

# Early stage adrenocortical carcinoma—what contributes to poor prognosis after adrenalectomy? A retrospective cohort study

Douk Kwon<sup>1</sup>, Cheong-Sil Rah<sup>2</sup>, Byung-Chang Kim<sup>1</sup>, Shin Jeong Pak<sup>3</sup>, Jae Won Cho<sup>4</sup>, Won Woong Kim<sup>1</sup>, Yu-mi Lee<sup>1</sup>, Jae Lyun Lee<sup>5</sup>, Dong Eun Song<sup>6</sup>, Ki-Wook Chung<sup>1</sup>, Tae-Yon Sung<sup>1</sup>

<sup>1</sup>Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

<sup>2</sup>Department of Surgery, Uijeongbu Eulji Medical Center, Eulji University School of Medicine, Uijeongbu, Korea

<sup>3</sup>Department of Surgery, Hanyang University College of Medicine, Seoul, Korea

<sup>4</sup>Department of Surgery, JinjuKorea Hospital, Jinju, Korea

<sup>5</sup>Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

<sup>6</sup>Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

**Purpose:** Adrenocortical carcinoma (ACC) is a rare primary carcinoma originating in the adrenal gland with a poor prognosis and a high recurrence rate. This study evaluated the risk factors associated with recurrence in patients with early stage ACC after curative surgical resection.

**Methods:** The present study retrospectively evaluated the risk factors for recurrence in 38 patients with stages 1 and 2 ACC who underwent curative resection between 1995 and 2020.

**Results:** Recurrence was observed in 21 patients (55.3%), with no significant difference between stages 1 and 2 ACC ( $P = 0.640$ ). The overall recurrence rate was higher in patients who underwent minimally invasive surgery than open adrenalectomy (71.4% vs. 51.6%). Of the 33 patients with gross tumor margins negative for malignancy, 16 (48.5%) experienced tumor recurrence, and all 5 patients with positive and unknown gross resection margins had recurrence. Recurrences were observed in 14 of the 30 patients (46.7%) negative for pathologic resection margins, 6 of the 7 patients (85.7%) with pathologically indeterminate margins, and 1 patient with pathologically positive margins.

**Conclusion:** The recurrence rates are high even in patients with early stage ACC, being higher in patients who undergo minimally invasive surgery than open adrenalectomy. Obtaining clear resection margins during surgery may reduce tumor recurrence; however, gross or pathologic margin safety was not a secure factor in preventing recurrence. None of the factors analyzed was a definitive predictor of poor prognosis.

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**Key Words:** Adrenocortical carcinoma, Adrenalectomy, Early stage, Recurrence

## INTRODUCTION

Adrenocortical carcinoma (ACC) is a rare primary carcinoma originating in the adrenal gland [1] with an annual incidence of 0.7–2.0 cases per million population [2-5]. ACC can present

as a functional adrenal tumor or can be detected incidentally by abdominal imaging modalities, such as CT and MRI scans performed to evaluate intraabdominal medical problems. Accurate characterization of ACC through imaging modalities is important to differentiate these tumors from benign adrenal

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Corresponding Author: Tae-Yon Sung

Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea

Tel: +82-2-3010-5862, Fax: +82-2-3010-6701,

E-mail: tysung@amc.seoul.kr

ORCID: https://orcid.org/0000-0002-2179-6269

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tumors. Moreover, the detection of early stage ACC may allow appropriate treatment [6].

CT scanning is a standard tool to evaluate adrenal tumors, with their sizes and enhancement patterns being critical in predicting their malignant potential. Size of  $\geq 4$  cm has a sensitivity of  $>93\%$  for identifying adrenal carcinomas [7], and a threshold of 10 Hounsfield units (HU) on pre-contrast CT scan has a sensitivity of 71% and a specificity of 98% for differentiating benign from malignant lesions [8]. The enhancement pattern of ACC is usually heterogeneous, with ACCs having less washout than benign adenomas. Indeed, ACCs are characterized by an absolute washout value of  $<60\%$  and a relative washout value of  $<40\%$  [9].

ACC has been associated with a poor prognosis and a high recurrence rate [1,5]. The 5-year disease-free survival (DFS) rate for patients with completely resected stage 1–3 ACC is about 30% [10,11]. Complete resection is considered the sole curative treatment for patients with early stage ACC and is the most important prognostic determinant of patient survival [12,13]. The completeness of resection can be determined by examination of resection margins, with both macroscopic and microscopic resection margin involvement predicting poorer patient prognosis [14].

Because ACCs have a high recurrence rate, many patients receive adjuvant treatment, such as chemotherapy and/or radiation therapy, following curative resection. To date, mitotane is the only approved pharmaceutical agent for ACC, although its ability to prevent local recurrence remains unclear [15-17].

The present study evaluated the risk factors associated with recurrence in patients with early stage ACC after curative surgical resection. Features on preoperative CT scans associated with malignant potential, as well as gross and pathologic resection margins, were especially evaluated.

## METHODS

### Ethics statements

The study was approved by the Institutional Review Board of Asan Medical Center, Seoul, Korea (No.2015-0376), which waived the requirement for informed consent due to the retrospective nature of this study. All methods were performed in accordance with the relevant guidelines and regulations.

### Study population

This retrospective study evaluated patients diagnosed with ACC who visited our tertiary center between 1995 and 2020. Patients aged  $\leq 18$  years and those lacking clinical records were excluded. Of the 109 patients identified, 93 (85.3%) were diagnosed with ACC and were treated in our center. ACC stage was classified according to the American Joint Committee

on Cancer 8th edition [11]. Because this study was designed to evaluate the prognosis of patients with early stage ACC, it included 38 patients, including 5 with stage 1 and 33 with stage 2 ACC who were candidates for curable surgical treatment.

### Study variables

Patients' clinical characteristics, CT scan findings, operation records, and pathological reports were collected. CT findings defined as being associated with malignant potential included adrenal tumor size of  $>4$  cm, pre-contrast density of  $>10$  HU, absolute washout of  $<60\%$ , and relative washout of  $<40\%$ . Adrenal tumors were evaluated on adrenal CT scans with contrast and on other types of dynamic abdominal-pelvic CT scans. Variables associated with malignant potential on CT scans were available only for 20 patients. Minimally invasive surgery (MIS) in this study included laparoscopic adrenalectomy and robot-assisted adrenalectomy.

Gross and pathologic adrenal gland resection margins were compared, with margins described as negative, positive, and unknown or indeterminate. Gross resection margins were determined intraoperatively by inspection using MIS instruments or palpation of the operative field during open adrenalectomy. Patients lacking information on gross margin safety were defined as having unknown gross resection margins. Patients with intraoperatively fragmented specimens within the specimen retrieval bag were defined as having indeterminate pathologic resection margins, as the actual negativity or positivity of the margins could not be determined. Mitotic activity and Ki-67 index were available only in 23 and 17 patients, respectively.

DFS was defined as the interval from the date of surgical resection to the date of first recurrence. Adjuvant treatment after adrenalectomy was defined as radiotherapy and/or chemotherapy, with the latter including treatment with cytotoxic agents, such as etoposide, doxorubicin, and cisplatin, as well as with mitotane.

### Statistical analysis

Continuous variables are presented as means  $\pm$  standard deviations and compared by the Mann-Whitney U-tests. Categorical variables are presented as absolute numbers and percentages and compared by the Fisher exact tests. All statistical analyses were performed using IBM SPSS ver. 26.0 for Windows (IBM Corp.), with the P-values of  $<0.05$  considered statistically significant.

## RESULTS

### Patient characteristics

The 38 patients included in the present study were of mean age of 48.4 years (range, 23–74 years) (Fig. 1), with no difference

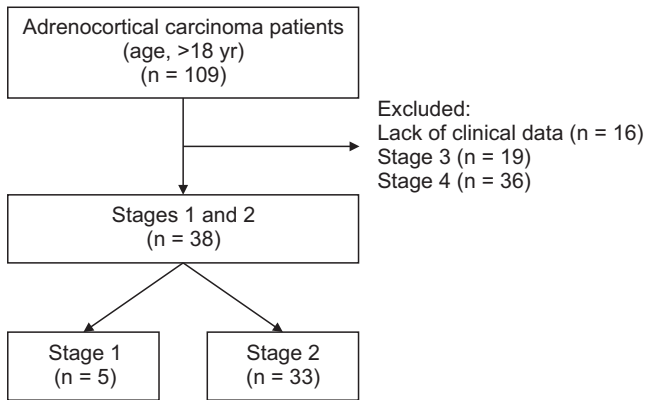


Fig. 1. Study population.

in age between patients with stage 1 and 2 ACC (Table 1). The mean follow-up duration was  $74.5 \pm 61.1$  months (range, 1–280 months) and the mean DFS was  $50.1 \pm 56.8$  months. The mean adrenal tumor size based on CT scan results was 9.5 cm (range, 2.5–27.0 cm), with tumor size being significantly larger in patients with stage 2 (10.4 cm) than stage 1 (4.0 cm) ACC, although all tumors of >5 cm were defined as stage 2 or T2 ( $P < 0.001$ ). Other individual variables on CT scans that correlated with malignant potential features included pre-contrast density of >10 HU, absolute washout of <60%, and relative washout of <40%. When 4 malignant potential features on CT scan were combined, 2 patients (50.0%) with stage 1 and 15 (93.8%) with stage 2 ACCs were classified accordingly.

Table 1. Clinicopathologic characteristics of patients with early stage adrenocortical carcinoma

Characteristic	Total population	Stage 1	Stage 2	P-value
No. of patients	38	5	33	
Age (yr)	$48.4 \pm 14.5$	$50.4 \pm 5.4$	$48.2 \pm 15.5$	0.900
Sex				
Female	17 (44.7)	3 (60.0)	14 (42.4)	0.640
Male	21 (55.3)	2 (40.0)	19 (57.6)	
CT scan findings				
Adrenal tumor size (cm)	$9.5 \pm 3.9$	$4.0 \pm 0.8$	$10.4 \pm 3.4$	<0.001
Pre-contrast density (HU)	$35.7 \pm 5.9$	$38.2 \pm 4.5$	$35.2 \pm 6.1$	0.323
Absolute washout (%)	$34.5 \pm 18.2$	$41.8 \pm 14.3$	$32.7 \pm 19.0$	0.385
Relative washout (%)	$19.3 \pm 13.0$	$25.4 \pm 9.4$	$17.7 \pm 13.5$	0.148
Adrenal tumor size >4 cm	34 (91.9)	2 (40.0)	32 (100)	0.001
Pre-contrast density >10 HU	29 (100)	5 (100)	24 (100)	NA
Absolute washout <60%	19 (95.0)	4 (100)	15 (93.8)	>0.999
Relative washout <40%	19 (95.0)	4 (100)	15 (93.8)	>0.999
Combination of 4 malignant potential features on CT scan				
No	3 (15.0)	2 (50.0)	1 (6.3)	0.088
Yes	17 (85.0)	2 (50.0)	15 (93.8)	
Surgical procedure				
Open adrenalectomy	31 (81.6)	1 (20.0)	30 (90.9)	0.002
Minimally invasive surgery	7 (18.4)	4 (80.0)	3 (9.1)	
Pathologic adrenal tumor size (cm)	$11.2 \pm 5.4$	$4.1 \pm 1.0$	$12.3 \pm 5.0$	<0.001
Gross resection margin				
Negative	33 (86.8)	4 (80.0)	29 (87.9)	0.239
Unknown	3 (7.9)	0 (0)	3 (9.1)	
Positive	2 (5.3)	1 (20.0)	1 (3.0)	
Pathologic resection margin				
Negative	30 (78.9)	4 (80.0)	26 (78.8)	0.923
Indeterminate	7 (18.4)	1 (20.0)	6 (18.2)	
Positive	1 (2.6)	0 (0)	1 (3.0)	
Mitotic activity	$9.7 \pm 8.7$	$10.0 \pm 9.2$	$9.7 \pm 8.9$	>0.999
Ki-67 index	$11.7 \pm 9.3$	$7.5 \pm 5.0$	$12.3 \pm 9.7$	0.618
Adjuvant treatment				
No	7 (18.4)	2 (40.0)	5 (15.2)	0.223
Yes	31 (81.6)	3 (60.0)	28 (84.8)	
Mitotane use				
No	15 (39.5)	2 (40.0)	13 (39.4)	>0.999
Yes	23 (60.5)	3 (60.0)	20 (60.6)	
Recurrence	21 (55.3)	2 (40.0)	19 (57.6)	0.640

Values are presented as number only, mean  $\pm$  standard deviation, number (%). HU, Hounsfield units; NA, not applicable.

Of the 38 patients, 31 (81.6%) underwent open surgery and 7 (18.4%) underwent MIS. Of the latter, 4 patients underwent laparoscopic transperitoneal adrenalectomy, 2 underwent laparoscopic retroperitoneal posterior adrenalectomy, and 1 underwent robot-assisted retroperitoneal posterior adrenalectomy. Of the 5 patients with stage 1 tumors, 4 (80.0%) underwent MIS, whereas, of the 33 patients with stage 2 tumors, 30 (90.9%) underwent open adrenalectomy.

Thirty-three of the 38 patients (86.8%) had clear gross resection margins. Information on gross resection margins was not available for 3 patients (7.9%) with stage 2 tumors, all of whom had undergone open surgery. Two patients (5.3%), 1 in each stage group, were reported to have positive resection margins. On pathologic reports, 30 patients (78.9%) presented with negative resection margins, 7 (18.4%) had indeterminate resection margins, and 1 (2.6%) with a stage 2 tumor presented with positive margins.

Of the 38 patients, 31 (81.6%) received adjuvant treatment, with 23 (60.5%) being treated with mitotane. Recurrence was detected in 21 patients (55.3%), including 2 (40.0%) with stage 1 and 19 (57.6%) with stage 2 ACC. DFS did not differ significantly in patients with stage 1 and stage 2 ACC ( $P = 0.384$ ) (Fig. 2).

### Risk factors for tumor recurrence

The mean adrenal tumor size on CT scans in patients who experienced tumor recurrence was 8.6 cm (Table 2), with the mean sizes of stages 1 and 2 tumors being smaller in patients who did than did not experience tumor recurrence. Nine patients (60.0%) with stage 2 tumors who experienced recurrence had a combination of all 4 malignant potential features on CT scan, compared with none in the stage 1 group. One patient with a stage 1 tumor who had no malignant features on CT scan experienced tumor recurrence. Recurrences were observed in 16 patients (51.6%) after open adrenalectomy

and in 5 patients (71.4%) after MIS. Recurrences were observed in 50% of the patients with stage 1 tumors who underwent MIS procedures, in 53.3% of the patients with stage 2 tumors who underwent open adrenalectomy, and in all 3 patients with stage 2 tumors who underwent MIS.

Gross and pathological resection margins did not differ significantly in patients who did and did not experience tumor recurrence ( $P > 0.05$ ). Recurrences were observed, however, in all 3 patients (100%) with no record of gross resection margins and in both patients (100%) with positive gross resection margins. Recurrences were also observed in 6 of the 7 patients (85.7%) with indeterminate pathologic margins and in 1 patient (100%) with positive pathologic resection margins. Tumor recurrence was also observed in 19 patients (61.3%) who received adjuvant treatment and in 14 (60.9%) who were treated with mitotane.

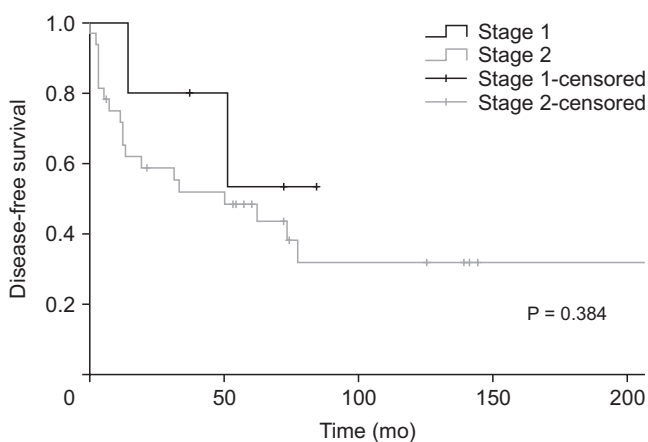
### Resection margin safety

Because pathologic resection margin is a more objective variable than gross resection margin, a subjective variable dependent on the surgeon's decision, indeterminate or positive pathologic resection margins were also evaluated. The clinicopathologic characteristics of these 8 patients are shown in Table 3. Tumor recurrence was observed in 7 of these 8 patients (87.5%). Tumor sizes varied from 4.0 cm to 14.0 cm, with 6 of these patients undergoing open adrenalectomy.

## DISCUSSION

This retrospective analysis of patients with early stage ACC sought to identify risk factors associated with recurrence. The recurrence rate in this study cohort was 55.3%, emphasizing the need for a comprehensive understanding of the variables contributing to ACC recurrence. Because CT scan results are crucial for characterizing adrenal tumors, previous CT results were re-evaluated to assess their significance. Factors identified as being associated with malignant potential on CT scans included tumor size  $>4$  cm, pre-contrast density  $>10$  HU, absolute washout  $<60\%$ , and relative washout  $<40\%$ . These factors, individually or in combination, were identified in most patients with ACC. Recurrence rates were similar in patients with stages 1 and 2 tumors who were positive for all 4 potentially malignant features (47.1% vs. 52.9%,  $P > 0.999$ ). The finding, that a substantial proportion of stage 2 patients exhibited all 4 malignant features, emphasizes the aggressive nature of these tumors and the need for early detection and intervention.

Open adrenalectomy was performed more frequently in patients with stage 2 than stage 1 ACCs, likely because the former tumors were larger. The recurrence rate was higher in patients who underwent MIS (71.4%) than in those who



**Fig. 2.** Kaplan-Meier analysis of disease-free survival rates in patients with early stage adrenocortical carcinoma.

**Table 2.** Clinicopathologic characteristics of patients with early stage adrenocortical carcinoma with and without tumor recurrence

Characteristic	Total population		Stage 1		Stage 2		P-value
	Non-recurrent	Recurrent	Non-recurrent	Recurrent	Non-recurrent	Recurrent	
No. of patients	17	21	3	2	14	19	
Age (yr)	46.1 ± 13.5	50.4 ± 15.4	46.7 ± 2.1	56.0 ± 1.4	45.9 ± 15.0	49.8 ± 16.1	0.377
Sex							
Female	8 (47.1)	9 (52.9)	1 (33.3)	2 (66.7)	7 (50.0)	7 (50.0)	0.497
Male	9 (42.9)	12 (57.1)	2 (100)	0 (0)	7 (36.8)	12 (63.2)	
CT scan findings							
Adrenal tumor size (cm)	10.7 ± 4.5	8.6 ± 3.1	4.3 ± 0.9	3.5 ± 0.7	12.0 ± 3.6	9.2 ± 2.8	0.008
Pre-contrast density (HU)	34.7 ± 7.7	36.6 ± 3.6	39.1 ± 6.1	36.7 ± 0.4	33.5 ± 7.9	36.6 ± 3.9	0.331
Absolute washout (%)	33.8 ± 16.9	35.3 ± 20.2	38.8 ± 16.0	50.6	31.6 ± 18.0	33.6 ± 20.7	0.681
Relative washout (%)	20.1 ± 13.8	18.4 ± 12.9	23.0 ± 9.9	32.5	18.8 ± 15.7	16.8 ± 12.6	0.758
Adrenal tumor size >4 cm	16 (47.1)	18 (52.9)	2 (100)	0 (0)	14 (43.8)	18 (56.3)	NA
Pre-contrast density >10 HU	14 (48.3)	15 (51.7)	3 (60.0)	2 (40.0)	11 (45.8)	13 (54.2)	NA
Absolute washout <60%	9 (47.4)	10 (52.6)	3 (75.0)	1 (25.0)	6 (40.0)	9 (60.0)	0.438
Relative washout <40%	9 (47.4)	10 (52.6)	3 (75.0)	1 (25.0)	6 (40.0)	9 (60.0)	0.438
Combination of 4 malignant potential features on CT scan							
No	2 (66.7)	1 (33.3)	1 (50.0)	1 (50.0)	1 (100)	0 (0)	0.438
Yes	8 (47.1)	9 (52.9)	2 (100)	0 (0)	6 (40.0)	9 (60.0)	
Surgical procedure							
Open adrenalectomy	15 (48.4)	16 (51.6)	1 (100)	0 (0)	14 (46.7)	16 (53.3)	0.244
Minimally invasive surgery	2 (28.6)	5 (71.4)	2 (50.0)	2 (50.0)	0 (0)	3 (100)	
Pathologic adrenal tumor size (cm)	12.9 ± 6.2	9.9 ± 4.3	4.7 ± 0.5	3.3 ± 1.1	14.7 ± 5.4	10.5 ± 3.9	0.016
Gross resection margin							
Negative	17 (51.5)	16 (48.5)	3 (75.0)	1 (25.0)	14 (48.3)	15 (51.7)	0.187
Unknown	0 (0)	3 (100)	-	-	0 (0)	3 (100)	
Positive	0 (0)	2 (100)	0 (0)	1 (100)	0 (0)	1 (100)	
Pathologic resection margin							
Negative	16 (53.3)	14 (46.7)	3 (75.0)	1 (25.0)	13 (50.0)	13 (50.0)	0.226
Indeterminate	1 (14.3)	6 (85.7)	0 (0)	1 (100)	1 (16.7)	5 (83.3)	
Positive	0 (0)	1 (100)	-	-	0 (0)	1 (100)	
Mitotic activity	10.8 ± 9.6	9.2 ± 8.5	20.0	5.0 ± 4.2	9.4 ± 9.5	9.9 ± 8.9	0.699
Ki-67 index	13.0 ± 5.9	11.0 ± 10.9	11.0	4.0	13.4 ± 6.5	11.7 ± 11.2	0.310
Adjuvant treatment							
No	5 (71.4)	2 (28.6)	1 (50.0)	1 (50.0)	4 (80.0)	1 (20.0)	0.138
Yes	12 (38.7)	19 (61.3)	2 (66.7)	1 (33.3)	10 (35.7)	18 (64.3)	
Mitotane use							
No	8 (53.3)	7 (46.7)	1 (50.0)	1 (50.0)	7 (53.8)	6 (46.2)	0.472
Yes	9 (39.1)	14 (60.9)	2 (66.7)	1 (33.3)	7 (35.0)	13 (65.0)	

Values are presented as number only, mean ± standard deviation, or number (%). HU, Hounsfield units; NA, not applicable.



**Table 3.** Clinicopathologic characteristics of patients with early stage adrenocortical carcinoma presenting with indeterminate or positive resection margins on pathologic reports

Patient No.	Pathologic resection margin	Stage	Age (yr)	Sex	Tumor size (cm)	CT findings				Surgical procedure	Gross resection margin	Mitotic activity	Ki-67 index	Adjuvant treatment	Mitotane use	Recurrence
						Pre-contrast density (HU)	Absolute washout (%)	Relative washout (%)	Relative washout (%)							
1	Positive	2	60	Male	5.9	34.32	0.95	0.55	Open	Negative	0	10	Yes	Yes	Yes	
2	Indeterminate	2	23	Male	12.0	NA	NA	NA	Open	Negative	NA	NA	Yes	Yes	Yes	
3	Indeterminate	2	66	Male	9.5	NA	NA	NA	Open	Negative	NA	NA	Yes	No	Yes	
4	Indeterminate	2	48	Female	14.0	35.68	34.26	21.33	Open	Negative	NA	NA	Yes	No	Yes	
5	Indeterminate	2	28	Female	9.0	31.15	20.82	10.65	Open	Negative	3	NA	Yes	No	No	
6	Indeterminate	2	53	Female	8.0	32.90	NA	NA	Open	Positive	6	4	Yes	Yes	Yes	
7	Indeterminate	1	55	Female	4.0	36.42	NA	NA	Minimally invasive	Positive	8	NA	Yes	Yes	Yes	
8	Indeterminate	2	47	Male	6.2	41.82	36.95	21.24	Minimally invasive	Negative	0	NA	Yes	Yes	Yes	

HU, Hounsfield units; NA, not applicable.

underwent open adrenalectomy (51.6%), although the difference was not statistically significant. All 3 patients with unknown gross resection margins and 2 patients with positive margins experienced tumor recurrence, suggesting that achieving clear resection margins during surgery would reduce the likelihood of poor prognosis. However, 48.5% of patients with negative gross resection margins experienced tumor recurrence.

Recurrences were also observed in 14 of the 30 patients (46.7%) with negative pathologic margins, although the recurrence rate was higher in patients with indeterminate pathologic margins (85.7%). Actual pathologic resection margin status could not be determined, however, in patients presenting indeterminate pathologic margins because these specimens were fragmented during their retrieval, thus limiting the actual effect of margin safety. Nevertheless, these findings emphasize the pivotal role of margin involvement in ACC prognosis, highlighting the importance of preserving specimen margins and comprehensively assessing gross margins during surgery.

Despite open surgery being associated with higher rates of positive/unknown gross margins and positive/indeterminate pathological margins, the recurrence rate was higher in patients who underwent MIS than open adrenalectomy. This finding suggests that unidentified tumor remnants may persist following MIS. The choice of surgical method for early stage ACC remains unclear and is likely influenced by factors other than margin involvement [10,18]. Overall, gross margin or pathologic margin safety after adrenalectomy itself was not able to determine the likelihood of poor prognosis in early stage ACC such as recurrence. Recurrence rates may be reduced, and prognosis improved by selecting the appropriate surgical method based on individual patient characteristics.

Adjuvant treatment, including radiation therapy and chemotherapy with agents other than mitotane, was not significantly associated with ACC recurrence in the present study. Treatment with mitotane, the only approved drug for ACC, was also not associated with the recurrence of early stage ACC. Proliferation markers, such as mitotic activity and Ki-67 expression, did not differ significantly in patients who did and did not experience tumor recurrence. Although these markers are recognized as prognostic factors and influence adjuvant treatment strategies, their utility in predicting recurrence in patients with early stage ACC remains uncertain [19,20].

This study had several limitations. Its retrospective, single-center design may have introduced selection bias and be responsible for potential missing data. The relatively small number of patients is also a limitation, precluding multivariable analysis. Nevertheless, these long-term follow-up results may offer valuable insights into the complexity underlying the recurrence of early stage ACC.

In conclusion, the rate of tumor recurrence is high in patients with early stage ACC. Factors associated with recurrence may

include MIS (vs. open adrenalectomy) and the lack of clear resection margins, including indeterminate pathologic resection margins. However, specimen margin safety after adrenalectomy was not a definitive predictive factor to determine poor prognosis in patients with early stage ACC. Treatment strategies should be tailored to individual cases. Further investigations into the factors influencing ACC recurrence are warranted to improve outcomes in patients with this rare malignancy.

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### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### ORCID iD

Douk Kwon: <https://orcid.org/0009-0003-0681-1867>

Cheong-Sil Rah: <https://orcid.org/0000-0001-8430-3129>  
 Byung-Chang Kim: <https://orcid.org/0000-0002-9634-403X>  
 Shin Jeong Pak: <https://orcid.org/0000-0002-9097-7135>  
 Jae Won Cho: <https://orcid.org/0000-0002-7775-5159>  
 Won Woong Kim: <https://orcid.org/0000-0003-3471-2068>  
 Yu-mi Lee: <https://orcid.org/0000-0002-8183-2604>  
 Jae Lyun Lee: <https://orcid.org/0000-0002-9420-7162>  
 Dong Eun Song: <https://orcid.org/0000-0002-9583-9794>  
 Ki-Wook Chung: <https://orcid.org/0000-0002-4418-1857>  
 Tae-Yon Sung: <https://orcid.org/0000-0002-2179-6269>

### Author Contribution

Conceptualization, Methodology: TYS, JLL, DES  
 Formal Analysis, Investigation, Visualization: DK  
 Data Curation: CSR, BCK, SJP, JWC, WWK, YL, KWC, TYS  
 Supervision: KWC, TYS  
 Writing – Original Draft: DK, TYS  
 Writing – Review & Editing: All authors

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