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Оригинален труд

THE IMPLEMENTATION OF PROGNOSTIC INDEX AND RISK GROUPING IN SURGICALLY TREATED CERVICAL CARCINOMA PATIENTS: A PROSPECTIVE VALIDATION STUDY

ПРИМЕНА НА ПРОГНОСТИЧКИОТ ИНДЕКС И ПОДЕЛБАТА ВО РИЗИЧНИ ГРУПИ КАЈ ХИРУРШКИ ТРЕТИРАНИ ПАЦИЕНТИ СО КАРЦИНОМ НА ГРЛОТО НА МАТКАТА: ПРОСПЕКТИВНА ВАЛИДАЦИОНА СТУДИЈА

Neli Basheska[1] and Slavica Veljanoska-Petreska[2]

[1]Department of Histopathology and Clinical Cytology, [2]Department of Gynecological Oncology, University Clinic of Radiotherapy and Oncology, Faculty of Medicine, University "Ss. Cyril and Methodius" Skopje, Republic of Macedonia

Abstract

Introduction. The objective of this prospective study was to validate the prognostic criteria defined by the results of our previous study in an independent population of surgically treated cervical carcinoma patients.
Methods. The study group consisted of 340 patients who underwent abdominal hysterectomy with pelvic lymphadenectomy as primary therapy. Based on the scores of the variables (blood vessel invasion, lymph node metastases, tumor diameter, degree of inflammatory reaction at the invasive front, and minimum thickness of uninvolved cervical stroma/parametrial extension) and calculated prognostic index (PI) values, the patients were divided into three prognostic groups.
Results. The 5-year disease-free survival (DFS) rates of the low, intermediate, and high-risk groups were 98,82%, 84,57%, and 74,01%, respectively. The differences in DFS rates were statistically significant (P<0,00001). In order to validate the model from our previous study, we have compared DFS rates between the groups. There was no difference in DFS rate between low-risk groups, although the majority of the patients in this study were not irradiated, while radiotherapy was administrated invariably to all the original study patients. Similarly, DFS did not differ significantly between the intermediate-risk groups, which could be expected since radiotherapy was administrated to majority of the patients in this study. In contrast, the high-risk group patients in this study had significantly higher DFS rate (74,01% vs. 44,24%, P=0,0010), probably as the result of the adjuvant chemotherapy administrated to 69% of them.
Conclusions. PI could be a sound and reliable basis for appropriate planning of the following therapeutical strategy of the surgically treated cervical carcinoma patients.

Correspondence to: Neli Basheska, Department of Histopathology and Clinical Cytology, University Clinic of Radiotherapy and Oncology, "Majka Tereza" 17, Skopje, R. Makedonija; Phone: 02 3147 892; Phone: 070 77 47 99; Fax: 02 31 11 430; E-mail: nbaseska@gmail.com

Key words: cervical cancer, prognostic factors, dDisease-free survival, prognostic index, prognostic groups

Апстракт

Вовед. Целта на оваа проспективна студија беше да се проверат прогностичките критериуми утврдени со резултатите на нашата претходна студија во независна популација од хируршки третирани пациенти со цервикален карцином.
Методи. Испитуваната група се состоеше од 340 пациенти кај кои како примарна терапија беше направена абдоминална хистеректомија со пелвична лимфаденектомија. Врз основа на одредените вредности од варијаблите (инвазија на крвните садови, лимфонодални метастази, туморски дијаметар, степен на воспалителна реакција во инвазивниот фронт и минимална дебелина на незафатена цервикална строма/параметријално зафаќање) и пресметаните вредности на прогностичкиот индекс (ПИ), пациентите беа поделени во три прогностички групи.
Резултати. Стапките на 5-годишното преживување без болест (ПББ) на ниско-, средно- и високоризичната група беа 98,82%, 84,57% и 74,01%. Разликите во стапките на ППБ меѓу прогностичките групи беа статистички значајни (P<0,00001). За да го провериме моделот од претходната студија, направивме споредба ППБ меѓу двете групи. Помеѓу ниско-ризични групи немаше разлика во стапките на ППБ, иако поголемиот дел од пациентите во оваа студија не беа зрачени, додека радиотерапија беше администрирана кај сите пациенти вклучени во оригиналната студија. Слично, ППБ не се разликуваше значајно помеѓу средно-ризичните групи, што би можело да се очекува со оглед дека радиотерапија беше администрирана и кај повеќето пациенти во оваа студија. Спротивно на тоа, пациентите од високо-ризична гру-

па во оваа студја имаа значајно повисока стапка на ППБ (74,01% наспроти 44,24%, P=0,0010), веројатно како резултат на адјувантната хемотерапија применета кај 69% од нив.
Заклучок. ПИ би можел да биде цврста и сигурна основа за соодветно планирање на терапевтската стратегија кај хируршки третирани пациенти со цервикален карцином.

Клучни зборови: карцином на грлото на матката, прогностички фактори, преживување без болест, прогностички индекс, прогностичка група

Introduction

The clinical behavior of carcinoma of the uterine cervix varies and covers a wide spectrum, from cases that are relatively indolent to those having a rapidly progressive course. For cervical carcinoma, clinical FIGO staging has been the most important single parameter influencing choice treatment and indicating outcome [1,2]. The overall 5-year survival rates range from 15% to 80% depending on the extent of disease [3]. Unfortunately, the 5-year survival for each stage has not improved significantly over the past 45 years. Many recent studies have suggested that this staging system is not capable of discriminating with regard to patient survival within and between stages [4].
Accurate staging is of utmost importance in determining the prognosis of carcinoma of the uterine cervix. It is well known that there is a significant disagreement between the neoplastic extension according to clinical FIGO classification, and the real extension of the tumor, according to pathological data from operative specimens or the postoperative stage. Thus, primary surgical treatment in patients with early stage cervical carcinoma allows for an accurate determination of the real extent of the disease. Histopathological analysis of the surgical specimens also allows identification of various histological features that significantly influence recurrence rate and survival in patients with early stage cervical carcinoma.
Traditionally, clinical and histopathological parameters such as regional lymph node metastases, tumor size, depth of stromal invasion, vessel invasion, parametrial involvement, and histological type are used to prognosticate and modify management options both in patients with early stage and locally advanced cervical carcinoma [3]. Many factors are still controversial in their prognostic significance including patient's age, surgical margin involvement, inflammatory stromal reaction, histological type and grade of differentiation.
Nevertheless, it has become increasingly clear that there exists a significant subpopulation of patients with apparent early invasive cervical carcinoma who are prone to treatment failure when managed by current standard surgical or radiotherapeutic techniques. This indicates the need for a more precise quantitative method for determining the prognosis in patients with cervical carcinoma in order to be able to individualize treatment as much as possible. A reliable marker of prognosis would therefore be very useful for identification of patients at low risk who could be offered more conservative therapy and patients at high risk who could be offered more intensive treatment.
Several years ago, in a prospective and retrospective study made by our Department, tumor invasion into blood vessels, pelvic lymph node metastases, tumor diameter, the degree of inflammatory cell infiltrate at the invasive front, and minimum thickness of uninvolved cervical stroma/parametrial extension were identified as the only independent and significant prognostic factors for disease-free survival (DFS) among 23 variables investigated by multivariate analysis, using Cox regression models [5]. In addition, the prognostic index (PI), defined by the model, was able to categorize the patients into three distinct risk groups. Differences in DFS rates between the low, intermediate, and high-risk groups were statistically significant. Thus, based on the data reported by two other recent randomized trials radiochemotherapy was recommended for the patients belonging to the high-risk group, while radiation alone was suggested for the intermediate-risk group patients [6,7].
The basic objective of this prospective study was to evaluate the results of the implementation of the prognostic index (PI) in determining the prognosis and individual planning of the postoperative therapy in an independent population of surgically treated patients with early stage invasive cervical carcinoma and to investigate whether treatment decisions based on this risk group division lead to better survival. The predictive value of the PI was assessed in relation to DFS of the patients divided in three prognostic groups. The prognostic influence of 12 various relevant histopathological and clinical variables on DFS of cervical cancer patients was also evaluated.

Materials and methods

Clinical and Histopathological Features

The study group consisted of a fairly homogenous population of 340 patients with early stage cervical carcinoma who underwent abdominal hysterectomy with pelvic lymphadenectomy as primary therapy at the University Clinic for Obstetrics and Gynecology in Skopje or the Special Gynecology and Obstetrics Hospital "Chair" in Skopje between January 2000 and December 2005. Their operative specimens were subjected to uniform histopathological workup at the Department of Histopathology and Clinical Cytology, at the University Clinic of Radiotherapy and Oncology, in Skopje. In some of the patients adjuvant postoperative irradiation and/or chemotherapy was administrated at the University Clinic of Radiotherapy and Oncology.

Originally, a total of 383 patients treated with radical hysterectomy and bilateral pelvic lymphadenecomy entered the study prospectively and consecutively. For the purpose of this study only the patients with early stage cervical carcinoma (pT1b1, pT1b2, pT2a and pT2b) whose operative specimens were subjected to uniform histopathological workup, with the determined value of the PI and all other relevant histopathological parameters, with known relevant information for adjuvant postoperative irradiation and/or chemotherapy and clinical follow-up data were included. Forty-three patients were excluded: 23 due to different treatment modality implemented (preoperative irradiation and/or chemotherapy), 5 with microinvasive cervical carcinoma (pT1a1/1a2), 4 with more advanced stage carcinoma, one with unspecified maximal tumor diameter, and 10 patients without clinical follow-up. The case series was finally made of 340 patients.

The operative specimens were fixed in 10% phosphate-buffered formalin for 24 hours. The surgical specimens were routinely examined and sections were taken according to the standard procedure for cervical cancer specimens from the sagittal and transversal area surface of uterine cervix leading to minimum of nine sections for each patient (mean 29±15). The mean number of resected pelvic lymph nodes was 35±13 (range 1-86). Subsequently, sections were routinely processed and paraffin embedded, and hematoxylin-eosin-stained to determine histology.

All patients were staged according to postoperative pTNM classification guidelines (UICC, International Union Against Cancer; 1997) [2]. In addition to tumor status (pT) and pelvic lymph node status (pN), further prognostic parameters included in the study were the morphometric and morphohistological characteristics including maximum diameter, depth of stromal invasion and thickness of uninvolved cervical stroma/parametrial extension, vaginal involvement, surgical margin involvement, histological type, grade of differentiation, blood vessel invasion and inflammatory infiltrate in the invasive front of the tumor.

Maximum diameter, depth of stromal invasion and thickness of uninvolved cervical stroma of the primary tumor were determined according to the measurements taken during the pathology examination. Tumors were classified according to the World Health Organization criteria [8], and graded using a modification of Broder's method [3]. When tumor cells were found in a distinctive vascular space, blood vessel invasion was recorded. In addition, the abundance of the lymphocytic-plasmacellular inflammatory infiltrate present was evaluated at the invasive front of the tumor [9,10].

The value of the PI was calculated for each patient by the following formula:

$$PI = 0{,}669215\ BVIi + 0{,}8094872\ pNi + 0{,}2195908\ TDi + 0{,}7449857\ INRi + 0{,}6726326\ TUSi$$

where *BVIi* equals 0 if there is no blood vessel invasion and *BVIi* equals 1 if blood vessel invasion is present; *pNi* equals 0 if pelvic lymph nodes are negative and 1 if there is lymph node metastasis present; *TDi* equals the value of the maximal tumor diameter in centimeters (continuous variable); *INRi* equals 0 if there is an abundant inflammatory infiltrate present in the invasive front of the tumor, *INRi* equals 1 if the inflammatory reaction is moderate and 2 if it is scarce; *TUSi* equals 0 if the thickness of uninvolved cervical stroma is more than 10 mm, *TUSi* equals 1 if the thickness is between 6 and 10 mm, *TUSi* equals 2 if the thickness is less than 6 mm and 3 if there is parametrial extension [5]. Based on the scores of the variables and calculated PI values the patients were divided into three prognostic groups. The patients with a PI value between 0 and 2,2 belong to the low-risk group, the intermediate-risk group patients are those with a PI value between 2,21 and 4,2, while patients with a PI value more than 4,2 are categorized in the high-risk group.

Clinical information, including patient age, FIGO stage, date of operation, postoperative treatment, and follow-up data (date and type of treatment failure or relapse, date and clinical status at follow-up through June 2007), were retrieved by reviewing each patient's complete medical records at the University Clinic of Radiotherapy and Oncology and computer data base records at the Department of Histopathology and Clinical Cytology. The age of the patients ranged from 22 to 69 years, with a median of 44 years. The patients were clinically staged as FIGO Stage IA (4), IB (168), IIA (126), IIB (12), or III (2), while 28 patients were unstaged.

Postoperatively, adjuvant therapy was given in patients belonging largely to the intermediate- or high-risk group. Radiotherapy consisted of 50 Gy in 25 fractions, 5 fractions a week, delivered to the pelvis in two or four fields. Chemotherapy consisted of either of cisplatin (75 mg/m2 on day 1) and fluorouracil (5-FU; 750 mg/m2 on days 1-5) or of carboplatin AUC 5 (on day 1) and 5-FU (750 mg/m^2 on days 1-5) for six cycles every 3 weeks. Adjuvant treatment was started 4-6 weeks after surgery.

Postoperative adjuvant pelvic radiotherapy was administrated to 7,2%(7/97), 90,1%(118/131) and 26,8%(30/112) of the patients belonging to the low-, intermediate-, and high-risk group, respectively. Radio- and chemotherapy was given to 1%(1/97), 5,3%(7/131) and 67%(75/112) of the patients belonging to the low-, intermediate-, and high-risk group, respectively, while 1,8%(2/112) patients belonging to the high-risk group received chemotherapy only. Due to intolerance, various complications or patients' refusal, radiotherapy in 7 cases (6 patients from the intermediate-risk group and one belonging to the high-risk group) and/or chemotherapy in 9 cases were incompletely administrated. In addition, intracavitary treatment of the vagina was administrated to 11 intermediate-risk group patients (in one patient as an exclusive therapy given) and 6 high-risk group patients. Brachytherapy dose was 5 Gy at 5 mm depth of the vaginal mucosa.

Patients receiving postoperative therapy were followed every 3 months during the first 3 years, every 6 months until the fifth year, and yearly thereafter at the University Clinic of Radiotherapy and Oncology. Untreated patients

were controlled by their gynecologists. Regular follow-up consisted of physical examination and vaginal vault smears; patients suggestive for metastatic disease underwent further investigation. Additional information about the length of disease-free and overall survival and clinical status of some patients were obtained from the contacts with the patients or their families. A detailed description of clinical and histopathological characteristics is given in Table 1.

Table 1. Clinicopathological characteristics and 5-year disease-free survival for 340 cervical cancer patients

Variables	Patients		Relapses		Disease-Free Survival Rate		Log rank	P value
	No.	%	No.	(%)	5 y	CI 95%		
Postoperative stage								
IB1	164	48,2	9	5,5	91,09%	85,1-97,0	11,66	0,0006
IB2	27	7,9	5	18,5	80,04%	64,3-97,0		
IIA	18	5,3	3	16,7	82,96%	65,3-100		
IIB	49	14,4	5	10,2	90,10%	80,8-99,4		
IIIB	82	24,1	21	25,6	72,62%	61,5-83,7		
Age (y)								
≤39	109	32,1	14	12,8	84,73%	77,1-92,4	0,01	0,9064
>39	231	67,9	29	12,6	84,29%	78,7-89,8		
Nodal status (pN)								
pN0	258	75,9	22	8,5	89,34%	84,8-93,8	16,84	<0,00001
pN1	82	24,1	21	25,6	69,71%	58,5-80,9		
Tumor status (pT)								
1b1	184	54,1	12	6,5	90,40%	84,8-96,0	8,99	0,0027*
1b2	40	11,8	8	20.0	78,74%	65,6-91,9		
2a	26	7,6	6	23,1	75.58%	58,6-92,6		
2b	90	26,5	17	18,9	79,02%	69,7-88,3		
Tumor diameter(cm)								
≤2	107	31,5	3	2,8	94,76%	88,9-100	16,03	0,0003
2.1 - 4	127	37,3	16	12,6	85,18%	78,3-92,1		
>4	106	31,2	24	22,6	74,40%	65,2-83,6		
Depth of invasion(mm)								
≤10	133	39,1	9	6,8	92,17%	86,8-97,6	12,18	0,023‡
11-20	149	43,8	16	10,7	85,77%	78,9-92,9		
>20	58	17,1	18	31,0	71,78%	61,0-82.5		
Thickness of US								
>10 mm	63	18,5	0	0	100%	-	10,19	0,0014*
6-10 mm	71	20,9	8	11,3	86,33%	77,3-95,3		
0-5 mm	116	34,1	18	15,5	80,74%	72,4-89,1		
parametrial extension	90	26,5	17	18,9	79,05%	69,8-88,3		
Vaginal involvement								
absent	291	85,6	27	9,3	88,09%	83,7-92,5	17,96	<0,00001
present	49	14,4	16	32,7	66,18%	52,1-80,3		
SM involvement								
absent	314	92,4	38	12,1	85,81%	81,5-90,1	1,03	0,3095
present	26	7,6	5	19,2	78,18%	58,9-97,4		
Histological type								
squamous	247	72,6	28	11,3	85,45%	80,1-90,8	2,98	0,2241
adenocarcinoma	44	12,9	4	9,0	88,59%	79,1-98,1		
mixed	44	12,9	9	20,5	77,88%	64,7-91,0		
adenoid basal#	2	0,6	1	50,0	-	-		
neuroendocrine#	3	0,9	1	33,3	-	-		
Grade (G)								
G1	55	16,2	1	1,8	98,15%	94,6-100	11,69	0,0006
G2	225	66,2	28	12,4	84,45%	78,9-90,0		
G3	60	17,6	14	23,3	73,92%	61,9-85,9		
Blood vessel invasion								
absent	160	47,1	9	5,6	92,24%	87,1-97,4	11,98	0,0005
present	180	52,9	34	18,9	78,15%	71,4-84,9		
Inflammatory reaction								
abundant	35	10,3	0	0	100%	-	8,91	0,0028
moderate	190	55,9	18	9,5	87,57%	81,8-93,3		
scarce	115	33,8	25	21,7	75,33%	66,8-83,9		

Legend: CI, confidence interval; Grade (G), grade of differentiation; G1, well differentiated; G2, moderately differrentiated; G3, poorly differentiated; No., number of patients, P, probability, SM, surgical margin; US, uninvolved stroma; y, years. *pertains only to differences between the first and all other categories; ‡ pertaining only to differences between the last and the other two categories; #survival rates for adenoid basal and neuroendocrine carcinomas were not calculated due to the small number of cases

Statistical Analysis

DFS curves were calculated from the date of operation to relapse or to the date of last follow-up. The 2 patients who died of intercurrent disease were considered as censored observations. Surviving patients were considered at the time of their last clinical control. For univariate analysis the percentage of DFS for each group was calculated using the Kaplan-Meier method and comparisons between groups were performed applying log-rank test. Chi-square and/or Fisher's exact test were used to compare differences in recurrence rate, while log-rank test was used to test differences in DFS between prognostic groups. Statistical analysis was performed using the SPSS statistical package. A P value of 0.05 or less was considered statistically significant and 95% confidence intervals (CI) were presented as well.

Results

In our case series the tumor was limited to the cervix with less than 4 cm in diameter in 164(48,2%) patients, while 27(7,9%) patients had a larger neoplasm. Local extension to the vagina and parametrial tissues was found in 18(5,3%) and 49(14,4%) patients, respectively. Pelvic lymph node involvement was found in 82(24,1%) patients. During the follow-up period (range, 16-89,7, mean, 39,7±22,2 months) recurrences were observed in 43 (12,6%) patients, 19(5,6) of whom died of cervical cancer. Two other patients died of intercurrent disease. The mean relapse-free period in recurrent cases was 19,9±14,5 (range 3,4-84,7) months. Six patients had locoregional (pelvic) recurrences with a mean disease-free interval of 36,6±25,1 months. Thirty-four patients had distant metastasis with a mean disease-free interval of 17,7±10,3 months, while in 3 patients both local recurrence and distant metastases developed, with a mean disease-free interval of 11,5±5,9 months. Distant metastases were localized in distant lymph nodes in 18, lungs in 11, musculoskeletal system in 10, liver in 4, and brain in 3 patients. Two hundred ninety-seven of the patients were relapse-free at the closing date of the study (June 2007). Median follow-up for patients without relapse was 37,9 months (range 40,9±22,2 months). The actuarial DFS rate for 340 cervical cancer patients at 5 years was 84,47% (95%CI=80-88,9).

The results of the univariate analyses are summarized in Table 1. Lymph node metastases, tumor status, large tumor diameter, deeper stromal invasion, smaller thickness of uninvolved cervical stroma/parametrial extension, vaginal involvement, poorer grade of differentiation, blood vessel invasion, and more scarce inflammatory reaction in the tumor's invasive front were highly significant predictors for a shorter duration of DFS in the univariate analysis (P<0,05). Age, surgical margin involvement, and histological type had no impact on DFS rate.

According to the value of the PI, the patients were categorized into three distinct risk groups: 97(28,5%) belonged to the low-risk group, 131(38,5%) to the intermediate-risk group and 112(32,9%) to the high-risk group. Recurrences were observed in 1%(1/97), 12,2%(16/131) and 23,2%(26/112) of the low-, intermediate-, or high-risk group patients, respectively. The 5-year DFS rates of the low, intermediate, and high-risk groups were 98,82%, 84,57% and 74,01%, respectively. Notably, a late local recurrence (85 months after the surgery) was observed in one of the patients belonging to the high-risk group, who refused adjuvant postoperative irradiation and chemotherapy. Differences in DFS rates between the low, intermediate, and high-risk groups were statistically significant (log rank test = 20,48, P<0,00001) (Figure 1).

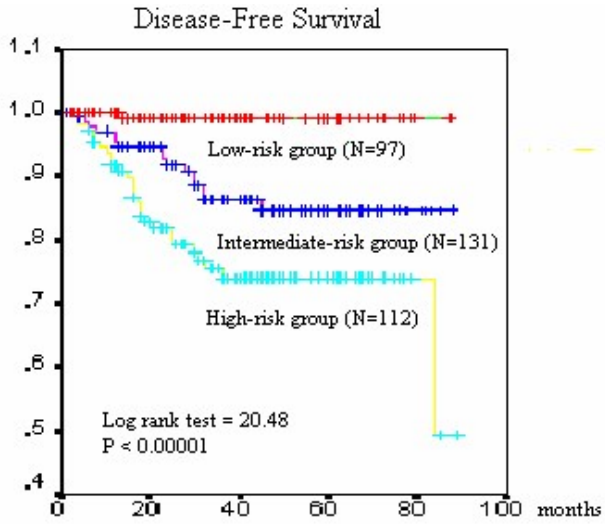

Fig. 1. Disease-free survival of the 340 patients from the prospective study (2000-07) distributed by the value of the prognostic index in three risk groups

Table 2. Recurrence rates and 5-year disease-free survival rates according to the value of the prognostic index

PI	Original study (1989-99)			Prospective study (2000-07)				P value*	P value#
	No.	Relapse (%)	5y DFS	No.	Relapse (%)	5y DFS	95%CI		
0-2,2	58	1 (1,7)	97,73%	97	1 (1,0)	98,82%	96,5-100	NS	NS
2.21-4,2	112	14 (12,5)	86,51%	131	16 (12,2)	84,57%	77,4-91,8	NS	NS
>4,.2	67	35 (52,2)	44,24%	112	26 (23,2)	74,01%	65,1-82,9	0,0000734	0,0010

Legend: CI, confidence interval; DFS, disease-free survival; No., number of patients, NS, not significant; P, probability, PI, prognostic index value; y, year. *Correlation between recurrence rates (chi-square or Fisher's exact test, as appropriate); #Correlation between disease-free survival rates (log rank test)

In order to validate the model from our previous study, we have compared the recurrence rates and DFS rates between the prognostic groups (Table 2). There was no difference in recurrence rate and DFS rate between low-risk groups, in spite of the fact that majority of the patients in this study were not irradiated, while radiotherapy was administrated invariably to all the cervical carcinoma patients included in the original study (Figure 2).

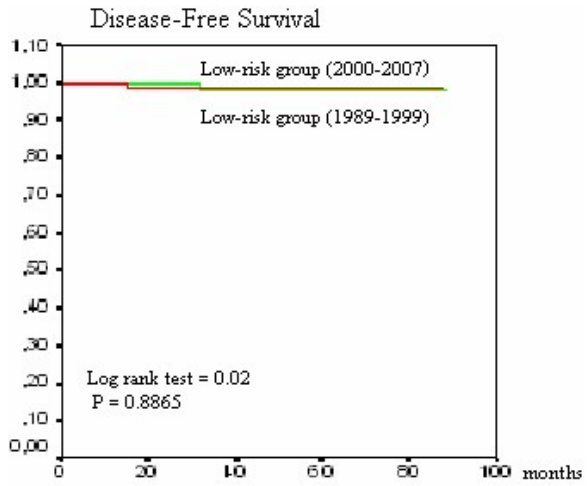

Fig. 2. Disease-free survival of the 58 patients belonging to the low-risk group in the original study (1989-99) and 97 low-risk group patients from the prospective study (2000-07)

Similarly, recurrence rate and DFS rate did not differ significantly between the intermediate-risk groups from both studies, which could be expected since radiotherapy was administrated to majority of the patients (125/131) in this study (Figure 3). In contrast, the high-risk group patients in this study had significantly lower recurrence rate and higher DFS rate probably as the result of the adjuvant chemotherapy administrated to 69% (77/112) of them (log rank test=10,79, P=0,0010) (Figure 4).

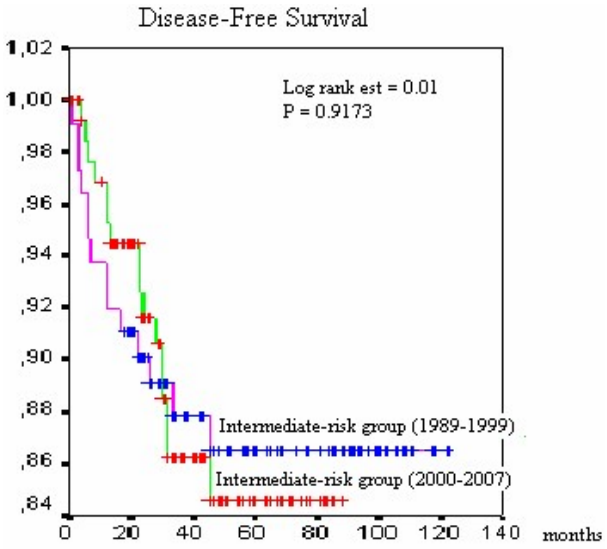

Fig. 3. Disease-free survival of the 112 patients belonging to the intermediate-risk group in the original study (1989-99) and 131 intermediate-risk group patients from the prospective study (2000-07)

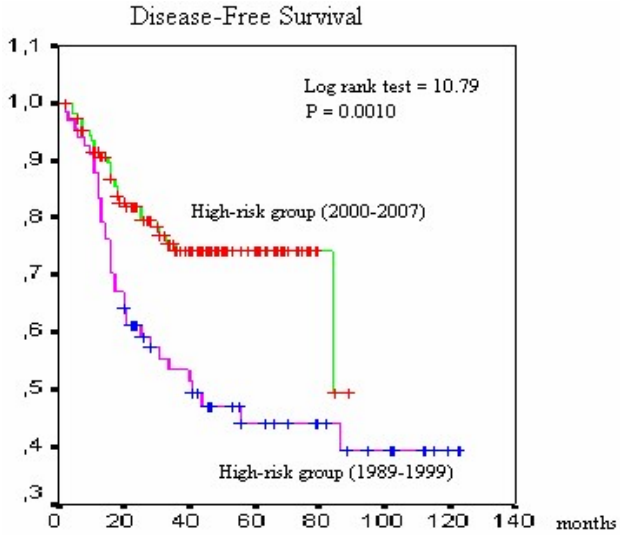

Fig. 4. Disease-free survival of the 67 patients belonging to the high-risk group in the original study (1989-99) and 112 high-risk group patients from the prospective study (2000-07)

Discussion

The current study confirmed previous data on prognostic factors in early stage cervical carcinoma, insofar as univariate analysis demonstrated that regional lymph node status, diameter, depth of stromal invasion and thickness of uninvolved cervical stroma/parametrial extension, vaginal involvement, grade of differentiation, blood vessel invasion and inflammatory infiltrate in the tumor's invasive front were of important prognostic significance in surgically treated early stage cervical cancer patients. At present, sufficient data have been reported in the literature to categorize lymph nodal status, tumor diameter, and depth of stromal invasion as independent risk factors because of their frequent association with increased cancer recurrence and mortality [5,7,9,11-20]. In addition, the prognostic significance of the third less frequently investigated morphometric parameter-thickness of uninvolved cervical stroma combined with parametrial extension - was also confirmed in this study [5,21,22]. The prognostic significance of vaginal involvement, a parameter incorporated in current staging systems, was also confirmed in our study, although conflicting results have also been reported [12,14]. In contrast to some other reports [19,23,24] the prognostic influence of surgical margin involvement on DFS was not confirmed in our study, which may be due to the small number of patients with positive margins [14,16]. Our data of the prognostic influence of tumor status (pT) as a parameter of postoperative pTNM classification on recurrence are in concordance with the results reported by Kainz, *et al*. [25].

With regard to histological type, it has been reported earlier that survival rate for patients with adenocarcinomas or mixed carcinomas was significantly poorer than that of patients with squamous cell carcinomas [12,17,20,24] Nevertheless, similar to our results, these data were not confirmed in other studies [13,16,23]. In our study tumor

grade was a predictive factor with regard to tumor recurrence. Yet, the reported data on the prognostic value of this parameter in surgically treated cervical cancer patients also are conflicting [10,13,14,16,19,20,22,23]. Similarly, the invasion of lymph-vascular spaces by tumor has been reported as an unfavorable prognostic factor by some investigators [9,11,14,26], whereas other analyses have not found this to be an independent risk factor [5,12]. On the other hand, the especially unfavorable prognosis of a tumor invasion into blood vessels communicated in the literature also became evident in our study group [10,26]. In the current study we have also confirmed the results of several previous studies [5,9,19,26], who reported that scarce inflammatory stromal reaction in the invasive front of the tumor was a significant predictive factor for lower disease-free and overall survival rate. Finally, as already reported in other studies, there was no association between patients' age and DFS [9,16,17].

However, it is well known that overall survival results of a study population are, among other factors, strongly influenced by the proportion of patients with a high and a low risk for treatment failure [11]. Therefore, one of the goals of developing a prognostic staging system is to define patients with similar risk for treatment failure that can be easily applied to an individual patient. Patients with similar risks can then be studied for effectiveness of different treatment modalities. In cervical carcinoma, clinical FIGO staging has been the international standard to compare treatment results. Many many studies have shown inaccuracy of clinical staging, making comparisons of treatment modalities based on FIGO stages difficult, if not impossible [5,11]. Thus, Kupets and Covens [4] based on their thorough assessment of the clinimetric properties of the current FIGO staging system for cervical carcinoma, conclude that it does not fully meet the majority of methodological criteria for a strong predictive tool. They also suggest a necessity of developing an improved prognostic index containing a complete array of independently prognostic variables.

Surgical staging in early stage cervical carcinoma patients preferentially treated with radical hysterectomy and pelvic lymph node dissection provides precise pathologic data that can identify patients with similar risks. Thus, individual parameters that predict poor prognosis have been the subject of many publications. Though most of these studies have used univariate analysis and reported a variety of risk factors, it is clear that many of these factors are interrelated. Multivariate analysis methods have been employed to define the best statistically significant combination of risk factors [5,11-16]. Using Cox's proportional hazards regression model, these studies have produced different sets of combined risk factors for surgically treated patients.

In the previous study we have evaluated the prognostic significance of 23 various clinicopathological parameters in early stage cervical carcinoma [5]. For that purpose we have selected a group of 237 cervical cancer patients which was homogenous for the type of therapy: all patients were submitted to radical surgery, followed by external pelvic radiation therapy according to hospital policy. In addition, selection criteria were based on the postoperative stage or the real extent of the tumor in the operative specimen. The hysterectomy specimens were subjected to identical histopathological work-up. Tumor invasion into blood vessels, pelvic lymph node metastases, tumor diameter, the degree of inflammatory cell infiltrate at the invasive front, and minimum thickness of uninvolved cervical stroma/parametrial extension were identified as the only independent and significant prognostic factors for DFS in our study. Using the models proposed by Kamura, *et al.* [12] and Lai, *et al.* [13], the PI, was calculated for each patient and three distinct risk groups were tentatively divided by two cut-off points set on the clinical basis. The estimated 5-year DFS rates for the low-, intermediate-, and high-risk group were 97,5%, 86,3% and 43,8%, respectively.

Delgado, *et al.* reported on 645 patients with FIGO Stage I squamous cell carcinoma and found clinical tumor size, lymph-vascular space involvement and depth of stromal invasion expressed in fractions of cervical thickness to be the best combined prognostic factors for 3-year DFS [14]. They proposed a scoring system which calculates a general relative risk (RR) by multiplication of relative risks of the three independent prognostic variables and identifies three separate risk groups for recurrence. Several years later, Van de Putte, et al. in their study of 221 patients with FIGO Stage I squamous cell carcinoma tried to validate and simplify the original model proposed by Delgado, *et al.* to a risk model based on two factors: tumor size and depth of stromal invasion [15]. In contrast, Kamura, *et al.* in a study of 345 patients with cervical carcinoma found the number of positive pelvic lymph nodal groups, histological type and tumor diameter to be the best combined risk factors for overall survival [12]. They proposed a prognostic index based on the three variables and created a system of three prognostic groups with significantly different survival curves. Subsequently, by comparing their results with previous two studies and introducing multivariate survival tree analysis, Sevin, *et al.* found depth of stromal invasion expressed in millimeters, lymph-vascular space involvement, lymph nodal metastasis and age to be the most important independent prognostic factors influencing 5-year DFS in a series of 301 patients with FIGO Stage I-II cervical carcinoma [11]. They also divided the patients into three risk groups with 5-year survival rates of 91%, 68% and 43%, respectively.

However, there were significant differences in the eligibility and selection criteria for adjuvant therapy used in these studies. In a large prospective Gynecology Oncology Group study of Delgado, *et al.* patients with aortic lymph node metastasis, other direct extension beyond uterus and nonsquamous histology were excluded. Postoperative irradiation in this study was given at the dis-

cretion of the physician in approximately 25% of patients [14]. Van de Putte, *et al.* implemented the same selection criteria, while in their study 9% of patients was given postoperative irradiation, 5,4% radiation and chemotherapy and 14% received chemotherapy only [15]. In their study Kamura, *et al.* included patients with FIGO stages IB-IIB, as well as 70 patients with depth of stromal invasion less than 3 mm [12]. Four patients with undifferentiated carcinomas were excluded, yet nine patients with small cell carcinoma were included. In this study 43% of the patients who had lymph nodal metastasis, parametrial extension and/or full thickness stromal invasion received irradiation. Sevin, *et al.* excluded patients with microinvasive and small cell carcinomas, while adjuvant irradiation was administrated to 22% of patients with histologically proven or positive surgical margins, vaginal involvement, parametrial extension or pelvic lymph node metastasis [11].

The current study has confirmed that PI implemented in our Department starting from January 2000, as an indicator of the patient's place in the prognostic spectrum could be a sound and reliable basis for an appropriate planning of the following therapeutical strategy of the surgically treated patients with cervical carcinoma. Thus, the 5-year survival rate for all the patients in the present study is in agreement with the reported rates in the 80% to 90% range for patients with FIGO stage IB-IIA tumors [7,16,17]. We were also able to reproduce the 5-year DFS rates for the low- and intermediate-risk group patients similar to the original study, while at the same time the low-risk group patients were spared of adjuvant irradiation therapy. Recurrences in our series were more often localized outside the pelvis (86%, 37/43), which may be partly due to the pelvic irradiation given to most of the patients belonging to the intermediate- and high-risk groups. A further argument for the usefulness of PI arises from the fact that the high-risk group patients, due to the administration of an adjuvant irradiation and chemotherapy have better prognosis than patients belonging to the high-risk group in the previous study treated by irradiation only. Despite the substantial number of patients refusing adjuvant irradiation (7) and/or chemotherapy (35), and the relatively small number of patients who did not complete irradiation (1) or chemotherapy (9), there was a profound decrease in recurrence and an improvement of DFS with the addition of chemotherapy to pelvic radiotherapy. These results are in agreement with the current view that radiotherapy for intermediate-risk postsurgical patients and chemoradiation for high-risk postsurgical patients are considered optimum treatments [7].

Conclusions

In conclusion, in the univariate analysis in our study the prognostic significance of majority of the clinicopathological variables investigated, was confirmed. In addition, based on the results of this prospective study, the individual value of the PI should be considered when an eventual postoperative therapy is planned and prognosis is determined in early stage cervical carcinoma patients. Its application clearly facilitates the recognition of those surgically treated patients with early stage cervical carcinomas that require a modified treatment approach. Besides exteranal validation study, we also recommend continuous monitoring of the criteria for determining the five significant independent prognostic parameters; along with a more rigorous implementation of the selection criteria and suggestions for an individual and modified therapeutic approach according to the PI value, as well as regular follow-up of all patients for early detection of recurrence.

Conflict of interest statement. None declared.

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