53.8% of patients), leading to more cases of radical resection and increasing survival.

In regard to treatment modalities that confer survival benefits, we assumed that all cases involved complete adrenalectomy. It is difficult to determine whether all 32 patients actually underwent 'complete' surgical resection because this study is based upon retrospective analysis. En bloc resection of local invasion, or metastatectomy was also performed in stage IV ACCs. According to several cases

of incidental findings in surgical fields, it is difficult to determine if lymphadenectomy was performed in all patients.

Early stage at diagnosis and radical surgical resection of localized primary or metastatic disease were found to be the most important prognostic factors influencing survival. The effect of adjuvant therapy on survival was indefinite, and other treatment modalities should be studied for survival benefits.

## CONCLUSION

ACC is a fatal disease with poor prognosis and a lack of efficient treatment options. According to this study, early stage at diagnosis and complete surgical resection were the most important prognostic factors associated with prolonged survival. The role of additional therapy remains controversial, and other treatment modalities should continue to be evaluated for efficacy.

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