

# Limited Prognostic Value of the 2004 International Union Against Cancer Staging Classification for Adrenocortical Carcinoma

## Proposal for a Revised TNM Classification

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This study was part of the German Adrenal Network Improving Treatment and Medical Education (GANIMED) and the European Network for the Study of Adrenal Tumors (ENSAT).

We are grateful to all colleagues who provided clinical data for the German Adrenocortical Carcinoma (ACC) Registry. We also appreciate the support of Uwe Maeder (Tumor Center, University Hospital Würzburg) in establishing the German ACC Registry database, and we are thankful to Michaela Haaf for documentation.

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The following hospitals/clinicians contributed clinical data from 4 or more patients who were included in the current analysis: University Hospital Würzburg, University Hospital Charite Berlin, University Hospital Düsseldorf, University Hospital Heidelberg (Michael Morcos); University Hospital Lübeck (Horst L. Fehm); University Hospital Marburg (Peter Langer); University Hospital Hannover/Hospital Deggen-dorf (Matthias Behrend); University Hospital Mainz (Christian Fottner); University Hospital Munich (Nicole Reisch); University Hospital Halle (Michael Brauckhoff); University Hospital Cologne (Wiebke Artl); University Hospital Freiburg (Felix Beuschlein); University Hospital Leipzig (Dagmar Führer); Marienkrankenhaus Hamburg (Wolfgang Saeger); University Hospital Tübingen (Karsten Müssig); Leopoldina Hospital Schweinfurt (Heiko Denecke); University Hospital Essen (Stephan Petersenn); University Hospital Münster (Karin Hengst); and University Hospital Hamburg, University Hospital Homburg/Saar, and University Hospital Bonn.

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**Received:** July 7, 2008; **Accepted:** August 21, 2008

**Published online:** November 24, 2008, © 2008 American Cancer Society

**DOI:** 10.1002/cncr.24030, www.interscience.wiley.com

**BACKGROUND:** Adrenocortical carcinoma (ACC) is a rare malignancy, and it was only in 2004 that the International Union Against Cancer (UICC) defined TNM criteria and published the first staging classification. However, to date, the prognostic value of the proposed classification has not been evaluated. **METHODS:** The German ACC Registry comprising 492 patients was searched for patients who were diagnosed between 1986 and 2007 with detailed information on primary diagnosis and a minimum follow-up of 6 months. Patients were assigned to UICC tumor stage, and disease-specific survival (DSS) was assessed. In addition, the contribution of potential risk factors for DSS was evaluated. **RESULTS:** In total, 416 patients with a mean follow-up of 36 months met the inclusion criteria (stage I, n = 23 patients; stage II, n = 176 patients; stage III, n = 67 patients; stage IV, n = 150 patients). Kaplan-Meier analysis revealed a stage-dependent DSS. However, DSS in patients with stage II ACC did not differ significantly from DSS in patients with stage III ACC (hazard ratio, 1.38; 95% confidence interval, 0.89-2.16). Furthermore, patients who had stage IV ACC without distant metastases had an improved DSS compared with patients who had metastatic disease ( $P = .004$ ). An analysis of different potential risk factors for defining stage III ACC revealed important roles in DSS for tumor infiltration in surrounding tissue, venous tumor thrombus (VTT), and positive lymph nodes; whereas tumor invasion in adjacent organs carried a prognosis similar to that of infiltration in surrounding tissue only. **CONCLUSIONS:** The 2004 UICC staging classification for ACC has significant limitations. On the basis of the current analysis, a revised classification with superior prognostic accuracy is proposed (the European Network for the Study of Adrenal Tumors classification). In this system, stage III ACC is defined by the presence of positive lymph nodes, infiltration of surrounding tissue, or VTT; and stage IV ACC is restricted to patients with distant metastasis. **Cancer 2009;115:243-50. © 2009 American Cancer Society.**

**KEY WORDS:** adrenal cancer, tumor staging, disease-specific outcome, prognosis.

**Adrenocortical** carcinoma (ACC) is a rare malignancy with an estimated annual incidence of only 0.5 to 2.0 per million population.<sup>1-4</sup> Accordingly, research in ACC is severely hampered; and, to date, reliable prognostic factors apart from tumor staging have not been firmly established.<sup>5-9</sup> However, in the past, different staging systems have been used<sup>4,10-14</sup> and none of them reached general acceptance.

The codification of staging systems has been a key process in oncology because of the related relevance and the associated treatment strategies. The tumor, lymph node, and metastasis (TNM) classification system proposed by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer is the most widely used classification to assess the local extension of the primary tumor, lymph node involvement, and the presence of distant metastasis. The purpose of this classification is to provide a powerful prognostic tool for predicting both disease-free and disease-specific survival in patients with cancer.

Since its first edition in 1968, TNM status has been a relevant outcome predictor in most tumor entities. However, it was only in 2004 that the UICC and the World Health Organization published the first staging classification based on TNM criteria for ACC.<sup>15</sup> This classification was based largely on earlier classification systems proposed

by Macfarlane<sup>10</sup> and the later modification by Sullivan et al.<sup>11</sup> It categorizes tumors  $\leq 5$ cm as stage I (T1N0M0) and tumors  $> 5$ cm as stage II (T2N0M0) if they do not fulfill criteria for stage III and IV. Criteria for stage III are tumor infiltration in the surrounding adipose tissue (T3) or at least 1 positive lymph node (N1), and criteria for stage IV are tumor infiltration into surrounding tissue and positive lymph nodes (T3N1), tumor invasion into adjacent organs (T4), or the presence of distant metastasis (M1) (Table 1). However, the prognostic value of the proposed UICC classification remains to be established.

Because of the rarity of ACC, large cohorts of patients for evaluation of staging systems are not readily available.<sup>13,14,16-20</sup> The largest series stems from the National Cancer Institute's Surveillance, Epidemiology, and End Results database, which includes 725 patients who were diagnosed between 1973 and 2000 in the US.<sup>4</sup> However, clinical information and follow-up data are rather limited in this cohort. The largest series of patients with ACC with more detailed clinical information comprised 253 patients collected between 1978 and 1997 in France<sup>14</sup>; and, more recently, a series of 202 patients from a single French center was reported.<sup>20</sup>

In 2003, the German ACC Registry was initiated with the objective of collecting well documented patients

**Table 1.** Staging System for Adrenocortical Carcinoma Proposed by the International Union Against Cancer in 2004

Stage	UICC/WHO 2004
I	T1, N0, M0
II	T2, N0, M0
III	T1-T2, N1, M0
IV	T3, N0, M0
	T1-T4, N0-N1, M1
	T3, N1, M0
	T4, N0-N1, M0

UICC indicates International Union Against Cancer; WHO, World Health Organization; T1, tumor  $\leq 5$  cm; T2, tumor  $> 5$  cm; T3, tumor infiltration into surrounding tissue; T4, tumor invasion into adjacent organs; N0, no positive lymph nodes; N1, positive lymph node(s); M0, no distant metastases; M1, presence of distant metastasis.

with ACC.<sup>21</sup> In this report, we have used the data from that registry to evaluate the prognostic value of the proposed UICC classification for ACC. Furthermore, based on the limitations of the current UICC classification evident from this analysis, we have used the German ACC Registry cohort to identify relevant prognostic factors. Consequently, we propose a revised TNM classification.

## MATERIALS AND METHODS

### *German Adrenocortical Carcinoma Registry*

The German ACC Registry was established in 2003 to characterize better the clinical course and the outcome of this disease in Germany. To this end, a structured evaluation form was developed to collect comprehensive information on diagnostic procedures, treatment, and follow-up. All "German Adrenal Network: Improving Medical Research and Education" (GAINMED) centers and the German Society of Pediatric Oncology Study Group for Malignant Endocrine Tumors in Childhood and Adolescence were contacted to include patients retroactively in this registry. In addition, a website (available at: [www.nebennierenkarzinom.de](http://www.nebennierenkarzinom.de) accessed on November 12, 2008) was created to provide all information required for patient enrollment. Starting in 2003, newly diagnosed patients were registered, and all registered patients were followed proactively.

Hospital reports, including copies of surgical and pathologic, reports were used as a data source. Participat-

ing physicians and patients were asked to provide follow-up information at the time of any relevant change in the course of the disease at least every 6 months. All data were entered into the database by trained medical personnel. The German ACC Registry is approved by the Ethics Committee at the University of Wurzburg, Germany, and all patients provided written informed consent.

### *Evaluation of the 2004 International Union Against Cancer Staging Classification for Adrenocortical Carcinoma*

The study was performed as prospective cohort study. To be included in the analysis, patients had to fulfill the following criteria: primary diagnosis between 1986 and 2007, detailed information on primary diagnosis (including information regarding tumor size, tumor infiltration into the surrounding tissue, lymph nodes status, tumor thrombus in the vena cava or renal vein, and distant metastasis) and sufficient follow-up data. The database was closed in March 2008 and contained 492 patients with ACC. Twenty-nine patients were excluded because of a primary diagnosis before 1986 ( $n = 16$  patients) or after October 2007 ( $n = 13$  patients), because it was judged that the quality of staging was not reliable before 1986, and a minimum follow-up of 6 months was considered necessary (unless the patient had died within 6 months). Thirty-one patients were excluded because of a lack of sufficient follow-up data. In 16 patients, detailed information on the diagnostic procedures at the time of primary diagnosis was missing. Therefore, in total, 416 patients were included for the analysis comprising 2186 follow-up datasets (median, 4 follow-up datasets per patient; range, 1-26 follow-up datasets per patient). Each patient was assigned to 1 of the 4 UICC tumor stages (see Table 1), and disease-specific survival was assessed by Kaplan-Meier analysis.

### *Analysis of Stage III Risk Factors*

Different criteria for stage III have been used in different patient cohorts.<sup>10-12,14,15</sup> However, the contribution of these different criteria for survival remains uncertain. Therefore, we analyzed the impact of the following potential risk factors on disease-specific survival: positive lymph

**Table 2.** Characteristics of the Patients at the Time of Primary Diagnosis (n = 416)

Characteristic	No. of Patients (%)
Mean $\pm$ SD age, y	46.7 $\pm$ 19.3
<b>Sex</b>	
Men	155 (37.3)
Women	261 (62.7)
Median tumor size [range], cm	11.3 [2.3-40]
Infiltration in surrounding tissue	138
Invasion in adjacent organs	50
Positive lymph node(s)	62
Tumor (thrombus) in vena cava or renal vein	58
<b>Distant metastases</b>	122
Lung	79
Liver	55
Bone	22
Others	18

SD indicates standard deviation.

nodes, infiltration in surrounding adipose tissue, invasion into adjacent organs, and tumors with venous tumor thrombus (VTT) in the renal vein or the vena cava. The role of each of these factors was analyzed separately by using patient groups that had only 1 of these factors. Patients without any of these risk factors and without distant metastases served as comparator group (n = 178 patients).

### **Evaluation of a New Staging Classification for Adrenocortical Carcinoma**

On the basis of the analysis of risk factors for stage III, a new staging classification for ACC was developed and analyzed in a fashion similar to that used for the evaluation of the UICC staging classification.

### **Statistical Methods**

Continuous parametric variables were reported as mean values  $\pm$  standard deviation. Continuous nonparametric variables were presented as the median values and range. Disease-specific survival was defined as the time elapsed from primary diagnosis to death because of ACC. Patients who were alive or who had died of other causes were censored. The Kaplan-Meier method was used to estimate survival functions with confidence intervals (CI), and differences were assessed with the log-rank statistic. Univariate

survival analysis and hazard ratios (HR) were calculated by using a Cox proportional-hazards regression model. Descriptive *P* values were provided for the assessment of differences between indicated groups of patients. Data were analyzed using the Statistical Package for Social Sciences version 15.0 (SPSS Inc., Chicago, Ill).

## **RESULTS**

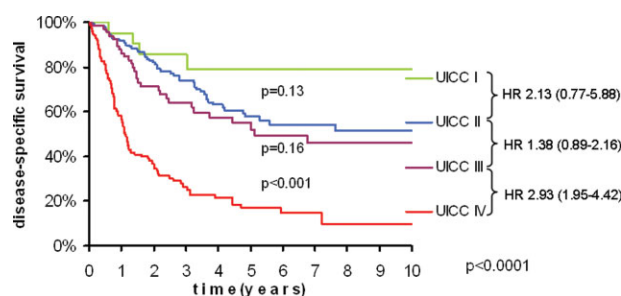
### **Evaluation of the 2004 International Union Against Cancer Staging Classification for Adrenocortical Carcinoma**

In total, 416 patients with ACC who met all inclusion criteria were included in the final analysis, as described in detail above. Patient's characteristics are listed in Table 2. One hundred ninety-three patients (46.4%) died of ACC, 10 patients (2.4%) died of other causes, and 213 patients were alive at the last follow-up. The average follow-up for the entire cohort was 36 months (median, 22 months; range, 0-247 months), the average follow-up for the patients who remained alive was 48 months (median, 32 months; range, 6-247 months). The median disease-specific survival was 46 months (95% CI, 34-58 months).

Survival analysis revealed a stage-dependent disease-specific survival (Fig. 1) with a 5-year disease-specific survival of 82% (95% CI, 69%-99%) for stage I, 58% (95% CI, 49%-68%) for stage II, 55% (95% CI, 42%-68%) for stage III, and 18% (95% CI, 10%-26%) for stage IV. However, survival for patients with UICC stage II disease did not differ significantly from survival for patients with stage I disease (*P* = .13) and stage III disease (*P* = .16). It is noteworthy that 3 of 4 patients with stage I disease who died of ACC suffered tumor spillage during surgery. If those 3 patients were excluded from the analysis, then the disease-specific survival for patients with stage I disease was significantly better than that for patients with stage II disease (*P* = .012).

### **Analysis of Stage IV Patients**

In the past, several authors suggested using distant metastases as the only criterion for stage IV.<sup>12,14</sup> Therefore, we also analyzed patients with UICC stage IV disease depending on the presence or absence of distant metastases. Figure 2 shows that patients without distant



**FIGURE 1.** Disease-specific survival stratified according to the 2004 International Union Against Cancer (UICC) staging classification for adrenocortical carcinoma (ACC). Disease-specific survival was defined as the time elapsed from primary diagnosis to death from ACC. Patients who were alive or who had died of other causes were censored. Four hundred sixteen patients were analyzed (stage I: n = 23 patients, 4 deaths, 19 censored; stage II: n = 176 patients, 55 deaths, 121 censored; stage III: n = 67 patients, 31 deaths, 34 censored; stage IV: n = 150 patients, 103 deaths, 47 censored). HR indicates estimated hazard ratio (95% confidence intervals are indicated in parentheses); *P*, log-rank *P* value assessing differences.

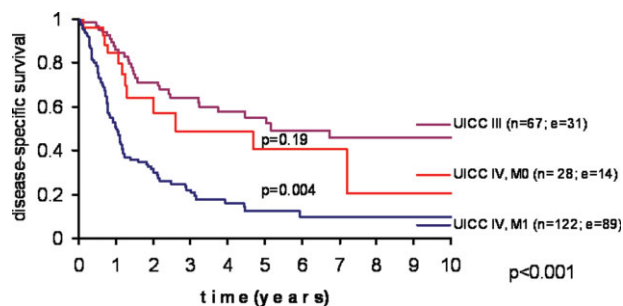
metastases (n = 27 patients) had considerably better survival than patients with distant metastases (n = 121 patients; HR, 0.44; 95% CI, 0.25-0.78; *P* = .004). In contrast, survival among patients who had UICC stage IV disease without distant metastases did not differ significantly from that of patients who had UICC stage III disease (*P* = .19) (Fig. 2).

### Analysis of Stage III Risk Factors

The clinical outcome of patients with either a positive lymph node (HR, 2.5; 95% CI, 1.2-5.7), or tumor infiltrating surrounding tissue (HR, 1.9; 95% CI, 1.2-3.0), or VTT in the large veins (HR, 2.7; 95% CI, 1.2-6.0) was significantly worse than the outcome of patients without any of these risk factors (Fig. 3a-c). However, in patients who had tumors infiltrating surrounding tissue (n = 56 patients), the criterion of invasion into adjacent organs did not have additional discriminative value (HR, 0.90; 95% CI, 0.34-2.41) (Fig. 3d).

### Proposal for a New Staging Classification for Adrenocortical Carcinoma

On the basis of these results, the following staging system was derived (Table 3): stage I, tumor size  $\leq 5$  cm without any risk factor (T1N0M0); stage II, tumor size  $> 5$  cm but

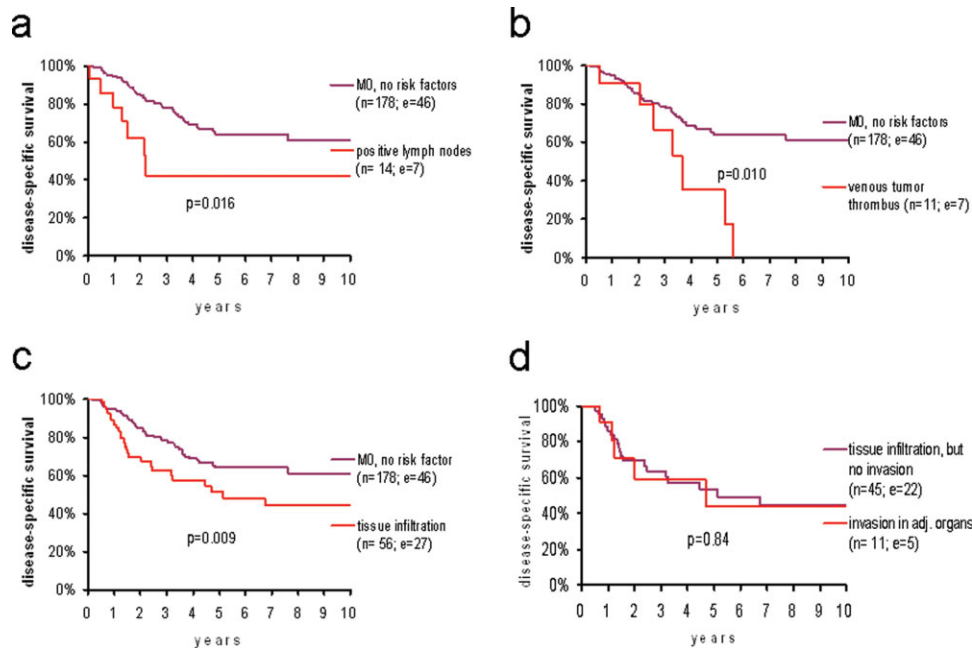


**FIGURE 2.** Disease-specific survival in patients with 2004 International Union Against Cancer (UICC) stage IV adrenocortical carcinoma (ACC) stratified according to the presence (M1) or absence (M0) of distant metastases and stage III ACC. *P* values were calculated with log-rank statistic. N indicates the number of patients per group; e, events (the number of patients who died of ACC).

still without risk factors (T2N0M0); stage III, tumor of any size with at least 1 of the following factors: tumor infiltration in surrounding tissue (T3), tumor invasion into adjacent organs or VTT in the vena cava or renal vein (T4), positive lymph node (N1), but no distant metastasis (M0); stage IV, the presence of distant metastases irrespective of tumor size or lymph node status (T1-T4N0-N1M1). By using our revised staging system (the European Network for the Study of Adrenal Tumors [ENSAT] classification) the 5-year disease-specific survival rate in this cohort was 82% (95% CI, 69%-99%) for stage I, 61% (95% CI, 51%-69%) for stage II, 50% (95% CI, 39%-61%) for stage III, and 13% (95% CI, 5%-21%) for stage IV. These data indicate improved outcome prediction compared with the 2004 UICC classification, because disease-specific survival now differs considerably between stage II and stage III (Fig. 4). When excluding the 3 patients who had stage I disease with intraoperative tumor spillage, again, the survival of patients with stage I disease is significantly better than that of patients with stage II disease (*P* = .027).

## DISCUSSION

Tumor staging based on the TNM classification is a dynamic process that aims at the optimum prediction of cancer-specific survival. Accordingly, for many tumor entities, the TNM system has been modified continuously to improve its accuracy. Therefore, it is to be expected that the first UICC staging system for ACC proposed in 2004 may need modification to achieve maximum



**FIGURE 3.** Analysis of the following potential risk factors defining stage III adrenocortical carcinoma (ACC): (a) positive lymph node(s), (b) tumors with venous tumor thrombus in the renal vein or the vena cava, (c) infiltration in surrounding adipose tissue, and (d) invasion in adjacent organs. The role of each of these factors was analyzed separately by using patient groups that harbored only 1 of these factors. Patients without any of these risk factors and without distant metastases served as comparator group (n = 178). N indicates the number of patients per group; e, events (the number of patients who died of ACC).

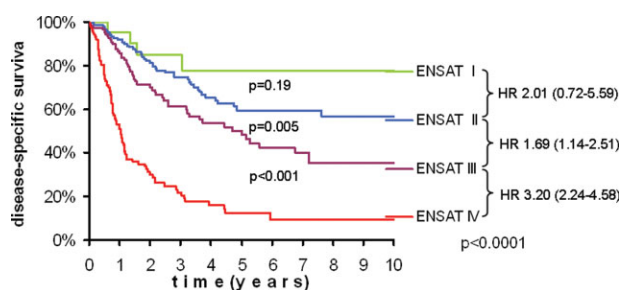
**Table 3.** New Staging System for Adrenocortical Carcinoma (European Network for the Study of Adrenal Tumors Classification 2008)

Stage	ENSAT 2008
I	T1, N0, M0
II	T2, N0, M0
III	T1-T2, N1, M0
	T3-T4, N0-N1, M0
IV	T1-T4, N0-N1, M1

ENSAT indicates European Network for the Study of Adrenal Tumors; T1, tumor ≤5 cm; T2, tumor >5 cm; T3, tumor infiltration into surrounding tissue; T4, tumor invasion into adjacent organs or venous tumor thrombus in vena cava or renal vein; N0, no positive lymph nodes; N1, positive lymph node(s); M0, no distant metastases; M1, presence of distant metastasis.

prognostic relevance. The major finding of our evaluation of the proposed UICC system is the observation that patients with stage II disease do not differ considerably in their disease-specific survival from patients with stage III disease. Furthermore, patients who have stage IV disease with documented distant metastases have a poorer survival than patients who have UICC stage IV disease without

distant metastases. These observations indicate the need for a major revision of the UICC tumor classification for ACC, and the revised staging system proposed in the current report has clearly improved prognostic potential. In fact, distant metastasis as a defining factor for stage IV disease already has been proposed by Lee et al<sup>12</sup> and also has been used in other cohorts of patients with ACC.<sup>14,18</sup> The basis for this strategy is related to the surgical approach to ACC. So long as the disease remains local and may be removed completely by surgery (R0 resection), the prognosis clearly is superior to a situation in which surgery no longer can achieve a complete resection and distant metastases obviously indicate systemic disease. With improving surgical techniques, the difference between invasion of surrounding tissue and invasion of adjacent organs has become of minor importance (Fig. 3d). In a recent study of patients with ACC who underwent radical resection, tumor stage had little prognostic value,<sup>22</sup> and those results support the dominant role of successful primary surgery for disease-specific survival. In the same line, the risk factors defining stage III disease that were identified and validated in our series are indicative of tumor spread either through local infiltration, or regional lymph node



**FIGURE 4.** Disease-specific survival stratified according to the new 2008 European Network for the Study of Adrenal Tumors (ENSAT) staging classification for adrenocortical carcinoma (ACC) using Kaplan-Meier analysis. Disease-specific survival was defined as the time elapsed from primary diagnosis to death from ACC. Patients who were alive or who had died of other causes were censored. Four hundred sixteen patients were analyzed (stage I: n = 23 patients, 4 deaths, 19 censored; stage II: n = 164 patients, 48 deaths, 116 censored; stage III: n = 107 patients, 52 deaths, 55 censored; stage IV: n = 122 patients, 89 deaths, 33 censored). HR indicates estimated hazard ratio (with 95% confidence intervals are indicated in parentheses); *P* indicates log-rank *P* value assessing differences.

involvement, or tumor thrombus in large veins. Irrespective of tumor size, these factors demonstrate a more aggressive tumor biology and, thus, an inferior prognosis.

A tumor size cutoff of 5 cm to differentiate between stage I and stage II disease seems to be arbitrary, and no significant difference in disease-specific survival emerged in our cohort. However, the number of patients with stage I disease was rather small, and different cutoffs in tumor size did not lead to improved separation of patients with stage II disease compared with stage I disease (data not shown).

It is important to note that patients with stage I disease who avoided tumor spillage during surgery had a significantly improved disease-specific survival compared with patients with stage II disease. In fact, tumor spillage during surgery obviously represents tumor spread and may justify classifying these patients with stage III or even stage IV disease. This also holds true for patients who undergo histologically incomplete resection (R1). Preliminary results from our series indicate that the survival of patients with incomplete resected stage II disease is similar or worse than that of patients with completely resected (R0) stage III disease (unpublished data). These observations strongly suggest that correct staging can be performed only after surgery and that the success of surgery should be taken into account. These aspects require fur-

ther analysis and validation and may lead to further modification of the UICC staging system in the future. The same may hold true for a potential subclassification of patients with stage IV disease, because patients with 1 or 2 metastatic lesions have a better prognosis than patients with  $\geq 3$  lesions.<sup>9</sup>

Our study had limitations: Although our series is by far the largest cohort of patients with ACC with full clinical annotation, our sample size still is small compared with similar studies in other tumor entities. Furthermore, our proposed new staging classification needs to be validated in a second independent cohort to fully establish the superiority of this approach.

In conclusion, our study demonstrates significant limitations of the 2004 UICC staging system for ACC, especially in the prognostic discrimination between stage II and III. Therefore, we propose a revision of the TNM system for this rare disease. The suggested ENSAT staging classification provides improved prognostic accuracy for disease-specific survival in ACC.

### Conflict of Interest Disclosures

Supported by grants from Deutsche Krebshilfe (grant 106 080 to B.A. and M.F. and grant 107111 to M.F.).

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