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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.

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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

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
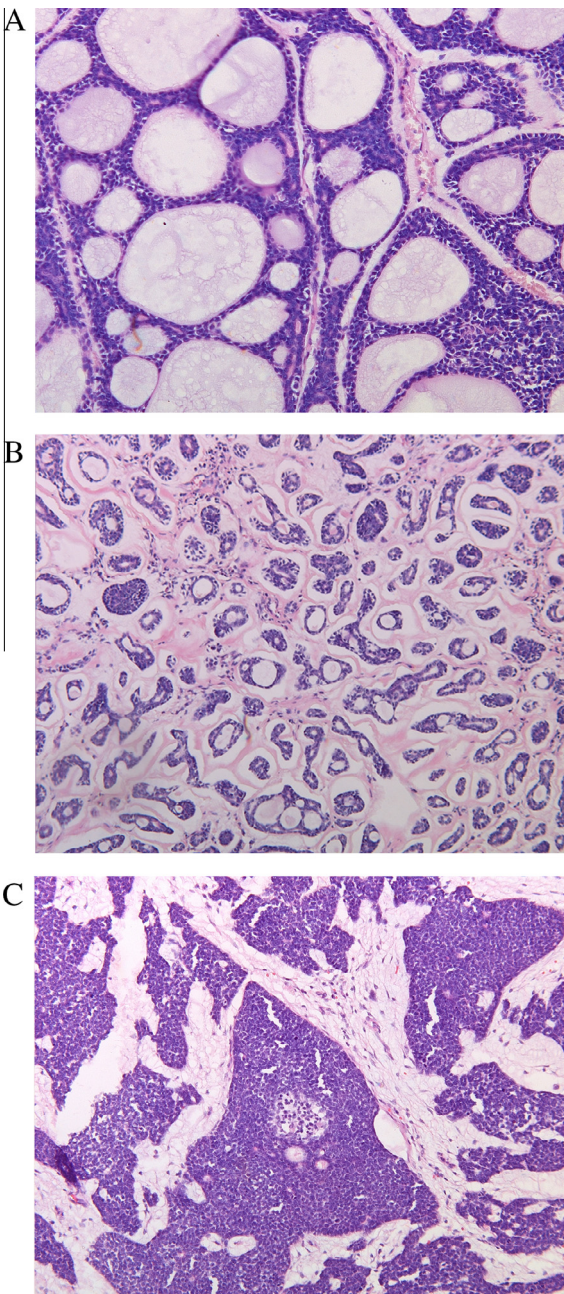

Fig. 1. (A) Cribriform, (B) tubular and (C) solid type ACC.

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].

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

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

Perzin/Szanto [10,11] Grade	Spiro et al. [12] Grade	Present study 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	