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Survival Analysis of Endometrial Carcinoma : Comparison Between Normal and Abnormal Cervical Cytology

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ABSTRACT

Introduction Preoperative malignant cervical cytology has been correlated with a higher surgicopathological stage or extrauterine metastasis of endometrial carcinoma patients. No study has identified cervical cytology as an independent prognostic factor of these patients.

Objectives To compare the survival of endometrial carcinoma patients between normal and abnormal cervical cytology, and to determine the independent prognostic factors of these patients.

Study design Historical cohort study.

Methods We retrospectively reviewed the preoperative cervical cytology and clinicopathological findings of 122 surgically staged endometrial carcinoma patients in Songklanagarind Hospital during 1987-1998. Survival analysis was conducted using Kaplan-Meier plots and Cox proportional hazards regression model.

Results Ninety-four patients (77.1%) had normal cervical cytology, and 28 patients (22.9%) had abnormal cervical cytology. The overall 5-year survival of endometrial carcinoma patients was 76.7%. Univariate analysis of the clinicopathologic prognostic factors showed that survival was significantly poorer in patients with abnormal cervical cytology ($p = 0.004$). The 5-year survival of patients with normal and abnormal cervical cytology was 83.6% and 56.8% respectively ($p = 0.001$). Survival was also significantly correlated with tumor stage ($p < 0.001$), histologic grading ($p = 0.011$), myometrial invasion ($p = 0.003$), adnexal metastasis ($p < 0.001$), pelvic or paraaortic lymph node metastasis ($p < 0.001$) and peritoneal cytology ($p < 0.001$). No association was found between survival and patients' age ($p = 0.085$), histologic type ($p = 0.482$) or cervical metastasis ($p = 0.388$). Multivariate analysis showed that abnormal cervical cytology ($p = 0.013$), nodal metastasis ($p = 0.009$) and peritoneal cytology ($p = 0.001$) were significant prognostic factors.

Conclusion Endometrial carcinoma patients with abnormal cervical cytology had significantly lower survival than those with normal cytology. Preoperative cervical cytology, nodal metastasis and peritoneal cytology were the independent prognostic factors of endometrial carcinoma patients.

Key words: endometrial carcinoma, survival, cervical cytology, pap smear, prognostic factor

Endometrial carcinoma is the fifth most common gynecologic malignancy in women worldwide.[1] In Songklanagarind Hospital, endometrial carcinoma is the third one with 21-34 initially diagnosed patients per year.[2] The incidence rate of these cases has been found to be increasing in recent decades.[3] About 90 % of women with endometrial carcinoma have vaginal bleeding or discharge as the only presenting complaint. Some women experience extragenital symptoms and less than 5 % of patients are asymptomatic. In the absence of symptoms, endometrial carcinoma is usually detected as the result of investigation of patients with abnormal cervical cytology.[4]

The study of cervical cytology in endometrial carcinoma has gradually improved. The importance of malignant or suspicious cell detected by cervical cytology had been demonstrated by several authors.[5-10] Desquamated endometrial cells detected by routine cervical cytology can be normal cells, benign changed cells or even malignant cells. Abnormal desquamation reflected by the presence of atypical endometrial cells is associated with adenocarcinoma and other endometrial lesions.[8] Women who are found to have malignant cells on Pap test are more likely to have a more advanced stage of disease.[5,6,11,12]

Although stage of disease is the most significant variable affecting survival, a number of other individual prognostic factors for disease recurrence or survival have been identified, including tumor grade, histopathology, depth of myometrial invasion, patients' age, and surgicopathological evidence of extrauterine disease spread. Peritoneal cytology has also been implicated as having prognostic importance.[13]

Several authors had demonstrated a significant correlation between preoperative malignant cervical cytology and a higher surgicopathological stage or extrauterine metastasis.[5-7,10,12] However, no study has identified cervical cytology as an independent prognostic factor of endometrial carcinoma patients. Thus, this study was undertaken in order to compare survival of endometrial carcinoma patients between normal versus abnormal cervical cytology, and to determine the independent prognostic factors affecting survival of these patients.

Material and Methods

In Songklanagarind Hospital, all patients with primary endometrial carcinoma are registered at the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology and Cancer Registry Unit.

Sample size calculation was based on the expected proportion of abnormal cervical cytology which is 28%, a 5-year survival of normal cervical cytology of 85% and a 95% power to detect a survival among abnormal cervical cytology of 60% with a type I error of $\alpha 0.05$. The total study time was 12 years accrual with 4.5 years extra-follow up. The required sample size was 119 patients, 33 abnormal cervical cytology and 86 normal cervical cytology.

After reviewing all cases who were registered during the period January 1987 and June 1998, a series of 122 consecutive patients fulfilling eligibility criteria with primary endometrial carcinoma was enrolled in this historical cohort study. The patients who had cervical cytology examined according to Papanicolaou classification within 6 months prior to surgery were included in the study. Those patients who were surgically staged with pathological report of the histologic type and grading, myometrial invasion, cervical involvement, adnexal involvement, pelvic and para-aotic lymph node involvement, and peritoneal cytological report were included in the study. Any patients who had two primary carcinomas or could not be followed up at anytime to confirm the status of dead or alive were excluded from the study.

The cervical specimens were obtained with an Ayre's spatula by VCE technique (vagina, ectocervix, endocervix). The cervical smears were interpreted by pathologists of the Department of Pathology, Songklanagarind Hospital. Cervical cytology class I (normal epithelium) and class II (inflammatory cell) of Papanicolaou classification were classified as normal cervical cytology. Cervical cytology class III (dysplastic cell), class IV (suspicious for malignant cell)

and class V (malignant cell) of Papanicolaou classification were classified as abnormal cervical cytology.

The patients were surgically staged by a standard protocol at Songklanagarind Hospital. The abdomen was opened with a midline vertical incision and sampling of peritoneal fluid for cytologic evaluation were taken on entry. All intra-abdominal and pelvic peritoneal surfaces were examined and biopsied at suspicious areas. After extrafascial total abdominal hysterectomy and bilateral salpingo-oophorectomy, tumor size, depth of gross myometrial invasion and cervical extension should be assessed intraoperatively. Patients with clear cell, serous, squamous or grade 2-3 endometrioid carcinoma, more than one-half of myometrial invasion, cervical or extrauterine metastasis and tumor size more than 2 cm had pelvic and paraaortic lymphadenectomy. Patients with grade 1 endometrioid carcinoma and less than or equal to one-half of myometrial invasion had pelvic and paraaortic lymph nodes palpation. Any suspicious pelvic and paraaortic lymph nodes should be removed for pathologic examination. All surgical specimens were reviewed by at least 2 pathologists of the Department of Pathology, Songklanagarind Hospital.

The histologic type was assessed in accordance with The Armed Forces Institute of Pathology. The histologic grading was assesed in accordance to FIGO grading system. The tumour staging, myometrial invasion, cervical extension, adnexal involvement, pelvic or paraaortic lymph node involvement were assesed in accordance with the FIGO surgical staging system. Myometrial invasion by tumor was categorized as superficial to moderate (less than or equal to one-half of myometrial thickness) and deep (more than one-half of myometrial thickness) invasion. Postoperative radiotherapy was given in cases of grade 1 and 2 tumors with deep myometrial invasion, grade 3 tumors with any degree of myometrial invasion, large tumors (> 2 cm) with superficial myometrial invasion, cervical or extrauterine or lymph node metastasis.

All deaths are registered by Medicine Statistical Unit and Cancer Regitry Unit of Songklanagarind Hospital and the Department of Provincial Administration, Ministry of Interior, according to death certificates issued by a physician stating the cause of death. All living patients were confirmed directly by calling, mailing and/or checking the last follow up at Songklanagarind Hospital, and checking the census records from the Had-Yai City Municipality.

Survival time was calculated from the date of histological diagnosis until the date of death or last follow up at Songklanagarind Hospital. Survival profiles of the entire group and of subgroups were examine using Kaplan-Meier plots. The Cox proportional hazards regression model was used to examined crude and adjusted hazard ratios of each variable and to identify those with independent association with survival. The significance of each variable in both uni- and multivariate models was assessed using the changes in log-likelihood of each model on removal of the variables from the model. In the multivariate analysis, all variables, except tumor stage which is constructed from the other individual prognostic factors, were initially included (full model) and the least significant variable was removed in a stepwise process until all remaining variables showed a statistical significant ($p < 0.05$) contribution to the fit of the model. This reduced model was considered to be the final model.

Table 1. Clinicopathologic variables of 122 endometrial carcinoma patients

Prognostic variables	Number	%
Age		
≤ 50 years	26	21.3
> 50 years	96	78.7
Cervical cytology		
Normal	94	77.0
Abnormal	28	23.0
Stage		
I	75	61.5
II	22	18.0
III	17	14.0
IV	8	6.6
Histologic type		
Endometrioid	113	92.6
Non-endometrioid	9	7.4
Histologic grade		
1	82	67.2
2	13	10.7
3	27	22.1
Myometrial invasion		
≤ one half	89	73.0
> one half	33	27.0
Cervical metastasis		
Negative	94	77.0
Positive	28	23.0
Adnexal metastasis		
Negative	106	86.9
Positive	16	13.1
Nodal metastasis		
Negative	114	93.4
Positive	8	6.6
Peritoneal cytology		
Negative	113	92.6
Positive	9	7.4

Results

The mean age of the patients was 54.8 years with a range of 30 to 82 years. Of the 122 patients, 94 (77.0%) patients had normal cervical cytology, 28 (23.0%) patients had abnormal cervical cytology comprising 3 (2.5%) dysplastic cell, 9 (7.4%) suspicious for malignant endometrial cell and 16 (13.1%) malignant endometrial cell. Histopathology comprised 113 (92.6%) endometrioid carcinoma, 2 (1.6%) papillary serous carcinoma, 3 (2.5%) clear cell carcinoma, 4 (3.3%) undifferentiated carcinoma. Of the 73 patients who had pelvic and paraaortic

lymphadenectomy, 8 cases (6.6%) had pelvic or paraaortic lymphnode matastasis. The tumor stage, grading, depth of myometrial invasion, cervical involvement, adnexal metastasis and positive peritoneal cytology are shown in Table 1.

The median follow up time of the patients was 6 years with a minimum of 0.02 years and maximum of 16.34 years. Of the 122 patients, 31 patients (25.4%) died from the endometrial carcinoma during the follow up period. Of these 31 patients who died, 19 (61.3%) had normal cervical cytology, 12 (38.7%) had abnormal cervical cytology.

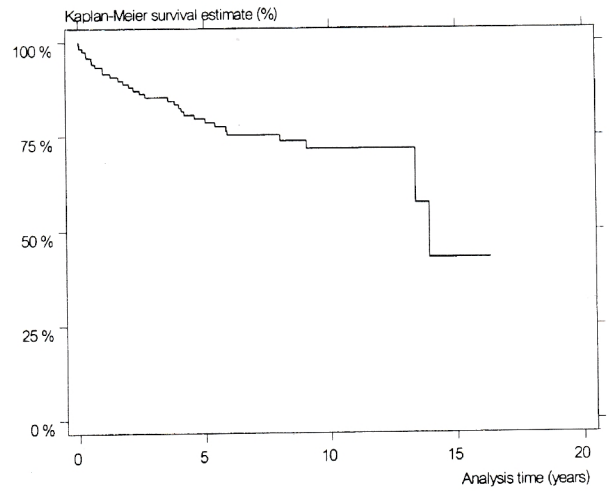

Fig. 1. Overall survival of the 122 endometrial carcinoma patients.

Fig. 1. shows the Kaplan-Meier survival profile of the 122 endometrial carcinoma patients. Five-year and 10-year survival were 76.7% (95% CI = 71.0-86.0) and 71.5% (95% CI = 61.0-79.6), respectively. The overall median survival time of the 122 endometrial carcinoma patients was 13.9 years (95% CI = 13.4-undetermined value).

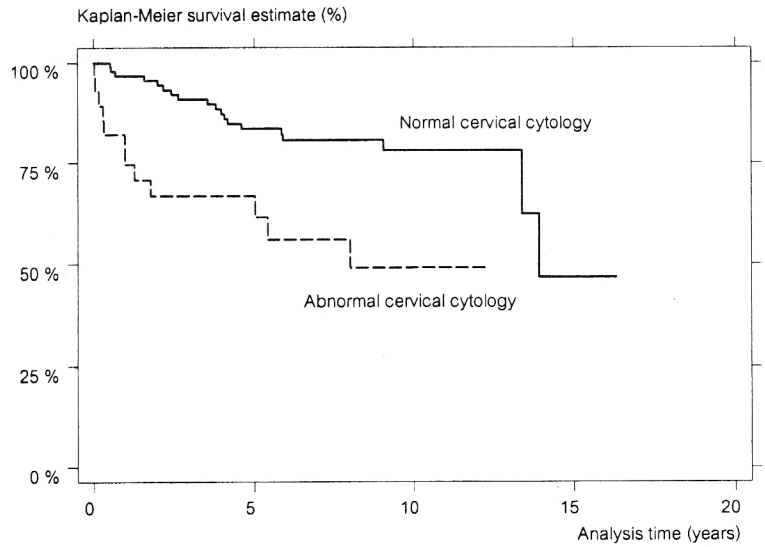

Fig. 2. Survival of the 122 endometrial carcinoma patients according to preoperative cervical cytology.

Fig. 2. shows the Kaplan-Meier survival profile of the patients with normal and abnormal preoperative cervical cytology. Five-year survival of normal and abnormal preoperative cervical cytology were 83.6% (95% CI = 73.9-90.0) and 66.8% (95% CI = 45.8-81.2), respectively and 10-year were 78.1% (95% CI = 66.5-86.1) and 49.1% (95% CI = 26.4-68.4), respectively (p = 0.001). The median survival times of the patients with normal and abnormal preoperative cervical cytology were 13.9 (95% CI = 13.4-undetermined value) and 8.0 years (95% CI = 1.27-undetermined value), respectively.

To determine if cervical cytology was a prognostic factor independent of other clinicopathological variables, the relationship of cervical cytology with other clinicopathologic variables and its association with survival after adjusting for other variables were examined.

Table 2. Relationship of preoperative cervical cytology with other clinicopathological variables of 122 endometrial carcinoma patients

Clinicopathological variables	Cervical Cytology		p*
	Normal (N = 94)	Abnormal (N = 28)	
Age			0.986
≤ 50 years	20	6	
> 50 years	74	22	
Stage			< 0.001
I	71	4	
II	13	9	
III	8	9	
IV	2	6	
Histologic type			0.442
Endometrioid	6	3	
Non-endometrioid	88	25	
Histologic grade			0.022
1	69	13	
2	9	4	
3	16	11	
Myometrial invasion			0.002
≤ one half	75	14	
> one half	19	14	
Cervical metastasis			< 0.001
Negative	81	13	
Positive	13	15	
Adnexal metastasis			0.001
Negative	87	19	
Positive	7	9	
Nodal metastasis			0.006
Negative	91	23	
Positive	3	5	
Peritoneal cytology			0.016
Negative	90	23	
Positive	4	5	

* p value from likelihood ratio test

Results of the univariate analysis of the association of preoperative cervical cytology with various clinicopathologic prognostic variables are shown in Table 2. Abnormal cervical cytology was significantly associated with advanced stage ($p < 0.001$), high grade ($p = 0.022$), deep myometrial invasion ($p = 0.002$), cervical involvement ($p < 0.001$), adnexal involvement ($p = 0.001$), pelvic or paraaortic lymph node metastasis ($p = 0.006$) and positive peritoneal cytology ($p = 0.016$). No association was found with patients' age ($p = 0.986$) or histologic type ($p = 0.442$).

Table 3. Univariate analysis of potential prognostic factors of 122 endometrial carcinoma patients

Prognostic variables	Hazard Ratio	95% CI	p*
Age			0.085
≤ 50 years	1		
> 50 years	2.54	0.77 - 8.38	
Cervical cytology			0.004
Normal	1		
Abnormal	3.16	1.51 - 6.64	
Stage			< 0.001
I	1		
II	1.72	0.52 - 5.66	
III	8.35	3.31 - 21.03	
IV	78.21	24.03 - 251.77	
Histologic type			0.482
Endometrioid	1		
Non-endometrioid	1.58	0.48 - 5.21	
Histologic grade			0.011
1	1		
2	2.04	0.66 - 6.27	
3	3.32	1.54 - 7.12	
Myometrial invasion			0.003
≤ one half	1		
> one half	3.08	1.48 - 6.40	
Cervical metastasis			0.388
Negative	1		
Positive	1.42	0.63 - 3.10	
Adnexal metastasis			< 0.001
Negative	1		
Positive	6.13	2.82 - 13.33	
Nodal metastasis			< 0.001
Negative	1		
Positive	11.55	4.68 - 28.51	
Peritoneal cytology			< 0.001
Negative	1		
Positive	12.31	5.08 - 29.80	

* p value from likelihood ratio test

Univariate analysis of the various clinicopathologic prognostic variables using the Cox proportional hazards regression model is shown in Table 3. Survival was significantly poorer in patients with abnormal cervical cytology (hazard ratio 3.16; 95% CI = 1.51-6.64, p = 0.004).

Significantly decreased survival was also noted in patients with advanced stage (p < 0.001), high grade (p = 0.011), deep myometrial invasion (p = 0.003), adnexal involvement (p < 0.001), pelvic or paraaortic lymph node metastasis (p < 0.001) and positive peritoneal cytology (p < 0.001). No statistically significant difference in survival was found with patients' age (p = 0.085), histologic type (p = 0.482) or cervical metastasis (p = 0.388).

Table 4. Multivariate analysis of potential prognostic factors of 122 endometrial carcinoma patients

Prognostic variables	Full model			Reduced model		
	Hazard Ratio	95% CI	p*	Hazard Ratio	95% CI	p*
Cervical cytology			0.041			0.013
Normal	1			1		
Abnormal	2.57	1.07 - 6.21		2.82	1.29 - 6.17	
Histologic type			0.612			
Endometrioid	1					
Non-endometrioid	1.47	0.34 - 6.25				
Histologic grade			0.477			
1	1					
2	1.79	0.51 - 6.31				
3	1.70	0.65 - 4.45				
Myometrial invasion			0.660			
≤ one half	1					
> one half	1.23	0.49 - 3.07				
Cervical metastasis			0.696			
Negative	1					
Positive	0.84	0.34 - 2.04				
Adnexal metastasis			0.527			
Negative	1					
Positive	1.54	0.42 - 5.67				
Nodal metastasis			0.102			0.009
Negative	1			1		
Positive	2.86	0.85 - 9.68		4.45	1.57 - 12.60	
Peritoneal cytology			0.026			< 0.001
Negative	1			1		
Positive	6.12	1.19 - 31.38		7.83	2.72 - 22.52	

* p value from likelihood ratio test

Results of the multivariate Cox proportional hazards regression analysis of various clinicopathologic prognostic variables are shown in Table 4. Tumor stage was excluded from the multivariate analysis because it is constructed from the other individual prognostic factors. Table 4 shows both the full model, containing all variables of interest, as well as the final reduced model, containing those variables which retained statistical significance. Preoperative cervical cytology was shown to be a significant prognostic factor for survival (hazard ratio = 2.82, 95% CI = 1.29-6.17, p = 0.013) even after adjustment for nodal metastasis (hazard ratio = 4.45, 95% CI = 1.57-12.6, p = 0.009) and peritoneal cytology (hazard ratio = 7.83, 95% CI = 2.72-22.52, p < 0.001).

Discussion

Twenty-eight to 79 percent of endometrial carcinoma patients have abnormal cervical cytology when initially diagnosed.[5,6,8,9,12,14-18] The significant factors that influence endometrial cellular shedding are higher stage,[6,10,11] higher tumor grade,[6,10,11] endocervical involvement,[7,10,11] and average surface area occupied by abnormal epithelium or a polypoid growth pattern.[10] The majority of the patients in this study were diagnosed at an early stage of the disease (stage I = 61.5%), had low grade tumor (grade I = 67.2%) and had low incidence of cervical metastasis (23.0%). Thus, abnormal cervical cytology was detected in only 23.0 % of these patients.

Patients with endometrial carcinoma who have malignant or suspicious cells detected by preoperative cervical cytology are at a higher risk of having poor prognostic factors including old age,[8] advanced FIGO stage,[5,6,11,12,18] poorer histopathology,[11,18] higher tumor grade,[6,10-12,18] deeper myometrial invasion,[11,12] higher incidence of cervical involvement,[7,11,12,18] extrauterine metastasis including positive peritoneal washing,[8,18] adnexal,[11] or lymph node metastasis [11,18] and also have a less favorable 5-year survival compared to those with normal cervical cytology.

Similarly, our study also demonstrated that endometrial carcinoma patients with abnormal preoperative cervical cytology had higher risk of having the other poor prognostic factors including advanced stage, high grade tumor, deep myometrial invasion, cervical involvement, adnexal involvement, pelvic or paraaortic lymph node metastasis and positive peritoneal cytology, but no significant association was found with patients' age or histologic type.

Fukuda et al. evaluated the correlation between preoperative cervical cytology and survival in 99 surgically staged patients with endometrial carcinoma. Univariate analysis showed that cervical cytology was related to survival (P = 0.018). However, multivariate analysis of cervical cytology, stage, grade, and myometrial invasion showed that preoperative cervical cytology was not a significant independent prognostic factor for survival.[11]

In this study, we were able to analyse the association between preoperative cervical cytology and survival of 122 endometrial carcinoma patients. Univariate analysis showed that survival was significantly lower in patients with abnormal preoperative cervical cytology, advanced stage, high grade tumor, deep myometrial invasion, adnexal metastasis, pelvic or paraaortic lymph node metastasis and positive peritoneal cytology. Although tumor stage had the strongest univariate association with survival, it was excluded from the multivariate analysis because tumor stage is constructed from the other individual prognostic factors including histologic grading, myometrial invasion, cervical metastasis, adnexal metastasis, pelvic or paraaortic lymph node metastasis and peritoneal cytology. Hence multivariate analysis of the various individual clinicopathologic prognostic variables, except tumor stage, showed that preoperative cervical cytology is still an independent prognostic factor for survival. Survival was also significantly lower in patients with nodal metastasis and positive peritoneal cytology.

Although there were significant associations between abnormal preoperative cervical cytology and the other poor prognostic factors, nevertheless after adjustment for all of these factors, preoperative

cervical cytology was proved to be an independent prognostic factor for survival.

According to the FIGO Annual Report on the Results of Treatment in Gynecological Cancer 2001, the total actuarial 5-year survival rate of all stages (surgical and clinical) of endometrial cancer was 76%.[19] Kristjan et al. reviewed the histology of 260 cases with endometrial carcinoma and reported the total age-adjusted 5- and 10-year relative survival rates were 76% and 75%, respectively,[20] similar to the overall 5-year and 10-year survival rate of the patients in this study, which were 76.7% and 71.5 %, respectively.

Mitchell et al. reported that the odds ratio of death was not statistically significantly different in endometrial cancer patients with malignant cervical cytology, compared to those with negative cytology.[16] In our study, the difference in 5-year survival between patients with abnormal cervical cytology (56.8%) and those with normal cervical cytology (83.6%) was statistically significant, as was the hazard ratio of death associated with abnormal cervical cytology after adjustment for other prognostic variables (HR = 2.82, 95% CI = 1.29-6.17).

In addition to histologic grade and type, cervical cytology is an another prognostic variable which can be assessed preoperatively. Therefore, preoperative identification of patients with abnormal cervical cytology should be a useful determinant in planning appropriate therapy either surgical staging or postoperative adjuvant radiotherapy.

Unlike patients with cervical cancer in whom cervical cytology screening may detect subclinical disease and improve patient survival, no survival advantage of such screening has yet been demonstrated for endometrial carcinoma patients. Nevertheless, the significant difference in survival of endometrial carcinoma patients with normal versus abnormal cervical cytology has clinical implications at initial evaluation of the prognosis of the patient who has any contraindication to surgery or denies surgical treatment, and it can be used in determining other treatment modalities, either radiotherapy or palliative care.

Although Pap test is inadequate and endometrial cytology is insensitive and too nonspecific to be used in routine screening for endometrial cancer even in a high risk population,[13] an abnormal result may facilitate the early detection of endometrial disease. Our recommendation is that preoperative evaluation of cervical cytology should be promoted in all of the initially diagnosed endometrial carcinoma patients. Further, our suggestion is to study the effect of adjuvant radiotherapy on survival of endometrial carcinoma patients with poor prognostic factors for tumor recurrence, comparing patients with normal and abnormal cervical cytology using a randomized controlled trial.

In conclusion, endometrial carcinoma patients with abnormal cervical cytology had significantly lower survival than those with normal cervical cytology. Preoperative cervical cytology, nodal metastasis and peritoneal cytology were independent prognostic factors of patients with endometrial carcinoma.

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