Thieme

The Prognostic Impact of Grading in FIGO IB and IIB Squamous Cell Cervical Carcinomas

Prognostischer Effekt von Grading bei FIGO-IB- und -IIB-Plattenepithelkarzinom der Cervix uteri

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ABSTRACT

Background Tumor grade is one of the more controversial factors, and the data regarding its prognostic impact in squamous cell carcinoma (SCC) of the uterine cervix are controversial.

Methods The histological slides of 467 surgically treated FIGO stage IB1 to IIB cervical SCC were re-examined regarding the prognostic impact of the histological tumor grade based on the degree of keratinization (conventional tumor grade) according to the WHO recommendation on recurrence-free and overall survival as well as on the prediction of pelvic lymph node involvement.

Results 46.0% presented with well-differentiated tumors (G1, n = 215), 30.6% with moderate (G2, n = 143) and 23.3% with poor differentiation (G3, n = 109). The recurrence-free survival was significantly reduced in patients with poorly differentiated tumors (G1: 81.4%, G2: 70.6%, G3: 64.2%; p = 0.008). There was no impact on overall survival. Because of the lack of survival differences between G1- and G2-tumors, they were merged into low-grade tumors, and their prognostic outcome was compared to the high-grade group (G3-tumors). Based on this binary conventional grading system there was a significantly longer recurrence-free (low-grade: 77.1% vs. high-grade: 64.2%; p = 0.008) and overall survival (low-grade: 76.0% vs. high-grade: 65.1%; p = 0.031) in the low-grade group. However, both the conventional three-tiered and the binary grading systems (separating tumors into a low- and high-grade group) failed to predict pelvic lymph node involvement (p = 0.9 and 0.76, respectively).

Conclusion A binary grading model for the conventional tumor grade (based on the degree of keratinization) in SCC of the uterine cervix may be suitable for the prognostic survival evaluation but failed to predict pelvic lymph node involvement.

ZUSAMMENFASSUNG

Hintergrund Tumorgrade gehören zu den umstrittenen Faktoren bei der Einschätzung von Tumoren, und die Daten zum prognostischen Effekt von Tumorgrading für das Plattenepithelkarzinom der Cervix uteri sind kontrovers.

Methoden Die histologischen Präparate von 467 operativ behandelten FIGO-IB1- bis -IIB-Plattenepithelkarzinome der Cervix uteri wurden einer erneuten Untersuchung unterzogen. Untersucht wurde u. a. der prognostische Effekt des histologi-

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schen Tumorgrads, basierend auf das Ausmaß der Keratinisierung (konventionelles Tumorgrading) gemäß der WHO-Empfehlung zum rezidivfreien Überleben und Gesamtüberleben sowie die prognostische Aussagekraft von Grading im Hinblick auf den Lymphknotenbefall in der Beckenregion.

Ergebnisse In 46,0 % der Präparate war der Tumor gut differenziert (G1, n = 215), in 30,6 % war er mäßiggradig differenziert (G2, n = 143), und in 23,3 % der Fälle war der Tumor schlecht differenziert (G3, n = 109). Bei Patientinnen mit schlecht differenzierten Tumoren war das rezidivfreie Überleben deutlich reduziert (G1: 81,4 %, G2: 70,6 %, G3: 64,2 %; p = 0,008). Es gab aber keine Auswirkungen auf das Gesamtüberleben. Weil es fast keinen Unterschied in den Überlebensraten zwischen G1- und G2-Tumoren gab, wurden diese als Low-Grade-Karzinome zusammengefasst, und das prognostische Ergebnis für diese Low-Grade-Tumoren wurde mit dem der High-Grade-Gruppe (G3-Tumoren) verglichen. Bei diesem binären konventionellen Gradingsystem war das rezidivfreie Überleben (Low-grade: 77,1 % vs. High-grade: 64,2 %; p = 0,008) und das Gesamtüberleben (Low-grade: 76,0 % vs. High-grade: 65,1 %; p = 0,031) der Low-Grade-Gruppe deutlich länger. Aber sowohl das konventionelle 3-stufige System als auch das binäre Gradingsystem (bei dem die Tumoren in Low-grade und High-grade unterteilt wurden) waren nicht in der Lage, prognostische Aussagen zum Befall von Beckenlymphknoten zu machen (p = 0,9 resp. 0,76).

Schlussfolgerung Beim Plattenepithelkarzinom der Cervix uteri eignet sich ein binäres Gradingsystem für konventionelle Tumorgrade (basierend auf das Ausmaß der Keratinisierung) zwar für die prognostische Einschätzung des Überlebens, es ist aber nicht in der Lage, prognostische Aussagen zum Befall der Beckenlymphknoten zu machen.

Introduction

There are several reports in the literature on survival and disease-free intervals and on their relationship to surgical-pathological factors in cervical carcinoma of the uterus [1–4]. Among these factors, pelvic lymph node involvement and tumor stage are well-established prognostic parameters. The histopathological grading of cervical cancer, however, is one of the more controversial factors, especially in squamous cell carcinomas (SCC) [2, 5, 6]. Historically, grading of cervical SCCs was performed using Broder's system or modifications thereof based on the degree of keratinization, cytological atypia and mitotic activity [7, 8]. This grading system has been adopted by the WHO classification and is still valid, but it tends to be vague and unprecise [6, 9]. Therefore, the present study was designed to evaluate the prognostic impact of the conventional grading based on the degree of keratinization within a large cohort of SCCs. A potential correlation of the conventional tumor grade with the recurrence-free and overall survival as well as pelvic lymph node metastases was used to determine the prognostic significance of grading in squamous cell cervical carcinomas. This may help to better define the role of tumor grade in cervical SCC and its possible consequences on clinical treatment decisions.

Material and Methods

Patients

Data from 467 consecutive squamous cell cervical cancer patients, clinically staged FIGO IB1 to IIB, who underwent upfront surgery were obtained from the files of the Institute of Pathology, University Hospital of Leipzig, Germany. Patients who received neoadjuvant therapy, those with incomplete local tumor resection and non-squamous cell histology were excluded from the study. Prior to the introduction of the TMMR-technique [10] at our institution, all women were treated by a radical abdominal hysterec-
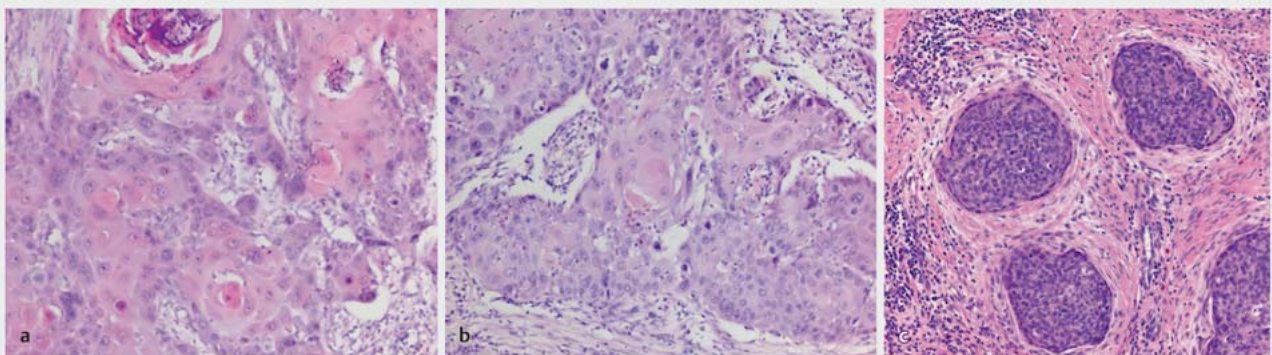
▶ **Fig. 1** Histologic images of different grades of squamous cell carcinoma of the uterine cervix. **a** G1: well-differentiated SCC: tumor cell nests with easily visible keratinization features (layered or cytoplasmic keratin). **b** G2: moderately differentiated SCC with focal keratinization within the tumor cells. **c** G3: tumor cell nests with squamous features without keratinization.

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tomy Piver type III [11]. All patients with parametrial involvement and/or lymph node metastases underwent adjuvant intracavitary radiotherapy (ICRT) and external beam chemoradiation.

Pathological examination

The pathological examination of the radical hysterectomy specimen was performed in a standardized manner [12]. All tumors were staged and classified according to the WHO and TNM-classifications [6, 13].

As a detailed description of the different grades is not included in the current WHO classification [6], tumors were graded in accordance to previous studies [14–17]. 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), the squamous morphology was only noticeable in a small area of the tumor, not exceeding 1% of the whole tumor. The moderately differentiated tumors (G2) showed an intermediate degree of squamous differentiation between the well- and poorly differentiated ones (▶ **Fig. 1 a** to **c**).

The original H&E-stained slides were re-examined on low power magnification (× 25). If necessary, the infiltrating tumor cell nests were screened at intermediate power fields (× 100) for single cell keratinization and intercellular bridges. Two to six slides per case were investigated (mean 2.7 per case).

Follow-up data

Follow-up data were retrieved from the medical records. Written informed consent was obtained from all patients. Additionally, 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 tests were used to analyze the survival data. Cox regression analyses were fitted to estimate the impact of grading. All statistical analyses were performed with IBM SPSS Statistics version 24.0.

Results

Grading and prognosis

A total of 467 cases were available for review. The patient characteristics are summarized in ▶ **Table 1**.

46.0% (n = 215) presented with well-differentiated tumors (G1), 30.6% (n = 143) showed moderate differentiation (G2) and 23.3% (n = 109) were poorly differentiated (G3).

The three grading groups were prognostically relevant for recurrence-free (p = 0.008; ▶ **Fig. 2 a**) but not for overall survival (p = 0.089; ▶ **Fig. 2 b**).
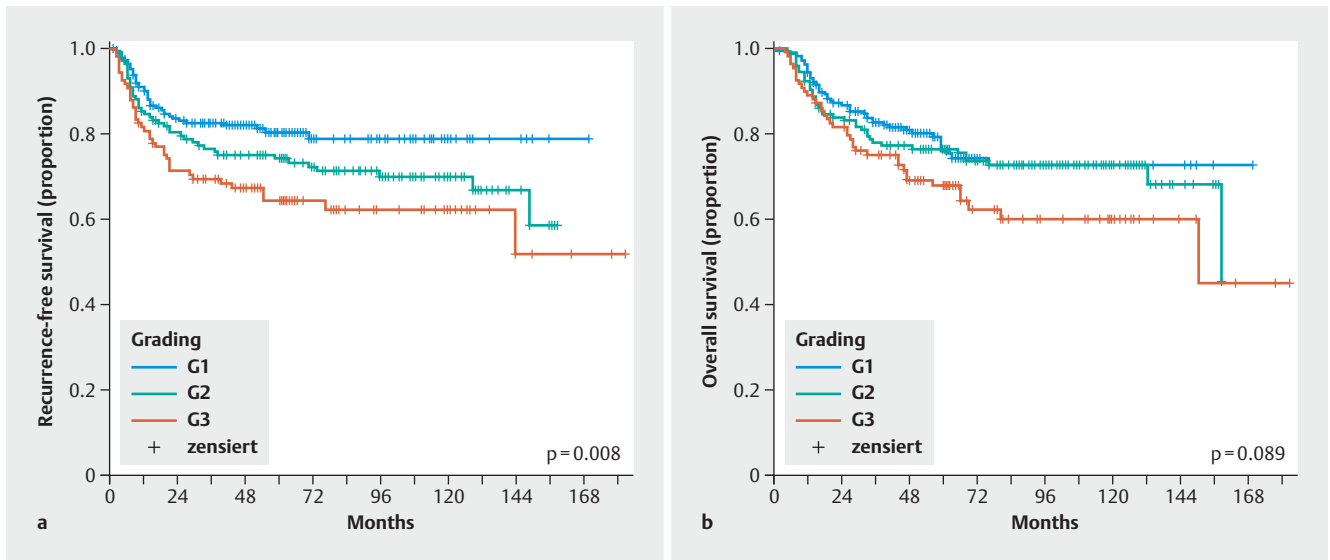
A separate analysis of well- and moderately differentiated tumors regarding recurrence-free and overall survival was performed and revealed no significant difference (p = 0.002 for 5-year recurrence-free survival and p = 0.033 for 5-year overall survival, ▶ **Table 2**). This is illustrated in ▶ **Fig. 2 b** where the survival curves are merging. Therefore, the well- and moderately differentiated carcinomas were merged into a low-grade group, whereas

▶ **Table 1** Patient characteristics (n = 467).

Follow-up (months)	
▪ Median (range)	69 (2–182)
Age (years)	
▪ Median (range)	41 (23–74)
▪ Mean ± SD	42 ± 11
Post-surgical stage distribution	
▪ pT1b1	233 (49.9%)
▪ pT1b2	55 (11.8%)
▪ pT2a	49 (10.5%)
▪ pT2b	130 (27.8%)
Pelvic lymph node involvement	
▪ No (pN0)	314 (67.2%)
▪ Yes (pN1)	153 (32.8%)
Tumor grade	
▪ G1	215 (46.0%)
▪ G2	143 (30.6%)
▪ G3	109 (23.3%)
Lymphovascular space involvement	
▪ None (L0)	169 (36.2%)
▪ Yes (L1)	298 (63.8%)
Recurrent disease	
▪ No	346 (74.1%)
▪ Yes	121 (25.9%)

▶ **Table 2** 5-year-recurrence-free (RFS) and -overall survival (OS) of the different grading groups using the conventional grading system for squamous cell carcinomas of the uterine cervix (p-values [Log rank test]).

	5-year recurrence-free survival	p-values	
G1	80.4% (95% CI: 74.7–86.0%)	p = 0.089 (G1 vs. G2)	p = 0.002 (G1 vs. G3)
G2	74.2% (95% CI: 66.9–81.5%)		
G3	64.4% (95% CI: 54.9–73.8%)	p = 0.162 (G2 vs. G3)	
		global: p = 0.008	
	5-year overall survival	p-values	
G1	76.4% (95% CI: 70.0–82.8%)	p = 0.603 (G1 vs. G2)	p = 0.033 (G1 vs. G3)
G2	76.4% (95% CI: 69.3–83.5%)		
G3	67.8% (95% CI: 58.6–77.0%)	p = 0.121 (G2 vs. G3)	
		global: p = 0.089	

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▶ **Fig. 2** Kaplan-Meier curves for the 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.
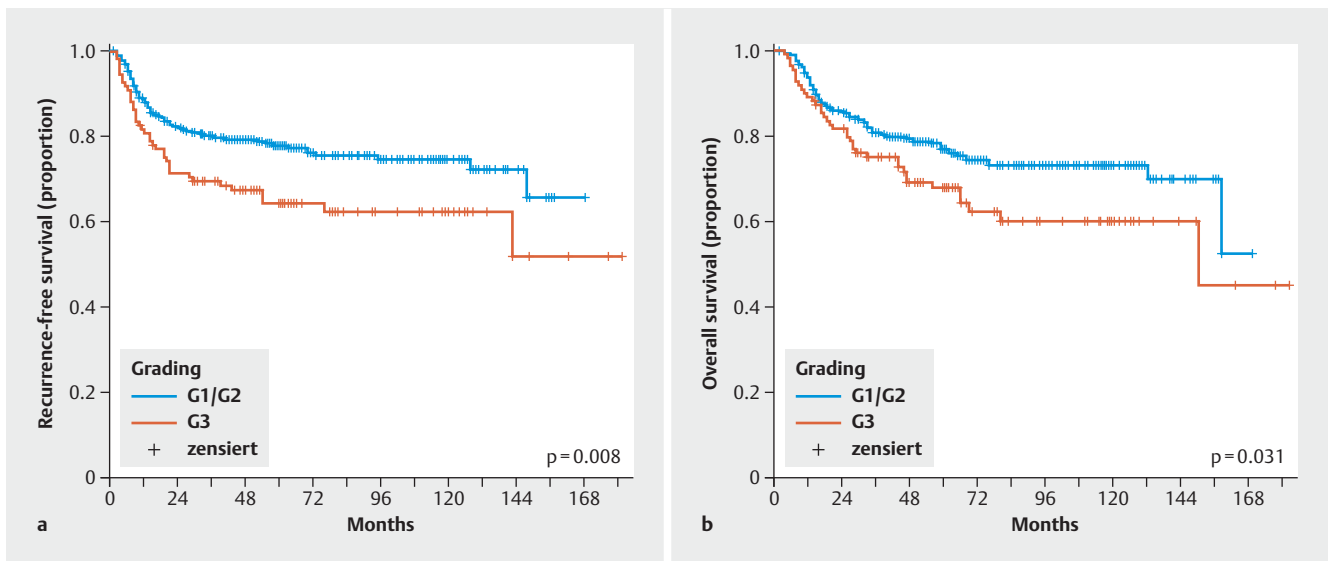
▶ **Fig. 3** Kaplan-Meier curves for the prognostic impact of conventional tumor grading in squamous cell carcinoma of the uterine cervix using a 2-tiered grading system (please see text). **a** Recurrence-free survival. **b** Overall survival.

the poorly differentiated carcinomas formed the high-grade group. 358/467 patients (76.6%) were found to have low-grade, 109/467 (23.3%) high-grade tumors.

As illustrated in ▶ **Fig. 3**, there was a significant difference between low- and high-grade tumors regarding the recurrence-free and overall survival, respectively. The 5-year recurrence-free survival for G1/G2 versus G3 tumors was 77.9% (95% CI 73.4–82.3%) versus 64.4% for the G3 tumors (95% CI 54.9–73.8%; p = 0.008). G1/G2 tumors showed a 5-year overall survival of 76.9% (95% CI 72.3–81.5%) versus 67.8% for the G3 tumors

(95% CI 58.6–77.0%; p = 0.031). The survival rates are shown in ▶ **Table 3**.

Grading and lymph node involvement

The frequency of pelvic lymph node involvement for the different grading systems used is presented in ▶ **Table 5**.

The conventional three-tiered grading system failed to predict pelvic lymph node involvement. The odds ratios for G1 versus G2 (0.98 [95% CI: 0.62–1.54]) and G2 versus G3 (1.08 [95% CI: 0.64–1.84]) were not statistically different. Also, the binary grading was

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▶ **Table 3** 5-year-recurrence-free (RFS) and -overall survival (OS) of the different grading groups using the conventional grading system for squamous cell carcinomas of the uterine cervix (p-values [Log rank test]).

	5-year recurrence-free survival	p-values
G1/G2	77.9% (95% CI: 73.4–82.3%)	p = 0.008
G3	64.4% (95% CI: 54.9–73.8%)	
	5-year overall survival	p-values
G1/G2	76.9% (95% CI: 72.3–81.5%)	p = 0.031
G3	67.8% (95% CI: 58.6–77.0%)	

▶ **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)	2.7 (95% CI: 1.8–3.9)	p < 0.001
Histological tumor grade		
▪ Low-grade (G1 + G2)	ref	
▪ High-grade (G3)	1.8 (95% CI: 1.2–2.6)	p = 0.003
Post-surgical stage		
▪ pT1b1	ref	
▪ pT1b2	2.2 (95% CI: 1.2–3.5)	p = 0.013
▪ pT2a	1.4 (95% CI: 0.7–2.8)	p = 0.373
▪ pT2b	2.4 (95% CI: 1.5–3.7)	p < 0.001
Overall survival		
Pelvic lymph node involvement		
▪ No (pN0)	ref	
▪ Yes (pN1)	2.8 (95% CI: 1.9–4.1)	p < 0.001
Histological tumor grade		
▪ Low-grade (G1 + G2)	ref	
▪ High-grade (G3)	1.7 (95% CI: 1.1–2.4)	p = 0.011
Post-surgical stage		
▪ pT1b1	ref	
▪ pT1b2	1.6 (95% CI: 0.9–3.0)	p = 0.107
▪ pT2a	1.7 (95% CI: 0.9–3.3)	p = 0.102
▪ pT2b	2.7 (95% CI: 1.7–4.1)	p < 0.001

unable to predict pelvic lymph node involvement (OR 1.07 [95% CI: 0.68–1.7]; p = 0.76).

Discussion

Clinical and postsurgical tumor stage as well as lymph node status are the most powerful predictors of outcome in cervical cancer [2–4]. The data regarding the prognostic impact of the tumor grade in squamous cell cancers (SCC) of the uterine cervix are controversial, and several approaches using different morphologic variables have been applied [15].

Historically, cervical SCCs were graded using Broder's system [7] or modifications thereof based on the degree of keratinization [8]. This particular grading system of cervical SCCs is currently mentioned in the last two editions of the WHO classification [6, 9] and is referred to as the conventional grading in order to separate it from other grading systems. In an earlier GOG-study, the three-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) [14]. In a small study of 97 patients, grading had an impact on overall survival [18]. Other studies including those with multivariate approaches showed no prognostic significance of conventional grading [1, 16]. In the present study, the conventional grading failed to show a prognostic impact on overall survival. There were no differences between well-differentiated (G1) and moderately differentiated (G2) tumors in regards to recurrence-free and overall survival (▶ **Fig. 2** and **Table 2**). After merging G1 and G2 tumors into low-grade tumors, the two-tiered conventional grading of cervical SCCs showed a prognostic im-

pact both on recurrence-free and overall survival (▶ **Fig. 3** and **Tables 2** and **3**).

In the present study, both the conventional three-tiered and the binary grading system failed to predict pelvic lymph node involvement (▶ **Table 5**).

In multivariate analyses including pelvic lymph node status, grading and the post-surgical tumor stage, the binary grading sys-

▶ **Table 5** Pelvic lymph node involvement within different grading groups.

Conventional grading					
	three-tiered grading system			**binary grading system**	
	G1 (n = 215)	G2 (n = 143)	G3 (n = 109)	low-grade (n = 358)	high-grade (n = 109)
pN0	67.4%	67.8%	66.1%	67.6%	66.1%
pN1	32.6%	32.2%	33.9%	32.4%	33.9%
p-value	p = 0.953			p = 0.764	

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tem was prognostically significant for recurrence-free as well as overall survival (▶ **Table 4**).

The advantage of the binary grading system may be the easier morphological categorization using only two rather than three different categories as well as the better reproducibility. While the conventional three-tiered grading system failed to predict prognosis, the binary system was useful in predicting both a reduced recurrence-free and overall survival. One limitation of the present study may be that it includes a variety of different stages of cervical carcinoma which may impact the results. The inclusion of different stages may also be responsible for the failure to predict pelvic lymph node involvement within the different grading groups.

Many attempts regarding the definition of grading systems on SCCs of the cervix uteri have been made [15]. Within that context, an invasive front grading was suggested [19]. This type of grading was first introduced in head and neck SCCs [20] 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. Very recently, tumor cell budding (evaluating tumor growth by cell nest size) was studied in cervical SCC [21]. The tumor budding as a variant of the grading of a malignancy was previously validated in esophageal, lung and oral SCC.

Furthermore, studies that discuss tumor grade as a prognostic factor give no detailed description of the grading system that was applied [22, 23]. At this point, there is no well-accepted and widely used grading system for cervical SCCs [24, 25], nor has one been recommended by the current WHO classification [6]. Because of these limitations, tumor grading is not listed as a required but rather a recommended feature in the most recent recommendations of the International Collaboration on Cancer Reporting [5] for cervical cancer. The German national guidelines for the diagnosis and treatment of cervical carcinoma point out that grading should not be used as a single factor for adjuvant treatment decision [26].

Finally, additional studies are required to define standardized and reproducible criteria for grading with stage-by-stage analyses and a multivariate approach.

Conclusions

A binary grading model for the conventional tumor grade (based on the degree of keratinization) in SCC of the uterine cervix may be suitable for the prognostic survival evaluation but failed to predict pelvic lymph node involvement.

Conflict of Interest

The authors declare that they have no conflict of interest.

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