Original Article

Adrenocortical Carcinoma: Clinical Presentation, Outcomes of Treatment and Survival Analysis from a 15-Year Experience

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Background: Adrenocortical carcinoma (ACC) is a rare malignant tumor of adrenocortical origin, often with an unfavorable survival. The estimated incidence is 0.7 to 2 per million per year.

Materials and Methods: The authors retrospectively reviewed all clinical data of the ACC patients that underwent surgical extirpation in the present study institution between January 2005 and December 2020. All demographic data, perioperative outcomes, survival, and predictive factors associated with mortality were analyzed.

Results: Twenty-three patients were included in the present study. The median (IQR) age was 51 (38 to 61) with females predominant at 78.3%. The median (IQR) tumor size was 8.3 (5.3 to 14.8) cm. with the left side predominant at 65.2%. The most common presentation was hormone-related symptoms at 52.2% and isolated hypercortisolism at 34.8%, was the most common hormonal excess. Complete resection (R0) was achieved in 82.6% of the patients. Following the European Network for the Study of Adrenal Tumors (ENSAT) staging system, 52.2% of the patients were in stage 2. Adjuvant therapies such as radiation, mitotane, and chemotherapy, were required in 47.7% of the patients. Eight patients (34.8%) were death during the median follow up of 44 months. The estimated 1-, 2-, and 5-year overall survivals were 78.3%, 73.9%, and 65.2% respectively. The ENSAT stage 3 to 4 (HR 1.61, 95% CI 1.16 to 21.5, p=0.03), nodal metastasis (HR 2.11; 95% CI 1.36 to 50.26; p=0.02), distant metastasis (HR 1.75; 95% CI 1.16 to 28.62; p=0.03), and the neutrophil to lymphocyte ratio (NLR) of 5 or more (HR 2.66; 95% CI 1.74 to 116.81; p=0.01) were significant factors associated with disease mortality in univariate analysis. NLR of 5 or more was the only significant factor (HR 2.51, 95% CI 1.2 to 126.84; p=0.03) in multivariate analysis.

Conclusion: ACC is a rare malignancy associated with aggressive behavior. Multidisciplinary approach with surgical removal is the mainstay of treatment. The high NLR of 5 or more is a significant factor associated with poor disease survival.

Keywords Adrenocortical carcinoma; Mitotane; Survival; Prognosis; Neutrophil to lymphocyte ratio

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Adrenocortical carcinoma (ACC), a malignant tumor of an adrenocortical origin, is a rare malignancy with an unfavorable prognosis. The estimated incidence is 0.7 to 2 per million per year[1]. ACC is more common in females and has a bimodal age distribution with peaks incidence in the first and the fourth to fifth decades of life.

The clinical presentations vary from incidental findings, hormonal excess symptoms, and compressive symptoms. About 50% to 79% of ACC presented with excess hormonal symptoms and glucocorticoid is the most common[2]. The majority of ACC occurs sporadically. However, ACC is related to various hereditary syndromes such as Li Fraumeni syndrome, Beckwith-Wiedemann syndrome, Lynch syndrome, and multiple endocrine neoplasia type 1[3].

The European Network for the Study of Adrenal Tumors (ENSAT) staging system is the most widely used in ACC staging. Clinical staging is a key factor in selecting the appropriate treatment[4]. Surgical resection of the tumor is the standard treatment for localized and locally advanced diseases. Moreover, surgical treatment in recurrent disease or metastasis may have a survival benefit in the selected patient[5].

Previous studies demonstrated prognostic

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factors associated with poor prognosis in ACC were advanced tumor stage, cortisol excess, older age, positive resection margin, high tumor grade, high mitotic count, and high Ki-67 index[6]. Currently, there are many interesting prognostic factors in solid organ malignancy. One of them, the pre-treatment neutrophil-to-lymphocyte ratio (NLR) is known as an independent prognostic factor in solid malignancies including ACC. The NLR in peripheral blood reflects the balance between systemic inflammation and immunity. Accordingly, the previous studies had used an NLR value of above 5, indicating a poor prognosis[7,8].

The present study aimed to evaluate the treatment outcomes of ACC in the authors' institution by reporting the survival outcomes and analyzing the predictive factors of the disease survival. Patients' demographic data and perioperative outcomes were also analyzed.

Materials and Methods

After the study protocol obtained approval from the Institutional Review Board of the Institution (COA No. 1562/2021), the authors retrospectively reviewed all clinical data of ACC patients underwent surgical extirpation in the present study from hospital between January 2005 and December 2020. All demographic data, perioperative parameters, and follow-up outcomes were recorded and analyzed.

Analyzed parameters included age, gender, clinical presentation, biochemical test, NLR, tumor size, tumor side, tumor extension, lymph node involvement, distance metastasis, ENSAT staging, surgical approach, operative times, estimated blood loss (EBL), length of hospital stay (LOS), pathologic findings such as margin status, Ki-67 index, and Weiss score, adjuvant therapy, current patient status such as remission, recurrence, or death, and length of follow up.

NLR was calculated by dividing the absolute neutrophil counts with the lymphocyte counts from peripheral blood preoperatively.

Patient managements

All patients completed the endocrinologic examination by the endocrinologist before surgery. Computed tomography (CT) chest and abdomen were performed to evaluate the primary tumor, tumor extension, and metastasis. Magnetic resonance imaging (MRI) was done instead in those contraindicated for CT scan.

For patients with hypercortisolism, hydrocortisone replacement was given preoperatively and subsequently taper dose in the postoperative period. The decision of adjuvant therapy was considered individually by the authors' multidisciplinary team. The follow-up protocol after surgery consisted of a contrasted CT scan of the chest and abdomen every six months for two to three years, afterward every year. Recurrent disease was defined as the presence of locally recurrent or distant metastasis in the radiologic study during follow-up.

Surgical techniques

The selection of surgical approach was individualized based on the patient's and the surgeon's preference. The contraindication for laparoscopic surgery was locally advanced ACC with suspected adjacent organ invasion. Large tumor size-only was not a contraindication for the laparoscopic approach in the present study.

Open surgery was made by L- or mirror-L or Chevron incision. Careful tumor resection with minimal tumor manipulation was the main principle in ACC surgery. En bloc resection of the tumor with the adjacent organ was performed in locally advanced disease according to the preoperative imaging and intraoperative findings.

The laparoscopic approach was performed by a lateral transperitoneal approach. Generally, three trocars were used for the left-side tumor and four trocars were used for the right-side tumor. The present study surgical techniques have been described previously[9]. All the vascular supplies of the small ACC were controlled by Ligasure, a vessel sealing device, Covidien-Medtronic. In the large ACC, Hem-o-lok Clip was used for controlling the large adrenal vein.

Data analyses

Statistical analyses were performed by using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as the median and interquartile range (IQR) and categorical variables were presented as numbers and percentages.

The predictive factors for overall survival (OS) were analyzed by univariate and multivariate Cox regression analysis. The relative risk was expressed as a hazard ratio (HR) and 95% confidence interval (CI). OS was analyzed with Kaplan-Meier analysis. Time from diagnosis to death was considered for calculating OS. Surviving patients were censored at the date of the last follow-up. Subgroup analysis for

OS was evaluated by the log-rank test. A p-values of less than 0.05 were considered statistically significant.

Results

Patient characteristics

During the study period, 23 patients were included. All demographic data are presented in Table 1. The median age at the time of diagnosis was 51 years (IQR 38 to 61). The peak incidence was in the sixth decade of life for 26.2%. The incidence of the tumor was predominant in the female gender at 78.3% and located on the left side at 65.2%. The median tumor size was 8.3 cm (IQR 5.3 to 14.8).

Hormonal-related symptoms were the most common clinical presentation at 52.2%. Adrenal incidentaloma and tumor-related symptoms such as abdominal or flank discomfort, were the presenting symptoms in 30.4% and 17.4%, respectively. Excessive hormonal excretion was found in 65.2% of patients. Isolated hypercortisolism was the most common functioning tumor at 34.8%, followed by excess co-secretion of cortisol and sex hormone at 26.1%. The median NLR was 4.4 (IQR 2.2 to 7.2) and 10 patients (43.5%) had NLR of 5 or more.

Table 1. Baseline patient's characteristics (n=23)

Variables	
Age (year); median (IQR)	51 (38 to 61)
Sex (female); n (%)	18 (78.3)
Tumor side (left); n (%)	15 (65.2)
Tumor size (cm); median (IQR)	8.3 (5.3 to 14.8)
Clinical presentation; n (%)	
Excess hormone-related symptoms	12 (52.2)
Adrenal incidentaloma	7 (30.4)
Tumor-related symptoms	4 (17.4)
Hormonal activity; n (%)	
Non-functioning tumor	8 (34.8)
Functioning tumor	15 (65.2)
• Hypercortisolism	8 (34.8)
• Excess cortisol and sex hormone	6 (26.1)
• Mineralocorticoid excess	1 (4.3)
NLR; median (IQR)	4.4 (2.2 to 7.2)

IQR=interquartile range; NLR=neutrophil-to-lymphocyte ratio

Perioperative outcomes and pathological reports

Details of perioperative outcomes are summarized in Table 2. Most of the patient underwent laparoscopic resection of the tumor (56.5%). One patient (4.3%) was converted to open resection due to tumor capsular tear. Sixteen patients or 69.6%, were performed adrenalectomy-only, while seven patients or 30.4%, were performed En-bloc adrenalectomy with adjacent organ resection. One patient was concomitantly performed with liver metastasectomy.

The median operative time was 140 minutes (IQR 90 to 209), and the median EBL was 150 mL (IQR 50 to 2,200). The median LOS was 11 days (IQR 7 to 16). One patient died postoperatively from pulmonary embolism and pneumonia with septicemia. For the staging, ENSAT stage 2 was the most common at 52.2%. Two patients or 8.7% had lymph node metastasis and four patients or 17.4% had distant metastasis with one in lung, one in liver, and two with both lung and liver metastasis.

A negative resection margin (R0) was achieved in 19 patients (82.6%). Unfortunately, Weiss score and Ki-67 index from the pathological reports were not available in all patients. Sixteen patients reported a Weiss score of 3 or more. The Ki-67 index was available in seven patients, four of them has a Ki-67 index of 10% or less and they were all alive until the last follow-up date. In contrast, three patients with Ki-67 index of more than 10% were dead during the follow-up period. The median length of follow-up was 44 months (IQR 11.8 to 82.4).

After surgery, eleven patients or 47.7% received the adjuvant treatment. Details of treatment are presented in Table 2. Only three patients received mitotane in the present study because the medication was unavailable in the present study country at the early period of the study.

Long term outcomes

After surgery, 17 patients (73.9%) had remission while six patients (26.1%) had residual disease. Adjuvant treatments were given to the patients with residual disease as radiation to the surgical bed or metastatic site, mitotane, and chemotherapy, depending on the patient's physical status and the availability of treatment.

In the remission group, four patients or 17.4%, developed metastasis during follow-up. The first patient was treated with radiofrequency ablation (RFA) at the liver metastasis site. The second patient was treated with trans-arterial chemoembolization (TACE) for liver metastasis and radiation therapy for spinal metastasis. The other two patients did not receive further treatment due to very poor general medical status.

Survival outcomes

At the last follow-up period, eight patients or

Table 2. Perioperative outcomes and long term follow up (n=23)

Variables	
Surgical approaches; n (%)	
Open	9 (39.1)
Laparoscopic	13 (56.5)
Laparoscopic converted to open	1 (4.3)
Surgical procedures; n (%)	
Adrenalectomy-only	16 (69.6)
En bloc with adjacent organ resection	7 (30.4)
Operative time (minute); median (IQR)	140 (90 to 209)
Estimated blood loss (mL); median (IQR)	150 (50 to 2200)
Length of stay (days); median (IQR)	11 (7 to 16)
Tumor stage (T), n (%)	
1	3 (13.0)
2	12 (52.2)
3	2 (8.7)
4	6 (26.1)
Nodal stage (N1); n (%)	2 (8.7)
Metastasis stage (M1); n (%)	4 (17.4)
ENSAT tumor stage; n (%)	
Stage I	3 (13.0)
Stage II	12 (52.2)
Stage III	4 (17.4)
Stage IV	4 (17.4)
Adjuvant treatment; n (%)	
Radiation therapy	7 (30.4)
Mitotane	1 (4.3)
Chemotherapy (Doxorubicin)	1 (4.3)
Radiation therapy + Mitotane	2 (8.7)
Follow up length (months); median (IQR)	44 (11.8 to 82.4)
Disease free; n (%)	13 (56.5)
Death; n (%)	8 (34.8)

IQR=interquartile range; ENSAT=European Network for the Study of Adrenal Tumors

Table 3. Univariate and multivariate analyses of factors associated with overall survival after surgery

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age at time of diagnosis		0.58		
<50 years	Reference			
≥50 years	0.4 (0.36 to 6.27)			
Sex (male)	0.19 (0.24 to 6.04)	0.81		
Tumor size		0.87		
<10 cm	Reference			
≥10 cm	0.12 (0.27 to 4.75)			
Left-side tumor	0.76 (0.12 to 1.87)	0.28		
Presence of symptoms	0.23 (0.25 to 6.31)	0.78		
Functioning tumor	3.88 (0.14 to 16508.56)	0.19		
NLR		0.01	2.51 (1.2 to 126.84)	0.03
<5	Reference			
≥5	2.66 (1.74 to 116.81)			
ENSAT stage		0.03	0.24 (0.26 to 6.33)	0.77
Stage 1 to 2	Reference			
Stage 3 to 4	1.61 (1.16 to 21.5)			
Lymph node metastasis	2.11 (1.36 to 50.26)	0.02		
Distant metastasis at time of surgery	1.75 (1.16 to 28.62)	0.03		
Surgical approach	0.12 (0.27 to 4.75)	0.89		
Capsular invasion	0.9 (0.49 to 12.28)	0.27		
Extension of surgery		0.99		
Adrenalectomy-only	Reference			
En bloc adjacent organ resection	0.01 (0.2 to 5.06)			
Complete resection (R0 resection)	0.99 (0.09 to 1.56)	0.18		
Adjuvant therapy	0.64 (0.45 to 7.96)	0.38		

NLR=neutrophil-to-lymphocyte ratio; ENSAT=European Network for the Study of Adrenal Tumors; CI=confidence interval

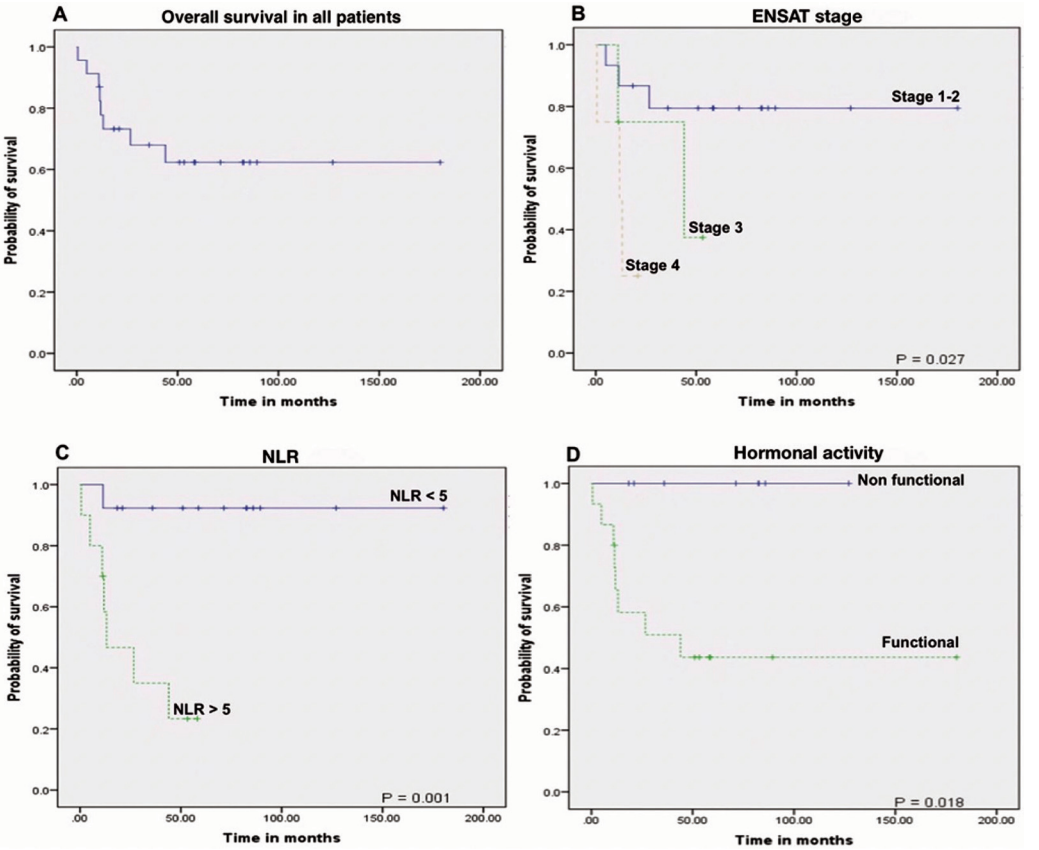

Figure 1. (A) Kaplan-Meier curves of overall survival according to all patients, (B) ENSAT stage, (C) NLR, and (D) functional status.

34.8% were dead. Factors associated with OS for the whole cohort are displayed in Table 3. On univariate analysis, high ENSAT tumor stage 3 to 4 (HR 1.61; 95% CI 1.16 to 21.5; p=0.03), nodal metastasis (HR 2.11; 95% CI 1.36 to 50.26; p=0.02), distant metastasis (HR 1.75; 95% CI 1.16 to 28.62; p=0.03), and high NLR of 5 or more (HR 2.66; 95% CI 1.74 to 116.81; p=0.01) were associated with worse survival. Multivariate analysis showed only high NLR of 5 or more was a significant predictive factor associated with poor disease survival (HR 2.51; 95% CI 1.2 to 126.84; p=0.03).

The median OS of all patients was not reached. The estimated 1-, 2-, and 5-year OS were 78.3%, 73.9%, and 65.2%, respectively (Figure 1A). Median survival was significant higher for patient with ENSAT stage 1 to 2 (p=0.02; Figure 1B), NLR of less than 5 (p=0.001; Figure 1C), and non-functioning tumor (p=0.01; Figure 1C).

Discussion

ACC is one of the most aggressive malignancies. Due to its rarity, the study of clinical characteristics, treatment outcomes, and predictive factors for disease survival are essential for obtaining knowledge about this disease.

In the present study, the authors analyzed the 15-year experiences of ACC treatment in the authors' tertiary care referral center. The patient's peak incidence was in the sixth decade of life, with the female (ratio 3.6:1) and left side (ratio 1.9:1) predominant. One-third of the present study patients presented with asymptomatic non-functioning adrenal incidentaloma and one-third had isolated hypercortisolism, which was comparable to the previous literature[10,11]. The increased use of cross-sectional imaging can increase the incidence of small asymptomatic ACC in the future. An uncommon clinical feature, isolated hyperaldosteronism, occurred in one patient in the present study. ENSAT stage 2 was the most common in 52.5% of the present study patients. Liver and lung were the most common metastasis site at the time of diagnosis.

Complete surgical removal of the tumor is the mainstay of ACC treatment associated with the highest rate of cure. The benefit of surgery can also

be found in more advanced stage[12,13]. Open surgery is considered the standard approach for large adrenal tumors with high suspicion of ACC. The role of laparoscopic surgery in ACC is controversial. The recent European Society of Endocrinology Clinical Practice Guidelines suggest laparoscopy is a choice of surgery for small, localized tumor sizes of less than 6 cm[4]. In the present study, 14 patients, including six patients with a tumor size between 6 and 10 cm, underwent laparoscopic surgery. Only one conversion occurred due to the tumor capsule disruption. Laparoscopic adrenalectomy was also a safe procedure in the selected patient with adrenal tumor size greater than 6 cm from the authors' previous study[9].

The benefits of medical treatment in the metastatic stage are limited, with unpredictable outcomes. Therefore, metastasectomy should be considered in the selected patient. This benefit was shown especially in ACC with liver metastasis[14,15]. One patient in the present study underwent resection of solitary liver metastasis, and this patient was the only patient with ENSAT stage 4 who was still alive until the end of the present study.

The ki-67 index is one of the pathologic prognostic markers for ACC, indicating aggressive behavior. A high Ki-67 index of more than 10 is associated with unfavorable outcomes[16]. Only seven patients or 30.4% in the present study had available information for the Ki-67 index. Therefore, the authors excluded this factor for the survival analysis. Interestingly, the three patients with a high Ki-67 index of more than 10 were dead while four patients with Ki-67 index of 10 or less were all alive at the end of the study.

Mitotane is recommended as adjuvant therapy in most cases due to the high disease recurrent rate[17]. From the retrospective data, mitotane can increase recurrence-free survival for 17 to 32 months[18]. In more advanced stages, combined chemotherapy may prolong the survival. Etoposide, doxorubicin, and cisplatin (EDP) are considered first-line chemotherapy. However, the objective response rate is only 23%, and the median duration of progression-free survival is five months[19]. The OS is poor, with a 5-year survival rate of 60% to 80% for localized disease, 35% to 50% for locally advanced disease, and 0% to 28% for metastatic disease[20].

In the present study cohort, only half of the patients received adjuvant treatment after surgery. This could be from a high proportion of completely resected ENSAT stage 1 to 2 patients in the study and the unavailability of mitotane at the early period of the present study.

Adjuvant radiation to the surgical bed has been recommended to combine with mitotane after incomplete resection. However, some complete resected patients in the present study received only adjuvant radiation to prevent local recurrence. Recent studies showed 56% to 100% efficacy of adjuvant radiation for local disease control. However, the advantage in OS was not identified[21,22]. Therefore, radiation therapy may be considered in selected patients.

In the present study, the all-cause mortality rate was 34.8%. The 5-year OS rate was 65.2%, which was comparable with the previous studies. Lim et al[10] presented the clinical outcomes from a multicenter study on 204 patients. The estimated 5-year OS and disease-specific survival were 65.4% and 70.6%, respectively. Souterio et al[11] showed the benefit of surgery and reported the highest OS at 66 months in the group of patients that achieved transient remission after surgery and the lowest OS at nine months in the group of palliative aim patients.

The tumor stage was one of the key factors in survival in ACC. The ENSAT staging has been summarized as a factor influencing survival in the previous study. Tella et al[23] presented the survival outcomes and predictors of survival in ACC from a large retrospective study of 3,185 patients. Increasing age, high comorbidity, high tumor grade, no surgical therapy, and stage 4 disease were associated with poor survival outcomes. However, in stage 4 disease, OS was significantly improved in patient treated with surgical removal, lymphadenectomy, postsurgical chemotherapy, or radiation. The present study subgroup analysis showed that 5-year OS was 80% in the localized disease in ENSAT stage 1 to 2, 50% in the locally advanced disease in ENSAT stage 3, and decreased to 25% in metastatic disease in ENSAT stage 4. The effect of the tumor stage on survival was also demonstrated by the univariate analysis.

The function of the tumor was also affected by the OS from subgroup analysis in the present study. None of the patients with non-functioning tumors died during the follow-up. This could be because most of the non-functioning ACC in the present study were ENSAT stages 1 to 2. This finding was supported from the result of Ayala-Ramirez et al[20] that the functioning tumor was the factor associated with poor survival. In contrast, Nair et al[24] reported hormonal overproduction did not related to the patient survival

Interestingly, NLR of 5 or more was a significant

predictor of survival in the present study cohort from both univariate and multivariate analyses. Patients with high NLR had a more than a twofold increased risk of death compared with patients with low NLR less than 5. However, the 95% CI was quite broad, due to the small study population and variation of data. This factor is recently obtaining interest for the potential factor predicting survival in ACC. Solak et al[7] found NLR was significantly higher in ENSAT stage 4 patients, patients with cortisol-secreting tumors, and patients with Ki-67 index greater than 10. Disease-specific survival and OS were also worse in patients with NLR greater than 3.9. de Jong et al[8] reported high NLR was strongly associated with poor OS.

NLR is a very simple and inexpensive tool. The potential hypothesis is the imbalance of immune response to the tumor cell. Tumor cell activates the systemic inflammatory response, which increases the neutrophil and decreases the lymphocyte[25]. Neutrophils can promote tumor progression by enhancing angiogenesis. In contrast, lymphocytes had an anti-tumor immune response. However, due to the rarity of ACC and the studies in NLR were limited, currently, there is no recommendation for the special additional neoadjuvant or adjuvant treatment in patients with high NLR of 5 or more.

The limitation of the present study was its retrospective nature from a single center. A small number of patients were included due to the rarity of the disease. Important clinical characteristics were incomplete such as Weiss score, Ki-67 index, mitotic count, detail of mitotane use, dose and type of radiation, and information on disease recurrence. The authors included only the patients who were performed the surgical resection. This could not reflect the entire population of ACC. The variety of treatments had made it difficult to assess the treatment outcomes. Multi-center study with a high volume of patients and long-term follow-up can confirm the present study's findings.

Conclusion

ACC is a rare endocrinologic malignancy associated with aggressive behavior. Management is a multidisciplinary approach, and surgical removal is the mainstay of treatment. The high NLR of 5 or more is a significant factor associated with poor disease survival.

What is already known on this topic?

ACC, a malignant tumor of an adrenocortical origin, is a rare malignancy with an unfavorable prognosis. Surgical resection of the tumor is the mainstay of treatment. The previously known prognostic factors associated with poor prognosis in ACC include advanced tumor stage, cortisol excess, older age, positive resection margin, high tumor grade, high mitotic count, and high Ki-67 index.

What this study adds?

High NLR was a significant predictor of survival in ACC. This factor is recently obtaining an interest because it is a very simple and inexpensive tool.

Conflicts of interest

The authors declare no conflict of interest.

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