Prospective Malignancy Grading of Invasive Squamous Carcinoma of the Uterine Cervix. Prognostic Significance in a Long-term Follow-up

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Abstract. *A multifactorial grading score (MGS) for invasive squamous cell carcinoma of the uterine cervix has demonstrated its capacity to predict survival in a 5-10 year perspective and metastasis frequencies, and is a valuable tool for treatment schedules. In this study it was shown that the power of prognosis is valid even up to 20 years. In this material from 619 cervical carcinoma patients the MGS scores turned out to remain as strong as earlier proven. Earlier studies have shown that MGS is superior to other mono- and multifactorial grading systems, histological differentiation into cell types, age, clinical stage, irradiation and DNA-analysis. Treatment of cervical squamous cell carcinoma is more specific today to meet the patients' need for instance to preserve fertility or to minimize operation and eventually radiotherapy. The MGS score is a strong prognostic tool in patients with cervical carcinoma.*

The problem of making a reliable prognosis before treatment in patients with invasive squamous cell carcinoma of the uterine cervix has been approached by studying mono- and multifactorial histopathological systems (1). Also clinical staging, TNM, has been used together with other elaborate diagnostic techniques, such as immunological, DNA analysis, chromosomal and computer-aided methods (1). The FIGO system has been most valid, although it cannot sufficiently predict the clinical outcome in individual patients (1). Therefore, a multifactorial histopathological malignancy grading system (MGS) in patients with invasive squamous cell carcinoma of the uterine cervix was developed and has been shown to have prognostic value (1, 4). In a 10-year follow-up (4), MGS was shown to be the sole prognostic factor when comparing MGS with histological differentiation, differentiation into cell type, age, clinical stage and irradiation. The aim of the present investigation is to verify if the MGS is still of significant importance in a larger number of patients followed-up after a longer time period with only minor changes of therapy during that period.

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Patients and Methods

Tissues from 619 patients with date of diagnosis ranging from 1981 to 2000 were examined. Patients were followed-up until April 2005. Causes of death were identified in the register of the Centre for Epidemiology at the National Board of Health and Welfare Stockholm, Sweden. The malignancy grading was performed on pre-treatment biopsies without knowledge of the further course of the disease.

A malignancy grading system including 8 parameters, each graded in a 1-4 points, was developed at the Department of Tumour Pathology at Radiumhemmet, Stockholm, to evaluate the biological activities of squamous cell carcinoma of the ENT region (3). A modification of that scheme was developed by RW for invasive squamous cell carcinoma of the uterine cervix (Table I) (4). The tumour cell population and the tumour-host relationship were considered separately. The evaluation of the tumour cell population was based upon the grading of tumour structure (P1), cell differentiation (P2), nuclear polymorphism (P3) and frequency of mitotic figures (P4) on a scale of 1 to 3. The tumour-host relationship was graded on a similar scale, by evaluation of the mode of invasion (P5) and the stage of invasion (P6), vascular invasion (P7) and the degree of lymphoplasmocytic infiltration (P8). These eight morphological parameters constituted the MGS, which could thus range from 8 to 24 points (1, 4, 5). It was of great importance that the biopsies were taken deep and fixed in a formalin buffer system of 0.17 M phosphate buffer at pH 7.0 at an effective vehicle osmolar pressure of 350mOsm/l (6).

Statistics. Survival was analysed using the Kaplan-Meier method and hypothesis tests were performed using the log-rank test. Cox regression analysis was used to analyse survival with adjustment for

Table I. *Parameters used for malignancy point grading.*

	Points		
Parameter	1	2	3
Tumour-cell population			
1. Structure	Exophytic, papillary and solid	Small cords and groups of cells	Marked dissociation
2. Differentiation in to cell type	Large cell no keratin	Large cell keratinisation	Small cell
3. Nuclear pleomorphism	>75% mature nuclei, few enlarged nuclei	75-25% mature nuclei moderate number of enlarged nuclei	<25% mature nuclei numerous irregular or anaplastic enlarged nuclei.
4. Mitosis	Single (0-1)	Moderate number (2-5)	Numerous (>5)
Tumour-host relationship			
5. Mode of invasion	Well-defined borderline	Cords, less marked borderline	Groups of cells or diffuse growth
6. Stage of invasion	Minimal stroma invasion or microcarcinoma	Nodular into submucosa and connective tissue	Massive, amongst muscle and vessels
7. Vascular invasion	None	Possible	Well-established within lumina of lymph or blood vessels
8. Cellular response (lymphoplasmocytic)	Marked (continuous rim)	Moderate (several large patches)	Slight or none (few small patches or no cells)

differences in age and calendar year. All tests were two-tailed and *p*-values of 0.05 or lower were considered statistically significant.

Results

There was a significant relation between survival and MGS (test for trend: $p<0.001$) among patients when divided into three groups according to MGS scores 0-15, 16-17, >17. This indicates that MGS has significant importance for survival (Figure 1). Adjusting for age and calendar year of diagnosis did not change this finding (Table II).

The tumour pattern and differentiation did not change over time in spite of intense vaginal smear controls, *e.g.* the same distribution of low and high grade squamous carcinomas turned out to be stable during the study period (Table II) in contrast to earlier findings in 310 consecutive patients FIGO I-IV. The frequency of low malignancy patients (<MGS 16) was found to decrease between years 1967 and 1988, probably as a result of screening activities (7).

Discussion

To predict the clinical outcome of invasive squamous cell carcinoma of the uterine cervix a variety of systems and methods, such as histopathology, clinical stage, operation and radiation models, as well as DNA measurements, have been used. Our group developed a grading system which in earlier studies could predict the clinical outcome in the short-term, *e.g.* 5-year survival (1, 2, 5, 7, 9) and metastasis frequencies (10).

The grading system has been used by several other groups. Graflund *et al.* (11) found the MGS highly significantly associated with pelvic gland metastases and disease-free survival rate in squamous cell carcinoma FIGO I-II. Bichel *et al.* (12) in 275 cases found crude survival of patients with an MGS index less than or equal to 14 was significantly better than patients with higher score. Kristensen *et al.* (13) in an analysis of 125 surgically treated patients FIGO 1B, found tumour size, depth of

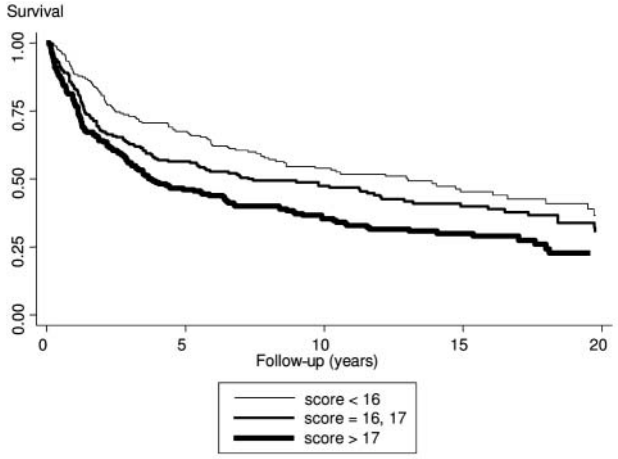

Figure 1. *Survival estimates by score in 619 patients. Score 1, means 8-15 points; score 2, 16-17; and score 3>17 points. The differences between groups was consistently maintained during the follow-up period of 5-24 years.*

invasion and grading of the invasive tumour front to be the main predictors of prognosis. Crissman *et al.* (14, 15) using a similar grading system of nine parameters, found that only vascular invasion predicted a poor outcome for FIGO stage IB while the grading system failed to predict patient survival for stage II and III.

This study reports a prospective study of graded material of invasive cervical carcinoma of 619 patients followed-up from five to 24 years. The end-point was cause of death. This was possible due to the unique Swedish personal number system, the so-called 10-figure system which allowed us to know if the patient was alive or dead. The cause of death is registered at the Centre for Epidemiology, National Board of Health and Welfare.

The biopsies were fixed in an appropriate buffer system to enable proper evaluation of the different parameters including vascular spaces. They were graded prospectively before treatment of the disease according to well-established treatment protocols. The MGS score was therefore fixed at the inclusion date and could not further be manipulated by, for *e.g.,* re-evaluation. To our surprise the predictive value of the MGS score persisted 20 years after the initial evaluation. This inexpensive, rapid, standard technique, in the hands of a well-trained histopathologist turned out to be the best longstanding predictive factor in spite of other sophisticated methods used in our group over the years (7, 8).

The treatment of cancer is more tailor-made today to meet the patients' need for instance to preserve fertility or to minimize operation and eventual radiotherapy. In this report we presented a strong prognostic tool.

Table II. *Analysis of scores and survival with adjustment for age and calendar year of diagnosis.*

Factor	RR	*P*-value	95%	CI
Age	1.03	<0.001	1.02	1.04
Calendar year	0.45	<0.001	0.38	0.54
MGS[1]				
0-15	0.82	0.146	0.64	1.07
16-17	1.00	-	reference	
18+	1.24	0.079	0.98	1.58

[1]Test for trend in scores: $p=0.002$; CI: confidence interval. RR: relative risk.

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