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A Revised Version of the TNM Classification Leads to Optimized Predictive Performance in Patients with Adrenocortical Carcinoma

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ABSTRACT

The prognostic stratification of the current AJCC/UICC TNM classification for adrenocortical carcinoma (ACC) has been validated in only a few studies. In this study, it was hypothesized that redefining the T category cut-off would result in a significant improvement in estimated stage-related survival. In 935 patients with ACC from the SEER database, optimal cut-off values based on tumor size were first determined to redefine T1 and T2 categories. Cox proportional hazards regression analysis and receiver operating characteristics (ROC) were then used to determine the prognostic value of the revised version. A new cut-off value of 9.5 cm tumor size was established to differentiate between T1 and T2 tumors, leading to a revised TNM classification. As a result, a more homogeneous distribution of patients with ACC across all stages was observed. Notably, the predictive value of the newly proposed TNM classification in the ROC analysis exceeded that of the 7th and 8th editions of the AJCC/UICC classification system. Finally, the prognostic superiority of the revised TNM classification was confirmed in a multivariate Cox proportional hazards regression model. In conclusion, the present study demonstrates that updating the current staging system with revised T1 and T2 categories significantly improves the prediction of cancer-specific survival (CSS) in patients with ACC.

* both authors contributed equally to this work

Introduction

Adrenocortical carcinoma (ACC) is an extremely rare tumor entity with an incidence of 0.5–2 per million population. In addition, ACC is associated with a very poor prognosis with a 5-year survival rate ranging from 16 % to 47 % depending on tumor stage [1–3]. Treatment of ACC depends on the stage of the disease and consists of surgical resection, radiotherapy and chemotherapy. Advanced tumor stages are largely reserved for radiotherapy and chemotherapy, primarily with mitotane [4–8].

A globally uniform system for the classification of tumor stages into T (tumor extension), N (lymph node metastasis), and M (distant metastasis) categories is essential for the prognostic assessment and thus for the decision on the respective stage-specific treatment strategy. Of note, until 2003, no TNM classification for ACC had been proposed by the American Joint Committee on Cancer (AJCC) or the Union Internationale Contre le Cancer (UICC), leading to different staging classifications for ACC without validation in appropriate cohort sizes [9–13]. Therefore, in 2004, the AJCC developed the TNM classification for ACC. Essentially, the 7th edition of the AJCC/UICC was based on the classifications proposed by Sullivan and Macfarlane [11, 13]. Accordingly, stage I disease was defined as tumors ≤ 5 cm in size without lymph node or distant metastases ($T_1N_0M_0$). Tumors without lymph node or distant metastases and with a size > 5 cm were considered stage II ($T_2N_0M_0$). ACC that invade adjacent tissues ($T_3N_0M_0$) or involve lymph nodes ($T_{1-2}N_1M_0$) were classified as stage III. Stage IV includes ACC with infiltration of surrounding tissue and lymph node metastases ($T_3N_1M_0$) or infiltration of adjacent organs ($T_4N_0M_0$) and the presence of distant metastases ($T_{1-4}N_{0-1}M_1$). However, this classification system showed weaknesses in two studies with large patient cohorts and has been questioned by others [14, 15]. Specifically, their data showed that disease-specific survival (DSS) did not differ significantly between stage II and stage III patients, who accounted for approximately 58 % of ACC cases. In addition, stage IV patients with distant metastases had significantly worse survival than stage IV patients without distant metastases [14, 16]. Another disadvantage of this classification was the unbalanced distribution of patients by tumor stage, with stage I and III tumors together accounting for only 21 % of patients [15]. These considerations led to a reclassification by the European Network for Study of Adrenal Tumors (ENSAT) consortium in 2008, which was then incorporated into the 8th edition of the AJCC/UICC for ACC.

According to this classification, stages I and II are still defined by tumor size, with the cut-off remaining at 5 cm, so that comparing stages I and II does not imply any prognostic differences. Thus, the main difference in this classification is that only tumors with distant metastases ($T_{1-4}N_{0-1}M_1$) are classified as stage IV, whereas stage III includes all ACCs with lymph node metastases ($T_{1-2}N_1M_0$) or tumors that invade the surrounding tissue ($T_{3-4}N_{0-1}M_0$). Overall, the reclassification in the 8th edition results in a significant prognostic difference only between stage II and III [14, 16]. Therefore, we hypothesized that redefining the cut-off value for T category should further improve the predictive accuracy of the TNM staging system. Using the Surveillance, Epidemiology, and End Results Program (SEER) database, the purpose of our study was to determine a new cut-off value for distinguishing T1 and T2 tumors and to evaluate the prognostic performance of the 7th and 8th editions of the AJCC/UICC staging system and our revised TNM classification, respectively.

Patients and Methods

Study population

Cancer registry data from the National Institutes of Health (NIH) Surveillance, Epidemiology, and End Results (SEER) program were retrieved on May 16th, 2022 using SEER*stat software version 8.4.0.1 and the SEER-17 registries released in November 2021 [17]. In the SEER-17 registries, which comprise cancer patients with diagnoses between 2000 and 2019, patients with ACC were identified according to histology code ICD-O-3 code 8370/3 (International Classification of Diseases for Oncology, third edition). The following registries are included in the SEER-17 registries: Alaska Native Tumor Registry, Connecticut, Atlanta, Greater Georgia, Rural Georgia, San Francisco-Oakland, San Jose-Monterey, Greater California, Hawaii, Iowa, Kentucky, Los Angeles, Louisiana, New Mexico, New Jersey, Seattle-Puget Sound, and Utah. Data were retrieved on May 16th, 2022.

Statistical analysis

The optimal cut-off value for tumor size to distinguish between T1 and T2 tumors was determined using the X-tile software [18]. The cut-off value with the lowest p-value from the log-rank χ^2 statistic was determined for the classification of T1 and T2 tumors with respect to CSS.

For each patient, the TNM stage was then determined using the TNM classification defined by the 7th or 8th edition of the AJCC/UICC or based on our revised version. Kaplan–Meier survival curves for each TNM stage, defined according to the 7th and 8th edition of the AJCC/UICC classification system and our revised classification, respectively, were generated for cancer-specific survival (CSS) and statistically analyzed using the log-rank test. Therefore, cancer-specific death was defined according to the SEER cause-specific death classification. Lifetime tables were used to determine 1-, 3-, and 5-year CSS rates. The prognostic accuracy of the 3 different classifications was determined for the 1-, 3- and 5- year CSS using the area under the curve (AUC) derived from the receiver operating characteristic (ROC). While a value of 1 represents the best model prediction, an AUC greater than 0.7 indicates a good model and a value of 0.5 means that the model is no better than predicting an event by chance alone. The statistical significance of the differences between the AUCs of the individual TNM classifications was tested with the DeLong test [19].

Finally, using Cox proportional hazards regression analysis, we tested the prognostic value of the AJCC/UICC staging system (7th and 8th edition) and our proposed revised TNM version for CSS. For risk factors with missing data, multivariate imputation by chained equations (MICE) was applied [20]. Therefore, the imputation method to be used for each column in data was specified as the classification and regression trees (CART) and the number of multiple imputations was set to 5. Adjustment of our multivariate Cox regression model was made for age, sex, treatment modality, race, marital status and laterality. Accuracy values were quantified using the concordance index (C-index), which is a modification of the AUC. The values of the C-index and thus the accuracy of the model prediction are interpreted in the same way

as the AUC. Statistical significance was assumed at a p-value < 0.05. The statistical analyses were conducted with the software R (version 1.4.1106) utilizing the packages readxl, pROC, mice, survival, and survminer [20–25].

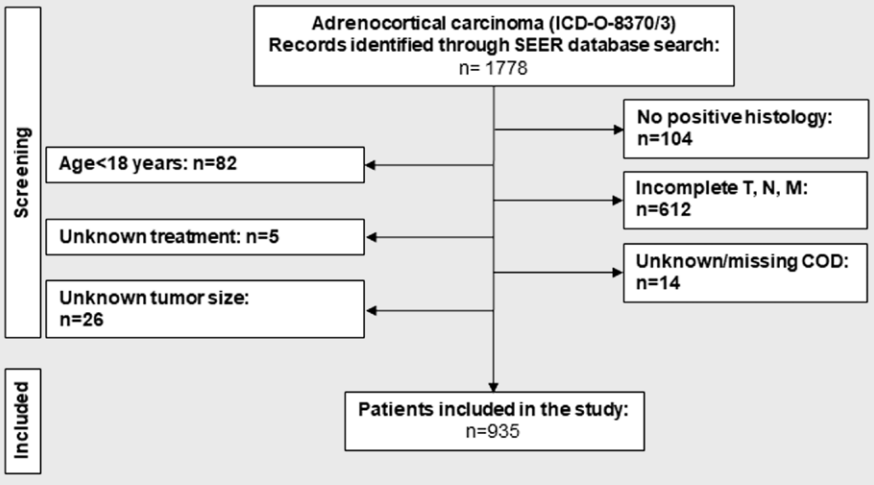
Results

A search of the SEER-17 registries, published in November 2021 and covering cancer patients with diagnoses between 2000 and 2019 [17], retrieved 1778 patients with a diagnosis of ACC (ICD-O-8370/3). Patients with the following characteristics were excluded from this study: no positive histology (n = 104), incomplete T, N, M status (n = 612), age < 18 years (n = 82), missing/unknown cause of death (COD; n = 14), unknown treatment modalities (n = 5), and unknown tumor size (n = 26). Finally, a total of 935 patients with histologically confirmed ACC were included in this study for further analysis (▶ **Fig. 1**). Of particular note, all of these patients were diagnosed between 2004 and 2019, thus our study population is composed only of patients after the introduction of the 7th edition of the TNM. Pathologic and demographic data, as well as treatment modalities, are summarized in ▶ **Tables 1** and **2**. The median age was 56 years (range: 18–91 years) and median tumor size was 105 mm (range: 5–800 mm). The most frequently assigned T category, defined by the 8th edition of the AJCC/UICC classification system, was T2 45.56 % (n = 426), followed by T3 23.74 % (n = 222), T4 23.53 % (n = 220), and T1 7.17 % (n = 67). In this cohort, 62.67 % (n = 586) patients were females and 37.33 % (n = 349) were males. Affected lymph nodes were detected in 11.76 % (n = 110) and distant metastases in 29.3 % (n = 274). Of these 935 patients, in 54.01 % (n = 505) ACC was located in the left, in 44.81 % (n = 419) the right adrenal gland, and in 1.18 % (n = 11) the localization was unknown. Among the included patients, 10.91 % (n = 102) were treated with chemotherapy or radiation alone and 82.67 % (n = 773) underwent surgery. In contrast, in 6.42 % (n = 60) no therapy was performed or recommended.

Of the patients who underwent surgery, 2.35 % (n = 22) received local tumor excision, 13.37 % (n = 125) simple/partial surgical removal of primary site, 45.45 % (n = 425) total surgical removal of primary site, 18.82 % (n = 176) radical surgery with resection in continuity with other organs, and 1.07 % (n = 10) received tumor debulking. Unfortunately, in 1.6 % (n = 15) patients no exact specification of the surgical procedure was available. A total of 168 patients (17.97 %) underwent radiotherapy and 405 (43.32 %) received chemotherapy (▶ **Table 2**).

Because tumor stages I and II differ only in tumor size, we used X-tile software [18] to assess whether a more prognostically relevant cut-off value for tumor size could be determined. This approach revealed that a tumor size of 9.5 cm has a substantially differential prognostic predictive value (data not shown). Therefore, we postulate a revised staging system that defines T1 tumors as ≤ 9.5 cm and T2 tumors as > 9.5 cm in size. Using this revised classification, we compared the distribution of patients among the different stages with that of the 7th and 8th edition of the AJCC/UICC classification system (▶ **Fig. 2a**). Hence, the new cut-off value of 9.5 cm resulted in a shift of 143 patients from stage II (n = 186) of the TNM 7th and 8th edition to stage I (n = 193) of our suggested classification system. Consequently, the revised stage I now includes 20.64 % of patients compared with 5.35 % previously, and our proposed stage II thus includes 19.89 % instead of 35.19 %. This also leads to a more balanced distribution of patients between these two tumor stages.

We then generated Kaplan–Meier survival curves (▶ **Fig. 2b–e**) and calculated the 1-, 3-, and 5-year CSS rates for each classification and tumor stage. Accordingly, the 1-, 3-, and 5-year CSS rates were 89.5 %, 69.5 %, and 58.7 % for stage I patients and 92.1 %, 71.6 %, and 63.4 % for stage II patients regardless of the edition. However, with our revised classification, the 1, 3, and 5-year CSS rates of stage I patients changed to 92.8 %, 78.1 %, and 69.1 % and to 90.7 %, 64.6 %, and 56.4 % in stage III patients, respectively. By revision of the 7th edition of the AJCC/UICC classification, CSS at 1, 3, and 5 years changed from 78.5 %, 47.8 %, and 38.3 % in tumor stage III to 73.8 %, 43.5 %, and 37.1 % and from 46.1 %, 22.1 %, and 17.4 % to 38.2 % 16.2 % and 10.2 % in tumor stage IV, respectively.



▶ **Fig. 1** Case selection from patients with ACC extracted from the SEER database.

▶ **Table 1** Patient characteristics.

Variable	Overall population (n = 935)
Age	
Median (range)	56 (18–91)
Gender n (%)	
Female	586 (62.67)
Male	349 (37.33)
Race n (%)	
White	780 (83.42)
Black	80 (8.56)
American Indian/Alaska Native	3 (0.32)
Asian or Pacific Islander	66 (7.06)
Unknown	6 (0.64)
Marital status n (%)	
Separated/Divorced/Widowed	161 (17.22)
Married/Domestic partner	552 (59.04)
Single	191 (20.43)
Unknown	31 (3.32)
Laterality n (%)	
Left	505 (54.01)
Right	419 (44.81)
Unknown	11 (1.18)
T category n (%)	
T1	67 (7.17)
T2	426 (45.56)
T3	222 (23.74)
T4	220 (23.53)
N category n (%)	
N0	825 (88.24)
N1	110 (11.76)
M category n (%)	
M0	661 (70.7)
M1	274 (29.3)
First malignant primary n (%)	
No	118 (12.62)
Yes	817 (87.38)
Tumor size (mm)	
Median (range)	105 (5–800)
Number of malignant tumors	
Median (range)	1 (1–5)

▶ **Table 2** Therapies of the included patients.

Treatment	Total (%)
Therapy	
Surgery	773 (82.67)
Chemotherapy/Radiation alone	102 (10.91)
Not performed/recommended	60 (6.42)
Surgery	
No surgery	162 (17.33)
Local tumor excision	22 (2.35)
Simple/partial surgical removal of primary site	125 (13.37)
Total surgical removal of primary site	425 (45.45)
Debulking	10 (1.07)
Radical surgery with resection in continuity with other organs	176 (18.82)
Surgery NOS	15 (1.60)
Radiation	
No/unknown	767 (82.03)
Yes	168 (17.97)
Chemotherapy	
No/unknown	530 (56.68)
Yes	405 (43.32)

NOS: Not otherwise specified.

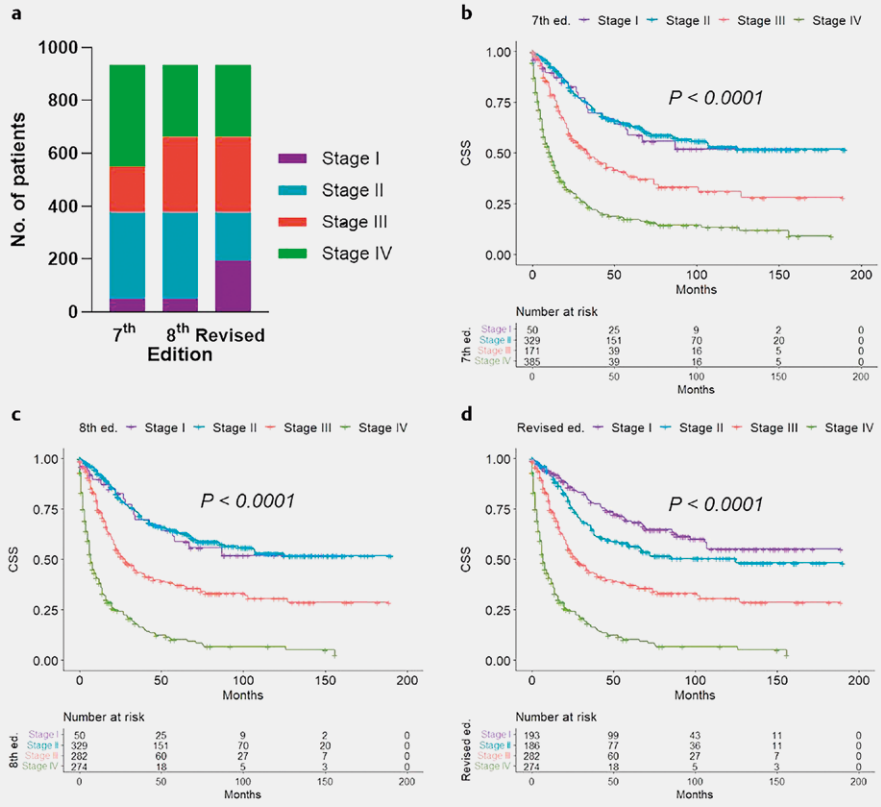
Note that survival rates for stages III and IV in our revised version remain unchanged from the 8th edition.

To compare the predictive power of the AJCC/UICC classifications (7th and 8th edition) with our suggested version, we next performed an ROC analysis for each classification (▶ **Fig. 3a–d**). The AUC of our revised version showed the highest values for the 1-, 3-, and 5-year CSS, respectively, when compared with the 7th and 8th edition of AJCC/UICC (▶ **Fig. 3e**). While the difference in the AUC for the 7th edition of the AJCC/UICC TNM classification and our proposed classification was significantly different for all time points, this was only true for the 3-, and 5-year CSS when comparing with the 8th edition, which supports an improved predictive power of our revised classification.

Finally, to determine the highest discriminatory power of the different TNM staging systems in predicting prognosis, we also performed Cox proportional hazards regression analysis adjusted for age, sex, race, marital status, tumor laterality, and type of therapy (surgery versus chemotherapy or radiotherapy alone), and assessed model performance for each TNM classification by assessing the C-index. Again, our suggested TNM classification showed not only the best prognostic discrimination between tumor stages (▶ **Table 3**), but also the highest predictive performance (C-index = 0.768; SE = 0.011) when compared with multivariate models that included the AJCC/UICC 7th (C-index = 0.764; SE = 0.011) or 8th edition (C-index = 0.767; SE = 0.011) TNM classification.

Discussion

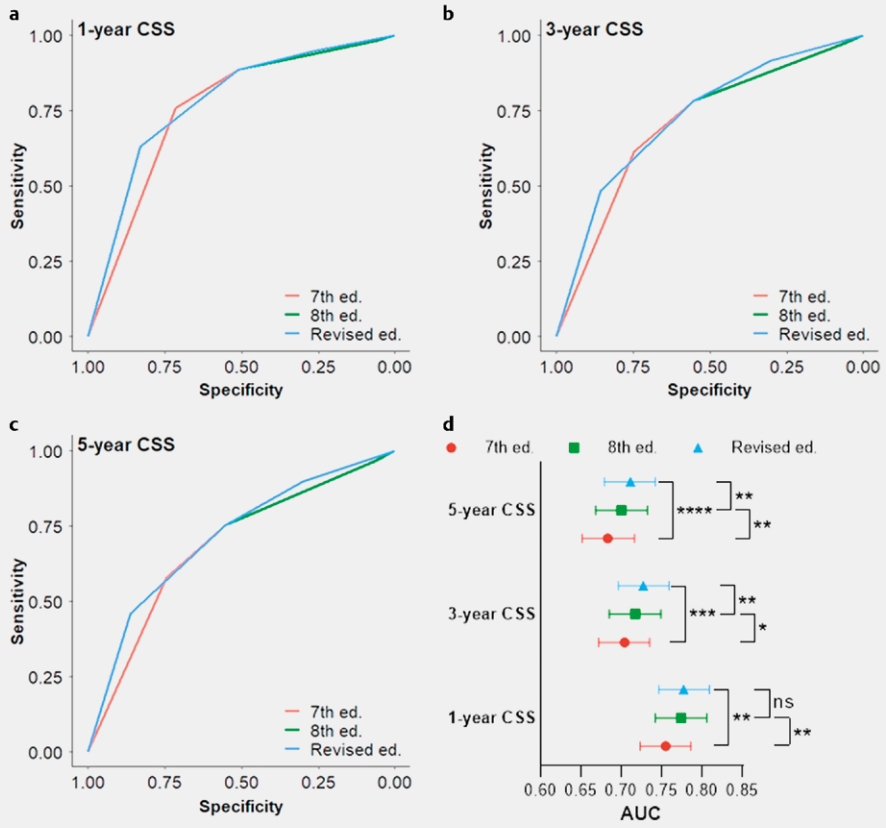
Reliable prognostic assessment after resection of ACC is essential for improved patient counseling regarding long-term outcomes, follow-up, and adjuvant therapy decisions. To date, the ENSAT staging system is commonly accepted as the standard prognostic factor in ACC despite considerable heterogeneity [14, 16, 26]. There are several factors driving the requirement for a unified and accurate staging system. An optimal staging system captures the most rel-



▶ **Fig. 2** Kaplan–Meier curves for cancer-specific survival according to the TNM stages. (**a**) Distribution of TNM stages according to the AJCC/UICC 7th or 8th edition and the revised staging system. Survival curves for the respective tumor stages defined on the basis of the (**b**) 7th, (**c**) 8th or (**d**) revised TNM classification. Ed.: Edition.

evant data regarding prognostic factors to maximize predictive accuracy with clinical relevance while remaining clinically practical. Staging systems facilitate the comparison of similar patient cohorts and their treatment. Especially for rare tumors such as ACC, it is important to collect internationally standardized data to obtain the largest possible cohort of patients to improve clinical research [26]. Therefore, in the present study, we took advantage of the SEER database and compared the 7th and 8th editions of the AJCC/UICC TNM classification in a large cohort of patients with ACC. Since the minority of tumors in our cohort were T1 according to the current TNM classification, but most were T2, differing only in size, we investigated whether there might be a prognostically better cut-off for tumor size. As a result, we were able to identify an alternative tumor size cut-off of 9.5 cm, which resulted in a more homogeneous distribution of tumor stages I and II, but also a better prediction of CSS. To date, only a few studies have compared the AJCC/UICC 7th and 8th edition TNM staging systems with respect to their prognostic relevance. In this context, recent studies have shown that DSS in stage II and III tumors can be better discriminated by the updated staging system, which is consistent with the results of our study [14, 16, 27]. Furthermore, we showed that a redefinition of the cut-off value for tumor size to distinguish T1 and T2 tumors leads to an improvement in prognostic accuracy. In both the 7th and 8th editions of the AJCC/UICC TNM classification system, the difference between CSS stage I and II was not distinguishable, as the survival curves for stage I and II overlapped almost completely. Moreover, only a small percentage of patients were classified as stage I, which in itself makes such classification highly questionable. Although Fassnacht and coworkers postulated in the past that other cut-offs did not lead to better prognostic discrimination between tumor stages I and II [16], we were now able to demonstrate a prognostic difference using our newly defined cut-off for T1/T2 tumors in a larger cohort of patients with ACC. However, whether this will lead to a different therapeutic regimen among current treatment options and thus better outcomes for patients requires further investigation. In addition, further subdivision of heterogeneous stage IV may be of interest in the future. In this context, Abdel-Rahman [27] and Libé et al. [28] proposed to subdivide stage IV into stages IVA and IVB, depending on the number of organs involved or distant metastases.

Furthermore, there is consensus that additional factors such as resection margins [29, 30], other histopathologic findings [28, 31, 32], hormonal activity [33], or age [34] should be taken into account in the future to achieve better risk stratification for recurrence and to estimate prognosis. Since several studies have previously demonstrated an association between the Ki67 labeling



▶ **Fig. 3** ROC curves and the corresponding AUC values for the respective TNM classification. The ROC curves were generated for the (**a**) 1-year, (**b**) 3-year, and (**c**) 5-year CSS according to the TNM classification of the 7th and 8th edition and the revised version as indicated and (**d**) the associated AUC values were determined and compared. *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.

index or mitotic rate and survival in ACC patients [2, 31, 32, 35], it may also be useful to include the mitotic index and other factors in a multivariable classification system [28, 36]. In this context, a comprehensive score was developed in 2015 that combines prognostic parameters such as tumor grade (G), resection status (R), age (A), and symptoms (S) into a single prognostic tool, the GRAS score, with a higher GRAS score associated with worse outcomes [37]. Recently, the ENSAT score has also been incorporated into the GRAS score, which is now called S-GRAS [38]. Compared with ENSAT staging and the Ki67 index, the S-GRAS score was shown to have better prognostic discrimination for both DSS and progression-free survival (PFS). Of note, the ENSAT stage is weighted higher compared to the other components of the S-GRAS score and has a stronger impact on PFS and DSS when calculating the score. However, in the S-GRAS score, ENSAT stages 1 and 2 are combined and scored as 0, whereas stages 3 and 4 are assessed separately with 1 and 2 points, respectively. It would therefore be interesting to investigate to what extent a redefinition of stages 1 and 2 and an adjustment of the S-GRAS score, especially with regard to the scoring of stages 1 and 2, could have an impact on the prognostic role of the S-GRAS and thus on the prediction of recurrence and response to mitotane therapy, and whether this could help to offer a new, improved treatment strategy to operated ACC patients [38].

ACC has a high risk of recurrence of approximately 60–80 percent despite complete tumor resection [39]. However, the evidence for adjuvant therapy is limited, with only a few data from randomized trials, and it is unclear whether patients at low risk of recurrence benefit in particular. Since 2007, mitotane has been considered the main chemotherapeutic agent for the treatment of ACC not only in advanced but also in the adjuvant setting [39, 40]. Initially, all patients received adjuvant mitotane as standard of care with the expectation of improving both overall survival (OS) and DSS [40]. However, due to the relevant spectrum of side effects, mitotane therapy has been increasingly questioned and investigated in several trials [41]. The first international randomized adjuvant trial, ADIUVO, compared the effect of adjuvant mitotane therapy versus active surveillance in a total of 91 patients with completely resected ACC and low or intermediate risk of recurrence (stage I–III, R0, Ki-67 ≤ 10 %) over a 10-year period. There was no significant difference in the primary endpoint of recurrence-free survival (RFS) or OS. The results suggest that mitotane should not be routinely administered to all patients to avoid potentially toxic treatment effects in these patients [39]. In this context, it would also be interesting to investigate the role of radiotherapy in adjuvant treatment according to tumor stage and prognostic assessment in randomized trials. Evidence suggests that patients with microscopic or macroscopic incomplete resection without evidence of distant

▶ **Table 3** Multivariate Cox regression analysis.

	HR	95% CI	p-Value	HR	95% CI	p-Value	HR	95% CI	p-Value
UICC/AJCC 7th edition									
I	Reference								
II	1.030	0.630–1.684	0.906						
III	2.015	1.217–3.336	*0.006*						
IV	3.727	2.315–6.001	*<0.0001*						
UICC/AJCC 8th edition									
I				Reference					
II				1.012	0.620–1.654	0.961			
III				2.165	1.334–3.515	*0.002*			
IV				4.712	2.897–7.664	*<0.0001*			
UICC/AJCC revised									
I							Reference		
II							1.428	1.011–2.016	*0.043*
III							2.570	1.890–3.494	*<0.0001*
IV							5.600	4.068–7.707	*<0.0001*
Therapy									
Not performed/recommended	Reference			Reference			Reference		
Surgery	0.150	0.108–0.209	*<0.0001*	0.173	0.124–0.243	*<0.0001*	0.174	0.124–0.243	*<0.0001*
Chemotherapy/Radiation alone	0.428	0.293–0.626	*<0.0001*	0.397	0.271–0.580	*<0.0001*	0.397	0.272–0.581	*<0.0001*
Laterality									
Left	Reference			Reference			Reference		
Right	1.024	0.854–1.228	0.798	1.045	0.872–1.252	0.634	0.980	0.811–1.184	0.535
Race									
White	Reference			Reference			Reference		
Black	0.799	0.565–1.129	0.203	0.801	0.566–1.132	0.209	0.801	0.567–1.133	0.210
American Indian/Alaska Native	1.070	0.264–4.332	0.925	0.920	0.228–3.711	0.906	0.915	0.227–3.692	0.901
Asian or Pacific Islander	0.851	0.578–1.253	0.415	0.833	0.566–1.227	0.356	0.830	0.563–1.222	0.344
Sex									
Female	Reference			Reference			Reference		
Male	1.010	0.835–1.220	0.922	0.990	0.819–1.196	0.913	0.980	0.811–1.184	0.832
Marital status									
Separated/Divorced/Widowed	Reference			Reference			Reference		
Married/Domestic partner	0.834	0.654–1.062	0.140	0.896	0.704–1.142	0.377	0.900	0.706–1.147	0.395
Single	0.860	0.633–1.168	0.333	0.911	0.671–1.236	0.548	0.923	0.680–1.253	0.609
Age	1.010	1.003–1.017	*0.004*	1.012	1.005–1.018	*0.001*	1.012	1.005–1.019	*<0.0001*

CI: Confidence interval; HR: Hazard ratio

metastases may benefit from radiotherapy, although randomized trials focusing on these specific subgroups are lacking [39].

However, when interpreting our data, we must acknowledge that our study may be limited by the inevitable limitations of a retrospective database analysis, such as bias due to unrecorded reasons for not receiving treatment and limitations due to missing variables or data. In addition, information on patients' comorbidities is lacking and coding reliability may vary. Although the SEER database is an excellent cancer registry with high reliability due to strict quality assurance and continuous updating, other prognostically relevant information such as resection status (R), hormone secretion status, tumor grading and mitotic index, as well as molecular pathology markers are not available for further analysis. Although our sample size appears relatively small compared with other database analyses, it is important to note that our study cohort of 935 patients is larger than most previous studies of ACC.

With the update of the staging system by the ENSAT consortium, the prediction of CSS has been significantly improved. In addition, the redefinition of T1 and T2 in this study resulted in a better distribution of the patient cohort and a more accurate distinction of CSS between stages I and II. In particular, the 3-year and 5-year survival rates are better differentiated in our proposed version compared to the established TNM classification systems.

Conclusion

The revised TNM classification for this rare tumor entity presented in this study proved to be effective and reliable. Already the update of the staging system by the ENSAT consortium improved the prediction of CSS. In addition, the redefinition of T1 and T2 in this study resulted in a more accurate distribution of the patient population and a more precise distinction of CSS between stages I and II. In particular, the 3-year and 5-year survival rates are more precise in our proposed version compared to the established TNM classification systems.

We propose to stratify these patients into different subgroups requiring different therapies according to their individual risk of recurrence. Furthermore, the establishment of prospectively validated prognostic risk calculators and the use of molecular profiling of ACC to accurately estimate the risk of recurrence, especially to guide adjuvant therapy, seems reasonable. However, the question of whether improved prognostic assessment leads to a change in treatment options needs to be addressed in future prospective studies. In addition, the extent to which the integration of additional potentially prognostic criteria into our proposed TNM staging system can improve the prognostic assessment of patients with ACC deserves further evaluation.

Author Contributions

Conceptualization, S.K., and A.K.; methodology, S.K., and A.K.; software, S.K., and A.K.; validation, S.D., S.K., I.E., M.S., F.L.G., S.H.L, C.R., T.L., W.T.K., and A.K; investigation, S.D., S.K., and A.K.; resources, S.D., S.K., I.E., M.S., F.L.G., S.H.L, C.R., T.L., W.T.K., and A.K.; data curation, A.K.; writing—original draft preparation, S.D., S.K., and A.K.; writing – review and editing, S.D., S.K., I.E., M.S., F.L.G., S.H.L, C.R., T.L, W.T.K., and A.K.; visualization, S.D., S.K., and A.K.; supervision, W.T.K., and A.K.; project administration, T.L., W.T.K., and A.K. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

Ethical review and approval were waived for this study, due to the data being publicly available and anonymous.

Informed Consent Statement

Patient consent was waived due to the data being publicly available and anonymous.

Data Availability Statement

All data relevant to the study are included in the article and can be accessed and analyzed via the SEER*Stat software after submitting a request for access to the SEER Research Plus database.

Conflict of Interest

The authors declare that they have no conflict of interest.

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