RESEARCH ARTICLE

Prognostic Factors of Adrenocortical Carcinoma: An Analysis of the Surveillance Epidemiology and End Results (SEER) Database

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Abstract

Objective: To define the prognostic factors associated with overall survival (OS) and cancer-specific survival (CSS) for adrenocortical carcinoma (ACC). **Patients and Methods:** We used the Surveillance, Epidemiology and End Results (SEER) database (1973-2014) to identify ACC patients. Correlated variables, including age, sex, race, tumor laterality, marital status at diagnosis, treatment of primary site, lymph node dissection, radiation therapy, chemotherapy, tumor size and tumor stage, were extracted. Univariate and multivariate Cox regression were used to define the prognostic factors. Harrell's concordance index (C index) was calculated to evaluate the discrimination ability for the prognostic predictive models. **Results:** There were 749 ACC patients identified from the database. The overall median survival time was 22 (95%CI, 18-25) months. In multivariate analysis, age, treatment, chemotherapy and tumor stage were independent risk factors for both overall and cancer-specific survival. Tumor stage had a dominant effect on the cancer prognosis. Additionally, the ENSAT stage had better discrimination than the AJCC stage group in different predictive models. **Conclusion:** Our study shows that age, treatment of primary site, chemotherapy and tumor stage were prognostic factors for overall and cancer-specific mortality in ACC patients. Among these factors, tumor stage had a dominant effect. The ENSAT stage was more discriminative than the 7th AJCC stage group. Further multi-center prospective validation is still needed to confirm these outcomes.

Keywords: Adrenocortical carcinoma- survival- prognosis- surgery- chemotherapy

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Introduction

Adrenocortical carcinoma (ACC) accounts for most of the primary adrenal gland malignancies. It is a fatal disease because of its rapid progression and high mortality risk (Kerkhofs et al., 2013; Else et al., 2014a). Almost two-thirds of patients experienced tumor recurrence within 2 years after curative surgery, including local recurrence and metastasis (Amini et al., 2016). Surgical resection of the primary tumor is still the unique curative treatment modality for non-metastatic ACCs (Stigliano et al., 2016). Adjuvant therapy in conjunction with surgery could delay tumor recurrence, but the improvement in the overall survival is controversial (Terzolo et al., 2007; Else et al., 2014b). Reoperation, mitotane therapy and chemotherapy are the pivotal choices for advanced and recurrent ACCs. The most responsive combination therapy, EDP-M (etoposide, doxorubicin, cisplatin with mitotane), was superior to the Sz-M (streptozotocin with mitotane) regimen and had a similar incidence of adverse events in the FIRM-ACT trial (First International Randomized Trial in Locally Advanced and Metastatic Adrenocortical Carcinoma Treatment) (Fassnacht et al., 2012). To facilitate consecutive adjuvant therapy, accurate risk evaluation before treatment is important for subsequent selection of the management strategy. Previous studies on predicting ACC survival are scarce due to the low incidence of ACC and lack of a large population. The aim of this study is to define the prognostic factors in ACC patients and to evaluate the discrimination ability of a different stage system using a population-based oncologic database.

Materials and Methods

Patients and Methods

Study population

The Surveillance, Epidemiology and End Results (SEER) database (1973-2014, Nov 2016 submission) was queried using the International Classification of Diseases for Oncology codes third edition (ICD-O-3). Primary consecutive screen conditions were set as the

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primary tumor site (Site recode B ICD-O-3/WHO 2008: Adrenal Gland), adults (age ≥18 years), histology type (ICD-O-3: 8370), and first primary tumor with survival time, unilateral tumor. After multiple rounds of screening, 749 records were identified. Related variable information was extracted, including age, sex, race, tumor laterality, marital status at diagnosis, treatment modality of primary site, regional lymph node dissection (RLND), radiation therapy, chemotherapy, tumor size, tumor stage, cause of death, survival status, and survival time. The clinical tumor stage was defined using the 7th edition of the American Joint Committee on Cancer (AJCC) staging system and European Network for the Study of Adrenal Tumors (ENSAT) stage system. The AJCC stage group consisted of stages I (T1N0M0), II (T2N0M0), III (T1~2N1M0 or T3N0M0) and IV (T3N1M0, T4N0M0 or TanyNanyM1). The ENSAT stage system consisted of stages I (T1N0M0), II (T2N0M0), III (T3~4N0M0 or T1~4N1M0) and IV (TanyNanyM1) (Fassnacht et al., 2009; Lughezzani et al., 2010). We also modified the tumor stage by merging stage I and stage II of AJCC stage group and ENSAT stage (sAJCC stage group: stage I/II, III, IV; sENSAT stage: stage I/II, III, IV). Considering some underutilized data (e.g., collaborative stages of tumor extension, tumor size, lymph nodes, and metastasis at diagnosis, but no concluded tumor stage), we re-staged the tumor stage of each case compatible with the UICC/AJCC T.N.M stage system based on the Collaboration Stage Data Collection System version 02.05 (CS version 02.05, http://web2.facs.org/cstage0205/adrenalgland/AdrenalGlandschema.html).

Statistical analysis

Continuous variables were presented as the median with interquartile range (IQR) in brackets. Category variables were presented as counts. For regression analysis, we used univariate Cox regression to screen potential confounding variables. Variables with $P \leq 0.1$ in univariate analysis were included in the multivariate Cox regression. The hazard ratio (HR) and 95% confidence interval (95% CI) was used to show the risks. The discrimination ability was calculated using the Harrell C index (C-index) (Harrell et al., 1982). All tests were two-sided, and a P value < 0.05 was considered statistically significant. All statistical analyses were performed using R software (Version 3.3.1, https://www.r-project.org) and Stata 15 (StataCorp LLC, TX, USA).

Results

The demographic characteristics are shown in Table 1. A total of 749 patients with a median age of 55 years (IQR 44-65) were identified between 1973 and 2014. The population con-sisted of 454 (60.6%) female and 205 (39.4%) male patients (pts). The main race was white race (631 pts, 84.4%). The locations of the lesions were similar (402 left and 347 right ACCs). The median tumor size was 11 cm with an IQR (8-15 cm). Marital status at diagnosis was redefined as married (440 pts) and unmarried (280 pts). Treatment modality included no surgery of primary site (198 pts) and surgery of primary site (545 pts). Regional lymph node removal was performed in 145 patients (20.1%) and 111 (14.8%) patients underwent adjuvant radiation therapy. Detailed tumor stages, including T.N.M stage, AJCC stage group and ENSAT stage, were listed in Table 1. Among the 749 patients, 486 patients died during the follow-up; 421 patients died of ACC-specific causes, and the other 65 died of other causes. The overall median survival time was 22

Table 1. Characteristics of the Study Population

Characteristics	Value	Number of population
Age	55 (44 - 65) years	749
Sex	Female	454 (60.6%)
	Male	205 (39.4%)
Race	Black	59 (7.9%)
	White	631 (84.4%)
	Other	58 (7.7%)
Laterality	Left	402 (53.7%)
	Right	347 (46.3%)
Marital	Married	440 (61.1%)
	Unmarried	280 (38.9%)
Treatment	Surgery of primary site	545 (73.4%)
	No surgery	198 (26.6%)
Regional LND	No	577 (79.9%)
	Yes	145 (20.1%)
Radiation	No/unknown	638 (85.2%)
	Yes	111 (14.8%)
Chemotherapy	No/unknown	433 (57.8%)
	Yes	316 (42.2%)
Tumor size	11 (8.0 - 15) cm	692
T stage	T1	38 (5.5%)
	T2	306 (44.6%)
	T3	150 (21.8%)
	T4	193 (28.1%)
N stage	N0	590 (86.3%)
	N1	94 (13.7%)
M stage	M0	460 (61.4%)
	M1	289 (38.6%)
AJCC stage group	I	30 (4.1%)
	II	230 (31.4%)
	III	101 (13.8%)
	IV	371 (50.7%)
ENSAT stage	I	30 (4.1%)
	II	230 (31.2%)
	III	189 (25.6%)
	IV	289 (39.1%)
sAJCC stage group	I/II	271 (36.2%)
	III	101 (25.2%)
	IV	371 (38.4%)
sENSAT stage	I/II	271 (36.5%)
	III	189 (13.6%)
	IV	289 (49.9%)
Survival status	Alive	263 (35.1%)
	Dead	486 (64.9%)

LND, lymph node dissection; AJCC, American Joint Committee on Cancer; ENSAT, European Network for the Study of Adrenal Tumors; sENSAT stage, simplified ENSAT stage; sAJCC stage group, simplified AJCC stage group.

Table 2. Predictors of Overall Survival for Adrenocortical Carcinoma

	Univariate analysis			Multivariate analysis		
Variables	Hazard Ratio	95% CI	P value	Hazard Ratio	95% CI	P value
Age	1.014	1.007-1.020	P < 0.001	1.015	1.007-1.022	P < 0.001
Sex			Reference Female			
Male	1.126	0.932-1.361	0.219			
Race			Reference Black			
White	1.043	0.741-1.469	0.809			
Other	1.095	0.690-1.738	0.701			
Laterality			Reference Left			
Right	0.987	0.820-1.189	0.894			
Marital			Reference Married			
Unmarried	0.974	0.800-1.185	0.79			
Treatment			Reference No surgery			
Surgery of primary site	0.214	0.175-0.263	P < 0.001	0.28	0.208-0.378	P < 0.001
Regional LND			Reference No			
Yes	0.819	0.645-1.041	0.103			
Radiation			Reference No/unknown			
Yes	1.05	0.802-1.373	0.725			
Chemotherapy			Reference No/unknown			
Yes	1.423	1.179-1.717	P < 0.001	0.772	0.602-0.990	0.042
Tumor size	0.998	0.983-1.014	0.826			
T stage			Reference T1			
T2	1.368	0.818-2.288	0.233	1.377	0.820-2.310	0.226
T3	2.196	1.293-3.729	0.004	2.388	1.386-4.114	0.002
T4	3.346	1.990-5.626	P < 0.001	1.599	0.929-2.754	0.09
N stage			Reference N0			
N1	3.094	2.383-4.018	P < 0.001	1.836	1.356-2.486	P < 0.001
M stage			Reference M0			
M1	4.018	3.314-4.871	P < 0.001	2.574	1.927-3.437	P < 0.001
AJCC stage group		Reference Stage I		Adjusted*		
II	1.185	0.650-2.159	0.58	1.199	0.657-2.188	0.555
III	2.144	1.151-3.995	0.016	2.341	1.252-4.378	0.008
IV	4.837	2.707-8.643	P < 0.001	3.562	1.969-6.443	P < 0.001
ENSAT stage		Reference Stage I		Adjusted*		
II	1.185	0.650-2.159	0.579	1.17	0.641-2.135	0.61
III	2.303	1.268-4.183	0.006	2.332	1.280-4.249	0.006
IV	6.196	3.454-11.114	P < 0.001	4.515	2.465-8.270	P < 0.001
sAJCC stage group		Reference Stage I/II		Adjusted*		
III	1.853	1.350-2.544	P < 0.001	2.01	1.459-2.769	P < 0.001
IV	4.188	3.349-5.236	P < 0.001	3.102	2.396-4.016	P < 0.001
sENSAT stage		Reference Stage I/II		Adjusted*		
III	1.991	1.530-2.592	P < 0.001	2.05	1.569-2.679	P < 0.001
IV	5.365	4.249-6.774	P < 0.001	4.024	3.014-5.373	P < 0.001

95% CI, 95% confidence interval; LND, lymph node dissection; AJCC, American Joint Committee on Cancer; ENSAT, European Network for the Study of Adrenal Tumors; sENSAT stage, simplified ENSAT stage; sAJCC stage group, simplified AJCC stage group; *, adjusted by age, treatment, chemotherapy.

(95%CI, 18-25) months. The median survival time were 57 months for ENSAT stage I, 67 months for stage II, 21 months for stage III and 7 months for stage IV.

Table 2 shows both univariate and multivariate analyses of the overall survival. In univariate analysis, age (P< 0.001), treatment modality of primary site (P< 0.001), chemotherapy (P< 0.001) and tumor stage (P< 0.001) were associated with overall survival. Sex, race, laterality, marital status, lymph node dissection, radiation therapy and tumor size were not significantly associated. In

Table 3. Predictors of Cancer Specific Survival for Adrenocortical Carcinoma

	Univariate analysis			Multivariate analysis		
Variables	Hazard Ratio	95% CI	P value	Hazard Ratio	95% CI	P value
Age	1.01	1.004-1.017	0.003	1.012	1.004-1.020	0.005
Sex			Reference Female			
Male	1.08	0.882-1.323	0.458			
Race			Reference Black			
White	1.242	0.839-1.838	0.28			
Other	1.301	0.779-2.171	0.315			
Laterality			Reference Left			
Right	0.989	0.811-1.206	0.912			
Marital			Reference Married			
Unmarried	0.93	0.753-1.148	0.498			
Treatment			Reference No surgery			
Surgery of primary site	0.206	0.166-0.256	P < 0.001	0.263	0.192-0.362	P < 0.001
Regional LND	Reference No					
Yes	0.88	0.685-1.130	0.317			
Radiation			Reference No/unknown			
Yes	1.121	0.848-1.482	0.424			
Chemotherapy			Reference No/unknown			
Yes	1.497	1.225-1.828	P < 0.001	0.771	0.591-1.005	0.055
Tumor size	1.001	0.985-1.018	0.886			
T stage			Reference T1			
T2	1.912	1.006-3.633	0.048	1.928	1.012-3.676	0.046
T3	3.057	1.586-5.891	0.001	3.365	1.723-6.572	P < 0.001
T4	4.815	2.523-9.186	P < 0.001	2.321	1.191-4.521	0.013
N stage			Reference N0			
N1	2.965	2.240-3.926	P < 0.001	1.718	1.250-2.363	0.001
M stage			Reference M0			
M1	4.229	3.444-5.193	P < 0.001	2.663	1.955-3.626	P < 0.001
AJCC stage group		Reference Stage I		Adjusted*		
II	1.744	0.806-3.772	0.158	1.777	0.820-3.848	0.145
III	3.084	1.396-6.812	0.005	3.393	1.531-7.520	0.003
IV	7.453	3.509-15.831	P < 0.001	5.472	2.548-11.752	P < 0.001
ENSAT stage		Reference Stage I		Adjusted*		
II	1.745	0.807-3.775	0.157	1.74	0.803-3.769	0.16
III	3.43	1.591-7.395	0.002	3.509	1.624-7.586	0.001
IV	9.537	4.475-20.322	P < 0.001	6.848	3.154-14.872	P < 0.001
sAJCC stage group		Reference Stage I/II		Adjusted*		
III	1.86	1.316-2.627	P < 0.001	2.021	1.425-2.866	P < 0.001
IV	4.501	3.535-5.732	P < 0.001	3.313	2.507-4.379	P < 0.001
sENSAT stage		Reference Stage I/II		Adjusted*		
III	2.068	1.554-2.751	P < 0.001	2.133	1.597-2.851	P < 0.001
IV	5.759	4.479-7.406	P < 0.001	4.236	3.104-5.781	P < 0.001

95% CI, 95% confidence interval; LND, lymph node dissection; AJCC, American Joint Committee on Cancer; ENSAT, European Network for the Study of Adrenal Tumors; sENSAT stage, simplified ENSAT stage; sAJCC stage group, simplified AJCC stage group; *, adjusted by age, treatment, chemotherapy.

multivariate Cox regression, age, treatment modality, chemotherapy and tumor T.N.M stage were independent risk factors. T2 stage patients have similar overall survival (HR 1.377, 0.820-2.310, P= 0.226). Chemotherapy was a protective factor with hazard ratio 0.772 (95%CI, 0.602-0.990).We used the above independent risk factors to construct survival models with the AJCC stage group or ENSAT stage system. The results consistently showed that mortality risk increased with the increase of the tumor stage. No survival difference between stages II and stage

Table 4. Discrimination Ability (Harrell C index) Comparison of Different Stage System Model

Predicted outcomes	Embedment of other factors	Harrell concordance index				
		T.N.M stage	AJCC stage group	ENSAT stage	sAJCC stage group	sENSAT stage
Overall mortality	No	0.721	0.698	0.718	0.697	0.717
Overall mortality	Embedment*	0.767	0.759	0.766	0.758	0.764
Cancer specific mortality	No	0.737	0.706	0.725	0.704	0.723
Cancer specific mortality	Embedment*	0.776	0.765	0.771	0.761	0.767

*, including age, treatment, chemotherapy; sENSAT stage, simplified ENSAT stage; sAJCC stage group, simplified AJCC stage group.

I was observed in the AJCC stage group and ENSAT stage systems. Table 3 shows both univariate and multivariate analyses of the cancer-specific survival. In univariate analysis, age (P< 0.001), treatment modality (P< 0.001), chemotherapy (P< 0.001) and tumor stage (P< 0.001) were correlated with cancer-specific survival. Sex, race, tumor location, marital status, lymph node dissection, radiation and tumor size did not affect the survival outcome. In accordance with the overall survival model, age, treatment modality and tumor T.N.M stage were independent prognostic factors in multivariate regression. Chemotherapy did not significantly improve cancer specific survival (HR 0.771, 0.591-1.005, P= 0.055). The effect size was marginal significance because when using efron method to deal with the ties, the hazard ratio was 0.748 (95%CI, 0.572-0.979, P=0.034). A multivariate model with age, treatment modality and AJCC stage group (or ENSAT stage) showed similar results as with aforementioned overall survival model. Stage I had no cancer-specific survival difference with stage II. As the clinical stage increased, the mortality risk also increased.

Table 4 shows the discrimination ability for predicting oncologic outcomes in ACCs. Compared with the models with the predictors of age, treatment modality, chemotherapy and tumor stage, the C index of the models with unique predictor of tumor stage (including T.N.M stage, AJCC stage group, or ENSAT stage) was not remarkably reduced in AJCC stage group and sAJCC stage group. Tumor stage was the mainstay in the prognostic models and contributed to the dominant predictive accuracy. Models with the ENSAT stage as a predictor had a larger C index than models with the AJCC stage group (Larger C index means better discrimination ability). These results consistently showed better discrimination ability for the ENSAT stage than for the AJCC stage group regarding overall survival and cancer-specific survival. Additionally, the ENSAT stage was much closer to the T.N.M stage.

Discussion

In this study, we defined four independent prognostic factors that affect overall and cancer-specific survival. Patients with younger age, surgical resection of primary lession, chemotherapy and low tumor stage had a better prognosis. Increased age decreased the overall survival. Along with the increase in age, the risk of death and tumor progression increased. On the other hand, the survival natural risk of elder increased by the age. The effect of primary site surgery decreased the overall and cancer specific mortality risk. This was consistent with previous studies. Considering this article derived from a observational cancer database. The selection bias probably contributed to the result. For example, patients with good conditions or good prognostic characteristics prone to receive surgical management and had better prognosis. Sex, race, marital status, tumor location, regional LND, radiotherapy and tumor size had no effect on the cancer survival in ACC patients. Moreover, we did not find any survival difference between stages I and stage II ACC patients in this study. Stage I is different from stage II in terms of tumor size with a cutoff of 5 cm, which could contribute to the laparoscopic indication. However, laparoscopic adrenalectomy was not strongly recommended in ACC management guidelines (Stigliano et al., 2016). Moreover, tumor size was not an independent prognostic factor in any model. The value of differentiating between stages I and II remains to be discussed. The staging system needs refinement. Our study also showed that the ENSAT stage system had better predictive ability than the AJCC stage group. The value of the C-index statistic ranges from 0.5 to 1 (100% correct prediction). The prognostic prediction model with a higher value of C-index was regarded as the better model. The C-index of the prognostic model with age, treatment, chemotherapy and ENSAT stage were 0.766 and 0.771 for overall and cancer-specific survival. We also modified the tumor stage by merging stage I and stage II into one category, and resulted in sAJCC stage group and sENSAT stage. Decreased C index was no more than 0.4%. The results showed relatively acceptable predictive ability for our prognostic model.

Compared with previous studies, our research did not adjust for some potential confounders. For instance, the clinical manifestation was concluded as a prognostic factor. Approximately 40-60% patients manifested clinical symptoms that were mainly derived from tumor-derived hormone excess (Fassnacht et al., 2011). Patients with functional tumors were deemed to have a poor prognosis in some studies (Ayala-Ramirez et al., 2013; Else et al., 2014b). In several studies (Else et al., 2014b; Margonis et al., 2016b), cortisol instead of androgen or other functional hormones affected the recurrence and overall survival. However, controversy remained about the impact of tumor hormone function (Loncar et al., 2015; Scollo et al., 2016). Surgery experience is important for tumor control. The surgical margins are somewhat related to the surgeon's experience. R1 (microscopically positive) and

(or) R^2 (macroscopically positive) patients have a poorer prognosis than R0 (microscopically negative) patients (Kim et al., 2016; Margonis et al., 2016a; Margonis et al., 2016b; Scollo et al., 2016). R0 was difficult to achieve, especially because skill was required. In Margonis' retrospective multi-center study, approximately 68.4% of R0 resection was achieved in ACC patients (Margonis et al., 2016b). Newly diagnosed cases should be referred to a centralized medical center (Hermsen et al., 2012; Abdel-Aziz et al., 2015). The surgical modality was also a critical factor. Open surgical resection was proven to have a significant survival benefit over laparoscopic surgery (Gaujoux et al., 2012; Miller et al., 2012; Cooper et al., 2013; Machado et al., 2015; Sgourakis et al., 2015; Autorino et al., 2016; Huynh et al., 2016). Therefore, open adrenalectomy was recommended in the guidelines (Funder et al., 2016; Stigliano et al., 2016), but not all studies were consistent (Lombardi et al., 2012; Fossa et al., 2013; Donatini et al., 2014). This may be derived from the small population in these studies. The necessity of regional lymph node resection is controversial (Reibetanz et al., 2012; Gerry et al., 2016; Nilubol et al., 2016). Lymphadenectomy was not a standard procedure of adrenalectomy in ACC treatment (Stigliano et al., 2016). Our results also did not support the survival benefit of lymph node dissection. Nevertheless, lymph node dissection could pathologically stage the lymph node stage from another perspective. The benefit of adjuvant mitotane administration after surgery remains controversial due to the low incidence of ACC, and no large randomized trial was performed (Terzolo et al., 2007; Fassnacht et al., 2012; Terzolo et al., 2013; Loncar et al., 2015; Maiter et al., 2016; Postlewait et al., 2016). Mitotane could be effective for certain patients. Predictors of response to mitotane therapy and other cytotoxic drugs could facilitate individualized treatment. Radiation was another palliative choice. However, there was no consensus on the ef-fect of adjuvant radiotherapy (Habra et al., 2013; Sabolch et al., 2015). Radiation therapy was deemed to ameliorate symptoms and reduce local recurrence (Fassnacht et al., 2006), but it did not improve the overall survival outcome (Stigliano et al., 2016).

There are numerous controversies in ACC treatment due to low incidence and scattered geographic distribution of this disease. The above controversies in different studies are possibly due to the sample size, number of events, and different adjusted models. Concise and sufficient predictive models are preferable in future studies. There are several limitations in our study. This study is based on the SEER database and, therefore, has the intrinsic bias of an observational study. The aforementioned confounders were not included because lack of the related data. Additionally, missing values pose a great challenge to the application of SEER data. In terms of the C index, our predictive models have relatively acceptable discrimination ability.

In conclusion, our study demonstrated that age, surgery of primary site, chemotherapy and tumor stage were prognostic factors for overall and cancer-specific mortality in ACC patients. Among these factors, tumor stage had a dominant effect. The ENSAT stage had better discrimination ability than the 7th AJCC stage group. Further multi-center prospective studies are still needed to validate these outcomes.

Conflict of interest

The authors declared no conflict of interest.

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