

The value of Pap test in women with endometrial cancer

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Abstract

Introduction: Endometrial cancer is the second most common gynecological tumor. There is still no recommended screening method for endometrial cancer. The application of transvaginal sonography, hysteroscopy and Pap test may prove useful in screening for this disease. Atypical glandular cells represent an important finding in Pap tests and they are related to histopathological verification of the endometrium. The aim of the study was to determine the usefulness of the Pap test in assessing the cervical infiltration, as well as to determine the significance of hormonal status and histopathological type of tumor in a pathological Pap test in patients with endometrial cancer.

Methods: The study was retrospective. The analysis included the data obtained from 62 operated patients diagnosed with endometrial cancer, medical history (menopausal status), histopathological findings after surgery (type and stage of the disease) and a preoperative Pap smear. The chi squared and Fisher's test were used.

Results: The difference in the prevalence of pathological Pap test in premenopausal and postmenopausal group of patients was not statistically significant. The difference in the prevalence of pathological Pap test in the group of endometrioid and non-endometrioid tumours of the uterine corpus had statistical significance. The difference in the prevalence of pathological Pap test compared to the present stage (I and II) was not statistically significant.

Conclusion: Pap smear does not correlate with menopausal status in women with endometrial carcinoma. Abnormal Pap test is more commonly found in cases of non-endometrioid tumours. Pap smears cannot be used to assess cervical involvement.

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Introduction

Endometrial carcinoma makes up 3.9% of all malignant tumors among women (200.000 patients) and 1.7% of all deaths (50.000) caused by malignant diseases. The rate of incidence increases with age. The incidence increases begins 5-10 years before menopause and the peak is reached at about 65-70 years of age (2). There is still no recommended screening test for endometrial cancer. The Pap test is not a routine in the diagnosis of endometrial abnormalities. Most authors believe that the

cytological diagnosis is not sufficiently sensitive in the detection of endometrial cancer (3). Cytology has low sensitivity due to anatomical reasons – cell desquamation must pass through the cervical canal and is thereby subject to degenerative changes. Cervical canal stenosis and reduced number of cells in the smear are common after menopause (3). The cytological sampling of the endometrium can be direct: from the uterus (including aspiration, brushing, rinsing), and indirect: the sampled cells are obtained from spontaneous desquamation through the cervical canal (4). Indirect tests are unreliable and cytologists encounter diagnostic difficulties in differentiating normal from abnormal endometrial cells, whereas direct tests are expensive and invasive and are only recommended for women at high risk of developing endometrial cancer (5).

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Atypical glandular cells are unusual but they represent an important finding in a Pap smear (6). The Bethesda system classifies atypical glandular cells (AGUS) as glandular cells with some degree of nuclear atypia, but which do not have the features of malignant carcinoma cells. The AGUS are present in 0.18 to 0.74% of all Pap smears. An important percentage of these patients has severe endometrial pathology, and these findings require a serious evaluation (6,7,8,9). The presence of an atrophic smear, greater than twice the size of an intermediate cell nucleus and the absence of clusters with irregular borders help in identifying endometrial carcinoma (7). Liquid-based Pap test can be useful in the diagnosis of endometrial carcinoma. The application of this test helps detect endometrial carcinoma with high sensitivity (10). The combination of cytological diagnosis, transvaginal ultrasound and hysteroscopy may be useful in selecting the patients who need to undergo histopathological sampling of endometrial tissue (11). The aim of the study was to determine the usefulness of the Pap test in assessing the cervical infiltration, as well as to determine the significance of hormonal status and histopathological type of tumor in a pathological Pap test in patients with endometrial cancer.

Methods

Samples

The study was retrospective and it included patients who had received surgical treatment for histopathologically verified endometrial cancer. There were 62 patients diagnosed with endometrial cancer. The analysis included the Pap test, medical history (menopausal status), histopathological reports after surgery and post-operative stage. The Pap test results were observed in relation to menopausal status, histological type and stage of tumor.

Statistical analysis

Comparison of the frequency of attribute characteristics between groups was performed with the chi square test or Fisher's exact probability test of the null hypothesis when expected frequency of some features was less than five. The statistical analysis was performed using SPSS software and $p < 0.05$ was considered significant.

Results

The research included 62 patients diagnosed with endometrial cancer. Pap test made during diagnostic procedures or preparation for surgical treatment was analyzed. There were 5 (8%) premenopausal patients and 57 (92%) postmenopausal patients. All premenopausal patients had normal Pap smears. Among the postmenopausal patients there were 12 cases (19.4%) of abnormal Pap smears. There was no difference in the presence of pathological Pap smear in premenopausal or postmenopausal groups of women ($P = 0.257$) (Table 1). In the study group (62 patients) there were 54 registered endometrioid types of tumor and 8 non-endometrioid types of tumor. The comparison of the patients with endometrioid and non-endometrioid types of tumors revealed that abnormal Pap test results were present in 10 (18.5%) patients with endometrioid type of tumor, whereas in non-endometrioid tumor type there were 2 patients (24%) with abnormal Pap test results ($\chi^2 = 6.92$, $p = 0.031$). (The difference in findings between the groups was statistically significant). Abnormal Pap test was significantly more common in non-endometrioid tumors. (Table 2). Pap test was compared with the determined histopathological stage of the disease where the material was removed surgically. In patients with an early stage of the disease, a normal Pap test was present in 89.7% and 10.3% in pathological cases, while in patients with other disease stages, a normal Pap

TABLE 1. Menopause and Pap tests ratio

Characteristics	Menopause		Total (n=62)	Comparison
	No (n=5)	Yes (n=57)		
Pap smear				$p=0.257$
Normal	5 (100.0%)	45 (78.9%)	50 (80.6%)	
Pathological	-	12 (21.2%)	12 (19.4%)	

TABLE 2. Relationship between Pap smear testing and hp-type endometrial cancer

Characteristics	Non-endometrioid type (n=8)	Endometrioid type (n=54)	Comparison
Pap smear			
Normal	6 (75.0%)	44 (81.5%)	$\chi^2=6.92$; $p=0.031$
Pathologic	2 (25%)	10 (18.5%)	

TABLE 3. Relationship between the stage and the Pap test.

Pap smear findings	Disease stage		Comparison
	I	II	
Normal	35 (89.7%)	13 (72.2%)	$p=0.123$
Abnormal	4 (10.3%)	5 (27.8%)	
Total	39 (100.0%)	18 (100.0%)	

test was found in 72.2% and abnormal in 27.8% of cases. Fisher's test did not confirm significant differences in the prevalence of individual findings of the Pap test for women with first and second stage of the disease ($p > 0.005$). Involvement of the cervix cannot be detected by Pap smears (Table 3).

Discussion

In our study pathological Pap smear was registered only in postmenopausal patients but this difference was not statistically significant. According to data (Bethesda 2001), the occurrence of endometrial cells in cervical cytology in women over 45 is often associated with endometrial cancer and endometrial hyperplasia (12), but other authors suggest that hormonal status is not relevant in terms of abnormal glandular cells in Pap smear (13). A comparison of the results of the Pap test revealed that abnormal Pap smears were significantly more frequent in a group of women with tumors with non-endometrioid histology. These tumors show more rapid progression, deeper myometrial involvement, more frequent lymphovascular invasion and cervical involvement (14). Cytology cannot be used as an independent method, but in combination with transvaginal ultrasound (TVS) it can be performed for patients with unfavorable hp types and cervical involvement. (3, 4, 5). Skaznik et al. (15) state that the unfavorable endometrial types of cancers had frequent abnormal Pap smears. The stages of endometrial cancer are based

on examination of tissue removed during an operation. Compared to earlier clinical staging, this method has an advantage. Most authors believe that surgical staging is reliable, particularly in the case of adverse findings of hp, in the case of cervical involvement and deep myometrial infiltration (15, 16, 17). Cervical infiltration has a worse prognosis, increases the incidence of metastases and local recurrence (18). In our research, Pap test results for patients with the disease in an early stage were normal in 89.7% of cases and abnormal in 10.3% of cases. On the other hand, Pap test results for patients with the disease in other stages were normal in 72.2%, and abnormal in 27.8% of cases. Fisher's test did not confirm significant differences in the prevalence of individual findings of the Pap test for women with first and second stage of the disease ($p > 0.005$). Involvement of the cervix cannot be detected by Pap test. Imaging methods may be applied in the evaluation of cervical involvement (19, 20). Other authors suggest that Pap smear is not suitable for the assessment of cervical infiltration in patients with endometrial carcinoma. The exceptions are patients with tumors of low grade endometrioid type, where a normal Pap smear indicates a very low risk of cervical involvement and low risk of lymph node metastasis (21).

Conclusion

Patients with endometrial cancer may have abnormal Pap smears regardless of hormonal status. If non-endometrioid type of tumor is present, abnormal Pap test is more common. Cervical involvement cannot be estimated by Pap tests.

Competing interests

The authors declare that they have no financial or personal relationship with people or organizations that could influence this work inappropriately.

References

1. Sankaranarayanan R, Ferlay J. Word-wide burden of gynecological cancer: the size problem, *Best Pract Res Clin Obstet Gynecol* 2006; 20:207-225.
2. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A et al. *Cancer Statistics 2005:CA Cancer J Clin* 2005; 55:10-30.
3. Mahovlić V. Endometriji. U: Ćorušić A, Babić D, Šamija M, Šobat H. *Ginekološka onkologija. Medicinska naklada, Zagreb* 2005, pp.42-47.
4. Broso P. Cervico-vaginal and endometrial cytology in the screening for endometrial cancer. *Minerva Ginecol*. 1995; 47(11): 503-507.
5. Tezuka F, Namiki T, Hifashiwai H. Observer variability in endometrial cytology using kappa statistics. *J Clin Pathol* 1992; 45: 292-294.
6. Kaferle JE, Malouin JM. Evaluation and management of the AGUS Papanicolaou smear. *Am Fam Physician* 2001; 63(11): 2239-2245.

7. Salomao DR, Hughes JH, Raab SS. Atypical glandular cells of undetermined significance favor endometrial origin, Criteria for separating low grade endometrial adenocarcinoma from benign endometrial lesions. *Acta Cytol* .2002;46(3):458-464
8. Saad RS, Takei H, Liu YL, Silverman JE, Lipscomb JT, Ruiz B. Clinical significance of a cytologic diagnosis of atypical glandular cells favor endometrial origin, in Pap smears. *Acta Cytol* 2006; 50(1):48-54.
9. Obenson J, Abreo F, Grafton WD. Cytohistologic correlation between AGUS and biopsy detected lesions in postmenopausal women *Acta Cytol*. 2000. 44(1):41-45
10. Zhou J, Tomashefski JJ, Khivami A. Diagnostic value of the thin layer, liquid-based Pap test in endometrial cancer: a retrospective study with emphasis on cytomorphologic features. *Acta Cytol* 2007; 51(5):735-741.
11. Minagawa Y, Sato S, Ito M, Onohara Y, Nakaoto S, Kigawa J. Transvaginal ultrasonography and endometrial cytology as a diagnostic schema for endometrial cancer. *Gynecol Obstet Invest* 2005; 59(3):149-154.
12. Ashfaq R, Sharma S, Duley T, Saboorian MH, Siddiqui MT, Warner C. Clinical relevance of benign endometrial cells in postmenopausal women. *Diagn Cytopathol* 2001; 25(4):235-238
13. Karim BO, Burroughs FH, Rosenthal DL, Alli SZ. Endometrial type cells in cervicovaginal smears: clinical significance and cytopathologic correlates. *Diagn Cytopathol* 2002; 26:123-127.
14. Rose P. Endometrial carcinoma. *N Engl J Med* 1996; 9(335):640-649.
15. Skaznik-Wikiel ME, Ueda SM, Frasure HE, Rose PG, Fleury A, Grumbine FC et al. Abnormal cervical cytology in the diagnosis of uterine papillary serous carcinoma: earlier detection of a poor prognostic cancer subtype? *Acta Cytol*. 2011; 55(3): 255-260.
16. Odicino F, Pecorelli S, Zigliani L, Creasman WT. History of the FIGO cancer staging system. *Int J Gynecol Obstet*. 2008;101:205-210
17. Creasman W M.D. Controversies in FIGO staging of corpus cancer. *J Gynecol Oncol* 2001; 6: 257-259.
18. Orr JW, Holimon JL, Orr PF. Stage I corpus cancer. Is teletherapy necessary? *Am J Obstet Gynecol* 1997; 176(4): 777-789.
19. Creasman WT, Morow CB, Bundy BN, Homesly HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer . A Gynecologic Oncology Group Study. *Cancer* 1987;60:2035-2041
20. Savelli L, Ceccarini M, Ludovisi M, Fruscella E, Iaco PA, Salizzoni E et al. Preoperative local staging of endometrial cancer: transvaginal sonography vs. magnetic resonance imaging. *Ultrasound Obstet Gynecol* 2008; 31: 560-566.
21. Sawicki W, Spiewankiewicz B, Steimachow J, Cendrowski K. The value of ultrasonography in preoperative assessment of selected prognostic factor in endometrial cancer. *Eur J Gynaecol Oncol* 2001; 24(3-4): 293-298.
22. Beshter DB, Deuel C, Gillis S, Glantz C, Angel C, Guzick D. Endometrial cancer. The potential role of cervical cytology in current surgical staging. *Obstet Gynecol* 2003; 101(2): 445-450.