Characteristics of Adrenocortical carcinoma in South Korea:

A registry-based nationwide survey

Short title: Adrenocortical carcinoma in Korea

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Abstract

Purpose

To evaluate the clinical characteristics and prognostic factors in patients with adrenocortical carcinoma (ACC) in South Korea.

Methods

A nationwide, registry-based survey was conducted to identify pathologically proven ACC at 25 tertiary care centers in South Korea between 2000 and 2014. Cox proportional hazard model and log-rank test were adopted for survival analysis.

Results

Two hundred four patients with ACC were identified, with a median follow-up duration of 20 months (IQR 5-52 months). The median age at diagnosis was 51.5 years (IQR 40-65.8 years), and ACC was prevalent in women (n=110, 53.9%). Abnormal pain was the most common clinical symptom (n=70, 40.2%), and ENSAT stage 2 was most common (n=62, 30.4%) at the time of diagnosis. One hundred sixty-nine patients underwent operation, while 17 were treated with other modalities. The remission rate was 48%, and median recurrence-free survival time was 46 months. Estimated 5-year recurrence-free rate was 44.7%. There were more women, large tumor, atypical mitosis, venous invasion, and higher mitotic count in cancer recurrence group. Estimated 5-year overall survival and disease-specific survival rates were 64.5% and 70.6%, respectively. Higher ENSAT stage and advanced pathologic characteristics were risk factors for all-cause mortality of ACC. Large tumor size and cortisol-secreting tumor were additional risk factors for ACC-specific death.

Conclusions

We report the first epidemiologic study regarding ACC in an Asian population. ENSAT stage 4; lymph node involvement; non-operative group; and invasion of vein, sinusoid, or capsule were associated with an increased risk for all-cause mortality.
Introduction

Adrenocortical carcinoma (ACC) is a rare disease with an estimated annual incidence of 0.7 to 2.0 per million population (1, 2). The prevalence of ACC varies depending on the circumstances under which patient data are collected. The reported frequency of ACC is derived from highly selected patient populations and may not reflect the prevalence rates observed in population-based studies. Combining the studies reported from 1982 to 2008, the ACC etiology of adrenal incidentaloma ranged from 0 to 14% (3-7). Further, studies including patients with symptoms or signs caused by hormone excess or an abdominal mass showed a higher prevalence of ACC within the group of adrenal incidentalomas, 10 to 15% (8-10). ACC can occur at any age, with a peak incidence between 40 and 50 years, and has a female predominance (55–60%) (2, 11). Most ACCs occur sporadically but rarely are related to various hereditary syndromes, including Li Fraumeni syndrome (12), multiple endocrine neoplasia type 1 (13), Beckwith-Wiedemann syndrome (14), Lynch syndrome (15), and others (16). Moreover, at least 50-60% of those with ACC show clinical hormone excess; the most common form is hypercortisolism (Cushing syndrome) (17).

Although the most common genetic alterations in ACC were TP53 and CTNNB1 mutations and CDKN2A and ZNRF3 homozygous deletions (18), the molecular and cellular mechanisms underlying the development of ACC have not been fully clarified; multi-omic studies demonstrated that only a minority of patients with ACC have pathogenic driver mutations (19, 20). Complete surgical removal can lead to cure (17). However, the prognosis of ACC remains a challenge. The median overall survival (OS) of all patients with ACC is approximately 3-4 years; therapeutic outcomes are heterogeneous (17). There are several known prognostic factors in patients with ACC, including clinical, pathological, and molecular factors (18). Clinical prognostic factors include advanced tumor stage, cortisol excess, and older age (18).
In addition, poor prognosis is associated with pathologic factors, including tumor grade, mitotic count, Ki-67 proliferation index (21), resection status (22), and results of p53 and CTNNB1 immunohistochemistry (18). Recently, progress in genomics has allowed research on the molecular prognostic markers of ACC (18). Nonetheless, there is a paucity of data on recurrence or survival in Asian patients with ACC. Understanding of the clinical characteristics and prognostic stratification of ACC in the Asian population is essential for proper management.

Here, we investigated epidemiologic data including clinical manifestations and imaging/pathologic findings of patients with ACC in South Korea. Based on these results, we aimed to analyze differences in characteristics according to remission, recurrence, and overall survival to identify prognostic factors of Asian patients with ACC.
Materials and methods

Data collection

We aimed to identify all patients aged 18 years and older diagnosed with or treated for ACC in South Korea and designed a patient cohort study with a retrospectively collected dataset. Among all 43 tertiary care institutions in South Korea, 25 participated in the data search for patients with ACC managed at their institutions. Multiple endocrinologists at each institution reviewed the medical records of all patients registered in this study to validate the diagnosis of ACC based on the following criteria: (1) diagnosed or treated by an endocrinologist between January 2000 and December 2014 and (2) reported by a pathologist via surgical resection or biopsy specimen. The registration process proceeded between June 2015 and March 2018. Patients with ACC were identified based on the following International Classification of Diseases, 10th revision (ICD-10) codes: C740 (primary malignant neoplasm of adrenal cortex, nonfunctioning adrenal carcinoma) and C749 (primary malignant neoplasm of adrenal gland, other type of adrenal cancer, unspecified adrenal cancer). Patients with metastasis to the adrenal gland were excluded.

The following data were collected from registered ACC patients: age at diagnosis, sex, body mass index, date of last visit, managing institution, clinical symptoms at diagnosis, comorbidities, results of biochemical and hormonal tests to confirm tumor functionality, abdominal computed tomography (CT) findings including size and pre-contrast Hounsfield unit (HU), pathologic findings including Ki-67 index and Weiss score, presence and location of distant metastasis at diagnosis, the first-line treatment modality, postoperative adjuvant therapy, and current progress including recurrence and mortality. Endocrinologists at each institution confirmed the presence of remission after surgery and the disease recurrence. Patient date of birth, initials, and home address were also collected to exclude duplicated subjects. In
In this study, the European Network for the Study of Adrenal Tumors (ENSAT)-staging system was used to evaluate clinical stage (9) because, among all proposed classifications, this system may provide the best survival discrimination in patients with ACC (18).

The institutional review board of each participating institution approved the current study based on the study protocol of Seoul National University Hospital (No.1505-051-671). The study was performed in accordance with the Declaration of Helsinki. The need to obtain informed consent from participants was waived due to the retrospective nature of this study.

**Statistical analysis**

Data were analyzed using IBM SPSS version 23.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as median (interquartile range, IQR). Categorical variables are presented as number (%). Comparisons between groups were conducted using Chi-square test, Mann–Whitney U test, and Fisher’s exact test. In addition, Cox proportional hazard model and log-rank tests were used to evaluate the prognosis of patients with ACC. Two-sided p values less than 0.05 were considered statistically significant.
Results

Baseline characteristics and clinical manifestations of the study population

As shown in Table 1, 204 patients diagnosed with ACC from 25 hospitals were included in the study. The median follow-up duration was 20 months (IQR 5 – 52 months). The median age was 51.5 years (IQR 40 – 65.8 years) and female patients were dominant (n=110, 53.9%). Among 188 patients with identifiable data of initial presentation at the time of diagnosis, 154 (81.9%) were symptomatic. The most common chief complaint was abdominal pain (n=70, 40.2%), followed by palpable abdominal mass (n=61, 33.9%). On abdominal CT images, the median tumor size was 85 mm (IQR 59 – 120 mm), with pre-contrast 34.4 HU (IQR 31.1 – 39.5 HU). Hypercortisolism (n=62, 47.7%), elevated serum dehydroepiandrosterone-sulfate (DHEA-S; n=21, 38.2%), elevated 24-hr urine 17-ketosteroid (n=16, 32.7%), and excessive aldosterone level (n=14, 11.5%) within obtainable data.

Table 2 shows the prevalence of ACC based on the ENSAT staging system and pathologic findings. By the ENSAT staging system, stage 2 (n=62, 30.4%) was the most common at the time of diagnosis, followed in order by stage 4 (n=58, 28.4%), stage 3 (n=35, 17.2%), and stage 1 (n=19, 9.3%). There were 56 available data of distant metastasis with multiple answers allowed: 34 in the lung, 32 in the liver, 13 in the bone, 3 in the brain, and 1 in the pericardial metastasis. The number of crude incidence cases is presented in Supplementary Figure 1.

Treatment and overall prognosis

Figure 1 summarizes the prognosis of patients with ACC who had data for treatment modality using a flowchart. A total of 169 patients underwent surgery (84.1%), 149 of which were total adrenalectomy. Among 32 patients who did not undergo surgical treatment, 17 had identifiable data regarding one or more alternative palliative treatment methods: 5 for cytotoxic chemotherapy, 5 for mitotane therapy, 3 for both chemotherapy and mitotane, 3 for both
mitotane and radiation therapy, and 1 for all three modalities.

After the first-line surgical treatment, 102 patients have reached remission of ACC, while 66 had remnant disease. Forty-nine cases of disease recurrence were reported during the follow-up period. In total cohort, there were 55 cases of mortality, which was most common in the non-remission group. Death was not reported in patients without recurrence.

**Disease remission and recurrence**

There were 36 patients who had missing data for remission state; the remaining 168 patients were included in the analysis of remission and recurrence. In 168 patients who had follow-up records, 102 (60%) achieved remission. Table 3 compares the characteristics of remission and remnant disease groups. Remission was more frequent in female patients (61.8% vs. 42.4%, p = 0.017), patients without symptoms at diagnosis (26.5% vs. 7.1%, p = 0.013), and patients without distant metastasis (95.6% vs. 26.8%, p < 0.001). The ENSAT stage was significantly different between the remission and non-remission groups: the proportion of stages 1 to 4 of remission-reached group was 14.3%, 53.8%, 27.5%, and 4.4% in order, while that of remnant disease group was 5.4%, 14.3%, 7.1%, and 73.2% (p for intergroup difference < 0.001). The remission group had smaller tumor size (91.5 mm vs 125 mm, p = 0.018) and lower mitotic count (9/50 HPF vs. 19.5/50 HPF, p = 0.030) than the remnant disease group. Age, BMI, hormonal functionality, lymph node metastasis, and operation type did not show statistical differences.

Among 102 cases of remission during the follow-up period, there were 49 recurrent cases. As shown in Table 4, ACC recurrence was reported more in the female population (73.5% vs. 50.9%, p = 0.019), with larger tumors (110 mm vs. 80 mm, p = 0.007), in tumors with venous invasion (60.6% vs. 24.2%, p = 0.006), and with higher mitotic count (15/50 HPF vs. 5/50 HPF, p = 0.015). There was no significant difference between groups regarding initial
presentation with symptoms or signs (67.6% vs. 79.4%, p = 0.272) or ENSAT stage (p = 0.948): stages 1 to 4 accounted for 16.3%, 51.0%, 26.5%, and 6.1% in non-recurrent group and 11.9%, 57.1%, 28.6%, and 2.4% in recurrent group, respectively.

**Mortality**

Fifty-five deaths (27%) were reported during the follow-up period. The median OS of total cohort was as 145 months (95% confidence interval [CI] 101.8 – 188.2) and estimated 5-year OS rate was 64.5%. Among the total cohort, there were 174 cases with known ENSAT stage. There were 19 and 29 events in stages 1-3 and stage 4, respectively. Estimated 5-year OS rates were 91.7%, 76.9%, 78.3%, and 30.3% from ENSAT stages 1 to 4, respectively. Kaplan-Meier curves and estimates of OS data according to ENSAT stage are plotted in Figure 2. The median survival of stage 4 advanced disease was 19 months while that of less-advanced disease (stages 1-3) was 138.4 months, and the OS rates significantly differed (Log-rank test p < 0.001).

Risk factors for mortality were assessed with univariable Cox proportional hazard models (Table 5). Since there were some missing values for variables regarding prognosis, it was not possible to create valid multivariable models due to small case numbers. For all-cause mortality, advanced ENSAT stage had the highest hazard ratio (HR) of 5.61 (95% CI 3.11 – 10.11), followed by sinus invasion in pathologic review (HR 5.50, 95% CI 1.93 – 15.71). The presence of lymph node metastasis, venous invasion, and capsular invasion were also statistically significant risk factors. Adrenalectomy was a protective factor (HR 0.11, 95% CI 0.06 – 0.19). HR was also calculated for ACC-specific mortality in univariable analysis (Table 5). Sinusoid invasion had the highest HR of 12.77 (95% CI 2.81 – 58.03), followed by ENSAT stage 4 disease (HR 5.62, 95% CI 2.89 – 10.90). Large mass size, higher pre-contrast HU on CT, and tumor functionality (especially hypercortisolism) were additional risk factors for ACC-specific mortality.
Discussion

ACC is an extremely rare but aggressive disease for which it is essential to obtain epidemiologic data, such as clinical characteristics and prognostic factors. The incidence rate of ACC was 0.5 to 2 cases per 1,000,000 person-years in previous reports (1, 23). In a population-based study conducted in the United States, Sharma et al. found that ACC incidence was higher in Caucasians, with a ratio of 6.3:1 (23). While racial, ethnic, and regional differences may exist, underestimation of cases from hospitals that were not included in the survey could be another explanation for the low incidence rate (Supplementary Figure 1). Additionally, the incidence rate has slightly increased in recent years. Recent high-resolution imaging studies and a nationwide health screening program could contribute to increased incidental identification of adrenal masses (24). ACC was diagnosed more frequently in females and in the 5th decade, consistent with previous studies (2, 22, 25-28).

The more symptomatic cases were observed in our study. There were 111 cases of abdominal pain and/or palpable abdominal mass as symptoms at diagnosis (59.4% of known information), which is a higher rate than previous studies. Iñiguez-Ariza et al. reported the mode of ACC discovery as follows: 42% incidentally found, 32% hormone excess, and 20% mass effect (29). Several patients reported no symptoms even when the mass was larger than 8cm. Since the data were collected by questionnaire retrospectively, the relationship between symptom and tumor size could not be concluded. In addition, our data contain the symptoms and signs at the time of diagnosis, which is not the same as the mode of ACC diagnosis. This point requires careful interpretation. In other words, it is hard to distinguish whether ACC was diagnosed due to the symptoms examined or whether ACC was found in testing for other symptoms or by accident in our dataset.

In diagnostic CT images, pre-contrast density was 34.4 HU, and median size was 85 mm. These findings were in accordance with known findings of ACC with higher pre-contrast HU and
large size (30-32). Mass heterogeneity, necrosis, calcification, and hemorrhage were also observed in CT images. There are previous reports on tumor laterality (26, 33-36), and left-side ACC was prevalent in the current study. ACC laterality is not fully explained in the current study. According to ENSAT stage (37), the majority of patients in this cohort presented with stage 2 (30.4%) ACC, consistent with previous findings (32). Common distant metastasis sites were lung, liver, and bone. Despite few (56 cases) identifiable records of the location of distant metastasis, the tendency of frequent metastatic sites was similar to previous studies (32, 38-42).

It is widely accepted that Weiss score of 3 or higher implies malignant potential of ACC, and Ki-67 index higher than 5% is only observed in malignancy. In the current study, there were 13 pathologic ACC cases with Weiss score of 1 or 2 and 11 cases with Ki-67 index of 1 to 5. We propose two possibilities for this result. First, there were some cases of Weiss score < 3 with aggressive disease course. Initially low-Weiss score tumors can progress to metastatic lesions during follow up. Pohlink et al. reported a case of Weiss 2 tumor that recurred 6 years later with lung metastases (43), and Papotti el al. reported myxoid type ACC cases with low Weiss score (44). Similarly, one patient with Weiss 2 score in our cohort showed distant metastasis at the time of diagnosis (ENSAT stage 4). Also, there were three patients with Weiss < 3 and ENSAT stage 3 and four patients with Weiss < 3 in whom the disease recurred after initial remission. Second, even though a higher Ki-67 index indicates malignant behavior, a low Ki-67 index does not always define benign behavior (45). Stojadinovic et al. reported Ki-67 overexpression in 35.5% of ACC cases (46). Our data include one ENSAT stage 4 patient with Ki-67 3%. These findings suggest that we should carefully evaluate and follow the progress of patients with low Weiss score and/or low Ki-67.

In Korea, surgical resection remains the mainstay of therapy, occurring in 84.1% of treated cases, consistent with other reports (21, 23, 40). Surgical removal of primary disease is often
curative and could yield survival benefits in advanced disease (21, 40). Of the 29 patients with information on adjuvant treatment modality, 4 received cytotoxic chemotherapy, 18 received mitotane, and 7 received radiation therapy. Data regarding mitotane dose, duration, and side effects were not included in the survey to determine therapeutic and adverse outcomes in a Korean ACC patient cohort. Although ACC was previously considered a radiotherapy-resistant disease, and there were contradictory results of adjuvant radiotherapy (47, 48), recent studies revealed 56-100% local disease control in the adjuvant setting (49-52) without an advantage in OS. Radiation therapy should be considered in selected patients to prevent local recurrence.

In this study, all-cause mortality rate was 27%, and 5-year OS rate was 64.5%, which is higher than previous studies, stating 5-year OS rate of 35-48% (6, 38, 53-56). Despite progress in understanding the molecular pathogenesis of ACC, tumor stage remains the main factor for predicting prognosis in patients with ACC. Five-year survival is reported to be 60–80% for tumors confined to the adrenal gland, 35–50% for locally advanced disease, and much lower in patients with metastatic disease (0-28%) (17, 18, 22, 31, 57, 58). As expected, higher ENSAT stage, lymph node metastasis, and the presence of venous, sinusoid, and capsular invasion were prognostic risk factors. Functioning tumors, especially ACC with cortisol excess, showed HR of 2.76 (95% CI 1.13 – 6.71, p = 0.025) for ACC-specific death but not for all-cause mortality. The poorer prognosis of cortisol-secreting tumors might be related to comorbidity with Cushing’s syndrome and its possible immunosuppressive effects that may promote tumor development and metastasis (6, 59). Nevertheless, the effect of cortisol secretion on survival of patients with ACC remains uncertain (18). Some studies reported that sex can affect survival rate (27, 36, 60), but we found no such relationship in this cohort. Therefore, prospective research with long-term follow-up is required to investigate the risk factors linked to survival and prognosis in Asian patients with ACC.

The major strength of our study is that we analyzed ACC data in an Asian population. To our
knowledge, this is the first nationwide multicenter cohort study of ACC conducted in Asia. Although ACC is a rare disease, this study was initiated with awareness of the demand for a Korean population-specific database. However, there were some limitations as well. First, because it was a retrospective registry-based study, there were missing data of several clinical variables. Multivariable Cox-proportional hazard models for disease outcome were not constructed due to this shortage, although multivariable models with risk factors would help to predict the prognosis for an individual case. Secondly, there were no detailed data on surgical resection type and not enough pathologic data which are considered prognostic factors. Data regarding Ki-67 index, an independent prognostic factor for predicting the survival of patients with ACC (18), were insufficient because few hospitals performed the Ki-67 index test. Weiss score is also considered an informative factor to assess the prognosis of ACC; however, the majority of our data had partial data of Weiss score components or small number of Weiss score. Instead, we analyzed each pathologic characteristic as well as the Weiss score to make the best use of our dataset. Third, this study could not cover all incident ACC cases in Korea since 25 of 43 tertiary hospitals of the country participated in the survey. In addition, we consider the rather short duration of follow-up as another shortage of our study. Therefore, future studies should include more detailed data on surgical treatment and pathologic findings in longer duration.

In conclusion, we report the first patient-based cohort study of 204 cases of ACC in Korea. Higher ENSAT stage and advanced pathologic characteristics were risk factors for all-cause mortality, and large tumor size and cortisol-secreting tumor were additional risk factors for ACC-specific death. The results of the current study may help with disease prognostication in an Asian population. Prognostic factors of ENSAT stage 4, advanced pathologic characteristics, and cortisol excess were generally in accordance with previously reported Western-population-based research. Identifying such prognostic factors and risk stratification are essential for ACC
treatment. In this context, patients with ACC should be managed by a multidisciplinary team including endocrinologists, surgeons, pathologists, oncologists, and radiologists.
DECLARATION OF INTEREST

The authors have nothing to disclose.

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Figure legends

Figure 1. Treatment and prognosis of patients with ACC.

The figures in each box indicates the number of patients. After the first-line treatment, 102 patients reached remission state. Among those with remission, 49 cases of disease recurrence were reported during the follow-up period. There were 55 mortality cases in total, 10 from the group of the missing data of treatment information. No mortality case of death was reported in patients without recurrence.

ACC adrenocortical carcinoma, Tx treatment

Figure 2. Kaplan-Meier estimates of survival of patients with ACC according to ENSAT stage.

Among a total cohort of 204 cases, 174 had known ENSAT stage. Median OS of these patients was 145 months (95% CI 101.8 – 188.2), and estimated 1-year, 2-year, and 5-year OS rates were 82.6%, 75.0%, and 64.5%, respectively. There were 19 and 29 events in stages 1-3 and 4, respectively. Mean survival of stages 1-3 was 138.4 months, and median survival of stage 4 was 19 months. ACC, adrenocortical carcinoma; CI, confidence interval; OS, overall survival
Table 1. Demographic characteristics of patients with ACC (Total n=204).

|                          | Available | n (%) | Median (IQR) |
|--------------------------|-----------|-------|--------------|
| **Sex**                  |           |       |              |
| Male                     | 94        | (46.1)|              |
| Female                   | 110       | (53.9)|              |
| **Age at diagnosis (years)** | 204       |       | 51.5 (40-65.8) |
| **BMI (kg/m²)**          | 147       |       | 23.3 (21.2-25.5) |
| **Symptom and sign at diagnosis** | 188       | 154  | (81.9) |
| Abdominal pain           | 174       | 70    | (40.2) |
| Abdominal mass           | 180       | 61    | (33.9) |
| Edema                    | 154       | 36    | (23.4) |
| Fatigue                  | 155       | 34    | (21.9) |
| Weight loss              | 160       | 23    | (14.4) |
| Central obesity          | 149       | 21    | (14.1) |
| **Underlying disease**   |           |       |              |
| Hypertension             | 198       | 81    | (40.9) |
| Diabetes mellitus        | 197       | 40    | (20.3) |
| Other malignancy         | 195       | 20    | (10.3) |
| Osteoporosis             | 178       | 12    | (6.7) |
| Ischemic heart disease   | 191       | 8     | (4.2) |
| Arrhythmia               | 193       | 7     | (3.6) |
| Heart failure            | 193       | 6     | (3.1) |
| Stroke                   | 191       | 4     | (2.1) |
| **Functioning tumor**    |           |       |              |
| Hypercortisolism         | 130       | 74    | (56.9) |
| Elevated serum DHEA-S    | 55        | 21    | (38.2) |
| Elevated 24hr urine 17-KS| 49        | 16    | (32.7) |
| Aldosterone excess       | 122       | 14    | (11.5) |
| **Abdominal CT finding** |           |       |              |
| Size (mm)                | 187       |       | 85 (59-120) |
| Pre-contrast HU          | 73        |       | 34.4 (31.1-39.5) |
|                          |   |         |         |
|--------------------------|---|---------|---------|
| Right : Left : Bilateral | 199| 91 : 103 : 5 |
| Heterogeneity (yes)      | 154| 148 (96.1)  |
| Necrosis (yes)           | 161| 104 (64.6)  |
| Calcification (yes)      | 162| 40 (24.7)   |
| Hemorrhage (yes)         | 161| 31 (19.3)   |

ACC adrenocortical carcinoma, IQR interquartile range, BMI body mass index, DHEA-S dehydroepiandosterone sulfate, 17-KS 17-ketosteroid, CT computed tomography, HU Hounsfield unit
Table 2. Stages and pathologic findings.

| ENSAT stage | Available | n (%)  | Median (IQR) |
|-------------|-----------|--------|--------------|
| 1           | 174       | 19 (9.3)|              |
| 2           | 62 (30.4) |              |              |
| 3           | 35 (17.2) |              |              |
| 4           | 58 (28.4) |              |              |
| Unknown     | 30 (14.7) |              |              |

Pathology

| Weiss score | Available | n (%)  | Median (IQR) |
|-------------|-----------|--------|--------------|
| ≤ 3         | 21 (34.4) |        |              |
| > 3         | 40 (65.6) |        |              |

| Size (mm)   | Available | Median (IQR) |
|-------------|-----------|--------------|
| 100 (64-130)|          |              |

| Ki-67 index | Available | Median (IQR) |
|-------------|-----------|--------------|
| 8 (4.5 – 16.3)|         |              |

| Mitotic count (/50HPF) | Available | Median (IQR) |
|------------------------|-----------|--------------|
| 10 (5-28.8)            | 100       |              |

| High nuclear grade (yes) | Available | n (%)  |
|--------------------------|-----------|--------|
| 62 (92.5)                | 67        |        |

| Atypical mitosis (yes)   | Available | n (%)  |
|--------------------------|-----------|--------|
| 26 (36.1)                | 72        |        |

| Diffuse architecture (yes) | Available | n (%)  |
|----------------------------|-----------|--------|
| 39 (83.0)                 | 47        |        |

| Clear cell component (yes) | Available | n (%)  |
|----------------------------|-----------|--------|
| 47 (74.6)                 | 63        |        |

| Necrosis (yes)  | Available | n (%)  |
|-----------------|-----------|--------|
| 122 (89.1)      | 137       |        |

| Venous invasion (yes) | Available | n (%)  |
|-----------------------|-----------|--------|
| 52 (48.61)            | 107       |        |

| Sinusoidal invasion (yes) | Available | n (%)  |
|---------------------------|-----------|--------|
| 23 (38.3)                 | 60        |        |

| Capsular invasion (yes)  | Available | n (%)  |
|--------------------------|-----------|--------|
| 80 (65)                  | 123       |        |

ENSAT European Network for Study of Adrenal Tumors, IQR interquartile range
### Table 3. Characteristics and findings according to remission after first-line treatment (n=168).

| Characteristic                                      | Remission (+), n=102 | Remission (-), n=66 | P value |
|-----------------------------------------------------|----------------------|---------------------|---------|
| Age at diagnosis (years)                            | 102                  | 66                  | 0.961   |
| Available data                                      | 49.5 (39.0-63.0)     | 50 (38.5-61.3)      |         |
| BMI (kg/m²)                                         | 75                   | 47                  | 0.839   |
| Available data                                      | 23.1 (20.9-25.9)     | 23.3 (21.4-25.5)    |         |
| Male                                                | 102                  | 66                  | 0.017   |
| Available data                                      | 39 (38.2)            | 38 (57.6)           |         |
| Initial symptom (yes)                               | 68                   | 42                  | 0.013   |
| Available data                                      | 50 (73.5)            | 39 (92.9)           |         |
| Functional tumor (yes)                              | 70                   | 42                  | 0.694   |
| Available data                                      | 40 (57.1)            | 26 (61.9)           |         |
| Distant metastasis (yes)                            | 91                   | 56                  | < 0.001 |
| Available data                                      | 4 (4.4)              | 41 (73.2)           |         |
| Lymph node metastasis (yes)                         | 6                    | 44                  | 1.000   |
| Available data                                      | 2 (33.3)             | 17 (38.6)           |         |
| CT                                                  |                      |                     |         |
| Tumor size (mm)                                     | 94                   | 61                  | 0.009   |
| Available data                                      | 76.5 (54.8-114.8)    | 100 (65-140)        |         |
| Pre-contrast HU                                      | 36                   | 18                  | 0.734   |
| Available data                                      | 35.0 (28.8-39.7)     | 34.4 (32.5-39.9)    |         |
| Complete adrenalectomy (yes)                        | 102                  | 50                  | 0.017   |
| Available data                                      | 90 (88.2)            | 44 (88)             |         |
| Pathology                                           |                      |                     |         |
| Weiss score                                         | 42                   | 13                  | 0.103   |
| Available data                                      | 4 (2-6)              | 6 (4-7)             |         |
| Tumor size (mm)                                     | 92                   | 41                  | 0.018   |
| Available data                                      | 91.5 (60.0-130.0)    | 125 (79.5-155)      |         |
| Ki67 index                                          | 24                   | 3                   | 0.393   |
| Available data                                      | 7.0 (3.5-10.8)       | 20 (3-20)           |         |
| Mitotic count (/50HPF)                              | 62                   | 28                  | 0.030   |
| Available data                                      | 9.0 (3.8-24.3)       | 19.5 (5.0-48.8)     |         |
| ENSAT stage                                         | 91                   | 56                  | < 0.001 |
| 1                                                   | 13 (14.3)            | 3 (5.4)             |         |
| 2                                                   | 49 (53.8)            | 8 (14.3)            |         |
| 3                                                   | 25 (27.5)            | 4 (7.1)             |         |
| 4                                                   | 4 (4.4)              | 41 (73.2)           |         |
| Death (yes)                                         | 75                   | 50                  | < 0.001 |
| Available data                                      | 13 (17.3)            | 32 (64)             |         |

* Continuous variables are presented as median (interquartile range), categorical variables as n (%).

Chi-square test, Fisher’s exact test, and Mann-Whitney U test were adopted for comparison.

HPF high power field
Table 4. Characteristics and findings according to presence of recurrence (n=102).

| Characteristic                  | Recurrence (-), n=53 | Recurrence (+), n=49 | P value |
|--------------------------------|----------------------|----------------------|---------|
| Age at diagnosis (years)       | 53                   | 49                   | 0.730   |
| BMI (kg/m²)                    | 43                   | 32                   | 0.748   |
| Male                           | 53                   | 49                   | 0.019   |
| Initial symptom (yes)          | 34                   | 34                   | 0.272   |
| Functional tumor (yes)         | 36                   | 34                   | 0.782   |
| CT                             |                      |                      |         |
| Right                          | 21 (41.2)            | 17 (35.4)            | 0.556   |
| Left                           | 30 (58.8)            | 31 (64.6)            |         |
| Tumor size (mm)                | 49                   | 45                   | 0.008   |
| Pre-contrast HU                | 21                   | 15                   | 0.810   |
| Necrosis (yes)                 | 41                   | 40                   | 0.381   |
| Hemorrhage (yes)               | 40                   | 40                   | 0.264   |
| Calcification (yes)            | 41                   | 41                   | 0.432   |
| ENSAT stage                    |                      |                      |         |
| 1                              | 8 (16.3)             | 5 (11.9)             |         |
| 2                              | 25 (51.0)            | 24 (57.1)            | 0.948   |
| 3                              | 13 (26.5)            | 12 (28.6)            |         |
| 4                              | 3 (6.1)              | 1 (2.4)              |         |
| Lymph node metastasis (yes)    | 4                    | 2                    | 1.000   |
| Surgery                        | 53                   | 49                   |         |
| Complete adrenalectomy         | 48 (90.6)            | 42 (85.7)            | 0.447   |
| Partial adrenalectomy          | 5 (9.4)              | 7 (14.3)             |         |
| Adjuvant therapy after surgery (yes) | 50              | 45                   | 0.313   |

(continued)
(continued)

| Pathology                             | Recurrence (-) | Recurrence (+) | P value |
|--------------------------------------|----------------|----------------|---------|
|                                      | Available data | Value *        | Available data | Value * |
| High nuclear grade (yes)             | 24             | 21 (87.5)      | 20       | 18 (90.0) | 1.000   |
| Atypical mitosis (yes)               | 26             | 6 (23.1)       | 20       | 10 (50.0) | 0.070   |
| Diffuse architecture (yes)           | 14             | 12 (85.7)      | 17       | 14 (82.4) | 1.000   |
| Clear cell component (yes)           | 22             | 16 (72.7)      | 18       | 14 (77.8) | 1.000   |
| Necrosis (yes)                       | 38             | 31 (81.6)      | 41       | 37 (90.2) | 0.338   |
| Venous invasion (yes)                | 33             | 8 (24.2)       | 33       | 20 (60.6) | 0.006   |
| Sinusoid invasion (yes)              | 21             | 5 (23.8)       | 18       | 9 (50.0)  | 0.108   |
| Capsular invasion (yes)              | 43             | 23 (53.5)      | 37       | 26 (70.3) | 0.168   |
| Weiss score                          | 20             | 4 (2-5)        | 22       | 5 (3-7)   | 0.174   |
| Tumor size (mm)                      | 47             | 80 (54-120)    | 45       | 110 (80-140) | 0.007 |
| Ki 67 index                          | 13             | 6 (4-8)        | 11       | 10 (3-20) | 0.123   |
| Mitotic count (/50HPF)               | 29             | 5 (2-12)       | 33       | 15 (5-35) | 0.012   |
| Death (yes)                          | 35             | 0 (0)          | 40       | 13 (32.5) | < 0.001 |

* Continuous variables are presented as median (interquartile range), categorical variables as n (%).

Chi-square test, Fischer’s exact test, and Mann-Whitney U tests were adopted for comparison.
Table 5. All-cause mortality and ACC-specific mortality Cox models (univariable analysis).

| Event / Available (n) | HR   | 95% CI        | P value |
|----------------------|------|---------------|---------|
| **All-cause mortality** |      |               |         |
| ENSAT stage 4 (vs. stage 1-3) | 48/174 | 5.61          | 3.11-10.11 | <0.001 |
| Lymph node metastasis (yes) | 32/65  | 2.45          | 1.19-5.05  | 0.016  |
| Adrenalectomy (yes) | 55/200 | 0.11          | 0.06-0.19  | <0.001 |
| **Pathology** |      |               |         |
| Venous invasion (yes) | 25/107 | 2.67          | 1.17-6.06  | 0.019  |
| Sinusoid invasion (yes) | 17/60  | 5.50          | 1.93-15.71 | 0.001  |
| Capsular invasion (yes) | 27/123 | 3.28          | 1.13-9.54  | 0.029  |
| **ACC-specific mortality** |      |               |         |
| CT size | 42/178 | 1.01          | 1.00-1.01  | 0.043  |
| CT pre-contrast HU | 16/73  | 1.04          | 1.01-1.08  | 0.009  |
| ENSAT stage 4 (vs. stage 1-3) | 38/174 | 5.62          | 2.89-10.90 | <0.001 |
| Hypercortisolism (yes) | 25/113 | 2.76          | 1.13-6.71  | 0.025  |
| Lymph node metastasis (yes) | 25/65  | 2.81          | 1.22-6.47  | 0.015  |
| Adrenalectomy (yes) | 44/200 | 0.08          | 0.044-0.16 | <0.001 |
| Adjuvant therapy after surgery (yes)* | 9/95  | 4.76          | 1.19-19.03 | 0.027  |
| **Pathology** |      |               |         |
| Venous invasion (yes) | 19/107 | 3.29          | 1.24-8.71  | 0.016  |
| Sinusoid invasion (yes) | 13/60  | 12.77         | 2.81-58.03 | 0.001  |

* Adjuvant therapy was analyzed in patient with complete surgical removal.

Only statistically significant variables are listed.
Figure 1. Treatment and prognosis of patients with ACC.
The figures in each box indicates the number of patients. After the first-line treatment, 102 patients reached remission state. Among those with remission, 49 cases of disease recurrence were reported during the follow-up period. There were 55 mortality cases in total, 10 from the group of the missing data of treatment information. No mortality case of death was reported in patients without recurrence. ACC adrenocortical carcinoma, Tx treatment.
Among a total cohort of 204 cases, 174 had known ENSAT stage. Median OS of these patients was 145 months (95% CI 101.8 - 188.2), and estimated 1-year, 2-year, and 5-year OS rates were 82.6%, 75.0%, and 64.5%, respectively. There were 19 and 29 events in stages 1-3 and 4, respectively. Mean survival of stages 1-3 was 138.4 months, and median survival of stage 4 was 19 months. ACC, adrenocortical carcinoma; CI, confidence interval; OS, overall survival.
Supplemental Table 1. Characteristics and findings according to presence of distant metastasis at diagnosis (n=174).

|                                | Distant metastasis (-), n=116 |                              | Distant metastasis (+), n=58 |                              | P value |
|--------------------------------|-------------------------------|------------------------------|-------------------------------|------------------------------|---------|
|                                | Available data | Value * | Available data | Value * |                   |
| Age at diagnosis (years)        | 116             | 51.5 (40.0-63.0) | 58             | 50.0 (40.8-67.0) | 0.691   |
| BMI (kg/m²)                     | 88              | 22.8 (21.0-25.4) | 43              | 23.3 (20.8-24.8) | 0.893   |
| Male                            | 116             | 47 (40.5)       | 58              | 35 (60.3)       | 0.014   |
| Initial symptom (yes)           | 68              | 52 (76.5)       | 38              | 33 (86.8)       | 0.199   |
| Functional tumor (yes)          | 83              | 48 (57.8)       | 31              | 21 (67.7)       | 0.335   |
| Lymph node metastasis (yes)     | 2               | 2 (100)         | 56              | 18 (32.1)       | 0.115   |
| Remission (yes)                 | 102             | 87 (85.3)       | 47              | 4 (8.5)         | < 0.001 |
| Recurrence (yes)                | 87              | 41 (47.1)       | 4               | 1 (25.0)        | 0.621   |
| CT Tumor size (mm)              | 111             | 76 (55-120)     | 55              | 100 (68-140)    | 0.007   |
| Pre-contrast HU                 | 48              | 34.2 (30.6-39.0)| 20              | 34.4 (31.6-39.5)| 0.701   |
| Complete adrenalectomy          | 114             | 98 (86.0)       | 30              | 27 (90.0)       | 0.764   |
| Pathology                       |                 |                 |                 |                 |         |
| Weiss score                     | 50              | 4 (2.8-6.0)     | 10              | 5.5 (3.8-7.3)   | 0.042   |
| Tumor size (mm)                 | 106             | 94 (60-130)     | 26              | 130 (82.3-163.8)| 0.016   |
| Ki67 index                      | 26              | 7 (4.5-16.25)   | 3               | 10 (3-20)       | 0.677   |
| Mitotic count (/50HPF)          | 71              | 8 (4-21)        | 21              | 25 (7.5-57.5)   | 0.001   |
| Death (yes)                     | 81              | 19 (23.5)       | 45              | 29 (64.4)       | < 0.001 |

* Continuous variables are presented as median (interquartile range), categorical variables as n (%).

Chi-square test, Fischer’s exact test, and Mann-Whitney test were adopted for comparison.
Supplemental Figure 1. Crude incidence of adrenal cortical carcinoma in Korea between 2000 – 2014.\textsuperscript{c1}