Survival of 231 cervical cancer patients, treated by radical hysterectomy, according to clinical and histopathological features

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Summary

Purpose of investigation: The purpose of the study was to estimate the five-year survival of cervical cancer patients after radical hysterectomy, taking into account clinical data and histopathological parameters.

Methods: 231 patients with invasive cervical carcinoma were diagnosed, surgically treated - Piver III – and followed-up. Histological examination of specimens was performed according to the British NHS-CSP guidelines.

Results: We discovered no statistical significance as regards age at diagnosis, age at menarche and menopause, and number of pregnancies, deliveries and abortions, in relation to survival. We concluded that the clinical stage according to FIGO classification influenced survival. Statistical significances were: Ia2 vs Ib, Ib vs IIa and IIa vs more advanced than IIa. The following histopathological parameters correlated with survival: depth of cervical invasion, primary lesion volume, and parametrial, uterine, vaginal and lymph node involvement. Using Cox's proportional hazards model we found that only lymph node status and FIGO staging were independent parameters correlating with survival and mortality risk in our study.

Conclusion: Prognostic indexes classifying patients at specific disease stages into different categories of risk should be based on histopathological features listed above. Such indexes are yet to be validated in larger, prospective studies conducted in different patient populations.

Key words: Cervical cancer; Clinical staging; Histopathological parameters; Lymph node metastases; Survival prognosis.

Introduction

The main risk factors for cervical carcinoma are well known. They were established and recognized on the basis of the results of combined multicenter studies [1, 2]. The survival of patients with invasive cervical carcinoma depends, first of all, on FIGO stage, but the presence of metastatic lymph nodes dramatically decreases the five-year survival rate [3]. The histological type of the tumor, tumor volume and parametrial involvement seem to be other important predictive factors [4, 5]. More aggressive treatment may be given to patients considered to be at an elevated risk of recurrence, whereas others with favorable prognoses may be spared the undesirable side-effects of an aggressive regimen [2]. Likewise, high-risk patients may be followed-up more closely via more sensitive diagnostic tests, whereas low-risk patients may be monitored in the standard fashion. Disease stage is by far the most important factor to consider when assessing the overall prognostic outlook and planning the therapeutic strategy. There are only a few statistical analyses of the survival of cervical cancer patients diagnosed and treated by the same surgical team. The purpose of the present study was to estimate the five-year survival of cervical cancer patients after radical hysterectomy, taking into account clinical data and histopathological parameters of the primary cervical lesion. Furthermore, we wanted to compare the results with those in other reports concerning patient characteristics associated with prognostic disadvantages.

Materials and Methods

We included into the study 231 well documented cases of patients with invasive cervical carcinoma. They were surgically treated between 1997 and 1999. The patients' age ranged from 27 to 79 years; mean age 48.82 ± 10.60 (± SD). Most patients developed cervical carcinoma between 40 and 50 years of age. We estimated cervical carcinoma clinical staging according to FIGO classification using standard techniques. Histologic examination of specimens obtained from the colposcopic-aimed biopsy from the cervix and the D&C procedure were criteria for diagnoses. Next, gynecological examination, cystoscopy, rectoscopy and standard imaging procedures as chest X-ray and ultrasound examination of the abdominal cavity were performed. All patients included into the study were staged Ia2 or more and were treated surgically - Piver III. Patients with cancer staged IIA and II B were qualified for surgical treatment by two experienced gynecologist-oncologists. Specimens obtained during the procedure, including cervices, were submitted in total to the Pathology Department and prepared for histological analysis. According to the British NHS-CSP guidelines cervices were "bread-sliced" and mucin stains were performed in all cases. We estimated the volume of the primary lesion from diameters recorded in the postoperative pathological report. After the surgical procedure patients were to be subjects of supplementary radiotherapy or were included in the

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group which was followed-up in the out-patient clinic of the gynecology department, and at regular 3-month intervals during the first two years and then twice yearly. Patients treated in radiotherapy departments were followed-up in those departments according to the same schedule. We analyzed survival by means of Kaplan-Meier estimation. The median follow-up period was 65,88 months (minimum 32,49 and maximum 92,06). We evaluated the association between survival and the following clinical parameters: patient's age at diagnosis (in three groups: under 40, under or equal to 50 and over 50), ages at menarche and menopause, menstrual cycle disorders, number of deliveries, number of abortions (spontaneous and induced), standard staging diagnosed by routine clinical examination (according to FIGO classification) as well as pathologic parameters: stage based on the postoperative pathological report, histologic type of tumor, depth of cervical invasion, size of primary lesion, lymph node metastasis status, and parametrial, uterine and vaginal involvement.

Statistical analysis

STATISTICA for Windows 6.0 Stat Soft, Inc., USA was used for statistical analysis. The chi-square test for determination of independence of the variable for histopathological parameters and the Kaplan-Meier method for survival analysis were applied. The statistical significance level was set at $p < 0.05$.

Results

Analyzing clinical features, we stated that age at menarche ranged from 10 to 20 years (median 14); mean 13.9 ± 2.2. Mean age at menopause was 45.3 ± 5.7 years; 139 (59.82%) patients were premenopausal and 92 (40.2%) postmenopausal at diagnosis. Most premenopausal patients had regular menstrual cycles; 14 (6.1%) women had cycles shorter than 26 days and seven (3.0%) had cycles longer than 31 days. The number of pregnancies among the patients ranged from 0 to 10; mean 3.07 ± 1.84 (median 3). Their mean delivery number was 2.56 ± 1.53; 67 (29.%) women reported two deliveries and 58 (25.1%) women three deliveries.

Eighty-six (37.23%) patients had undergone abortions; 14 (6.06%) women had had more than two. Most reported abortions – 63 (27.27%), were spontaneous, and 37 (16.02%) women had undergone induced abortions.

We present clinically staged groups according to FIGO classification. Almost half of the analyzed group (48.5%) were patients in Stage Ib and 14.5% were patients in stages more advanced than IIa.

Histologically, squamous cell carcinomas were predominant, representing 88.7% of cases. Among the squamous carcinomas, 69 (29.9%) were large cell keratinizing type and 136 (58.9%) were large cell non-keratinizing type. There were 26 (11.3%) adenocarcinomas. Postoperative pathological reports confirmed cervical invasion deeper than 10 mm in 167 cases. In 81 cases the tumor volume was over 40 cm^3 (the most numerous group). We confirmed uterine involvement in 71 (30.7%) cases, parametrial involvement in 21 (9.1%) cases and vaginal invasion in 73 (31.6 %) patients (Table 1).

We discovered no statistical significance as regards age at diagnosis, age at menarche and menopause, and number of pregnancies, deliveries and abortions, in relation to survival. We observed that patients reporting more than four pregnancies tended to have a shorter survival time ($p = 0.10$). We concluded that the clinical stage according to FIGO classification and pathological parameters influenced survival. When analyzing clinical stage and survival we divided the patients into five groups: Ia2, Ib1, Ib2, IIa and those at stages more advanced than IIa (Figure 1). We concluded that there were statistically significantly shorter survival periods in consecutive groups ($p < 0.001$).

The following histopathological parameters correlated with survival: depth of cervical invasion, primary lesion volume, and parametrial, uterine, vaginal and lymph node involvement. Detailed data concerning FIGO stage and frequency of lymph node metastases are presented in Table 2. We found a relationship between depth of cervical invasion and survival when comparing invasion up to 10 mm vs invasion over 10 mm – Figure 2. We categorized the volume of the lesion into three groups: below 1 cm^3, 1-40 cm^3 and over 40 cm^3 and concluded that it statistically influences survival. We observed shorter survival times in patients categorized in the third group (tumor volume over 40 cm^3) – Figure 3. Invasion of the uterus (Figure 4) and vaginal invasion (Figure 5) statisti-

Table 1. — *Pathological findings in cervical cancer patients.*

	Total group n = 231	%	p value (related to survival)
Squamous cell carcinoma			
large cell non-keratinizing	136	58.9	0.15
large cell keratinizing	69	29.9	
Adenocarcinoma	26	11.3	
Depth of cervical invasion			
3-10 mm	64	27.7	0.001
invasion > 10 mm	167	72.3	
Volume of primary lesion			
< 1 cm^3	51	22.1	
1-10 cm^3	34	14.7	< 0.001
10-40 cm^3	65	28.1	
> 40 cm^3	81	35.1	
Corpus invasion			
not over internal isthmus	160	69.3	0.003
over internal isthmus	71	30.7	
Vaginal invasion			
–	158	68.4	0.005
+	73	31.6	
Parametrial invasion			
–	210	90.9	< 0.001
+	21	9.1	

Table 2. — *FIGO stage and lymph node metastases.*

FIGO stage	Number of patients	Patients with lymph node metastases (%)
Ia2	34	1 (3)
Ib1	38	18 (47)
Ib2	74	21 (28)
IIa	51	21 (41)
IIb and more	34	12 (35)
Total group	231	73 (32)

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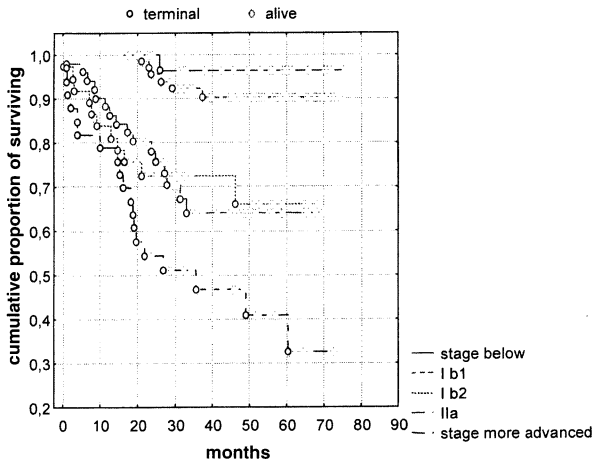
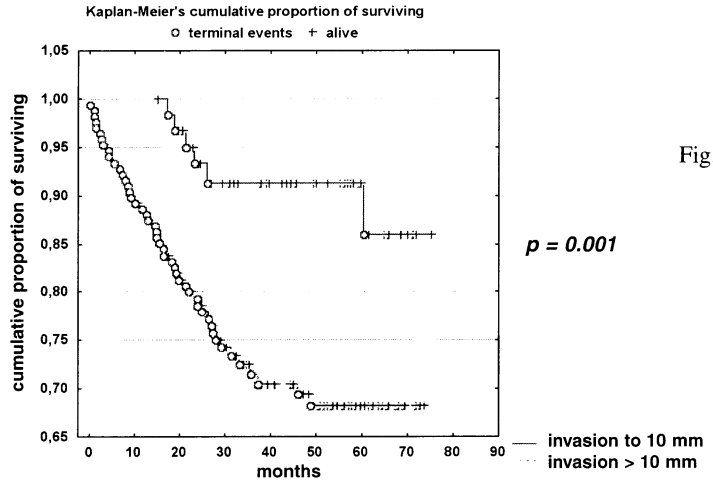


Fig. 2



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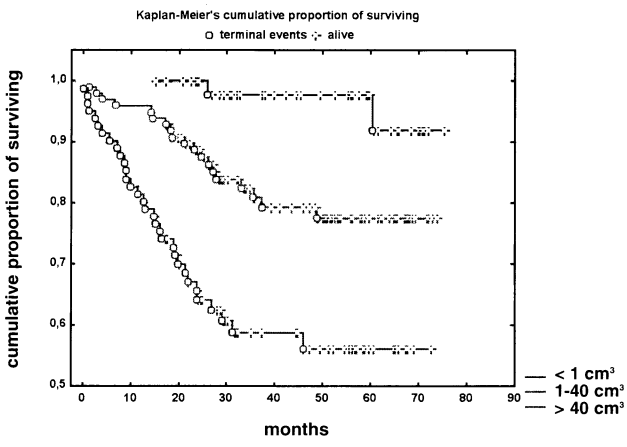

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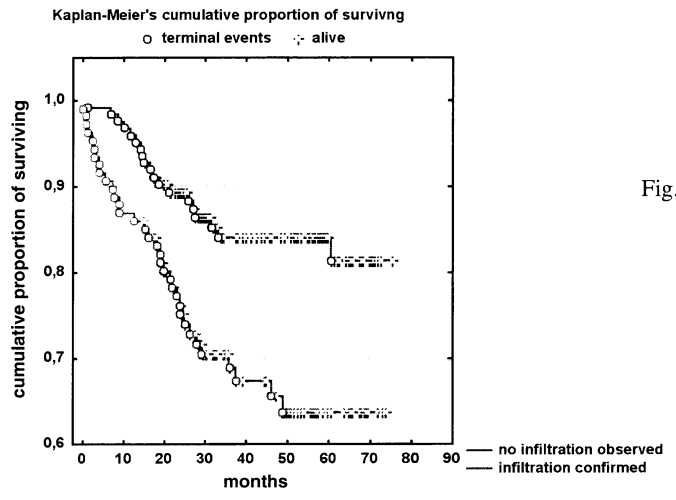

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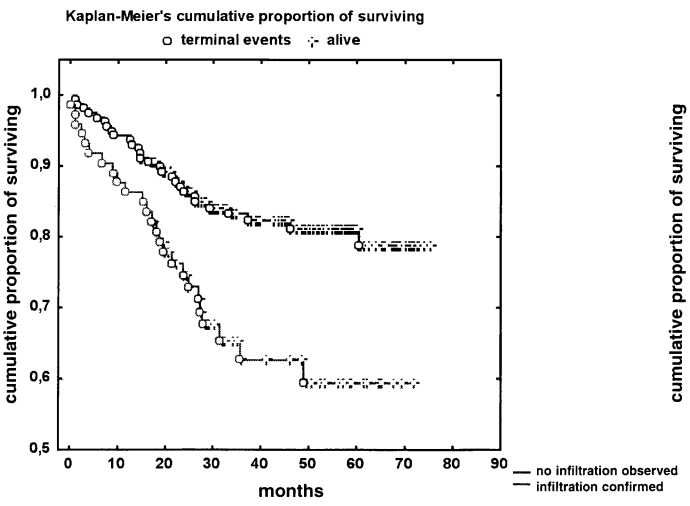

Fig. 6

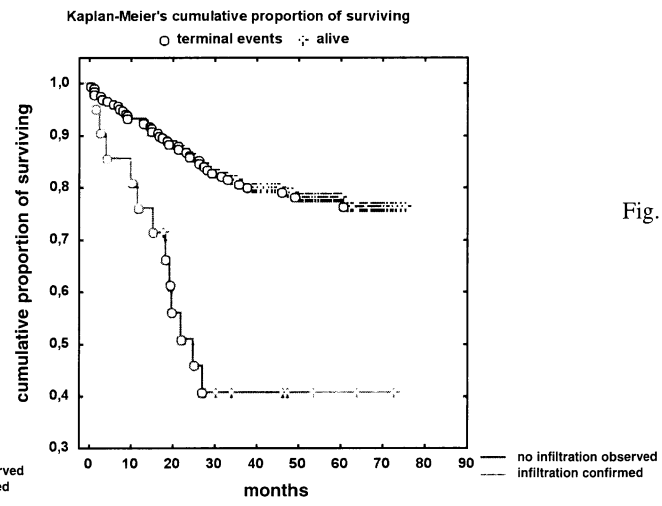

Figure 1. — Kaplan-Meier survival curves stratified for clinical staging (according to FIGO classification) in cervical cancer patients.
Figure 2. — Kaplan-Meier survival curves stratified for cervix invasion to 10 mm and deeper than 10 mm in cervical cancer patients.
Figure 3. — Kaplan-Meier survival curves stratified for primary lesion volume in cervical cancer patients.
Figure 4. — Kaplan-Meier survival curves stratified for tumors infiltrating and not infiltrating the uterus in cervical cancer patients.
Figure 5. — Kaplan-Meier survival curves stratified for tumors infiltrating and not infiltrating the vagina in cervical cancer patients.
Figure 6. — Kaplan-Meier survival curves stratified for tumors infiltrating and not infiltrating the parametrium in cervical cancer patients.

cally significantly shortened survival, as well as invasion of the parametrium – Figure 6 and lymph node involvement – Figure 7. We evaluated the association of independent clinicopathological variables with survival in cervical carcinoma patients with the Cox's proportional hazards model. In statistical analysis we took into account pathological parameters, lymph node status and FIGO staging. Data are presented in Table 3.

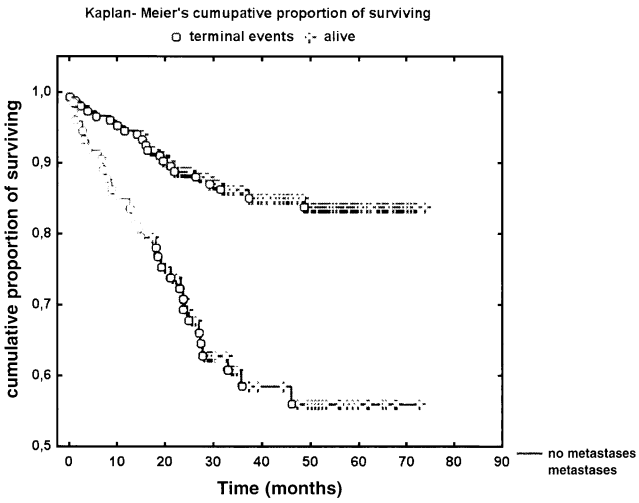

Figure 7. — Kaplan-Meier survival curves stratified for presence of lymph node metastases.

Table 3. — . *Results of the Cox's proportional hazards model in analyzed clinical and histopathological parameters.*

Analyzed data	p value	Relative risk
Clinical FIGO staging	< 0.001	2.15
Lymph node metastasis	< 0.001	2.53
Primary lesion volume	0.13	2.63
Depth of cervix invasion	0.59	0.71
Corpus invasion	0.17	1.25
Parametrial invasion	0.49	0.77
Vaginal invasion	0.94	0.98

Discussion

Recent epidemiological studies have revealed deceleration of the earlier dramatic reduction of incidence and mortality rates associated with cervical cancer in certain countries. This does not apply to Poland, however, where mortality from cervical cancer is still over 50% [2]. Additionally, there are reports of an increased risk among selected groups of women. In our study we discovered no statistical significance as regards age at diagnosis, age at menarche and menopause, and number of pregnancies, deliveries and abortions in relation to survival. In contrast, most studies reveal that the age of the patient is a risk factor for a poorer outcome. Data presented by Kosary [1] concerning over 17,000 cases of invasive cervical cancer diagnosed between 1973 and 1987 and categorized by age into 10-year intervals, with the youngest category under 30 and the oldest over 70, unequivocally confirmed a positive correlation between age and risk of death. However, in another study, Brewster *et al.* [6], after adjusting for mortality not related to cancer, tumor stage and histology, found no differences in survival between younger vs older women. Older age is often connected with a lower socioeconomic status and poor performance status at the time of diagnosis. Even in developing countries, higher socioeconomic status is associated with advantageous survival among cervical cancer patients [7]. Similarly, "not active" and "bedridden" status at the time of diagnosis has been reported to be an independent predictor of survival among patients at Stages Ib through IVb [8]. Analyzing clinical stage and survival we divided the patients into five groups: Ia2, Ib1, Ib2, IIa and stages more advanced than IIa. We found statistically significantly shorter survival in consecutive groups ($p < 0.001$). FIGO stage has a strong correlation with disease-free interval and overall survival in most studies [1]. This is not surprising, since stage summarizes the essential information from three dimensions of disease burden: the extent of the local primary tumor, the degree of regional involvement, and the existence of distant involvement and metastases. However, conventional FIGO staging for cervical carcinoma does not take into account important information from postoperative histopathological examination, especially that concerning pelvic lymph node status. In the present work Kaplan-Meier survival curves stratified in regard to patients with and without lymph node involvement showed statistical significance ($p < 0.001$). According to US SEER data [1], overall survival rates are 25 to 65% lower within stages among women with positive lymph node status compared with those who are node-negative. In a Japanese study [3] it was found that the 5-year survival rate decreased substantially with increased number of affected lymph node sites: 92% for none, 88% for one affected site, 72% for two sites, and 64% for three or more sites. Other important and independent determinants of survival are histological type and degree of differentiation. Analysis of a very large cohort of patients [1] showed that the survival of women with squamous cell carcinomas of the cervix was comparable to that of those with adenocarcinomas, whereas women with carcinomas of adenosquamous histology had an approximately 30% greater risk of death compared with those with other histological types, after controlling for other prognostic factors. In our study, similar to the others [9], squamous cell carcinomas were predominant, comprising 88.7% of cases. Among the squamous carcinomas, 69 (29.9%) were of large cell keratinizing type and 136 (58.9%) were of large cell non-keratinizing type. There were 26 (11.3%) cases of adenocarcinomas. Probably as a result of having a relatively homogeneous group of patients, according to histology, we did not observe statistical significance as regards the histological type of cervical carcinoma. We found that the depth of cervical invasion affected survival (up to 10 mm vs over 10 mm; $p = 0.001$), and the volume of the lesion

also significantly influenced survival ($p < 0.001$). These observations support data presented by Lai *et al.* [10], where depth of stromal invasion and tumor size were significant factors as regards recurrence-free and overall survival. The depth of stromal invasion should not be regarded as a valuable pretreatment parameter, the majority of patients being evaluated by histologic examination. Tumor size estimation was far from accurate by means of pelvic examination. MR imaging has been confirmed to be an attractive way of measuring tumor size and depth of stromal invasion in cervical carcinoma. However, magnetic resonance imaging (MRI) will not pick up microscopic foci of tumor, for example in the parametrium or lymph nodes. Invasion of the uterus and vaginal invasion significantly shortened survival ($p = 0.003$ and $p = 0.005$, respectively), as did invasion of the parametrium ($p < 0.001$). The significant influence of parametrial involvement on survival is a result of the association with pelvic node involvement. Seventy percent of the patients with parametrial involvement in a series reported by Winter *et al.* [11] had positive pelvic lymph nodes. Parametrial involvement in patients with negative pelvic nodes is associated with slightly poorer survival, which does not differ significantly from that among patients with a negative parametrium and negative pelvic nodes [11]. Lymph node involvement, which significantly shortened survival ($p < 0.001$), is very sensitive poor prognostic factor [12]. The frequency of parametrial involvement and pelvic lymph node involvement is closely associated with the size of the primary tumor [4, 5, 13, 14]. A large primary tumor is very often connected with uterine involvement and vaginal invasion, which are risk factors for a poor prognosis, as mentioned above. Using Cox's proportional hazards model we found that only lymph node status and FIGO staging were independent parameters correlated with survival and mortality risk in our study. Many authors have attempted to compute prognostic indexes and have classified patients at specific disease stages into different categories of risk, with varying results [15]. Such indexes are yet to be validated in larger studies conducted in different patient populations. Our data support universal application of the histopathological features listed above in prognostic studies.

References.

[1] Kosary C.L.: "FIGO stage, histology, histologic grade, age and race as prognostic factors in determining survival for cancers of the female gynaecological system: an analysis of 1973-1987 SEER cases of cancers of the endometrium, cervix, ovary, vulva, and vagina". *Semin. Surg. Oncol.*, 1994, *10,* 31.

[2] Duarte-Franco E., Franco E.L.: "Determinants of patient survival in cervical cancer: an overview". *CME J. Gynecol. Oncol.,* 2001, *6,* 173.

[3] Kamura T., Shigematsu T., Kaku T., Shimamoto T., Saito T., Sakai K. *et al.*: "Histopathological factors influencing pelvic lymph node metastases in two or more sites in patients with cervical carcinoma undergoing radical hysterectomy". *Acta Obstet. Gynecol. Scand.,* 1999, *78,* 452.

[4] Baltzer J., Köpcke W.: "Tumor size and lymph node metastases in squamous cell carcinoma of the uterine cervix". *Arch. Gynecol.,* 1979, *227,* 271.

[5] Piver M.S., Chung W.S.: "Prognostic significance of cervical lesion size and pelvic node metastases in cervical carcinoma". *Obstet. Gynecol.,* 1975, *46,* 507.

[6] Brewster W.R., DiSaia P.J., Monk B.J., Ziogas A., Yamada S.D., Anton-Culver H.: "Young age as a prognostic factor in cervical cancer: results of a population-based study". *Am. J. Obstet. Gynecol.,* 1999, *180,* 1464.

[7] Schrijvers C.T., Mackenbach J.P.: "Cancer patient survival by socio-economic status in seven countries: a review of six common cancer sites". *J. Epidemiol. Community Health.*, 1994, *48,* 441.

[8] Sankaranarayanan R., Nair M.K., Jayaprakash P.G., Stanley G., Varghese C., Ramadas V. *et al.*: "Cervical cancer in Kerala: a hospital registry-based study on survival and prognostic factors". *Br. J. Cancer,* 1995, *72,* 1039.

[9] Hagen B., Skjeldestad F.G., Halvorsen T., Strickert T., Tingulstad S., Lorenz E., Onsrud M.: "Primary treatment of cervical carcinoma. Ten years experience from one Norwegian health region". *Acta Obstet. Gynecol. Scand.,* 2000, 79, 1093.

[10] Lai C.H., Hong J.H., Hsueh S., Ng K.K., Chang T.C., Tseng C.J. *et al.*: "Preoperative prognostic variables and the impact of postoperative adjuvant therapy on the outcomes of Stage IB or II cervical carcinoma patients with or without pelvic lymph node metastases: an analysis of 891 cases". *Cancer,* 1999, *85,* 1537.

[11] Winter R., Haas J., Reich Lahousen M., Tamussino K.: "Prognostic significance of parametrial involvement in cervical cancer". *CME J. Gynecol. Oncol.,* 2001, *6,* 204.

[12] Takeda N., Sakuragi N., Takeda M., Okamoto K., Kuwabara M., Negishi H. *et al.*: "Multivariate analysis of histopathologic prognostic factors for invasive cervical cancer treated with radical hysterectomy and systematic retroperitoneal lymphadenectomy". *Acta Obstet. Gynecol. Scand.*, 2002, *81,* 1144.

[13] Ayhan A., Celik H., Coskun F., Baykal C., Salman M.C., Askan G.: "Restaging in gynaecological cancers". *Eur. J. Gynaecol. Oncol.,* 2005, *26,* 25.

[14] Burghardt E., Pickel H.: "Local spread and lymph node involvement in cervical cancer". *Obstet. Gynecol.,* 1978, *52,* 138.

[15] Shaw M.C., Wolfe C.D., Devaja O., Raju K.S.: "Development of an evidence-based algorithm for the management of cervical cancer". *Eur. J. Gynaecol. Oncol.,* 2003, *24,* 365.

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