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The European Network for the Study of Adrenal Tumors staging system is prognostically superior to the international union against cancer-staging system: A North American validation

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ABSTRACT

Background: A reclassification of the International Union Against Cancer (UICC) staging system for adrenocortical carcinoma (ACC) patients has recently been proposed by the European Network for the Study of Adrenal Tumors (ENSAT) to better discriminate between cancer-specific mortality (CSM) risk strata. We formally tested the validity of the modified staging system in a large North American population-based cohort.

Methods: Kaplan–Meier survival curves depicted CSM rates in the overall population and after stratification according to the 2004 UICC or the 2008 ENSAT-staging system. Cox regression models addressing CSM tested the prognostic value of respectively the UICC or the ENSAT-staging system. Harrell's concordance index quantified the accuracy of the standard versus the modified staging system.

Results: In the overall population ($n = 573$), the CSM-free survival rates at 1, 3, and 5 years were, respectively, 62.9%, 47.0%, and 38.1%. No statistically significant differences in survival were recorded between 2004 UICC stages II and III patients ($p = 0.1$). Conversely, a statistically significant difference was observed between 2008 ENSAT stage II and stage III patients ($p < 0.001$). The 2008 ENSAT-staging system showed higher accuracy (83.0%) in predicting 3-year CSM rates, relative to the 2004 UICC-staging system (79.5%) ($p < 0.001$).

Conclusion: Our study corroborates the superior accuracy of the ENSAT-staging system for ACC relative to the 2004 UICC-staging system. In consequence, the 2008 ENSAT-staging system may warrant consideration in the next update of staging manuals.

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1. Introduction

Adrenocortical carcinoma (ACC) is a rare solid tumour, with an estimated incidence of 0.5–2.0 per million population.[1–3] ACC is characterised by a poor prognosis, with 5-year cancer-specific mortality (CSM) free survival rates between 16% and 38%.[1,3,4] The prognostic stratification of patients with ACC is crucial, since the survival of those patients may be very different.[2,3,5–7] To date, only tumour stage has been consistently found as an independent predictor of CSM.[6–14] Nonetheless, other variables, such as patient age,[7,8,12] type of treatment[9,10,12,13] and tumour grade[7,11,13] emerged as CSM predictors in select studies.

The first tumour, node and metastasis (TNM) classification was proposed in 2004 by the International Union Against Cancer (UICC).[15] This scheme was largely based on the classification systems proposed by Macfarlane[16] and Sullivan.[17] It classifies tumours $\leqslant$ 5 centimeters (cm) as stage I ($T_1N_0M_0$) and tumours > 5 cm as stage II ($T_2N_0M_0$) if these do not fulfill the criteria for stages III and IV. Stage III ACC infiltrates the surrounding adipose tissue ($T_3N_0M_0$) or invades at least one lymph node ($T_{1-2}N_1M_0$). Stage IV ACC indicates infiltration of surrounding adipose tissue and at least one positive lymph node ($T_3N_1M_0$), tumour invasion into adjacent organs ($T_4N_{0-1}M_0$) or the presence of distant metastases ($T_{1-4}N_{0-1}M_1$) (Table 1).

Recently, Fasschnat et al. showed that the stratification based on the 2004 UICC-staging system failed to accurately discriminate between the prognoses of stages II and III patients.[18] To circumvent this limitation, the European Network for the Study of Adrenal Tumors (ENSAT) proposed a modification of the 2004 UICC-staging system.[18] The derived 2008 ENSAT-staging system reclassified stage III and stage IV ACC.[18] The 2008 ENSAT stage III denotes the presence of nodal metastases, irrespective of T stage ($T_{1-4}N_1M_0$), or tumour extension into surrounding adipose tissue, or invasion of adjacent organs ($T_{3-4}N_0M_0$). Conversely, the 2008 ENSAT stage IV ACC only includes tumours with established distant metastases ($T_{1-4}N_{0-1}M_1$) (Table 1).

Table 1 – Comparison between the 2004 UICC-staging system and the 2008 ENSAT-staging system for adrenocortical carcinoma.

Stage	2004 UICC-staging system	2008 ENSAT-staging system
I	$T_1N_0M_0$	$T_1N_0M_0$
II	$T_2N_0M_0$	$T_2N_0M_0$
III	$T_{1-2}N_1M_0$	$T_{1-2}N_1M_0$
	$T_3N_0M_0$	$T_{3-4}N_{0-1}M_0$
IV	$T_{1-4}N_{0-1}M_1$	$T_{1-4}N_{0-1}M_1$
	$T_3N_1M_0$	
	$T_4N_{0-1}M_0$	

UICC: International Union Against Cancer; ENSAT: European Network for the Study of Adrenal Tumors; T_1: tumour $\leqslant$ 5cm; T_2: tumour > 5 cm; T_3: tumour infiltration into surrounding adipose tissue; T_4: tumour invasion into adjacent organs; N_0: absence of positive lymph nodes; N_1: at least one positive lymph node; M_0: absence of distant metastases and M_1: presence of distant metastases.

Although the prognostic discrimination was better when the ENSAT cohort was used for a head-to-head comparison of the modified ENSAT versus the standard 2004 UICC-staging system, no external validation has been performed to prove the value of the 2008 ENSAT-staging system in an independent cohort. To address this limitation, we formally tested the prognostic ability of the 2008 ENSAT-staging system using Harrell's concordance index (c-index) and we compared it with the 2004 UICC-staging system.

2. Materials and methods

2.1. Study population

Within 16 Surveillance, Epidemiology and End Results (SEER) registries, patients with ACC were identified using the International Classification of Diseases for Oncology codes (second and third edition). Specifically, primary tumour location codes (ICD-O-2 C74.0 and C74.9 codes) and histology codes (ICD-O-3: 8010, 8140 and 8370) were used for patients diagnosed between the years 1988 and 2006,[19] which resulted in the identification of 1206 patients affected by adrenocortical carcinoma. The 16 SEER registries include the Atlanta, Detroit, San Francisco-Oakland, Seattle-Puget Sound, San Jose-Monterey and Los Angeles metropolitan areas, as well as the states of Connecticut, Hawaii, Iowa, New Mexico, Utah, Georgia, California, Kentucky, Louisiana and New Jersey. The characteristics of the SEER population are comparable to the general population of the United States.[19]

Patients younger than 18-years of age at the time of ACC diagnosis were excluded from the current analysis ($n = 50$). Further exclusions consisted of patients with unknown tumour size ($n = 292$), unknown TNM classification ($n = 442$) and unknown treatment type ($n = 3$) for a total of 633 patients excluded. These criteria resulted in 406 surgically treated and 167 non-surgically managed ACC patients. Subsequently, patients were grouped into stages according to the 2004 UICC-staging system, as well as according to the 2008 ENSAT-staging system (Table 1). The cause of death was defined according to SEER specific cause of death code (code 32020). For the purpose of this analysis, deaths from other causes were considered as censored events.

2.2. Statistical analysis

Kaplan–Meier survival curves depicted CSM rates in the overall population and after stratification according to either the UICC or the ENSAT classification. The log-rank test was used for comparison of CSM rates between different groups. The life-table method was used to determine CSM rates at 1, 2 and 5 years after diagnosis or surgery.

Cox regression models addressing CSM tested the prognostic value of, respectively, the UICC or the ENSAT-staging system (I–II versus III versus IV). Adjustment was made according to age, gender (male versus female), race (Caucasian versus Other), treatment type (surgery versus no surgery) and year of diagnosis. It is noteworthy that for UICC and ENSAT I and II stages, patients needed to be combined due to the rarity of stage I ($T_1N_0M_0$) disease ($n = 19$ in both staging schemes). Cox regression coefficients were first used to

quantify the univariable accuracy of either staging schemes in predicting 3-year CSM. Subsequently, multivariable Cox regression coefficients were used to quantify the 3-year prognostic ability of the two staging schemes in combination with all other covariables. Univariable and multivariable accuracy values were quantified according to Harrell's concordance index.[20] The latter represents a modification of the receiver operating characteristic (ROC) derived area under the curve (AUC), for time-to-event analyses that include censored events. In accuracy analyses, a value of 100% indicates perfect prediction versus 50% which is equivalent to the toss of a coin. The decision to test the prognostic ability of the variables in the prediction of 3-year CSM rates was based on the observation that approximately half (53.0%) of the cancer-related events occurred within 3 years following ACC treatment or diagnosis. The statistical significance of the differences between various accuracies was tested using the DeLong method for comparisons of related AUCs.[21] Additionally, we graphically explored the ability of the two staging systems in predicting 3-year CSM rates using the *val.prob* method. The latter allows testing the agreement between predicted and observed CSM rates within a plot, where a 45 degree line represents perfect correlation between predicted and observed survival.

All reported *p*-values are two-sided and statistical significance was set at $\leqslant 0.05$. Statistical analyses were performed with S-Plus Professional software (MathSoft Inc., Seattle, Washington).

3. Results

The study population consisted of 573 patients diagnosed with ACC between 1988 and 2006 within 16 SEER registries (Table 2). The majority was female (55.7%) and Caucasian (86.0%). The mean and median tumour size was 11.8 and 11.0 cm. Overall, 65.6%, 5.3% and 29.1% of patients were, respectively, treated with surgery only, surgery and adjuvant radiotherapy, and without surgery. The majority of patients (43.6%) were diagnosed in the most contemporary year tertile (2001–2006).

In the overall population, the CSM-free survival rates at 1, 3, and 5 years were, respectively, 62.9%, 47.0%, and 38.1% (Fig. 1). After stratification according to the UICC-staging system, the 5-year CSM-free survival rates were 73.9% versus 63.8% versus 57.1% versus 12.5% for, respectively, stages I ($n = 19$), II ($n = 182$), III ($n = 46$) and IV ($n = 326$) ACC (Fig. 2A). No statistically significant survival difference was recorded between UICC stages II and III patients (log-rank test: $p = 0.1$). Similarly, no statistically significant survival difference was recorded between UICC stages I and II ($p = 0.6$) and stages I and III patients ($p = 0.3$).

After stratification according to the 2008 ENSAT-staging system, the 5-year CSM-free survival rates were 73.9% versus 63.8% versus 44.1% versus 6.9% for, respectively, stages I ($n = 19$), II ($n = 182$), III ($n = 105$) and IV ($n = 267$) ACC (Fig. 2B). A statistically significant CSM difference was recorded between all disease stages (all log-rank tests: $p < 0.001$), except for the comparisons between ENSAT stages I and II ($p = 0.6$) and stages I and III patients ($p = 0.06$). It is noteworthy that only 19 stage I patients were available and 4 events occurred during follow-up.

Table 2 – Characteristics of the study population of patients diagnosed with adrenocortical carcinoma ($n = 573$) between 1988 and 2006 within 16 SEER registries.

Variables	Overall population ($n = 573$)
Age (years)	
Mean (median)	53.1 (54.0)
Range	18–93
Gender	
Male	254 (44.3%)
Female	319 (55.7%)
Race	
Caucasian	493 (86.0%)
Other	80 (14.0%)
Tumour size (cm)	
Mean (median)	11.8 (11.0)
Range	1–35
Treatment type	
Surgery only	376 (65.6%)
Surgery + radiotherapy	30 (5.3%)
No surgery	167 (29.1%)
Year of diagnosis	
1988–1994	143 (25.0%)
1995–2000	180 (31.4%)
2001–2006	250 (43.6%)
2004 UICC stage	
Stage I	19 (3.3%)
Stage II	182 (31.8%)
Stage III	46 (8.0%)
Stage IV	326 (56.9%)
2008 ENSAT stage	
Stage I	19 (3.3%)
Stage II	182 (31.8%)
Stage III	105 (18.3%)
Stage IV	267 (46.6%)
Cancer-specific mortality rates	
3 year	53.0%
5 year	61.9%

UICC: International Union Against Cancer and ENSAT: European Network for the Study of Adrenal Tumors.

In univariable Cox regression analyses, patients with UICC stages III and IV ACC were 1.5 ($p = 0.1$) and 5.6 times ($p < 0.001$) more likely to succumb to ACC than patients with stages I and II ACC (Table 3). Conversely, patients with ENSAT stages III and IV had a 1.9 and 7.7-fold higher CSM rate then patients with stages I and II ACC ($p < 0.001$) (Table 3). In multivariable Cox regression models, only tumour stage ($p < 0.001$) and surgical resection ($p < 0.001$) achieved independent predictor status. Specifically, patients who were treated non-surgically had a 2.2–2.8-fold higher CSM rate relative to their surgically treated counterparts ($p < 0.001$).

The univariable predictive accuracy of the 2004 UICC-staging system for 3-year CSM predictions was 79.5% versus 83.0% of the 2008 ENSAT-staging system (Fig. 3). The difference in accuracy between the two staging systems was statistically

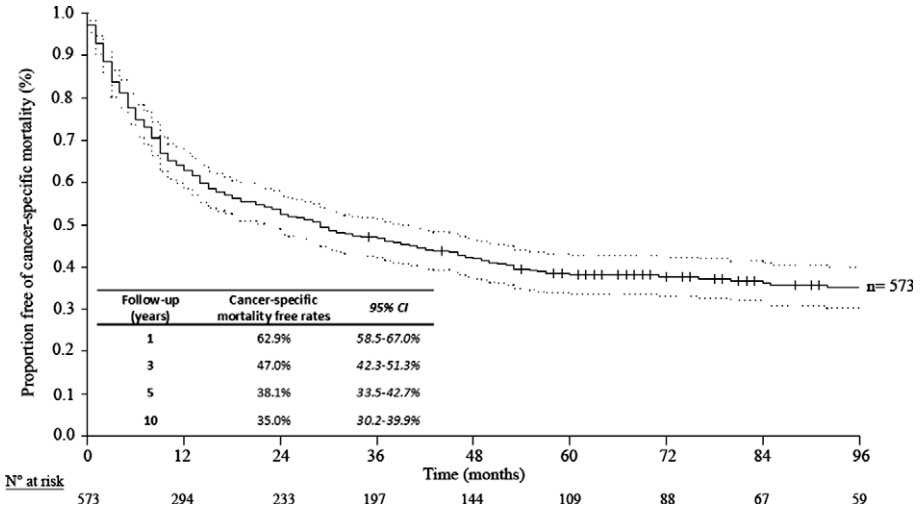

Fig. 1 – Kaplan–Meier plot depicting cancer-specific mortality rates in the overall population of ACC patients (n = 573).

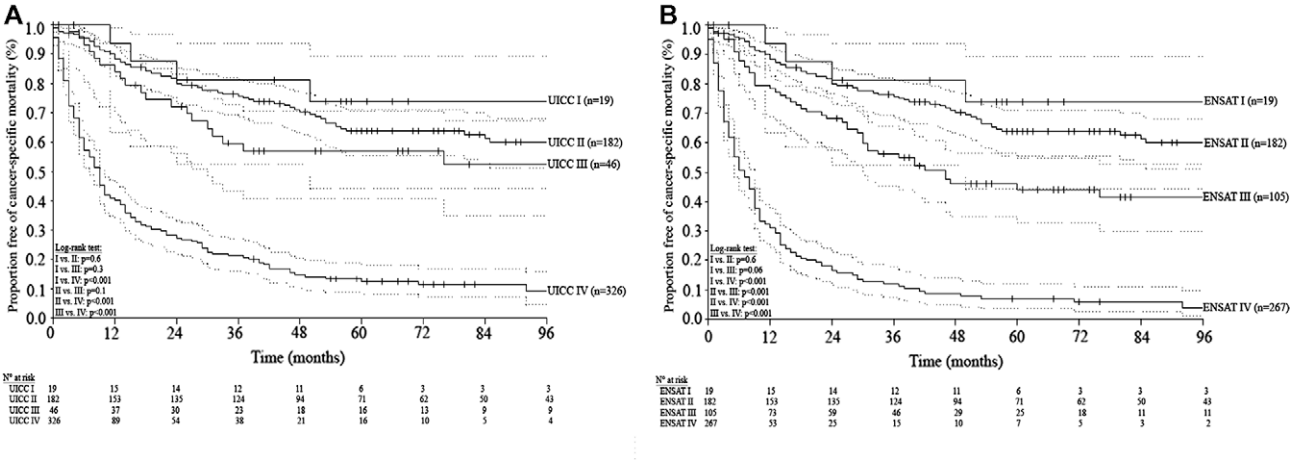

Fig. 2 – Kaplan–Meier plots depicting cancer-specific mortality rates after stratification according to the 2004 UICC-staging system (A), as well as according to the 2008 ENSAT-staging system (B).

significant according to the DeLong method for related AUCs ($p < 0.001$). Similarly, the accuracy of the multivariable model including the ENSAT-staging system (86.2%) was statistically significantly higher than the multivariable model that included the UICC-staging system (84.4%) ($p = 0.003$). Finally, the calibration plot for the 2004 UICC-staging system showed more important departures from ideal predictions than for the 2008 ENSAT-staging system (Fig. 3).

4. Discussion

Prognostication in any malignancy is important for initial treatment selection, adjuvant or salvage therapy, type and frequency of follow-up, as well as for the interest of the patients and the treating physicians.[22,23] In ACC, only two treatment modalities may affect the natural history of the disease. Surgery for patients with non-metastatic disease represents the mainstay therapy.[2–4,9,10,24–26] Those with locally advanced disease may benefit from adjuvant systemic mitotane.[25] Conversely, systemic therapy has little impact on metastatic, unresectable or incompletely resected (R1) disease.[8,27,28] Finally, the role of adjuvant or palliative radiotherapy in ACC treatment has not been extensively evaluated.[29,30] In consequence, the objective of prognostication in ACC is mainly to provide patients and their treating physicians with the most accurate estimates of remaining survival. Unfortunately, few prognostic schemes are capable of fulfilling this need. Until recently, only the 2004 UICC-staging system was capable of classifying the survival of individuals with ACC.[15]

Recently, Fassnacht et al. examined the ability of the 2004 UICC-staging system to discriminate between prognoses of stage I versus II versus III versus IV ACC patients.[18] Little discriminant ability existed when stages II and III were compared. Moreover, UICC stage IV individuals with peri-adrenal fat invasion and positive lymph nodes ($T_3N_1M_0$) or with invasion of adjacent viscera ($T_4N_{0-1}M_0$) fared significantly better than stage IV patients with distant metastases.[18] These two observations prompted a revision of stage groupings and re-

sulted in a proposal for a new staging system.[18] Within the new staging system, stages III and IV groupings were modified. The new stage III grouping resulted in the inclusion of patients with lymph node metastases, irrespective of T stage, and of patients with invasion of adjacent viscera.[18] Conversely, the new stage IV grouping resulted in the inclusion of only patients with distant metastases.[18]

The rationale behind this type of reclassification results from the observation that patients who represent surgical candidates and who may benefit from extensive resections, fare substantially better than individuals with distant metastases for whom this option can no longer be offered.[9,10] Despite the attractiveness of such hypothesis, to date no study confirmed the validity of the proposed ENSAT stage groupings.

In the current study, we hypothesised that the 2008 ENSAT-staging system may provide the same or better stratification than was reported by Fassnacht et al.[18] Since stratification of Kaplan–Meier curves only represents a subjective measure of discrimination, we complemented the assessment of the novel staging scheme with a formal measure of accuracy, namely Harrell's concordance index (c-index).[20] The latter provides a numeric value between 50% and 100%, where 50% is equivalent to the toss of a coin. Conversely, 100% represents perfect predictions. Since the assessment of one-staging scheme requires a comparison with an established benchmark, we tested the discriminant ability of the 2004 UICC-staging scheme using the same criteria, as for the novel (ENSAT)staging scheme. To complement the overall accuracy estimates, we also examined the calibration of predicted prognoses for both the ENSAT and the UICC-staging systems (Fig. 3). This step is equally important, since even highly accurate models may show poor calibration between predicted and observed survival.

Our results showed better stratification of the Kaplan–Meier survival curves when the 2008 ENSAT-staging scheme was used, relative to the 2004 UICC-staging system (Fig. 2). The reclassification of patients with stage III and stage IV offered a greater separation between patients with stage II and stage III. Additionally, patients with stage IV disease fared significantly worse in the new classification than in the original UICC-staging system. This is reflective of the exclusive grouping of individuals with distant metastases within this category. Better separation between patients of stages II and III

Table 3 – Cox regression analyses addressing cancer-specific mortality in the overall population of patients with adrenocortical carcinoma ($n = 573$). The area under the curve (AUC) reflects the prognostic value of individual variables (column), as well as of multivariable models in predicting cancer-specific mortality.

Predictors	Univariable analysis		Multivariable analysis with 2004 UICC stage	Multivariable analysis with 2008 ENSAT stage
	p-value HR (95% CI)	3-year AUC of individual predictor variables	*p*-value HR (95% CI)	*p*-value HR (95% CI)
2004 UICC stage	$p < 0.001$		$p < 0.001$	
Stages I and II (Referent)	1.0	79.5%[a]	1.0	–
Stage III	1.45 (0.9–2.4)		1.43 (0.9–2.4)	
Stage IV	5.58 (4.2–7.4)		4.51 (3.3–6.1)	
2008 ENSAT stage	$p < 0.001$			$p < 0.001$
Stages I and II (Referent)	1.0	83.0%[a]	–	1.0
Stage III	1.93 (1.3–2.8)			1.87 (1.3–2.7)
Stage IV	7.73 (5.7–10.4)			6.18 (4.5–8.5)
Surgical resection	$p < 0.001$	69.0%	$p < 0.001$	$p < 0.001$
Yes (Referent)	1.0		1.0	1.0
No	2.13 (1.9–2.4)		2.76 (2.1–3.6)	2.20 (1.6–2.9)
Gender	$p = 0.4$	52.6%	$p = 0.6$	$p = 0.5$
Female (Referent)	1.0		1.0	1.0
Male	1.09 (0.9–1.4)		0.94 (0.7–1.2)	1.08 (0.8–1.4)
Race	$p = 0.04$	53.2%	$p = 0.3$	$p = 0.4$
Caucasian (Referent)	1.0		1.0	1.0
Other	1.38 (1.0–1.9)		1.19 (0.9–1.6)	1.14 (0.8–1.6)
Age	$p = 0.04$		$p = 0.2$	$p = 0.1$
Continuously coded	1.01 (1.0–1.02)	58.7%	1.00 (0.9–1.01)	1.01 (0.9–1.01)
Year of diagnosis	$p = 0.9$	52.7%	$p = 0.07$	$p = 0.07$
Continuously coded	0.99 (0.9–1.02)		0.98 (0.9–1.0)	0.98 (0.9–1.0)
3-year AUC of multivariable models			84.4%[a]	86.2%[a]

AUC: area under the curve; HR: hazard ratio; CI: confidence intervals; UICC: International Union Against Cancer; and ENSAT: European Network for the Study of Adrenal Tumors.

[a] AUCs comparison using the DeLong method: $p \leqslant 0.003$.

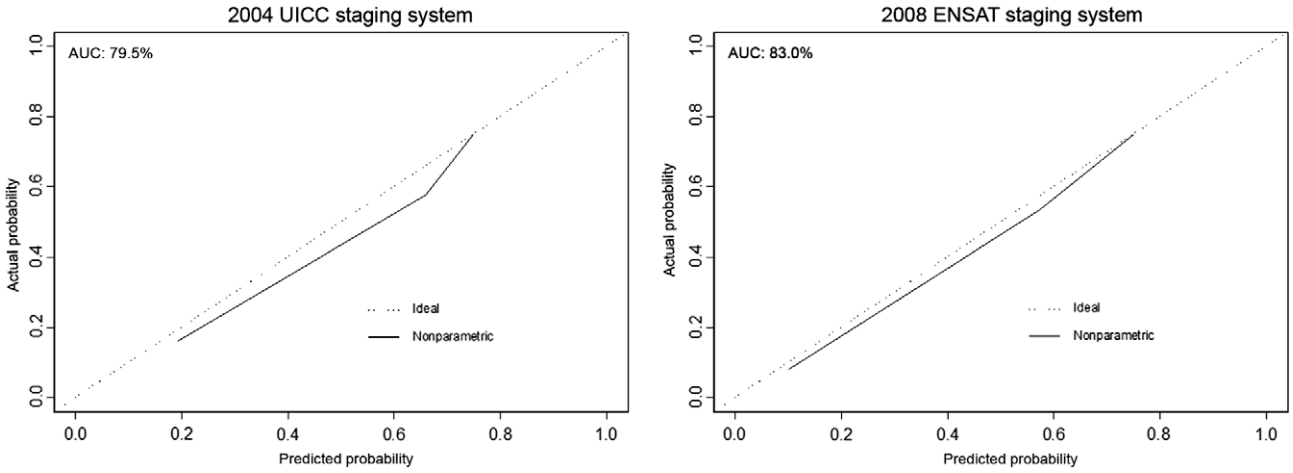

Fig. 3 – Calibration plots depicting the accuracy of the 2004 UICC and the 2008 ENSAT-staging systems in predicting cancer-specific mortality at 3 years after ACC diagnosis or treatment.

was related to the inclusion of individuals with peri-adrenal fat invasion and positive lymph nodes ($T_3N_1M_0$) or the inclusion of individuals with invasion of adjacent viscera ($T_4N_{0-1}M_0$) among stage III patients.

Accuracy tests confirmed the improved stratification observed in Kaplan–Meier plots. The univariable and multivariable accuracy tests showed that the 2008 ENSAT-staging scheme was, respectively, 3.5% and 1.8% more accurate than the 2004 UICC-staging scheme for 3-year CSM predictions (Table 3). This difference achieved statistical significance ($p \leqslant 0.003$). Moreover, the 2008 ENSAT-staging system showed better calibration relative to the 2004 UICC-staging system (Fig. 3).

It is noteworthy that among other covariates, only surgical treatment achieved independent predictor status ($p < 0.001$). Conversely, no differences in CSM rates were observed for patient gender, race and age. Similarly, more contemporary years of diagnosis were not associated with a statistically significant difference in CSM, which indicates the need for more effective therapies, especially in patients with advanced ACC stages.

Based on the appearance of the Kaplan–Meier curves, overall accuracy values and calibration properties, it appears that the ENSAT-staging scheme is better suited for prognostic stratification of ACC patients. In consequence, the ENSAT modifications may warrant consideration for adoption by the UICC in the next iteration of the TNM-staging system. This observation is based on two distinct populations. One stems from a contemporary European dataset.[18] The other, as described in the current study, originates from the largest North-American tumour registry, namely the SEER database. These two datasets represent the two biggest repositories of ACC patients and provide highly generalisable results.

One of the limitations of the current analysis consists of the paucity of stage I ($T_1N_0M_0$) ACC patients. Those individuals contributed only 3.3% of all ACC patients ($n = 16$). This limitation was also shared by the ENSAT population, where stage I patients contributed to only 5.5% ($n = 23$).[18] In consequence, it may be suggested that the original UISS and the ENSAT-proposed modification should also consider modifying the definition of stage I ACC. Lack of patients that qualify for inclusion into this category within the two largest ACC databases represent a valid argument to question the criteria for stage I patients. Lack of apparent discriminant ability of stage I ACC relative to stage II ACC is purely related to sample size limitations that are due to excessively narrow definition for this substage. In clinical practice, the existing evaluation and management criteria do not require treatment or work-up for adrenal masses less than 5 cm, unless such masses are associated with symptoms or have high intensity signal in T2 MRI imaging.[31,32]

Several other limitations of our study warrant mention. Due to the rarity of ACC, the sample size ($n = 487$) is relatively small when compared to other tumour types. Moreover, lack of information about the extent and the completeness of the surgical resection (R0 versus R1) represented other limitations. Finally, the SEER database does not provide any information regarding delivery of mitotane chemotherapy. This limitation is also shared with the Fassnacht et al. study.[18]

In conclusion, our findings corroborate the validity of the ENSAT modifications of the UICC-staging system for ACC. In consequence, these modifications may warrant consideration in the next update of the UICC-staging manual. Moreover, stage I may also necessitate a reappraisal, as very few patients qualify for inclusion in this category.

Conflict of interest statement

None declared.

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REFERENCES

1. Wajchenberg BL, Albergaria Pereira MA, Medonca BB, et al. Adrenocortical carcinoma: clinical and laboratory observations. *Cancer* 2000;**88**(4):711–36.
2. Ng L, Libertino JM. Adrenocortical carcinoma: diagnosis, evaluation and treatment. *J Urol* 2003;**169**(1):5–11.
3. Allolio B, Fassnacht M. Clinical review: adrenocortical carcinoma: clinical update. *J Clin Endocrinol Metab* 2006;**91**(6):2027–37.
4. Dackiw AP, Lee JE, Gagel RF, Evans DB. Adrenal cortical carcinoma. *World J Surg* 2001;**25**(7):914–26.
5. Vassilopoulou-Sellin R, Schultz PN. Adrenocortical carcinoma. Clinical outcome at the end of the 20th century. *Cancer* 2001;**92**(5):1113–21.
6. Paton BL, Novitsky YW, Zerey M, et al. Outcomes of adrenal cortical carcinoma in the United States. *Surgery* 2006;**140**(6):914–20 [discussion 9–20].
7. Bilimoria KY, Shen WT, Elaraj D, et al. Adrenocortical carcinoma in the United States: treatment utilization and prognostic factors. *Cancer* 2008;**113**(11):3130–6.
8. Luton JP, Cerdas S, Billaud L, et al. Clinical features of adrenocortical carcinoma, prognostic factors, and the effect of mitotane therapy. *New Engl J Med* 1990;**322**(17):1195–201.
9. Lee JE, Berger DH, el-Naggar AK, et al. Surgical management, DNA content, and patient survival in adrenal cortical carcinoma. *Surgery* 1995;**118**(6):1090–8.
10. Icard P, Goudet P, Charpenay C, et al. Adrenocortical carcinomas: surgical trends and results of a 253-patient series from the French Association of Endocrine Surgeons study group. *World J Surg* 2001;**25**(7):891–7.
11. Stojadinovic A, Ghossein RA, Hoos A, et al. Adrenocortical carcinoma: clinical, morphologic, and molecular characterization. *J Clin Oncol* 2002;**20**(4):941–50.
12. Abiven G, Coste J, Groussin L, et al. Clinical and biological features in the prognosis of adrenocortical cancer: poor outcome of cortisol-secreting tumors in a series of 202 consecutive patients. *J Clin Endocrinol Metab* 2006;**91**(7):2650–5.
13. Kebebew E, Reiff E, Duh QY, Clark OH, McMillan A. Extent of disease at presentation and outcome for adrenocortical carcinoma: have we made progress? *World J Surg* 2006;**30**(5):872–8.
14. Assie G, Antoni G, Tissier F, et al. Prognostic parameters of metastatic adrenocortical carcinoma. *J Clin Endocrinol Metab* 2007;**92**(1):148–54.
15. De Lellis RA, Lloyd RV, Heitz PU, Eng C. *Pathology and genetics of tumors of endocrine organs*. Lyon (France): IARC; 2004.
16. Mcfarlane DA. Cancer of the adrenal cortex: the natural history, prognosis and treatment in the study of fifty cases. *Ann R Coll Surg Engl* 1958;**109**:613–8.
17. Sullivan M, Boileau M, Hodges CV. Adrenal cortical carcinoma. *J Urol* 1978;**120**:660–5.
18. Fassnacht M, Johanssen S, Quinkler M, et al. Limited prognostic value of the 2004 International Union Against Cancer staging classification for adrenocortical carcinoma: proposal for a Revised TNM Classification. *Cancer* 2009;**115**(2):243–50.
19. Ries LAG MD, Krapcho M, et al. SEER Cancer Statistics Review, 1975–2004, National Cancer Institute. Bethesda, MD. <http://seer.cancer.gov/csr/1975-2004/>, based on November 2006 SEER data submission, posted to SEER website [last accessed: January 2007]. November.
20. Harrell Jr FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;**15**(4):361–87.
21. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;**44**(3):837–45.
22. Karakiewicz PI, Briganti A, Chun FK, et al. Multi-institutional validation of a new renal cancer-specific survival nomogram. *J Clin Oncol* 2007;**25**(11):1316–22.
23. Walz J, Gallina A, Saad F, et al. A nomogram predicting 10-year life expectancy in candidates for radical prostatectomy or radiotherapy for prostate cancer. *J Clin Oncol* 2007;**25**(24):3576–81.
24. Libe R, Fratticci A, Bertherat J. Adrenocortical cancer: pathophysiology and clinical management. *Endocr Relat Cancer* 2007;**14**(1):13–28.
25. Terzolo M, Angeli A, Fassnacht M, et al. Adjuvant mitotane treatment for adrenocortical carcinoma. *New Engl J Med* 2007;**356**(23):2372–80.
26. Schteingart DE, Doherty GM, Gauger PG, et al. Management of patients with adrenal cancer: recommendations of an international consensus conference. *Endocr Relat Cancer* 2005;**12**(3):667–80.
27. Abraham J, Bakke S, Rutt A, et al. A phase II trial of combination chemotherapy and surgical resection for the treatment of metastatic adrenocortical carcinoma: continuous infusion doxorubicin, vincristine, and etoposide with daily mitotane as a P-glycoprotein antagonist. *Cancer* 2002;**94**(9):2333–43.
28. Wooten MD, King DK. Adrenal cortical carcinoma. Epidemiology and treatment with mitotane and a review of the literature. *Cancer* 1993;**72**(11):3145–55.
29. Fassnacht M, Hahner S, Polat B, et al. Efficacy of adjuvant radiotherapy of the tumor bed on local recurrence of adrenocortical carcinoma. *J Clin Endocrinol Metab* 2006;**91**(11):4501–4.
30. Polat B, Fassnacht M, Pfreundner L, et al. Radiotherapy in adrenocortical carcinoma. *Cancer* 2009;**115**(13):2816–23.
31. Grumbach MM, Biller BM, Braunstein GD, et al. Management of the clinically inapparent adrenal mass ("incidentaloma"). *Ann Intern Med* 2003;**138**(5):424–9.
32. Reinig JW, Doppman JL, Dwyer AJ, Johnson AR, Knop RH. Adrenal masses differentiated by MR. *Radiology* 1986;**158**(1):81–4.