Acta Radiologica Oncology 24 (1985) Fasc. 2

FROM THE DEPARTMENT OF PATHOLOGY, UNIVERSITY HOSPITAL, S-221 85 LUND, AND THE DEPARTMENT OF CANCER EPIDEMIOLOGY, RADIUMHEMMET, KAROLINSKA SJUKHUSET, S-104 01 STOCKHOLM, SWEDEN.

INVASIVE SQUAMOUS CELL CARCINOMA OF THE UTERINE CERVIX

IX. Construction of a partial index in a histopathologic malignancy grading system

H. WILLÉN and G. EKLUND

Abstract

A malignancy grading system (MGS) for invasive squamous cell carcinoma of the uterine cervix, consisting of four items for the tumour-cell population and four items for the tumour-host relationship, proved to have a good prognostic capacity. A correlation analysis based on 161 patients with invasive squamous cell carcinoma of the uterine cervix in stages I and II was evaluated. The relationships between survival/lethality ratio (S/L) and all single items, MGS, and a reduced partial index were compared. The study showed good agreement with previous studies on another partial index. The MGS had the best predictive value. The items of the tumour-cell population had no significant predictive value. According to a regression analysis, items for the tumour-host relationship or the items vascular invasion and host-cellular response alone could be used without any substantial loss of predictive capacity compared with the MGS. However, the MGS remains the most complete and adequate classification for invasive squamous cell carcinoma of the uterine cervix.

A histopathologic malignancy grading system (MGS) for carcinoma of the uterine cervix has previously been introduced (15, 16). Several retrospective reviews have shown that a total malignancy score is correlated to survival/lethality (13–15, 18).

In earlier studies, a partial index, where only certain parameters are considerd, was recommended (12). The reliability of such a partial index should be tested in further studies in order to ensure that the parameters chosen in the original studies as having a high predictive value were not favoured by chance. Based on this re-evaluation a new partial index is proposed.

Material and Methods

The material consisted of 208 patients with invasive squamous cell carcinoma of the uterine cervix stages I A to II B (7) treated at the Division of Gynecologic Oncology at the University Hospital, Lund, during the years 1969 to 1970. The boundary between stages I A and I B in cases where cone biopsy was performed was established according to the system of FRICK et coll. (8). The follow-up period was at least 10 years, but only the first 8-year period is described in this report. This was done in order to allow a comparison with a previous study (12). Patients who had received less than 60 per cent of the intended radiation dose in point A were excluded (10 patients). No attention was otherwise paid to the tumour dose. Patients who had received external irradiation exclusively were included. The material was thus reduced to 198 patients.

When the histopathologic malignancy grading was retrospectively performed, 30 patients were excluded who could not be evaluated with respect to all histologic parameters or had a biopsy of poor quality (thus leaving 168 patients).

Accepted for publication 29 May 1984.

Patients who died from intercurrent disease within 4 years after diagnosis of disease were also excluded, leaving 161 patients for analysis. As regards the clinical stages, 23 of these patients had stage I A, 59 had stage I B, 53 had stage II A, and 26 had stage II B.

The grading of the histopathologic parameters was performed retrospectively on pretreatment biopsies, without knowledge of the treatment and the further course of the disease.

The tumour-cell population parameters, namely structure (P1), differentiation into cell type (P2), nuclear polymorphism (P3), and mitosis (P4), and the tumour-host relationship parameters, mode of invasion (P5), stage of invasion (P6), vascular invasion (P7) and host-cellular response (P8), were recorded separately. Each parameter was graded from 1 to 3 points. Thus, after summing up the parameter values the score (MGS) permitted a grading from 8 to 24 points totally. The distributions of the parameters and the MGS have been reported by WILLÉN et coll. (19).

The predictive values of the malignancy grading system and a partial index were compared with the aid of correlation and stepwise linear multiple regression analyses, BMDP2R, and life table analysis according to Kaplan & Meier, BMDPL1 (5).

Results

The correlations between each of the histopathologic parameters and the survival/lethality ratio (S/L, S coded O, L coded 1) as well as the MGS are given in Table 1. The highest correlation to S/L was reached by the complete MGS, followed by vascular invasion (P7), host-cellular response (P8) and stage of invasion (P6). With respect to rank those findings were in total accordance with previous results (12).

The strength of the correlations was also similar in both materials. A significant difference existed, however, in the correlations between P5 (mode of invasion) and survival. The correlation coefficient in the present material, for this variable, was 0.155 while in the Uppsala study it was 0.392.

All parameters except P4 (mitoses) showed a highly significant correlation to the MGS ($p<0.001$).

Table 2 shows the correlations between pairs of the eight items included in the MGS. The correlations were generally quite low. Particularly striking were the negative correlations between mitoses (P4) and the other variables. The correlation within the tumour-cell population variables (P1–P4) was poor throughout. Among the tumour-host relationship (P5–P8) variables, the correlation was somewhat higher, but still quite low. When the correlation

Table 1

Product-moment correlations between different histopathologic parameters and survival/lethality (S=O/L=1) after 8 years and the MGS

Variable	S/L at 8 years	MGS
P1 Structure	0.226**	0.286***
P2 Differentiation into cell type	0.193*	0.421***
P3 Nuclear polymorphism	0.125	0.355***
P4 Mitoses	0.022	0.139
P5 Mode of invasion	0.155*	0.431***
P6 Stage of invasion	0.265***	0.635***
P7 Vascular invasion	0.404***	0.626***
P8 Host-cellular response	0.341***	0.426***
MGS	0.516***	

Significance: * $p<0.05$, *** $p<0.001$.

Table 2

Correlation coefficients, r, between the eight items included in the MGS

	P1	P2	P3	P4	P5	P6	P7	P8
P1	1.00							
P2	0.19	1.00						
P3	0.00	−0.04	1.00					
P4	−0.28	0.06	−0.16	1.00				
P5	0.07	0.10	0.05	−0.10	1.00			
P6	0.16	0.15	0.03	0.08	0.22	1.00		
P7	0.10	0.19	0.03	0.01	0.22	0.25	1.00	
P8	0.26	0.03	0.01	−0.29	0.00	0.21	0.17	1.00

Significance: $p<0.05$ corresponds to $r \geq 0.16$, $p<0.01$ to $r \geq 0.20$, $p<0.001$ to $r \geq 0.26$.

Table 3

Stepwise multiple regression analysis. Dependent: Survival/lethality (0/1 code) at 8 year control. Independent: P1, P2, P3, P4, P5, P6, P7 and P8. Inclusion level: $t \geq 2.0$ corresponding to $p \leq 0.05$. Program: BMDP2R, 1981. Material: 161 cases

Variable in equation	Regression coefficient	Standard error
P7 Vascular invasion	0.170***	0.034
P8 Host-cellular response	0.138***	0.035

P1–P6 candidated, but were not included. Multiple $R=0.489$. Order of inclusion: P7, P8. Significance: ***$p<0.001$.

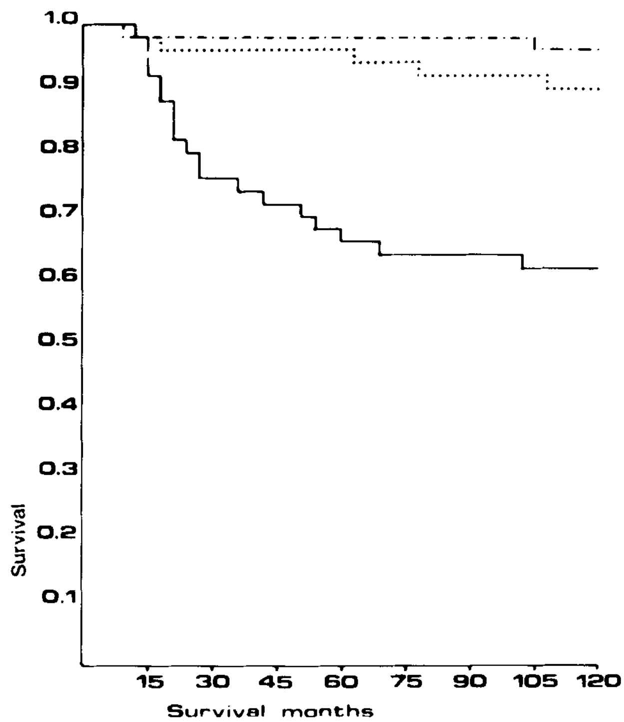

Fig. 1. Survival curves for the partial index based on P7+P8, 2 to 6 points. 2 p (n=56 –·–), 3 p (n=53 ····), ≥4 p (n=59 ——).

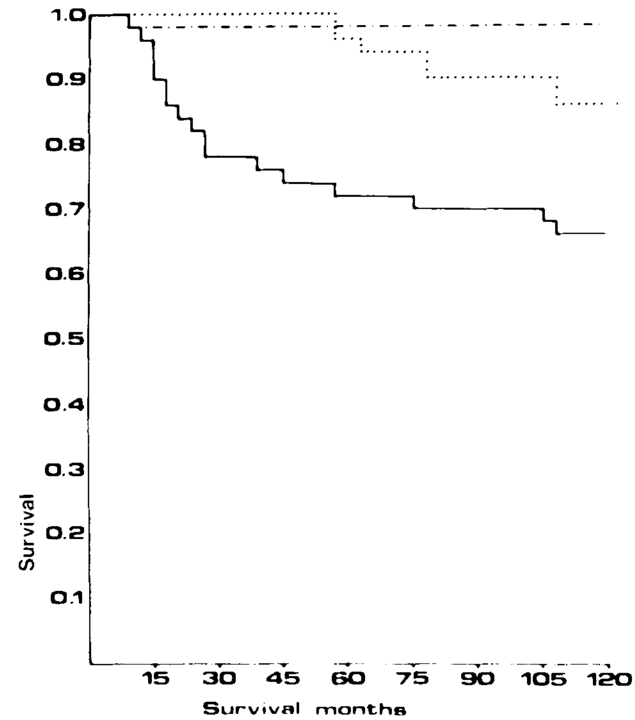

Fig. 2. Survival curves for the 3 MGS classes. ≤13 p (n=67 –·–), 14 p (n=34 ····), ≥15 p (n=67 ——).

table was considered, it did not appear feasible to eliminate any of the items because of the low correlation between them. This would mean that the parameters constituting the MGS are relatively independent. A multiple stepwise linear regression analysis was performed (Table 3), to study the possibility of reducing the number of parameters. Vascular invasion (P7), followed by host-cellular response (P8), exhibited strong significance, $p<0.001$, but no other parameters reached the inclusion level.

The results indicate that it would be possible to reduce the number of variables considerably without loss of predictive capacity. In order to illustrate the strength of various simple combinations of the parameters, they were subjected to a correlation analysis (Table 4).

Among the combinations made by four items, the parameters representing the tumour-cell population (P1–P4) were relatively poorly correlated to the S/L. The tumour-host relationship (P5–P8) showed a considerably higher correlation to both S/L and MGS. The index recommended by STENDAHL et coll. (12), which includes mitoses, was not the most successful, but not significantly inferior to the seemingly best combination. Thus, combinations of the tumour-host parameters showed the highest correlations (Table 4).

The partial index based on a combination of two items only (2–6 points), vascular invasion and host-cellular response (P7+P8), could identify low and high risk patients (Table 5). The table was the basis for a comparison between the correlations to S/L for P7+P8 and FIGO stages. The correlation was significantly stronger ($p<0.05$) for P7+P8 than for stages I A to II B. The difference between the correlations was 0.23 (0.49–0.26). This simple combination P7+P8 gave as good correlation to S/L as the best index composed of three or four items. Comparison between the survival curves for P7+P8 (Fig. 1) and an MGS classification (Fig. 2) revealed that the simple combination P7+P8 (vascular invasion and host-cellular response) seemed to have the same predictive capacity as the MGS. In Figs 1 and 2, the materials are divided into three patient groups.

Discussion

The collection of information by the use of qualitative and quantitative parameters requires analysis of the prognostic values of each parameter and of all

Table 4

Correlation between, on the one hand different item combinations, and on the other S/L (8 years) and the MGS in 161 patients

Combination	S/L 8 years	MGS
P1+P7	444	665
P5+P7	379	690
P7+P*	487	689
P5+P7+P8	474	766
P1+P5+P7	414	721
P1+P5+P7+P8	493	774
P4+P5+P7+P8	476	813
P1+P2+P3+P4	252**	610
P5+P6+P7+P8	483	856
2×P7+P5+P8	480	761
2×P7+P1+P5+P8	495	773
2×P7+P4+P5+P8[1]	481	796
1.235×P7+P8[2]	489	699

Significance: **p<0.01. All other correlations p<0.001.
All other correlations significant at 1% level.
[1] Partial index according to STENDAHL et coll. (12).
[2] Weights proportio ! to regression coefficient in Table 3 (1.235=0.170/0.138).

Table 5

Partial index 2–6 points P7+P8 (vascular invasion and host-cellular response) and clinical staging I A to II B (FIGO) qualified 1–4 compared with survival/(survival+lethality) in 161 patients (per cent of survials in parentheses)

P7+P8 (points)	1 I A	2 I B	3 II A	4 II B	Total	
2 (min.)	16/16	19/19	11/11	7/8	53/54	(98)
3	5/5	22/22	13/14	7/10	47/51	(92)
4	2/2	6/8	15/17	4/6	27/33	(82)
5		6/7	2/8	1/2	9/17	(53)
6 (max.)		1/3	0/3		1/6	(17)
Total	23/23 (100)	54/59 (92)	41/53 (77)	19/26 (73)	137/161 (85)	

combinations together. Generally, parameters chosen for the partial index should be easy to evaluate, should correlate to survival as well as to the MGS, and add further prognostic information.

A previous investigation on the reproducibility of a histopathologic malignancy grading system (17) showed that some parameters were more difficult to evaluate than others. Structure, cell type, vascular invasion, and cellular response were easier to evaluate as compared with nuclear polymorphism, mitoses, mode of invasion, and stage of invasion, which most often depended on biopsy quality and subjective factors associated with the histopathologic evaluation. A histopathologic malignancy index proved capable of discriminating patients with carcinoma of the uterine cervix with respect to the prognosis (13, 14). Eight histopathologic items graded from 1 to 3 add up to constitute the malignancy index. By regression analysis the number of items could be reduced to 4: mitoses (P4), mode of invasion (P5), host-cellular response (P8), and vascular invasion (P7), the latter was attributed double weight. The predictive value of the partial index seemed to be as good as the malignancy index (MGS) itself. These calculations were obtained upon material from patients in stage II only and confirmed on a material in stages I, III and IV. In pilot studies, however, there is a risk that favourable combinations attract attention (12).

In the present analysis, 168 patients received an adequate complete treatment and had a biopsy of a proper quality for evaluation of all histopathologic parameters (P1–P8). A considerable number of patients were excluded (see section on Material and Methods). One of the reasons for this was an incomplete recording of different items, particularly stage of invasion (P6), vascular invasion (P7), and host-cellular response (P8). In this analysis, 15 cases were excluded because of missing registration of P6, P7 and P8. The question is, whether transition to a partial index can give satisfactory prognostic information when some but not all items are recorded. From Table 4, it is obvious that tumour-cell population items (P1–P4) were less informative. A partial index not based on parameters of the tumour-host relationship (especially P7 and P8) will scarcely be of much value.

P1–P4 items showed a weak correlation to the S/L in this as well as in an earlier investigation (12). In particular, P4 (mitoses) was of dubious worth and had no prognostic value by itself, but nevertheless was included in the index by those authors. The present analysis supports the possibility that this item has been favoured by chance. Assessments of mitotic activity are often used in routine surgical pathology (11). Among factors with an influence upon assessment, a delay in fixation, which may allow the majority of mitoses to terminate, resulting in unreliable evaluation of mitotic activity, might be relevant (9). The estimated number of mitoses depends on the section thickness as well (6). CHI et coll. (3) found variable frequency and distribution of mitotic figures within the different tissue layers in dysplasia and carcinoma in situ of the uterine cervix. However, there may be an underestimation of the value of the mitosis parameter in the study of invasive squamous cell carcinoma of the uterine cervix.

Some differences exist in the composition of the present material and that of the Uppsala material. Our series was extended to stage I A to II B, which resulted in a lower MGS score. The reduced index obtained may be less successful when applied to stage III cancers.

In the present report, the partial index based on parameters representing the tumour-host relationship (P5–P8) showed a strong correlation to the S/L and MGS ($p<0.001$).

Mode of invasion (P5) was included as a second parameter in the regression analysis of the Uppsala material but not at all in our study. It should be noted that a score of three for P5 was much less common in our material ($n=10$) than in the Uppsala series ($n=40$), which may explain the lower correlation, but inter-observer variation must also be considered. As the material in the present study had a different stage composition and was dominated by cases with a low score, the lower S/L correlation of this material, compared with the Uppsala material, was not surprising. Furthermore, the lethality at the 8-year follow-up was considerably lower in the Lund material. Further comparison between the Uppsala and Lund materials will be published later.

Vascular invasion has proved to be a valuable prognostic parameter in this, as well as in earlier studies (2, 12, 15). Vascular invasion was evaluated in association with other variables, but it was not clear whether it should be given independent weight in treatment planning. BOYCE et coll. (2) showed that vascular invasion alone contributed prognostic information beyond that available from lesion size and extracervical spread.

The cellular response was very intense in the group of patients without death and recurrences and seemed to be an indication for a low death risk, although the exact mechanism involved is not known. A beneficial effect of this factor on prognosis has now been reported for squamous cell carcinoma of the uterine cervix (1) and for several other neoplasms (10).

The results of the present analysis are in agreement with those of the Uppsala report (12). Nevertheless, there seem to be several reasons for the use of a new partial index. Summing up the Uppsala and Lund materials, the original partial index (P4+P5+2 P7+P8) still remains as the combination which shows the highest correlation to the S/L mean.

This index, however, includes the mitoses item (P4) which had no prognostic value by itself in the Uppsala study or in the present investigation. In both studies, vascular invasion was the most important variable according to a stepwise multiple regression analysis and was given double weight in the original partial index. This parameter, however, has practical disadvantages such as possible observer errors and technical errors. Shrinkage or fragmentation of the biopsy specimen may give spaces with an intima-like covering, especially in a retrospective, inadequately fixed material.

On the other hand, the more reliable tumour-host relationship items combination (P5+P6+P7+P8) was comparable with the original partial index.

It seems important to include parameters of the host-cellular response in the partial index, as these parameters showed a highly significant correlation to S/L as well as to the MGS. Further reduction to only three items (P5+P7+P8) also gave a good correlation to MGS and S/L. A surprisingly good correlation to S/L was obtained when only two items, P7+P8 (vascular invasion and cellular response), were used (demonstrated in Figs 1 and 2). An index based on P7+P8 showed a significantly stronger correlation to the outcome than the FIGO classification in stages I A to II B. The same superiority has earlier been observed for MGS (19).

Serious differences have been reported between histologic evaluations made by various pathologists and also between evaluations of the same sections made by individual pathologists at different times (4, 17). Evaluation and reproducibility of the two parameters P7 and P8 are easier if the biopsy quality is good and the definitions of the parameters are consistently applied. The influence of different fixative methods on the estimation of vascular invasion has been studied by WILLÉN et coll. (18). With an improved fixation, tissue shrinkage and sectioning artefacts could be reduced to a minimum. Vessels remained open, which facilitated the analysis of vascular invasion. A new reproducibility study of the MGS and of a partial index with only the P7+P8 items on a prospective material, using both traditional and improved fixative methods, is in progress.

Reproducibility and training problems limit the use of the complete MGS score to a small exclusive group of super-specialized squamous cell carcinoma experts or gynecologic pathologists, while evaluation of vascular invasion and host-cellular response can be included in the routine surgical pathology.

Nevertheless, the MGS remains at present the most complete and adequate prognostic classification for invasive squamous cell carcinoma of the uterine cervix.

ACKNOWLEDGEMENTS

Financial support was received from the University and University Hospital, Lund, and John and Augusta Persson's Foundation.

Request for reprints: Dr Helena Willén, Department of Pathology, University Hospital, S-221 85 Lund, Sweden.

REFERENCES

1. BALTZER J., LOHE K. J., KÖPKE W. and ZANDER J.: Histological criteria for the prognosis in patients with operated squamous cell carcinoma of the cervix. Gynecol. Oncol. 13 (1982), 184.
2. BOYCE J. G., FRUCHTER R. G., NICASTRI A. D. et coll.: Vascular invasion in stage I carcinoma of the cervix. Cancer 53 (1984), 1175.
3. CHI C. H., RUBIO C. A. and LAGERLÖF B.: The frequency and distribution of mitotic figures in dysplasia and carcinoma in situ. Cancer 39 (1977), 1218.
4. COCKER J., FOX H. and LANGLEY F. A.: Consistency in the histological diagnosis of epithelial abnormalities of the cervix uteri. J. clin. Path. 21 (1968), 67.
5. DIXON W. J. (Editor): BMDP. Statistical software, 1981. University of California Press, Berkeley, Calif. 1981.
6. ELLIS P. S. J. and WHITEHEAD R.: Mitosis counting — a need for reappraisal. Hum. Path. 12 (1981), 3.
7. FIGO — Fédération Internationale de Gynécologie et Obstétrique: Classification and staging of malignant tumours in the female pelvis. Acta obstet. gynec. scand. 50 (1971), 1.
8. FRICK H. C., JONOSKI N. A., GUSBERG S. B. and TAYLOR H. C.: Early invasive cancer of the cervix. Amer. J. Obstet. Gynec. 85 (1963), 100.
9. GRAEM N. and HELWEG-LARSEN K.: Mitotic activity and delay in fixation of tumour tissue. Acta path. microbiol. scand. sect. A. 87 (1979), 375.
10. KHOO S. and MACKAY E. V.: Relation of cell-mediated immunity in woman with genital tract cancer to origin, histology and clinical stage and subsequent behaviour of neoplasm. J. Obstet. Gynaecol. Brit. Commonw. 81 (1974), 229.
11. SILVERBERG S. G.: Reproducibility of the mitosis count in the histologic diagnosis of smooth muscle tumours of the uterus. Hum. Path. 7 (1976), 451.
12. STENDAHL U., EKLUND G. and WILLÉN R.: Invasive squamous cell carcinoma of the uterine cervix. IV. Analysis of a histopathologic malignancy grading system and construction of a partial index. Acta radiol. Oncology 20 (1981), 289.
13. — — — Prognosis of invasive squamous cell carcinoma of the uterine cervix. A comparative study of the predictive values of clinical staging IB–III and a histopathologic malignancy grading system. Int. J. Gynecol. Path. 2 (1983), 42.
14. — — WILLÉN H. and WILLÉN R.: Invasive squamous cell carcinoma of the uterine cervix. III. A malignancy grading system for indication of prognosis after radiation therapy. Acta radiol. Oncology 20 (1981), 231.
15. — WILLÉN H. and WILLÉN R.: Classification and grading of invasive squamous cell carcinoma of the uterine cervix. Acta radiol. Oncology 18 (1979), 481.
16. — — — Invasive squamous cell carcinoma of the uterine cervix. I. Definition of parameters in a histopathologic malignancy grading system. Acta radiol. Oncology 19 (1980), 467.
17. — — — Invasive squamous cell carcinoma of the uterine cervix. II. Reproducibility of a histopathologic malignancy grading system. Acta radiol. Oncology 20 (1981), 65.
18. WILLÉN H., WILLÉN R. and STENDAHL U.: Invasive squamous cell carcinoma of the uterine cervix. VII. Influence of vehicle osmolarity on biopsy quality. Acta radiol. Oncology 22 (1983), 257.
19. — EKLUND G., JOHNSSON J.-E., STENDHAL U. and TROPÉ C.: Invasive squamous cell carcinoma of the uterine cervix. VIII. Survival and malignancy grading in patients treated by irradiation in Lund 1969–1970. Acta radiol. Oncology 24 (1985), 41.