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Histopathological grading of adenoid cystic carcinoma of the head and neck: Analysis of currently used grading systems and proposal for a simplified grading scheme

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SUMMARY

Background: Histopathological grading of adenoid cystic carcinoma (ACC) is a controversial issue. It is generally agreed that solid type ACC has a relatively poor prognosis. However, the amount of solid regions within this often mixed type tumor that predicts a poor prognosis is not firmly established. Some authors stipulate that the presence of a solid component regardless of the amount is a poor prognosticator where others argue that the amount should be taken into consideration. Two grading systems most commonly used are those described by Perzin et al./Szanto et al. and Spiro et al., respectively. They report that prognosis of ACC is poor if >30% and >50% of the tumor volume has a solid growth pattern, respectively.

Material and methods: The described grading systems are applied to a series of 81 surgically treated cases of ACC at the VU University Medical Center, Amsterdam, The Netherlands. Moreover, we introduced an alternative grading system, in which the presence of a solid component, irrespective of its amount, is considered. All three systems of grading were tested for inter-observer concordance and prediction of prognosis.

Results: Inter-observer concordance for grading ACC according to Perzin et al./Szanto et al. and Spiro et al., proved to be moderate with Kappa Scores of 0.393 and 0.433, respectively. Our alternative grading system yielded inter-observer concordance with a Cohen's kappa result of 0.990. All systems were comparable in discriminating patients with poor clinical outcome. Histopathological grade proved to be an independent prognosticator.

Conclusion: The presence of any solid component in ACC is a negative prognosticator, and can histopathologically be diagnosed with a high reliability. These results suggest to merely register the presence or absence of a solid tumor component since its inter-observer variability is very low, its reproducibility is high and its predictive value is comparable to the traditional grading systems used.

Introduction

Adenoid cystic carcinoma (ACC) of the head and neck is one of the most prevalent malignant salivary gland neoplasms [1]. ACC in general has a protracted course. It is notorious for its poor disease free survival due to frequent local recurrences and – often indolent – distant metastases. The treatment of choice is surgery, when feasible followed by radiotherapy (RT).

Regarding its histological features ACC predominantly presents as a mixed tumor, consisting of tubular, cribriform and/or solid growth patterns. The tumor is mostly classified according to the predominant pattern; the solid subtype is considered a high grade tumor with poor prognosis, first recognized as such in 1958 by Patey and Thackray [2].

Compared to cribriform and tubular types, solid type ACC shows a high percentage of loss of heterozygosity (LOH), more chromosomal aberrations and somatic mutations and a high expression of p53 [3–8]. Some authors speculate that the risk of nodal metastases is higher when solid ACC is present [9].

For ACC, two different histopathological grading systems are currently used. These are one grading system described by Perzin

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et al. [10] and Szanto et al. [11] and one by Spiro et al. [12] We will refer to these grading systems as Perzin/Szanto and Spiro, resp. Both grading systems can discriminate patients with a poor prognosis, based upon the amount of solid component present in the tumor. In the Perzin/Szanto system, ACC is considered high grade if more than 30% of the tumor consists of a solid component. In the Spiro system, more than 50% of solid parts are considered high grade. In these grading systems, the amount of tumor to be investigated is not (clearly) defined [10–12].

Next to these established schemes, we studied the usefulness of a new histopathological grading system scoring the mere presence of solid type ACC in the histological specimen, irrespective of its amount. The main goal was to provide a reliable grading system with good reproducibility and with a low inter-observer variability, which are prerequisites for a practical grading system. Furthermore, the importance of histopathological grading relative to other known prognosticators such as T-stage and N-status is investigated.

Materials and methods

One-hundred and five patients with ACC attended our institution for treatment between 1979 and 2009, and of these, 87 patients were treated surgically. During this period, treatment strategies remained unchanged.

Of these 87 patients, H&E stained slides were available for review in 81 cases which were included in this study. All available slides – almost always plural per case – were revised and graded independently by two expert head and neck pathologists (EB and IVDW). In case of discordant grading an agreement was reached. Grading was carried out according to the currently used systems by Perzin/Szanto and Spiro, respectively [10–12]. The definitions of these grading systems are shown in Table 1. The histopathological criteria of this predominantly mixed type tumor were scored according to the criteria of the World Health Organization (WHO) [1]. The three types of ACC are shown in Fig. 1.

For analysis, specimens were subdivided in low and high grade ACC. This was done according to the definitions in the original papers [10–12]. According to these definitions, low grade ACC consists of Perzin/Szanto grade I (predominantly tubular, no solid) and II (predominantly cribriform, <30% solid) and Spiro grade I (mostly tubular/cribriform, occasional solid). High grade ACC thus consists of Perzin/Szanto grade III (>30% solid component) and Spiro grade II (substantial solid; >50%) and III (only solid).

An additional scoring system was introduced which reported the presence or absence of solid type ACC in the specimen, regardless of the amount or further composition of this predominantly mixed type tumor. We considered this a new grading system, defined as Solid± (S±).

A Cohen's kappa test was performed to analyse inter-observer variability for the different grading systems. The Cohen's kappa test is a reliable and often used test for measuring inter-observer variability with values ranging from 0 to 1.00, where values of >0.70 are considered satisfactory [13].

Table 1
Definitions of grading systems as used in current literature and the S± system.

Perzin/Szanto [10,11]	Spiro et al. [12]	Present study
Grade	Grade	Solid/no solid
I. Predominantly tubular, no solid	I. Mostly tubular or cribriform, occasional solid	S+
II. Predominantly cribriform, <30% solid	II. Mixed with substantial solid (>50%)	S–
III. Solid component > 30%	III. Only Solid	

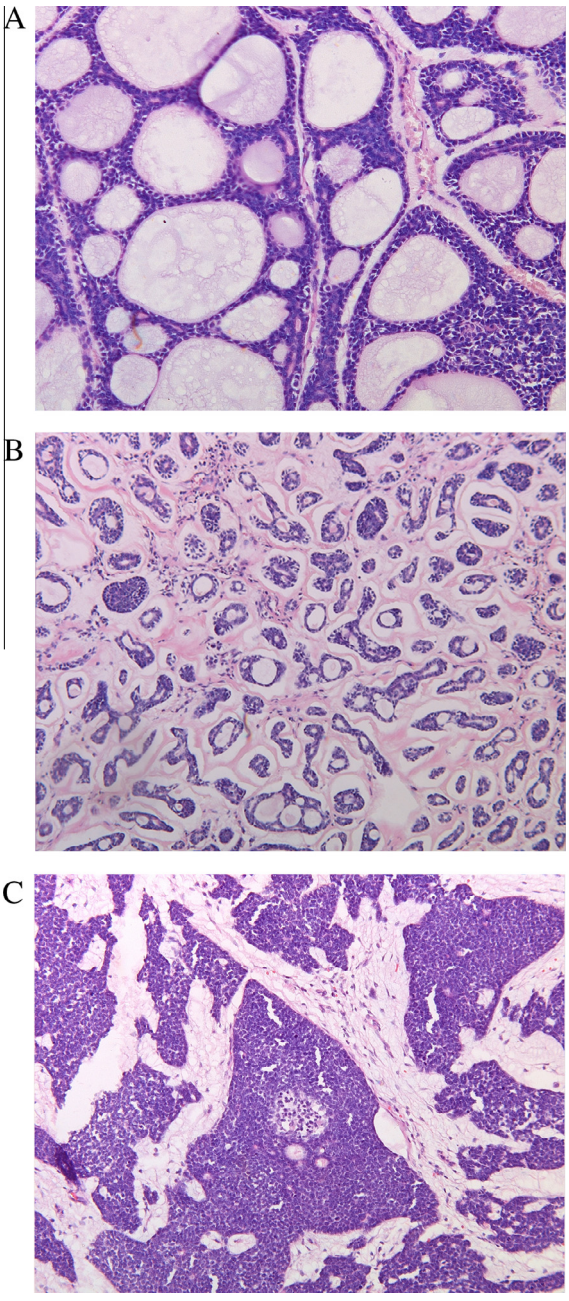

Fig. 1. (A) Cribriform, (B) tubular and (C) solid type ACC.

Possible additional prognostic factors registered were TNM stage (retrospectively staged according to UICC, 7th edition) [14], treatment modalities, perineural invasion (defined as extension of epithelial tumor cells around nerves), metastases, microscopic margins, type of salivary gland involved, gender and age. Uni- and multivariate survival analyses were performed using the Log rank and Cox regression test with SPSS statistical software version 15.0 (IBM, New York, USA). The different survival parameters scored were local control rate (LCR), distant disease free survival (DDFS), disease free survival (DFS), disease specific survival (DSS) overall survival (OS) and hazard ratios (HR) with confidence intervals (CI).

A Harrell's concordance index (C-index) – a test for assessing prediction performance in survival analyses – was calculated to

measure the predictive power of the three grading systems on survival [15].

Results

One hundred and five cases of previously untreated ACC were identified, of which 87 underwent surgery with curative intent, followed by radiotherapy in the majority of cases (93%). Patients' age ranged from 19 to 87 year (mean 57.3 year). Of the 87 surgically treated cases, 81 histological specimens were available for review. Forty-one patients were female (51%) and 41 cases involved the major salivary glands (51%). The demographic, tumor and treatment characteristics are shown in Table 2. 35/81 (43%) specimens contained solid type ACC regardless of the amount.

Application of the grading systems according to Perzin/Szanto and Spiro resp. by two expert pathologists showed that the designation of grade in 50/81 (62%) tumors differed, solely on the basis of the different criteria in the two grading systems. This is due to the defined cut off point for the relative amount of solid tumor (30% vs. 50%, respectively). This sometimes even led to a two grade difference (i.e. a mixed tumor with >30% and <50% solid component is Perzin/Szanto grade III and Spiro grade I). Moreover, a Cohen's kappa test was done to analyse the inter-observer variability of the different grading systems based on the original grading. Results showed values of 0.393 (fair) for Perzin/Szanto, 0.433 (moderate) for Spiro and 0.990 (almost perfect) for S±.

In order to actually determine the true clinical relevance of grading as such, both a univariate and a multivariate analysis were done. Univariate analysis showed that LCR, DDFS, DFS, DSS and OS all were significantly related (p-range <0.001–0.011) to tumor grade, irrespective of the grading system used, and to stage. Multivariate analysis for DSS with stepwise implementing of the prognostic factors *T*-stage and *N*-status was performed separately for the three grading systems. Table 3 shows a comparable outcome for all three grading systems.

In 10 cases (11%), positive lymph nodes were found at first presentation. In 9 out of these 10 cases pathology specimens were available for revision and showed high grade tumor in 6/9 patients (67%) and presence of solid type tumor in 8/9 cases (89%).

The 5, 10 and 20-year DSS and OS rates for the different grading systems (Perzin/Szanto, Spiro and S±) are shown in Table 4. Fig. 2 show the Kaplan Meier curves for DSS for a maximum follow up of 20 years for Perzin/Szanto, Spiro and S±, respectively. The results all show high significance with a poor survival for high grade (Perzin/Szanto grade III, Spiro grade II and III and S+) tumors. DSS and OS are also related to tumor stage (data not shown). Since it is generally assumed that stage is the strongest prognosticator for ACC [16], effects of stage on survival in low and high grade tumors is shown separately (Figs. 3A–3D). Finally, a Harrell's C-index was calculated to evaluate the actual predictive power of the grading systems used in this study. This shows that all three grading systems have a comparable predictive strength (Table 5).

Table 2
Clinicopathological data of 81 reviewed cases of ACC.

Gender		
Male	40 (49%)	
Female	41 (51%)	
Age	19–87 year (mean 57.3 year)	
Major/Minor		
Major	41 (51%)	
Minor	40 (49%)	
Histology/Grade	Perzin/Szanto	Spiro
I	19 (23%)	58 (72%)
II	40 (49%)	12 (15%)
III	22 (27%)	11 (14%)
Solid		
Yes	45 (56%)	
No	36 (44%)	
UICC[a]-stage		
I	20 (25%)	
II	25 (30%)	
III	8 (10%)	
IV	28 (35%)	
N-stage		
N1	2 (2%)	
N2a	1 (1%)	
N2b	4 (5%)	
N2c	2 (2%)	
N3	0	
Perineural invasion		
Yes	63 (78%)	
No	14 (17%)	
NR[b]		4 (5%)
Surgical margins		
⩾5 mm	10 (12%)	
1 < 5 mm	9 (11%)	
<1 mm	62 (77%)	
Postoperative RT		
Yes	75 (93%)	
No	6 (7%)	

[a] Union for international cancer control.
[b] Not reported.

Discussion

The debate on the role and actual importance of histopathological grading of ACC has been on-going for some decades. Some authors advocate that ACC should be predominantly solid to be of influence on outcome where others stipulate that the presence of a solid pattern regardless of its quantity encompasses a high grade tumor [17–22]. The results of the present study concur with the latter.

One could argue that its importance is limited, for treatment strategies – surgery ± RT – remain unchanged so it bears no clinical consequence. On the other hand, the quest for identifying adjuvant treatment targets for ACC has been disappointing so far. Grading based upon the presence of solid growth pattern seems to be an independent prognosticator according to the present study and should be taken into account as such, as is the case for T-stage and N-status, thus providing the clinician and the patient with additional prognostic information.

Although the definition of the currently used grading systems is rather different, they are both used. Difficulty is however encountered using these systems [17]. For both grading systems used, the defined cut-off point is difficult to calculate and prone to error. These could be reasons that tumor stage is considered more indicative for prognosis than grade – as reported by Spiro et al. – and that histology is often described according to the predominant pattern rather than as a numeric grade [16].

In the present study, all but one case with lymph node metastases contained solid type tumor, supporting the assertion by Myers et al. that there is a higher likelihood of lymph node metastases in solid type ACC [9]. Besides the histological subtype, recent reports emphasize the possible importance of the proliferative marker Ki-67, where a high index correlates with poorer outcome [23,24].

We suggest to exclude or confirm the mere presence of a solid component and to report it as such through the S± grading system. The Cohen's kappa test – a proven reliable measure for inter observer variability – shows a slightly better outcome for Spiro compared to Perzin/Szanto which is in accordance with the study by Therkildsen et al. [14,25,26]. However, both results show only fair to moderate values for inter-observer variability. The S± grading

Table 3
Multivariate analysis (cox regression) with hazard ratio's (HR) and 95% confidence intervals (CI) for 81 histologically reviewed cases. Separate analysis for Perzin/Szanto, Spiro and S±.

	HR	95% CI		HR	95% CI		HR	95% CI
Perzin/Szanto			Spiro			Solid		
I	1.0		I	1.0		No	1.0	
II	1.7	0.6–4.4	II	3.6	1.6–8.2	Yes	3.9	1.7–9.1
III	5.7	2.2–15.2	III	6.2	2.5–15.3			
T-stage								
1	1.0			1.0			1.0	
2	12.3	1.6–95.0		13.1	1.6–102.0		5.7	0.7–44.9
3	24.8	2.8–219.0		25.6	2.9–227.7		9.9	1.1–85.5
4	26.7	3.4–206.8		29.3	3.7–230.2		13.3	1.7–103.6
N-status								
N0	1.0			1.0			1.0	
N+	4.1	1.7–9.7		4.1	1.7–10.0		5.1	2.0–12.8

Table 4
Five, ten and twenty-year disease specific-and overall survival for Perzin/Szanto, Spiro and Solid±.

	Perzin/Szanto ($p < 0.001$)			Spiro ($p < 0.001$)			S± ($p < 0.001$)	
	I	II	III	I	II	III	No	Yes
5 year DSS[a] (%)	90	75	36	82	39	27	90	53
5 year OS[b] (%)	90	75	36	82	39	27	90	53
10 year DSS (%)	73	60	22	66	26	13	73	37
10 year OS (%)	73	55	22	62	26	13	70	34
20 year DSS (%)	58	48	11	52	0	0	64	26
20 year OS (%)	50	20	11	35	0	0	45	19

[a] Disease specific survival.
[b] Overall survival.

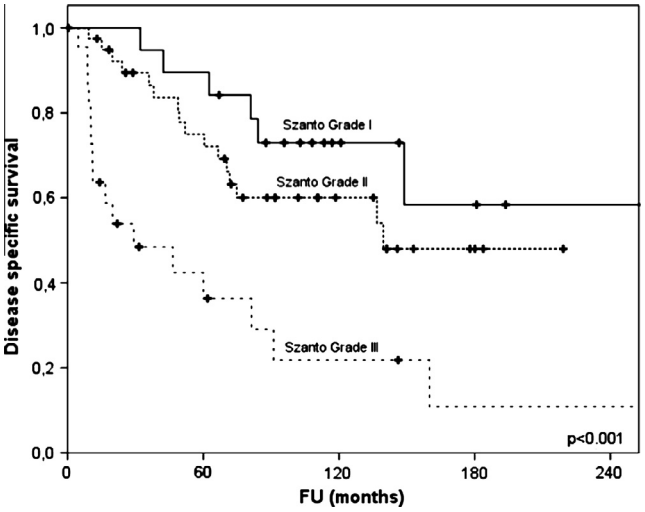

Fig. 2A. DSS for grading according to Szanto (Log Rank, significance $p < 0.05$).

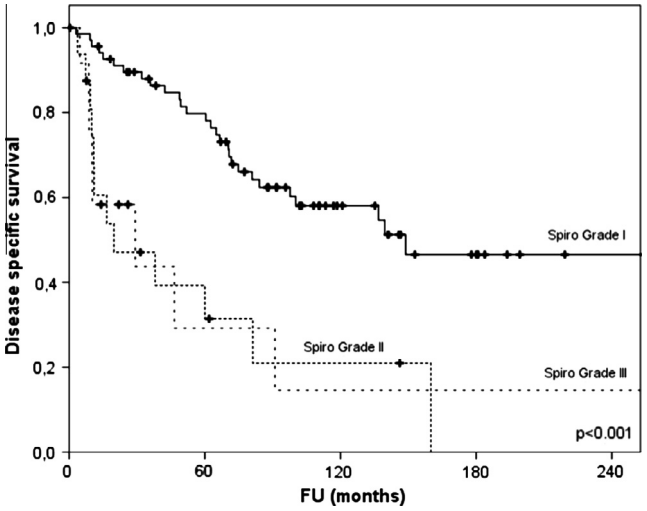

Fig. 2B. DSS for grading according to Spiro (Log Rank, significance $p < 0.05$).

system however has a Cohen's kappa result of 0.990, which resulted in an excellent correlation.

The Harrell's C-index shows that the predictive power of this grading system is equal to that of the other two grading systems. In previous studies, contradictory results are reported on the clinical relevance of grading [24,27]. However, the present study confirms through multivariate analysis that grade is an independent prognosticator which is in accordance with the study from da Cruz Perez et al. who report somewhat the same HR for solid type ACC (3.9 vs. 3.6, respectively) [27]. According to the results in this study, it is rather questionable to describe ACC histology according to its predominant pattern for the mere presence of solid type tumor despite predominance of another subtype seems to be of significant influence on survival.

According to the present study, high T-stage and N+-status remain the most powerful negative prognosticators. Because of the reliability, reproducibility and predictive power of the S± grading system we regard this grading system as a meaningful adjunct to the currently used grading systems, for grade has a significant impact on survival [11,12,24,27,28].

Conflict of interest statement

None declared.

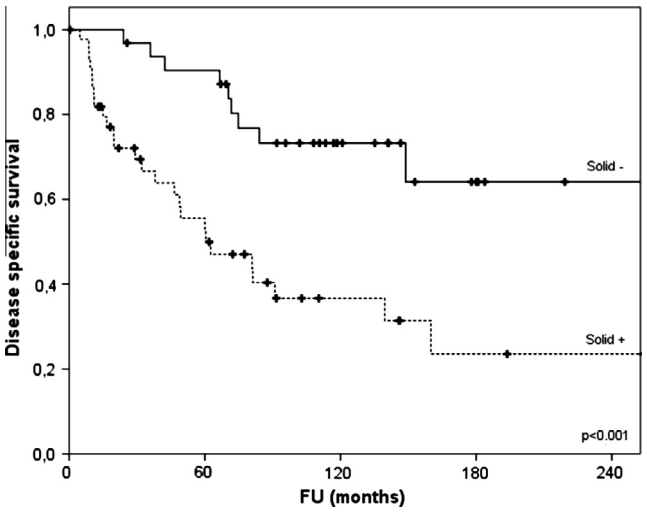

Fig. 2C. DSS for grading according to S± (Log Rank, significance $p < 0.05$).

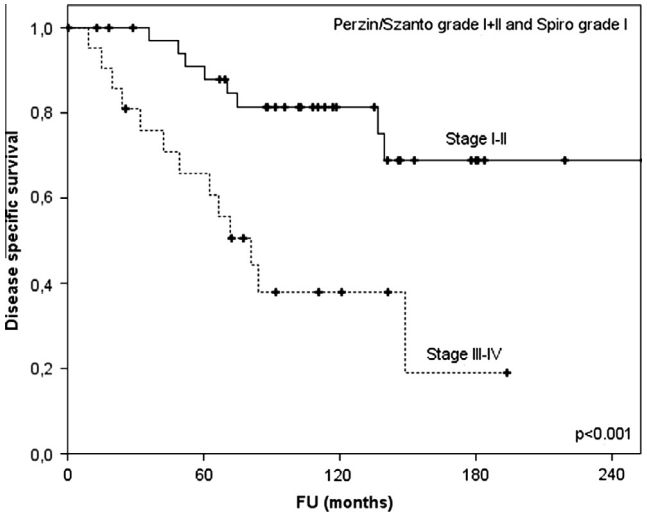

Fig. 3A. DSS for low grade ACC subdivided for early (I–II) and advanced stage (III–IV) disease (Log Rank, significance $p < 0.05$).

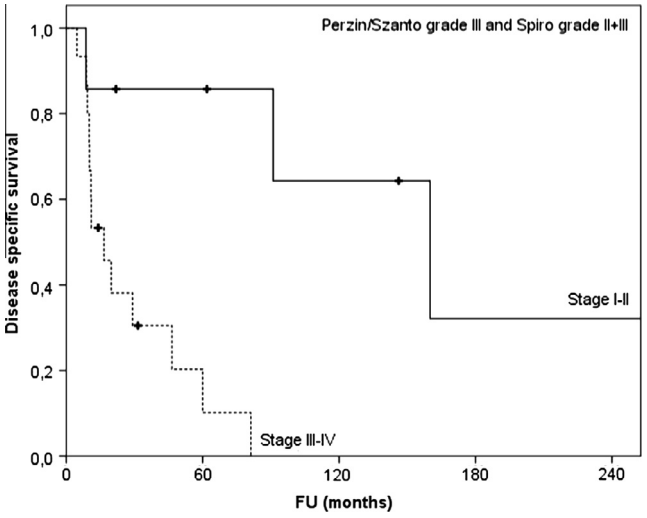

Fig. 3B. DSS for high grade ACC subdivided for early (I–II) and advanced stage (III–IV) disease (Log Rank, significance $p < 0.05$).

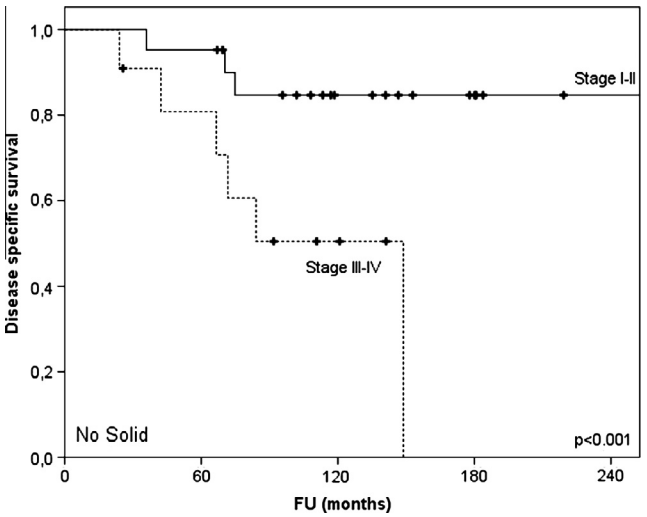

Fig. 3C. DSS for non-solid ACC subdivided for early (I–II) and advanced stage (III–IV) disease (Log Rank, significance $p < 0.05$).

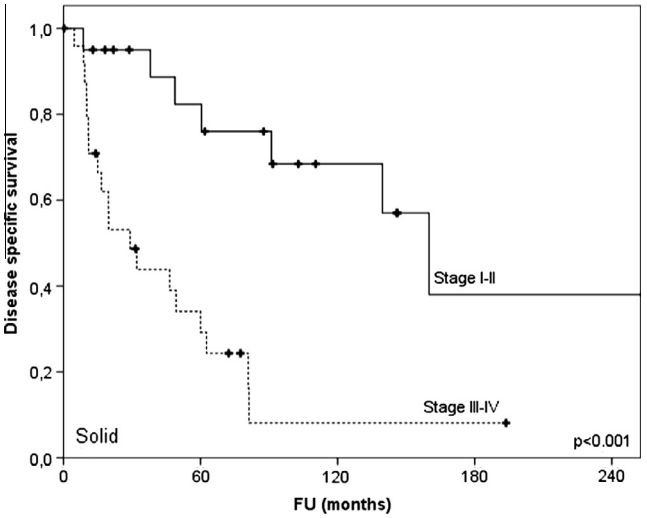

Fig. 3D. DSS for solid ACC subdivided for early (I–II) and advanced stage (III–IV) disease (Log Rank, significance $p < 0.05$).

Table 5
Harrell's C-index (H C) for all three grading systems.

	Perzin/Szanto		Spiro		S±	
	H C	95% CI	H C	95% CI	H C	95% CI
LCR[a]	0.62	0.52–0.72	0.63	0.55–0.71	0.61	0.51–0.70
DDFS[b]	0.64	0.56–0.73	0.63	0.56–0.70	0.62	0.54–0.70
DFS[c]	0.64	0.56–0.72	0.63	0.57–0.69	0.60	0.52–0.67
DSS[d]	0.66	0.58–0.74	0.65	0.59–0.72	0.65	0.57–0.73
OS[e]	0.66	0.58–0.73	0.64	0.58–0.70	0.64	0.57–0.71

[a] Local control rate.
[b] Distant disease free survival.
[c] Disease free survival.
[d] Disease specific survival.
[e] Overall survival.

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