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Prognostic relevance of low-grade versus high-grade FIGO IB1 squamous cell uterine cervical carcinomas

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Abstract

Purpose Tumor grade is one of the more controversial factors with limited prognostic information in squamous cell carcinomas (SCC) of the uterine cervix.

Methods Histologic slides of 233 surgically treated cervical SCC (FIGO IB1) were re-examined regarding the prognostic impact of the WHO-based grading system, using the different degree of keratinization, categorizing the tumors in G1, G2 and G3 (conventional tumor grade).

Results 45.1% presented with well-differentiated tumors (G1), 29.2% with moderate (G2) and 25.8% with poor differentiation (G3). Tumor grade significantly correlated with decreased recurrence-free and overall survival. However, detailed analyses between G1- and G2-tumors failed to show any correlation with either recurrence-free or overall survival. G1- and G2-tumors were therefore merged into low-grade tumors and were compared to the high-grade group (G3-tumors). This binary conventional grading system showed an improved 5-years recurrence-free (low-grade: 90.2% vs. high-grade: 71.6%; $p = 0.001$) and overall survival rates (low-grade: 89.9% vs. high-grade: 71.1%; $p = 0.001$) for low-grade tumors. On multivariate analysis adjusted for lymph node metastasis, high-grade tumors represented a hazard ratio of 2.4 (95% CI 1.3–4.7) for reduced recurrence-free and 2.4 (95% CI 1.2–4.6) for overall survival. High-grade tumors showed a significantly higher risk for pelvic lymph node involvement [OR 2.7 (95% CI 1.4–5.5); $p = 0.003$]. The traditional three-tiered grading system failed to predict pelvic lymph node metastases.

Conclusion A binary grading model for the conventional tumor grade (based on the degree of keratinization) in SCC of the uterine cervix may allow a better prognostic discrimination than the traditionally used three-tiered system.

Keywords Cervix · Cancer · Prognosis · Grading · Histopathology · Treatment · Squamous cell · Survival

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Introduction

Regardless of the treatment modalities, parametrial invasion and lymph node involvement are well-accepted prognostic factors in carcinomas of the uterine cervix (Takeda et al. 2002; Vinh-Hung et al. 2007; Wagner et al. 2013). One of the most controversial factors of all histopathological prognosticators is tumor grade (Singh and Arif 2004), especially in squamous cell carcinomas (SCC). Previous studies showed a prognostic impact on survival (Delgado et al. 1990; Vinh-Hung et al. 2007). Several other studies failed to show a prognostic impact (Takeda et al. 2002; Wagner et al. 2013; Zaino et al. 1992). Especially large studies evaluating the SEER data base include a variety of different tumor stages and treatment approaches (Vinh-Hung et al. 2007; Wagner et al. 2013) which may impact the results.

Additionally, squamous cell and adenocarcinomas were not usually analyzed separately.

Traditionally, cervical SCCs are graded based on the degree of keratinization, cytological atypia and mitotic activity (Broders 1926; Wentz and Reagan 1959). This grading system has been adopted by the WHO classification and is still in use (Stoler et al. 2014; Wells et al. 2003). The present study was designed to evaluate the prognostic impact of tumor grade within a cohort of surgically treated and histopathologically staged SCCs.

Materials and methods

Data form consecutive patients with upfront surgery were obtained from our medical files. Patients who received any neoadjuvant treatment, those with incomplete tumor resection and tumors of other histologic type than pure squamous cell carcinomas were excluded from the study. Patients who showed microinvasive disease and those with parametrial involvement after histopathologic examination were also excluded. Prior to the introduction of the TMMR-technique (Höckel et al. 2003) all women were treated by radical hysterectomy Piver type III (Piver et al. 1974) at our institution. All patients with histologically proven lymph node involvement were treated with combined adjuvant radiation therapy without concurrent chemotherapy.

The pathological examination was performed in a standardized manner (Kurman and Amin 1999). All tumors were classified and staged according to the WHO- and TNM-classification (Brierley et al. 2017; Stoler et al. 2014).

Because there is no detailed description of different grades for SCC of the uterine cervix in the current WHO classification (Stoler et al. 2014), tumors were graded in accordance to previous studies (Delgado et al. 1990; Stock et al. 1994; Travis et al. 2004; Zaino et al. 1992). In well-differentiated tumors (G1) the tumor cell nests were composed of keratinocyte-like cells with easily visible keratinization features (layered or cytoplasmic keratin). In the poorly differentiated tumors (G3) squamous morphology was only noticeable in a small area of the tumor. The moderately differentiated tumors (G2) showed an intermediate degree of squamous differentiation that was between the well- and poorly differentiated ones.

The original H&E-stained slides were re-examined on low-power magnification ($\times 25$). If necessary, the infiltrating tumor cell nests were screened at intermediate-power fields ($\times 100$) for single cell keratinization and intercellular bridges.

Follow-up information was obtained from the medical charts. Written informed consent was obtained from all patients. The study was approved by the Institutional Review Board.

Recurrence-free survival (RFS) was calculated from the day of diagnosis until tumor recurrence or end of follow-up. Overall survival (OS) was calculated from the day of diagnosis until death or end of follow-up. Kaplan–Meier survival curves and log rank test were used to analyze survival data. Cox regression analyses were fitted to estimate the impact of grading. Odds ratios (OR) with 95% confidence intervals (CI) were determined to describe the chance (risk) for pelvic lymph node involvement depending on tumor grade. All statistical analyses were performed with IBM SPSS Statistics version 24.0.

Results

A total of 233 cases with a median follow-up of 71 (range 2–182) months were available for review. The patient characteristics are summarized in Table 1.

45.1% of the tumors were well-differentiated (G1), 29.2% showed a moderate differentiation (G2) and 25.8% were poorly differentiated (G3). There was a significant decrease in both recurrence-free and overall survival with increasing tumor grade (Fig. 1; Table 2). The detailed statistical analyses between the different grading groups failed to show a difference between well (G1) and moderately (G2) differentiated tumors both in recurrence-free as well as in overall survival (Table 2). As illustrated in Fig. 1, the Kaplan–Meier

Table 1 Patient characteristics ($N = 233$)

|	
Follow-up (months)	
Median (range)	71 (2–182)
Age (years)	
Median (range)	39 (23–67)
Mean $\pm$ SD	40.7 $\pm$ 10.4
Post-surgical stage distribution	
pT1b1	233 (100%)
Pelvic lymph node involvement	
No (pN0)	189 (81.1%)
Yes (pN1)	44 (18.9%)
Histological tumor type	
Squamous cell carcinoma	233 (100%)
Tumor grade	
G1	105 (45.1%)
G2	68 (29.2%)
G3	60 (25.8%)
Lymphovascular space involvement	
None	109 (46.8%)
Yes	124 (53.2%)
Recurrent disease	
No	195 (83.7%)
Yes	38 (16.3%)
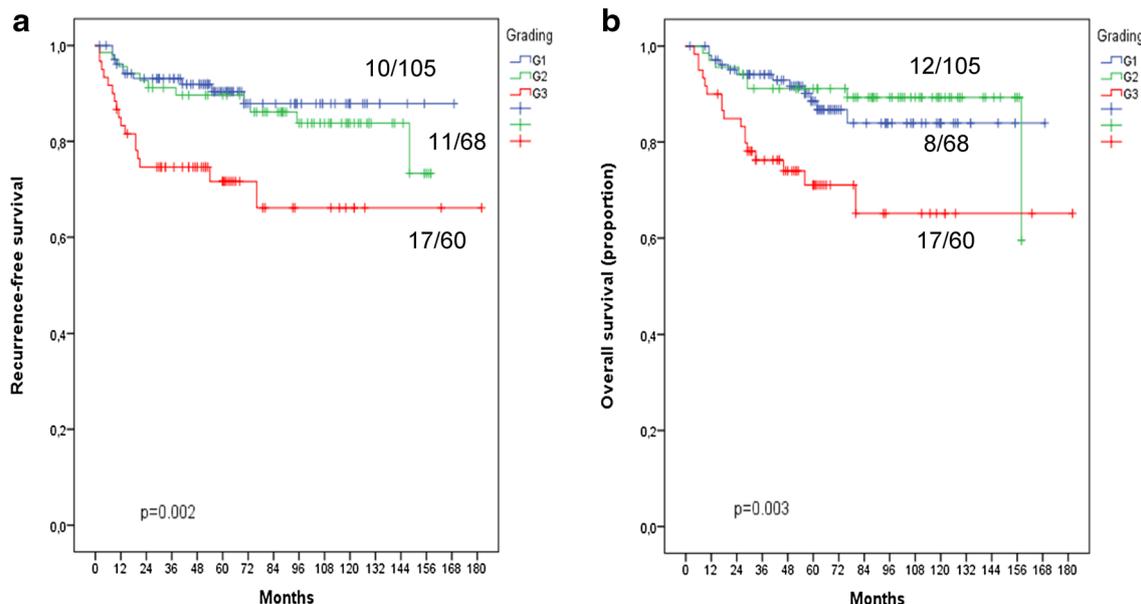
Fig. 1 Kaplan–Meier curves for prognostic impact of conventional tumor grading in squamous cell carcinoma of the uterine cervix using a 3-tiered grading system (please see text). **a** Recurrence-free survival. **b** Overall survival

Table 2 5-year rate for recurrence-free (RFS) and overall survival (OS) for the different grading groups using the conventional three-tiered grading system for squamous cell carcinomas of the uterine cervix

	5-year recurrence-free survival	p-values
G1	90.4% [95% CI: 84.3% - 96.5%]	
G2	89.6% [95% CI: 82.4% - 96.9%]	p=0.576
G3	71.6% [95% CI: 59.5% - 83.7%]	p=0.016

p=0.001 (G1 vs. G3)

global: p=0.002

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	5-year overall survival	p-values
G1	88.5% [95% CI: 81.6% - 95.4%]	
G2	91.1% [95% CI: 84.4% - 97.9%]	p=0.594
G3	71.1% [95% CI: 58.7% - 83.4%]	p=0.006

p=0.004 (G1 vs. G3)

global: p=0.003

Table 3 5-year rate for recurrence-free (RFS) and overall survival (OS) for the different grading groups using a binary approach for the conventional grading system for squamous cell carcinomas of the uterine cervix

	5-year recurrence-free survival	p values
Low-grade (G1/G2)	90.2% (95% CI 85.7–94.7%)	0.001
High-grade (G3)	71.6% (95% CI 59.5–83.7%)	

	5-year overall survival	p values
Low-grade (G1/G2)	89.9% (95% CI 85.2–94.6%)	0.001
High-grade (G3)	71.1% (95% CI 58.7–83.4%)	

survival when compared to the high-grade group [90.2% (95% CI 85.7–94.7%) versus 71.6% (59.5–83.7%); $p = 0.001$; Table 3 and Fig. 2]. The 5-year overall survival rate was significantly higher in the low-grade compared to the high-grade group [89.9% (95% CI 85.2–94.6%) versus 71.1% (95% CI 58.7–83.4%); $p = 0.001$; Table 3 and Fig. 2b]. In the multivariate Cox regression analysis that included the pelvic lymph node status and binary tumor grade, there was a 2.4-fold increase in the risk for recurrent disease and death from the tumor for high-grade tumors (Table 4).

The frequency of pelvic lymph node involvement within the different grading is summarized in Table 5.

Overall, between the conventional three-tiered tumor grading and the pelvic lymph node involvement was a significant association ($p = 0.009$).
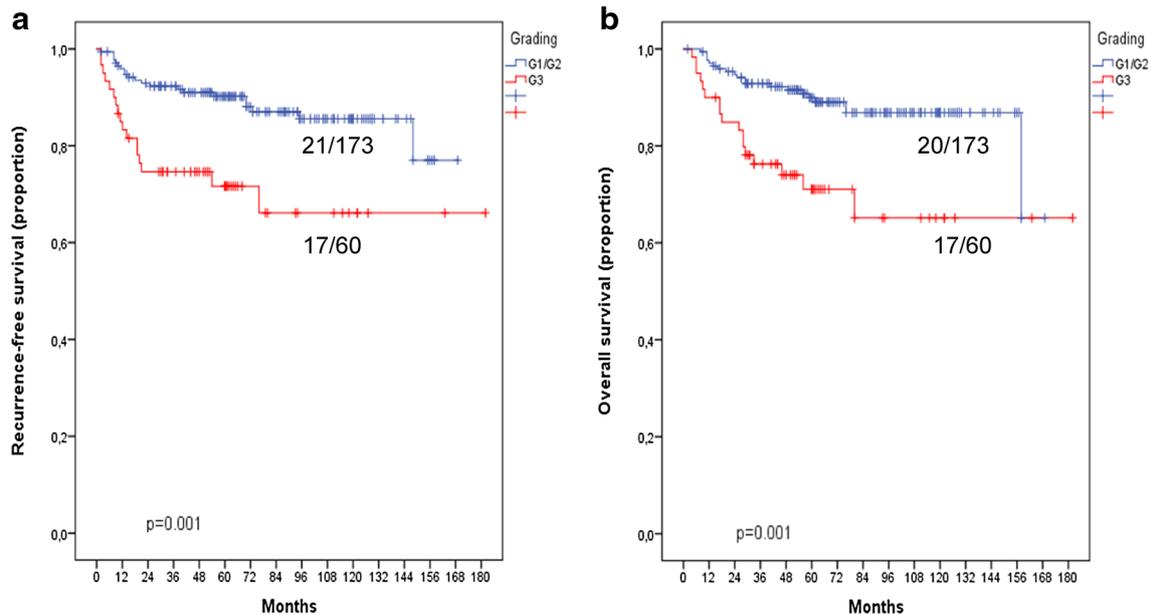
curves for recurrence-free as well as for overall survival run closely together.

For further analyses, a binary grading model was established. The G1- and G2-tumors were merged into a low-grade group, whereas the G3-tumors formed the high-grade group. The majority of the tumors were part of the low-grade group (173/233; 74.2%) and 25.8% showed high-grade morphology. Patients within the low-grade group were found to have a significantly increased 5-year recurrence-free

Fig. 2 Kaplan–Meier curves for the prognostic impact of conventional tumor grading in squamous cell carcinoma of the uterine cervix using a 2-tiered grading system (please see text). **a** Recurrence-free survival. **b** Overall survival

Table 4 Cox regression analyses for recurrence-free and overall survival

	HR	*p* values
Recurrence-free survival		
Pelvic lymph node involvement		
No (pN0)	Ref.	
Yes (pN1)	3.3 (95% CI 1.7–6.4)	< 0.001
Histological tumor grade		
Low-grade (G1 + G2)	Ref.	
High-grade (G3)	2.4 (95% CI 1.3–4.7)	0.009
Overall survival		
Pelvic lymph node involvement		
No (pN0)	Ref.	
Yes (pN1)	4.0 (95% CI 2.1–7.7)	< 0.001
Histological tumor grade		
Low-grade (G1 + G2)	Ref.	
High-grade (G3)	2.4 (95% CI 1.2–4.6)	0.011

The risk for lymph node involvement for G2 tumors compared to G1 tumors was increased slightly [OR = 1.52 (95% CI 0.65–3.56)] and not significantly. More pronounced by a factor of about two was the risk for lymph node involvement for G3 tumors related to G2 tumors [OR = 2.16 (95% CI 0.94–4.95); $p < 0.05$].

However, using the binary grading system, there was a relevant and significant increased risk for lymph node involvement for high-grade tumors compared to low-grade tumors [OR 2.74 (95% CI 1.38–5.47), $p = 0.003$].

Table 5 Pelvic lymph node involvement within different grading groups

	Conventional grading				
	Three-tiered grading system			Binary grading system	
	G1 (*n* = 105)	G2 (*n* = 68)	G3 (*n* = 60)	Low-grade (*n* = 173)	High-grade (*n* = 60)
pN0	87.6%	82.4%	68.3%	85.5%	68.3%
pN1	12.4%	17.6%	31.7%	14.5%	31.7%
p value	0.009			0.003	

Discussion

Lymph node status, tumor stage and tumor size are the most powerful and well-accepted prognostic factors in cervical carcinoma (Piura et al. 2006; Singh and Arif 2004; Takeda et al. 2002; Wagner et al. 2013). Data about the impact of histopathological tumor grade are more controversial, particularly in squamous cell cancers of the uterine cervix (SCC; Singh and Arif 2004).

Historically, cervical SCCs were graded using Broders system (Broders 1926) or modifications thereof based on the degree of keratinization (Wentz and Reagan 1959). This particular grading system of cervical SCCs is still mentioned in the last two WHO classifications (Stoler et al. 2014; Wells et al. 2003) and is referred to as conventional grading in order to differentiate it from other grading systems.

In an earlier GOG study, the 3-year disease-free interval correlated significantly with the conventional tumor grade (G1: 90.6%, G2: 86.0% and for G3: 76.1%; $p = 0.001$; 4). Metindir and Bilir (2007) reported that tumor grade was a prognostic factor regarding 5-year disease-free survival. In a larger study of 331 node-negative patients with FIGO stages IB–IIA, grading had no prognostic relevance regarding 5-year disease-free survival (Sartori et al. 2007). Tumor grade was no predictor for vaginal and/or parametrial invasion or pelvic lymph node involvement in FIGO stage IB patients (Koleli et al. 2014; Kong et al. 2016; Silva-Filho et al. 2005; Xie et al. 2016).

In the present study, conventional tumor grade was of prognostic impact both on recurrence-free and overall survival (Fig. 1; Table 2). However, separate analyses revealed no difference between well-differentiated (G1) and moderately differentiated (G2) tumors with regard to recurrence-free and overall survival (Fig. 1; Table 2). After merging G1 and G2 tumors into low-grade tumors, this two-tiered conventional grading showed a statistically more powerful impact both on recurrence-free and overall survival (Fig. 2; Table 3). The prognostic power of the two-tiered conventional grading persisted in multivariate analyses including lymph node status (Table 4). The high-grade tumors showed a hazard ratio of 2.4 (95% CI 1.3–4.7) and of 2.4 (95% CI 1.2–4.6) for recurrent disease and death from the disease, respectively.

With an odds ratio of 1.52 (95% CI 0.65–3.56) there was no difference regarding the risk of pelvic lymph node involvement using the three-tiered conventional grading system. Using the binary grading system, high-grade tumor represented a near threefold increase in the frequency of pelvic lymph node metastases [OR 2.74 (95% CI 1.38–5.47); $p = 0.003$].

The advantage of the present study may be the analysis of a well-defined study population including only histopathologically staged T1b1-tumors with pure squamous cell histology treated by a primary surgical approach.

Many attempts regarding the definition of grading systems for SCCs of the cervix uteri have been made (Kristensen et al. 1999; Stock et al. 1994). An invasive front grading was suggested by Kristensen et al. (1999). This type of grading was first introduced in head and neck SCCs (Bryne et al. 1992) and evaluates the degree of keratinization, nuclear pleomorphism, pattern of invasion and peritumoral host response at the infiltrative edge of SCCs. In cervical cancer, however, data on this grading system are very limited (Kristensen et al. 1999). Not uncommonly, studies assessing tumor grade as a potential prognostic variable provide no details on the grading system applied. The definition of grading criteria is also an issue in large multicenter investigations such as the SEER analyses (Macdonald et al. 2009; Sartori et al. 2007; Vinh-Hung et al. 2007).

The dilemma of the definition of a grading system in carcinomas with squamous cell histology is not limited to the uterine cervix but is also evident in lung cancer (Kadota et al. 2017; Travis et al. 2004). A recent study evaluated the grade of tumor budding in pulmonary SCC (Kadota et al. 2017). Tumor budding was initially described in colorectal cancer and is defined as the presence of isolated small tumor nests composed of < 5 tumor cells within the stroma of the invasive front of the tumor (Karamitopoulou et al. 2013; Prall 2007). A high number of tumor buds is associated with poor outcome both in colorectal adenocarcinomas and squamous cell cancers of the lung (Kadota et al. 2017; Karamitopoulou et al. 2013). Studies have shown that tumor cell budding may be associated with epithelial–mesenchymal transition and increased cell migration (Kalluri and Weinberg 2009; Taira et al. 2012). Similar to the different patterns of invasion including a finger-like and spray-like growth pattern in SCC of the uterine cervix (Horn et al. 2006, 2012), tumor budding signifies the histopathologic feature of tumor cell dissociation. The invasive front grading (Kristensen et al. 1999) and growth pattern analyses at the invasive tumor front (Horn et al. 2006) may be included in future approaches to define a grading system in SCC of the uterine cervix.

At the present time, no particular grading system(s) has achieved universal acceptance nor has one been recommended by the most recent WHO classification (Stoler et al. 2014). According to the most recent International Collaboration on Cancer Reporting (ICCR 2017) recommendations for cervical cancer, grading of SCCs of the uterine cervix has uncertain clinical value. Finally, additional studies are required to define standardized and reproducible criteria for the grading of SCC of the uterine cervix.

Compliance with ethical standards

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