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Prognostic factors in stage III–IV adrenocortical carcinomas (ACC): an European Network for the Study of Adrenal Tumor (ENSAT) study

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Background: The clinical course of advanced adrenocortical carcinoma (ACC) is heterogeneous. Our study aimed primarily to refine and make headway in the prognostic stratification of advanced ACC.

Patients and methods: Patients with advanced ENSAT ACC (stage III or stage IV) at diagnosis registered between 2000 and 2009 in the ENSAT database were enrolled. The primary end point was overall survival (OS). Parameters of potential prognostic relevance were selected. Univariate and multivariate analyses were carried out: model 1 'before surgery'; model 2 'post-surgery'.

Results: Four hundred and forty-four patients with advanced ENSAT ACC (stage III: 210; stage IV: 234) were analyzed. After a median follow-up of 55.2 months, the median OS was 24 months. A modified ENSAT (mENSAT) classification was validated: stage III (invasion of surrounding tissues/organs or the vena renalis/cava) and stage IVa, IVb, IVc (2, 3 or >3 metastatic organs, including N, respectively). Two- or 5-year OS was 73%, 46%, 26% and 15% or 50%, 15%, 14% and 2% for stages III, IVa, IVb and IVc, respectively. In the multivariate analysis, mENSAT stages (stages IVa, IVb, or IVc, respectively) were significantly correlated with OS ($P < 0.0001$), as well as additional parameters: age ≥50 years ($P < 0.0001$), tumor- or hormone-related symptoms ($P = 0.01$ and 0.03, respectively) in model 1 but also the R status ($P = 0.001$) and Grade (Weiss >6 and/or Ki67 ≥20%, $P = 0.06$) in model 2.

Conclusion: The mENSAT classification and GRAS parameters (Grade, R status, Age and Symptoms) were found to best stratify the prognosis of patients with advanced ACC.

Key words: adrenocortical carcinoma, prognostic factors, ENSAT, GRAS

introduction

Adrenocortical carcinoma (ACC) is a rare malignancy with an estimated yearly incidence of 0.7–2.0 cases per million inhabitants [1, 2] and a very aggressive behavior [2–5]. Historically, the prognosis of ACC was shown to be mainly driven by the presence of metastases and tumor resecability [6]. More recently, the European Network for the Study of Adrenal Tumors (ENSAT) classification of TNM stages and the resection status has refined prognostication [4, 5, 7].

Advanced ACC, defined as tumor stage III, in the case of locoregional spread, or stage IV, in the case of distant metastases, represent 18%–26% and 21%–46% of ACC at diagnosis, respectively

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[2–5]. Treatment options for such patients are limited [8, 9], and no predictors of response have been validated. The best way to stratify the prognosis of advanced ACC continues to fuel debate. Indeed, several studies suggest that patients with stage III disease and positive lymph nodes (N1) or vena cava invasion could have a similar prognosis to that of those with stage IV disease [7, 10, 11]. The number of tumor-involved organs in patients with stage IV ACC has been reported to be useful for refining the prognosis of these patients as well [12]. Furthermore, several studies also claim that age, hormone secretion, the Weiss score and/or proliferative index and the resection (R) status may also exert an impact on the prognosis of these patients [13–17]. Better prognostic stratification is therefore needed in advanced ACC [8, 9].

The objective of this retrospective study was to refine the prognostic classification of patients with advanced stage III and stage IV ACC at diagnosis. To achieve this goal, the ENSAT registry, comprising a large number of ACC patients treated in expert centers in four European countries, was utilized.

patients and methods

patient and data collection

From 1 January 2000 to 31 December 2009, 463 patients with stage III or IV ACC followed up in 16 expert referral centers in four European countries (Germany, France, Italy and The Netherlands) were consecutively registered in the ENSAT ACC Registry. Inclusion criteria were: a confirmed histological diagnosis of ACC, stage III–IV disease at imaging and/or surgery carried out within 3 months of the diagnosis, age >18 years and available follow-up data.

Data collected included: age, sex, modality of tumor diagnosis [defined as : incidental, symptom-related either to the tumor mass (i.e. abdominal pain) or hormone secretions (glucocorticoids, mineralocorticoids, androgens hypersecretion) or other/unknown], ENSAT or UICC TNM classifications (tumor size, invasion of adjacent tissue/organs or vena cava/renalis vein, lymph node or distant metastases), involved organs, tumor grade based on the pathological analysis of the primary tumor [defined as the Weiss score (≤6/>6) or Ki67 percentage (<20%/≥20%)], the R status at first surgery (complete resection:R0; microscopic residual disease:R1; macroscopic residual disease:R2, resection not-known: Rx).

The ENSAT registry was approved by the local ethics committees of all participating centers and all patients included had given their written informed consent.

evaluation of different stage III–IV definitions and tumor grading systems

In order to validate the best way to stratify the TNM classification of advanced ACC patients, four different TNM classification systems were compared before the final prognostic analysis: the UICC, ENSAT and two proposed modified ENSAT classifications (mENSAT).

The two mENSAT classifications were constructed as described in supplementary Figure S1A and B, available at *Annals of Oncology* online by analyzing independently the prognostic influence of N status and venous invasion. In addition, stage IV was categorized into subgroups according to the number of tumor-involved organs (IVa: 2, IVb: 3, IVc: >3 organs).

In order to classify the tumor grade, three different classifications were analyzed as described in supplementary Figure S2A–C, available at *Annals of Oncology* online, by analyzing the prognostic influence of the Weiss score, Ki67 or a combination of both parameters.

Patients whose Weiss score and Ki67 were both missing, as well as patients who have no adrenalectomy, were excluded from the analysis.

Parameter selection and combinations were carried out graphically, using the Kaplan–Meier and the Hall–Wellner confidence intervals of each curve. The parameters considered to best reflect the tumor burden and the tumor grade were those allowing the greatest discrimination of patients in terms of overall survival (OS), graphically.

statistics

Descriptive analyses were carried out using means and standard deviations for quantitative variables, and comparisons were carried out using the Student test (or non-parametric Wilcoxon test if non-normally distributed). Qualitative variables were expressed as percentages and comparisons were carried out using the χ^2 test.

The primary end point was OS, defined as the interval between the date of the diagnosis of stage III or IV ACC and death due to any cause. Surviving patients were censored at the date of the last follow-up. Follow-up data were last updated in November 2012. The median follow-up was estimated by the reverse Kaplan–Meier method (Schemper's method).

Survival rates and 95% confidence intervals were estimated by the Kaplan–Meier method. The log-rank test was used to compare survival curves. The parameters significantly associated with OS in the univariate analysis ($P < 0.05$) were further tested in the multivariate analysis. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were estimated using Cox's proportional hazards regression model in the multivariate analysis, with the lowest risk group as the reference group. All tests were two sided.

Variables, as well as cut-off thresholds, are presented in supplementary Table S1, available at *Annals of Oncology* online: they were analyzed for their potential prognostic value in the univariate analysis.

Two multivariate analyses were carried out: *model 1* (before-surgery) analyzed all prognostic parameters available at the time of ACC diagnosis. *Model 2* (post-surgery) analyzed all prognostic parameters including the pathological grade and R status in patients who underwent adrenalectomy. The statistical analysis was conducted using SAS software version 9.2.

results

population characteristics and follow-up data

Four hundred and sixty-three cases were reviewed: 15 were excluded because <18 years old and 4 because lost at follow-up. Thus, 444 patients constituted the study population: 210 (47%) were ENSAT stage III and 234 (53%) stage IV. The main population characteristics are summarized in Table 1.

Supplementary Table S2, available at *Annals of Oncology* online describes the different treatments received by the patients during the first year of therapy. Patients with stage III underwent significantly more frequently surgery than those with stage IV: no surgery was carried out in 6 ENSAT stage III patients and in 54 ENSAT stage IV patients.

The median follow-up of patients was 55.2 (range 0–139) months. The median OS was 24 (21.6–27.7) months. The 2- and 5-year survival rates were 50% (CI 45%–55%) and 27% (CI 23%–31%), respectively.

selection of the best TNM and pathology classifications in advanced ACC patients

N-positive status but not venous invasion outcome was found to overlap with stage IV outcome (supplementary Figure S1A and B, available at *Annals of Oncology* online). Therefore, the first mENSAT classification was considered to better stratify the prognosis of patients with stage III–IV ACC. It defined stage III

Table 1. Clinical and pathological characteristics of 444 patients with advanced adrenocortical carcinoma

Parameters	*n* of patients (%)	*n* of assessable patients
Patients	444	444
Age(years)		
<50	200 (45%)	444
≥50	244 (55%)	
Gender		
Male	173 (39%)	444
Female	271 (61%)	
Modality of diagnosis		
Tumor-related symptoms	163 (37%)	444
Hormone-related symptoms	144 (32%)	
Incidentally	65 (15%)	
Other/unknown	72 (16%)	
ENSAT stage		
III	210 (48%)	444
IV	234 (52%)	
Modified ENSAT stage (mENSAT)		
III	177 (40%)	444
IVa	139 (31%)	
IVb	65 (15%)	
IVc	63 (14%)	
Tumor (T)		
T1	11 (2%)	444
T2	97 (22%)	
T3	140 (32%)	
T4	196 (44%)	
Regional lymph nodes (N1)		
Y	98 (22%)	444
N	202 (45%)	
Unknown	144 (32%)	
Organ metastases (M1)		
Lung		
Y	152 (34%)	444
N	292 (65%)	
Liver		
Y	125 (28%)	444
N	319 (72%)	
Bone		
Y	32 (7%)	444
N	412 (93%)	
Adrenalectomy		
Y	384 (86%)	444
N	60 (14%)	
R status in resected patients		
R0[a]	150 (39%)	384
R1	34 (9%)	
R2	91 (24%)	
Rx	109 (28%)	
Weiss score		
≤ 6	174 (53%)	327
>6	153 (47%)	
Ki 67 (%)		
<20	103 (46%)	226
≥ 20	123 (54%)	
Death		
Y	301 (68%)	444
N	143 (32%)	
Alive		
With disease or recurrence	76 (53%)	143
Without disease	63 (44%)	
Unknown	4 (3%)	

[a]Primary including metastases in 43 patients.

as T3–4N0M0 and stage IVa, IVb, IVc according to the number of tumor-involved organs (including the primary tumor and the 'N' as 'organ'): 2, 3 or >3, respectively (supplementary Table S3, available at *Annals of Oncology* online). ENSAT and mENSAT classifications were found to be more informative than their UICC counterpart (Figure 1A–C).

Regarding pathological grading, prognostic information but also the number of available data were taken into account. Both Ki67 and the Weiss score significantly discriminated OS outcome in the univariate analysis. However, Ki67 had not been documented in a significant number of patients. The Weiss score and/or Ki67 were available in 340 patients and the combination of the two pathological parameters allowed us to significantly discriminate two subgroups of patients, in terms of OS (supplementary Figure S2A–C, available at *Annals of Oncology* online) and to apply this pathological classification.

prognostic factors for OS

univariate analysis. In the univariate analysis, the following parameters were significantly inversely associated with OS: age ≥50 years, tumor or hormone-related symptoms at diagnosis, ENSAT, mENSAT classification, the R status, Weiss score >6 and Ki67 ≥20% (supplementary Table S1, available at *Annals of Oncology* online).

In the mENSAT classification, stage III, IVa, IVb and IVc were significantly associated with OS. In particular, the median OS in stage III, IVa, IVb and IVc was 60.8 (CI 39.8–81.5), 21.2 (CI 15.7–25.9), 12.1 (CI 9.4–14.9) and 13.6 (CI 8.6–15.8) months, respectively. Specifically, 2-year OS was 73% (CI 66%–79%), 46% (CI 37%–54%), 26% (CI 16%–37%) and 15% (CI 7%–25%) for stages III, IVa, IVb and IVc and 5-year OS was 50% (CI 44%–60%), 15% (CI 8%–22%), 14% (CI 6%–24%) and 2% (CI 0.01%–9%) for stages III, IVa, IVb and IVc, respectively.

multivariate analysis: models 1 and 2. In the multivariate analysis (model 1), the following parameters were significantly and independently associated with an increased risk of death: age ≥50 years ($P < 0.0001$), tumor- or hormone-related symptoms ($P = 0.01$, 0.03, respectively), the mENSAT stage (all $P < 0.0001$) (Table 2). When Nx patients were excluded or considered as a separate subgroup, the results remained unchanged.

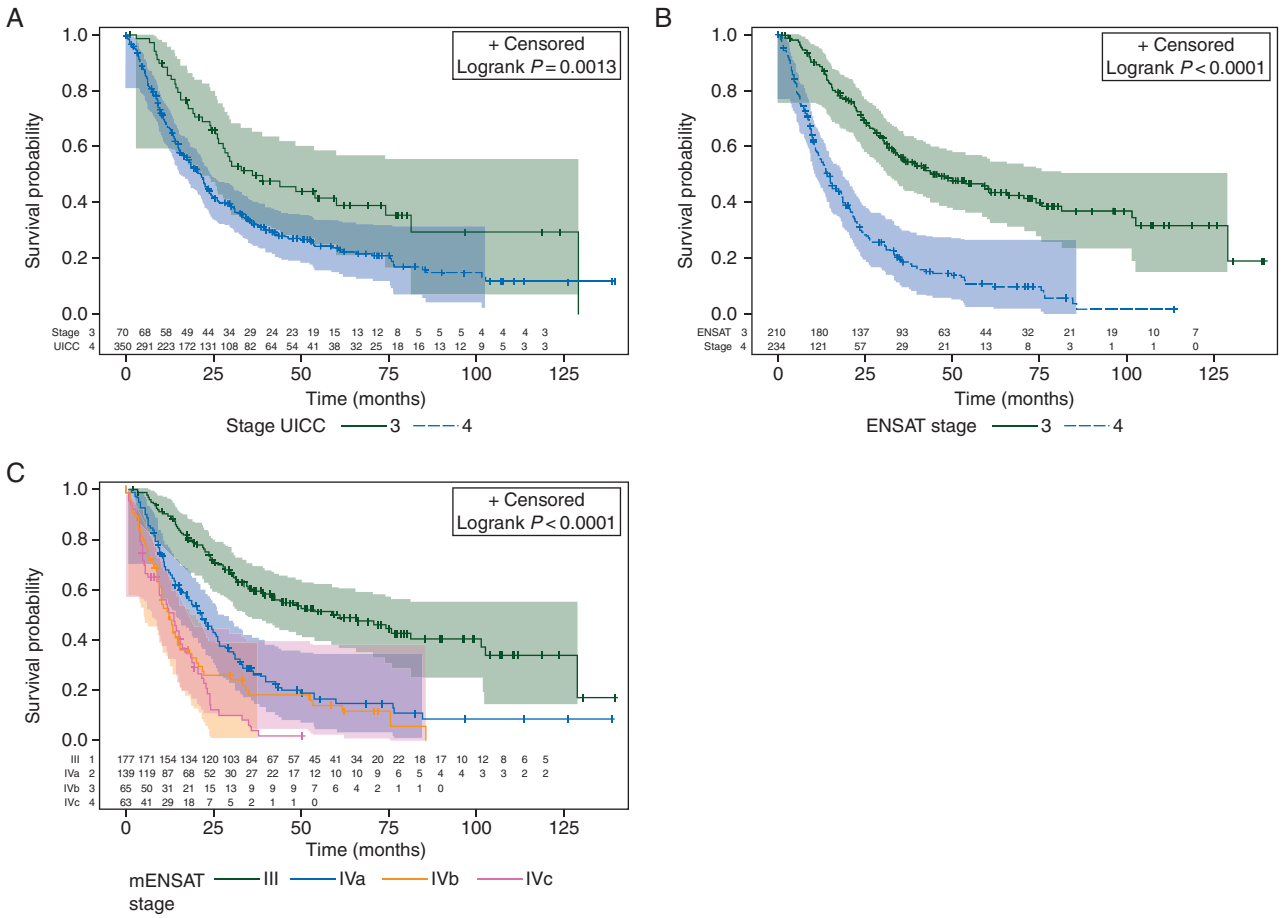

Figure 1. Overall survival according to UICC (A), ENSAT (B) and m-ENSAT (C) TNM classifications in 444 advanced adrenocortical carcinoma patients.

Table 2. Multivariate analyses (models 1 and 2)

	Model 1 (n = 444 patients)			Model 2 (n = 340 patients)		
	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Age						
<50 years	1	1		1	1	
≥50 years	1.6	1.3–2.1	<0.0001	1.3	1.01–1.8	0.04
Modality of diagnosis						
Incidentally	1	1		1	1	
Tumor mass	1.7	1.1–2.5	0.01	1.8	1.1–2.8	0.01
Hormone hypersecretion	1.6	1.05–2.4	0.03	1.5	0.97–2.5	0.06
Other or unknown	1.2	0.8–1.9	0.40	1.05	0.6–1.8	0.83
Modified ENSAT stage						
III	1	1		1	1	
IVa	2.6	2.0–3.5	<0.0001	2.1	1.5–2.9	<0.0001
IVb	3.6	2.5–5.1	<0.0001	2.4	1.5–3.7	<0.0001
IVc	5.1	3.6–7.3	<0.0001	4.3	2.7–6.5	<0.0001
Tumor grade	NA					
Weiss ≤6 and Ki <20				1	1	
Weiss >6 and or Ki ≥20				1.3	0.99–1.7	0.06
R status	NA					
R0				1	1	
R 1, 2, X				1.6	1.2–2.2	0.001

Model 1: prognostic model with clinical variables, without pathology and the R status; model 2: prognostic model with clinical variables, with pathology and the R status.
NA, not applicable.

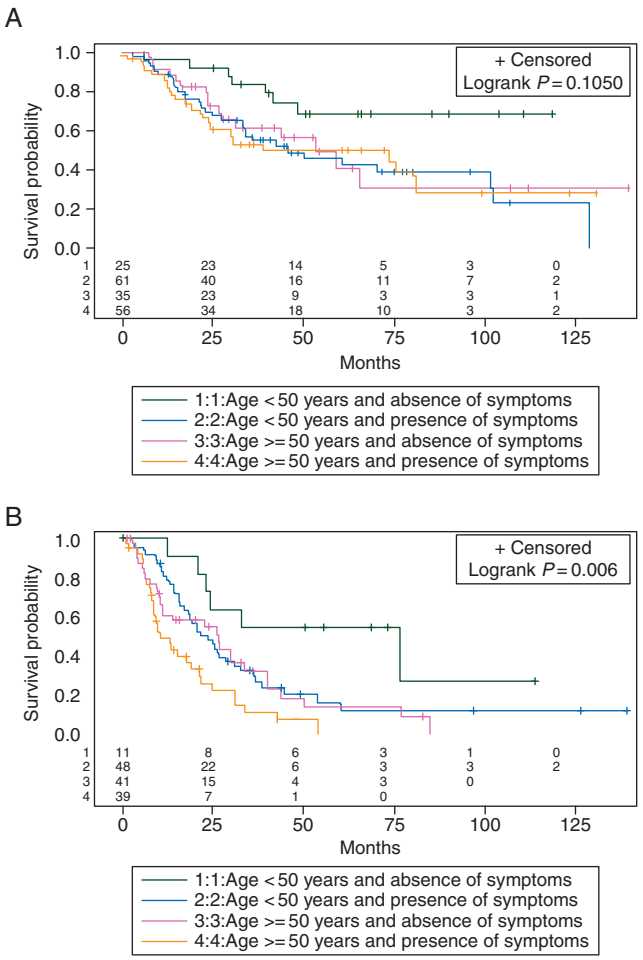

Figure 2. Kaplan–Meier curves of overall survival according to age and the modality of the diagnosis (model 1) in mENSAT stage III (A) and stage IVa (B).

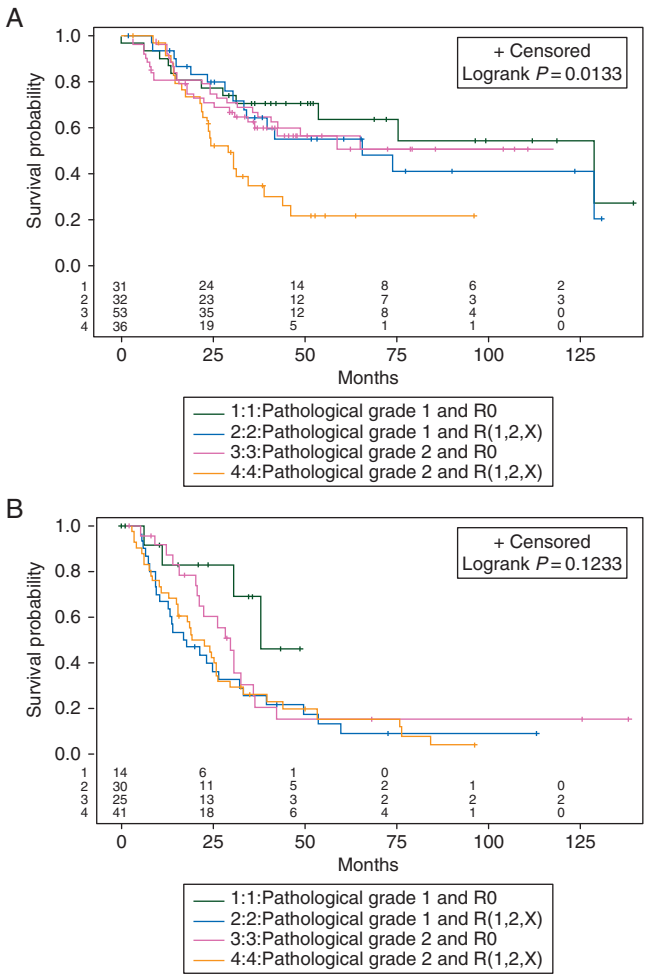

Figure 3. Kaplan–Meier curves of overall survival according to the tumor grade (Weiss ≤6 and Ki <20 versus Weiss >6 and/or Ki ≥20) and the resection status (R0 versus R1, R2, Rx) (model 2) in mENSAT stage III (A) and stage IVa (B).

With model 2, the following parameters were significantly associated with an increased risk of death: age ≥50 years ($P < 0.04$), tumor-related symptoms ($P = 0.01$), the mENSAT stages (all $P < 0.0001$) and the R status ($P = 0.001$). The HR of the tumor grade (Weiss >6 and/or Ki67 ≥20%) reached 1.3 and the hormone-related symptoms at diagnosis was 1.5, with a *P*-value that tended to be significant for both variables ($P = 0.06$). When Rx patients were excluded or considered as a separate subgroup, the results remained unchanged.

In the following section, the acronym 'GRAS', used to designate Grading (G), the R status (R), Age (A) and Symptoms (S), defined as tumor- or hormone-related symptoms at diagnosis, corresponds to these parameters.

combining prognostic parameters. We then attempted to refine the prognostic classification of ACC by combining the mENSAT stage with the GRAS parameters. Age ≥50 years and/or presence of symptoms were first combined with mENSAT stages III and IVa in model 1 (Figure 2A and B). Unfavorable grading or the R status was subsequently combined with the same mENSAT stages in model 2 (Figure 3A and B).

Figures 2 and 3 show that these GRAS parameters significantly affect the prognosis of mENSAT stage III or IVa. Five-year OS of mENSAT stage III was 50% but ranged from 68%, for age <50 years and an incidental tumor (Figure 2A) in model 1 to 22% when tumor grading and the R status were unfavorable in model 2 (Figure 3A).

Five-year OS of mENSAT stage IVa was 15% but ranged from 0% to 55% when age and functional symptoms were unfavorable or favorable in model 1 (Figure 2B), respectively, and ranged from 16% to 46% when tumor grading and the R status were unfavorable or favorable in model 2 (Figure 3B).

discussion

This collaborative study of the ENSAT network allowed us to refine the prognostic classification in a large and typical group of patients with advanced ACC defined as stage III or synchronous stage IV disease [3, 5, 12]. We propose a new mENSAT TNM classification and confirm the prognostic value of four additional prognostic parameters named 'GRAS' parameters.

The tumor stage, best defined by the mENSAT classification, was confirmed as the keystone of the prognostic stratification. We investigated the prognostic role of the N status together with venous invasion and we found that the N1 status plays a deleterious prognostic role comparable to stage IV ACC, as previously

reported [7, 10]. In addition, we confirmed the prognostic value of the number of tumor-involved organs, including the primary and lymph node involvement [12]. On the basis of these results, we created a new prognostic TNM classification restricted to patients with advanced ACC, the mENSAT stage III–IV classification, which allowed us to unambiguously discriminate the prognostic outcomes of four categories of patients namely, stage III, IVa, IVb and IVc with 5-year OS rates of 50%, 15%, 14% and 2%, respectively. In this new classification, the N1 status shifts tumors from ENSAT stage III to the mENSAT stage IV category (i.e. IVa, if the N1 is isolated). In contrast, the prognosis of ACC with venous invasion was found to be comparable to that of other subgroups of stage III N0 disease. However, a limitation of our study is the fact that vena cava or vena renalis invasion was not accurately documented in all cases [5]. Furthermore, it should be borne in mind that the N classification used in our study refers to both imaging and pathological classifications and future refinements are expected. These results may suggest that surgical excision of the ACC primary tumor including venous invasion is better handled by ACC surgeons than lymph node dissection whose putative role has only been underlined recently [11, 18].

In addition to the mENSAT classification, we validated for the first time, after optimization and adjustment for the tumor burden in advanced ACC, four additional prognostic parameters, designated GRAS, that were found to affect the prognosis of each mENSAT stage.

Indeed, 5-year OS of stage III patients ranged between 60% and 70% in patients <50 years-old with an incidentally discovered ACC or with an R0 status and favorable tumor grading but dropped to 22% when the tumor grade and the R status were both found to be unfavorable. Five-year OS for patients with stage IVa disease was 15% but ranged from 0 to 55% in patients with favorable or unfavorable GRAS parameters, again suggesting an overlap between patients with stage III and IVa disease. The validation of the precise prognostic roles of each parameter and the combination of GRAS parameters require additional studies in larger and independent group of patients to better understand the magnitude of their influence for each stage. Meanwhile, standardization, including quantification when feasible, of the analysis of each prognostic parameter is required.

Age was expressed as a binomial parameter according to the median in this study which may be optimized. Also future studies should investigate more precisely how far the magnitude and subtypes of secretions affect the prognosis [13, 15]. The prognostic influence of the Weiss score in comparison to the Ki67 index, but also standardization of their analyses in all patients and comparisons of the informative value of the primary and metastasis require further studies.

The R0 status of the primary was identified as a major prognostic parameter in our study, suggesting that the benefit of the R0 status applies not only to stage III but also to stage IV. However, the R status can be considered a surrogate for the tumor burden but also reflects the surgeon's expertise which is difficult to analyze objectively. In addition, the best time to perform R0 resection remains to be more precisely defined.

The strengths of this study include the large number of patients based on national expert European networks together with prolonged follow-up allowing robust conclusions in this rare cancer. The limitations of this study include its retrospective nature explaining the lack of consistency for pathological, R and N status reports. In addition, as for all prognostic studies, the impact of therapeutic intervention was not analyzed which may affect the results. Standardization and further validations of the mENSAT-GRAS parameters are however warranted in a prospective cohort of patients as well as the analysis of the added value of the recently published molecular classification of ACC patients [19].

conclusion

The mENSAT classification was found to best stratify the prognosis of advanced ACC patients. After adjustment to the mENSAT classification, four additional prognostic 'GRAS' parameters were found. Prospective validation of this new prognostic system is expected.

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disclosure

The authors have declared no conflicts of interest.

references

1. Golden SH, Robinson KA, Saldanha I et al. Clinical review: prevalence and incidence of endocrine and metabolic disorders in the United States: a comprehensive review. J Clin Endocrinol Metab 2009; 94: 1853–1878.
2. Kerkhofs TM, Verhoeven RH, Van der Zwan JM et al. Adrenocortical carcinoma: a population-based study on incidence and survival in the Netherlands since 1993. Eur J Cancer 2013; 49: 2579–2586.
3. 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: 891–897.
4. Lughezzani G, Sun M, Perrotte P et al. 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. Eur J Cancer 2010; 46: 713–719.
5. 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: 243–250.
6. Schulick RD, Brennan MF. Long-term survival after complete resection and repeat resection in patients with adrenocortical carcinoma. Ann Surg Oncol 1999; 6: 719–726.
7. Bilimoria KY, Shen WT, Elaraj D et al. Adrenocortical carcinoma in the United States: treatment utilization and prognostic factors. Cancer 2008; 113: 3130–3136.
8. Berruti A, Baudin E, Gelderblom H et al. Adrenal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; 23(Suppl 7): vii131–vii138.
9. Baudin E. Adrenocortical carcinoma. Endocrinol Metab Clin North Am 2015; 44 (2): 411–434.
10. Do Cao C, Leboulleux S, Borget I et al. Prognosis of stage III adrenocortical carcinoma after radical resection: a French retrospective multicentric study from the COMETE Network. European Congress of Endocrinology 2011, Abstract, P. 70.
11. Turbendian HK, Strong VE, Hsu M et al. Adrenocortical carcinoma: the influence of large vessel extension. Surgery 2010; 48: 1057–1064; discussion 1064.

12. Assie G, Antoni G, Tissier F et al. Prognostic parameters of metastatic adrenocortical carcinoma. J Clin Endocrinol Metab 2007; 92: 148–154.
13. 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: 2650–2655.
14. Volante M, Bollito E, Sperone P et al. Clinicopathological study of a series of 92 adrenocortical carcinomas: from a proposal of simplified diagnostic algorithm to prognostic stratification. Histopathology 2009; 55: 535–543.
15. Berruti A, Fassnacht M, Haak H et al. Prognostic role of overt hypercortisolism in completely operated patients with adrenocortical cancer. Eur Urol 2014; 65: 832–838.
16. Miller BS, Gauger PG, Hammer GD et al. Proposal for modification of the ENSAT staging system for adrenocortical carcinoma using tumor grade. Langenbecks Arch Surg 2010; 395: 955–961.
17. Stojadinovic A, Ghossein RA, Hoos A et al. Adrenocortical carcinoma: clinical, morphologic, and molecular characterization. J Clin Oncol 2002; 20: 941–950.
18. Reibetanz J, Jurowich C, Erdogan I et al. Impact of lymphadenectomy on the oncologic outcome of patients with adrenocortical carcinoma. Ann Surg 2012; 255: 363–369.
19. Assie G, Letouze E, Fassnacht M et al. Integrated genomic characterization of adrenocortical carcinoma. Nat Genet 2014; 46: 607–612.

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Bevacizumab/high-dose chemotherapy with autologous stem-cell transplant for poor-risk relapsed or refractory germ-cell tumors

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Background: High-dose chemotherapy (HDC) using sequential cycles of carboplatin/etoposide is curative for relapsed germ-cell tumors (GCT). However, outcomes of high-risk patients in advanced relapse remain poor. We previously developed a new HDC regimen combining infusional gemcitabine with docetaxel/melphalan/carboplatin (GemDMC), with preliminary high activity in refractory GCT. Given the high vascular endothelial growth factor expression in metastatic GCT and the synergy between bevacizumab and chemotherapy, we studied concurrent bevacizumab and sequential HDC using GemDMC and ifosfamide/carboplatin/etoposide (ICE) in patients with poor-risk relapsed or refractory disease.

Patients and methods: Eligibility criteria included intermediate/high-risk relapse (Beyer Model), serum creatinine ≤1.8 mg/dl and adequate pulmonary/cardiac/hepatic function. Patients received sequential HDC cycles with bevacizumab preceding GemDMC (cycle 1) and ICE (cycle 2). The trial was powered to distinguish a target 50% 2-year relapse-free survival (RFS) from an expected 25% 2-year RFS in this population.

Results: We enrolled 43 male patients, median age 30 (20–49) years, with absolute refractory ($N = 20$), refractory ($N = 17$) or cisplatin-sensitive ($N = 6$) disease, after a median 3 (1–5) prior relapses. Disease status right before HDC was unresponsive ($N = 24$, progressive disease 22, stable disease 2), partial response with positive markers (PRm^+) ($N = 8$), PRm^- ($N = 7$) or complete response ($N = 4$). Main toxicities were mucositis and renal. Four patients (three with baseline marginal renal function) died from HDC-related complications. Tumor markers normalized in 85% patients. Resection of residual lesions ($N = 13$) showed necrosis ($N = 4$), mature teratoma ($N = 2$), necrosis/teratoma ($N = 3$) and viable tumor ($N = 4$). At median follow-up of 46 (9–84) months, the RFS and overall survival rates are 55.8% and 58.1%, respectively.

Conclusions: Sequential bevacizumab/GemDMC–bevacizumab/ICE shows encouraging outcomes in heavily pretreated and refractory GCT, exceeding the results expected in this difficult to treat population.

ClinicalTrials.gov: NCT00936936.

Key words: bevacizumab, gemcitabine, docetaxel, high-dose chemotherapy, autologous transplantation, germ-cell tumors

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