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Original Research

The Impact of Cervical Pap Smear on The Prognostic Risk Groups of Endometrial Carcinoma

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ABSTRACT

Objective: To investigate the importance of preoperative cervical Pap smear in patients with endometrial cancer and the impact of it on the prognostic risk groups of endometrial cancer.

Methods: The preoperative cervical cytology results of 423 patients who underwent staging surgery for endometrial cancer between the years of 2010 and 2020 in the gynecological oncology clinic of the tertiary center were examined in a retrospective observational study. The relations between cervical Pap smear results and pathological prognostic factors of endometrial cancer such as tumor histology, tumor size, FIGO grade, lymphovascular space invasion and FIGO stage were evaluated in detail. The impact of cervical cytology results in the prognostic risk groups (molecular classification unknown) specified in the ESGO/ESTRO/ESP (2020) guideline was also examined. SPSS version 25.0 program was used in the analysis of the data.

Results: Abnormal cervical Pap cytology was present in 12.1% (n= 51) of the patients included in the study. Significantly more abnormal cervical cytology was observed in the high prognostic risk groups (p= 0.017), tumors with non-endometrioid histologic types (p= 0.001), and patients with adnexal involvement (p= 0.007). In the subgroup analysis of endometrioid type endometrial adenocarcinomas, as the FIGO grade increased, the rate of abnormal cervical cytology increased significantly (p= 0.014).

Conclusions: Pre-operative cervical cytology abnormality may predict the need for intra-operative systematic surgical staging and postoperative adjuvant therapy.

Keywords: Endometrial cancer, prognostic risk, cervical cytology, FIGO stage, adjuvant therapy

INTRODUCTION

Pap smear screening tests are widely applied all over the world and provide an opportunity to detect cervical pathologies at an early stage [1]. However, there is currently no standardized effective screening method for endometrial cancer. Anatomically, the continuity of the uterine cavity with the cervix offers the opportunity to examine the endometrial cells shed from the upper genital tract in Pap smear samples. Studies have reported that cytology tests can detect endometrial cancers at a rate of approximately 45% [2]. It is also promising that up to 80% of

endometrial cancer can be detected with new molecular analyzes in Pap smear samples [3]. However, the issue that arouses more curiosity than the diagnostic adequacy of the cytology is whether it has prognostic significance in preoperative and postoperative management of patients with endometrial cancer.

The prognosis is highly dependent on the stage of the disease and tumor histology. Factors such as tumor grade, lymphovascular space invasion (LVSI), myometrial invasion (MI), lymph node involvement, and peritoneal cytology positivity, which can also be obtained from the final pathology reports are effective on the prognosis of the disease. In the ESGO (European Society of Gynecological Oncology)/ESTRO (European Society for Radiotherapy and Oncology)/ESP (European Society of Pathology) guidelines, prognostic risk groups (low, moderate, high-intermediate, high, advanced and metastatic) were established with all these factors and adjuvant treatment according to these prognostic risk groups were reported [4]. The significance of abnormal Pap smear sampling is unknown in the prognostic risk groups. The possible integration of abnormal Pap smear tests to the prognostic risk assessment may open an era for the reorganization of all risk groups in the future.
In this study, our aim is to analyze the correlation between the Pap smear results and the pathological factors and the prognostic risk groups of endometrial carcinoma and discuss it in the light of current literature.

Main Points;

- Abnormal Pap smear results prior to endometrial cancer surgery can predict the need for intraoperative systematic staging and postoperative adjuvant therapy.
- The study evaluated the correlation between preoperative cervical Pap smear results and pathological factors in endometrial cancer, including tumor histology, tumor size, FIGO grade, lymphovascular space invasion, and FIGO stage.
- Abnormal cervical cytology was significantly associated with high prognostic risk groups, non-endometrioid histologic types, and adnexal involvement.
- In the subgroup analysis of endometrioid type endometrial adenocarcinomas, the rate of abnormal cervical cytology increased significantly with higher FIGO grades.
- Pre-operative cervical cytology abnormality may have implications for the selection of intraoperative staging procedures and postoperative adjuvant therapy in endometrial cancer patients.

MATERIALS AND METHODS

Patients (n=733) who were operated for endometrial cancer between the years 2010-2020 were assessed for eligibility to the retrospective observational study. Written informed consent was obtained from all patients included in the study. The study started with the approval of the local ethics committee with the approval number 2021/17 and all steps were carried out in accordance with the principles of the Declaration of Helsinki. The medical records of the patients were accessed by examining the archive module and patient files of the Health Information System.

Cervical samples were taken with an endocervical brush and prepared with the Thin Prep Processor (Cytyc, Boxborough, MA, USA). The samples were examined by the expert gyneco-pathologist at our institute. Cytological evaluations were reviewed according to the Bethesda 2014 system [5]. Smear results which were negative for malignancy and had signs of inflammation and infection were classified in the normal cytology group. All results other than normal cytology were evaluated as abnormal cytology. Endometrial cells over 40 years of age were classified as benign endometrial cells. Patients with insufficient Pap smear results were excluded from the study. In addition, patients with cervical intraepithelial neoplasia (CIN) lesion in the cervix and patients with second primary malignancy were excluded from the study. As a result, 423 patients who had Pap smear results within 6 months before the operation and had adequate surgical staging were included in the study (Fig. 1).

Data from final pathology results, such as tumor size, histopathological type, FIGO grade, MI, cervical stromal involvement, LVSI, lymph node involvement, cytology of peritoneal washing, adnexal involvement, parametrial involvement, FIGO stage, postoperative residual disease, distant metastasis were evaluated. Then, patients were classified into low, moderate, high-intermediate, high, advanced and metastatic risk groups according to the prognostic risk groups (molecular classification unknown) defined in the ESGO/ESTRO/ESP (2020) guidelines [4]. Correlations between the Pap smear results and the pathological factors and the prognostic risk groups of endometrial carcinoma were analyzed.

The data were evaluated by using IBM SPSS Statistics 25.0 (IBM Corp., Armonk, New York, USA) statistical package program. In the tables, continuous variables are presented as mean±standard deviation, while categorical variables are presented as numbers

(N) and percentage (%). Chi-Square test was used to compare categorical variables. Comparisons between groups were made using the Independent Samples T-Test for continuous variables. P<0.05 was considered statistically significant.

RESULTS

The mean age of the patients included in the study was 56.5±0.5 years (range= 29-82 years of age). The rates of abnormal and normal Pap tests were 12.1% (n=51) and 87.9% (n=372), respectively. Endometrioid adenocarcinoma was diagnosed in 82% (n=347) of the patients. The mean tumor diameter was calculated as 36.9±1.3mm (range= 1-150 mm). And, 77.1% (n=326) of the patients were in FIGO Stage 1, 48.9% (n=207) were in the low prognostic risk group. Clinico-pathological features of the study patients are given in Table 1.

The mean age was similar between the groups of patients with normal (56.3±0.5 years) and abnormal (58.1±1.5 years) Pap smear test (p= 0.198). In addition, tumor size, myometrial invasion, cervical involvement, LVSI, positivity of peritoneal cytology, involvement of lymph nodes and FIGO stage did not differ between the groups of normal and abnormal Pap test. Histology of non-endometrioid tumor type (p= 0.001), patients with adnexal involvement (p= 0.007) and the patients in the high prognostic risk group (p= 0.017) were found to be statistically significantly higher in the abnormal cervical cytology group. Pap test with malignant cells were detected mostly in non-endometrioid type tumors with a rate of 66.7%, and normal Pap test was detected mostly in endometrioid type tumors with a rate 90.5%. The rate of abnormal cytology was found to be 29.4% in the advanced and metastatic risk prognostic groups (Fig. 2). The results of all detailed analysis are given in Table 2.

Table 1. Clinico-pathological features and prognostic factors in patients who were surgically staged due to endometrial cancer (N= 423).

	N	%
Cytology		
Negative		
Normal	319	75.4
Inflamation	19	4.5
Infection	34	8.0
Positive		
ASC-US	18	4.3
ASC-H	4	0.9
HSIL	3	0.7
AGC, FN	13	3.2
AGC, NOS	1	0.2
AEC, NOS	5	1.2
Benign Endometrial Cells	4	0.9
Malignant Cells	3	0.7
Hystopathology Results		
Endometrioid Adenocarcinoma	347	82.0
Non-endometrioid Adenocarcinoma		
Serous Carcinoma	28	6.6
Carcinosarcom	15	3.6
Clear Cell Carcinoma	12	2.8
Mixt Carcinoma	9	2.1
Undifferentiated Carcinoma	7	1.7
Mucinous Carcinoma	5	1.2
MI		
< 50%	301	71.2

≥ 50%	122	28.8
Cervical Involvement		
No	368	87.0
Yes	55	13.0
Adnexal Involvement		
No	392	92.7
Yes	31	7.3
LVSI		
No	295	69.7
Yes	128	30.3
Peritoneal Cytology		
Negative	397	93.9
Positive	26	6.1
Lymph Node Involvement *		
Only Pelvic	18	
Only Paraaortic	3	
Pelvik and Paraaortic	19	
FIGO Stage		
I		
IA	264	62,4
IB	62	14,7
II	31	7,4
III		
IIIA	9	2,1
IIIB	4	0,9
IIIC1	15	3,5
IIIC2	18	4.3
IV		
IVA	3	0,7
IVB	17	4.0
Prognostic Risk Groups †		
Low	207	48.9
Intermediate	37	8.8
High-Intermediate	73	17.3
High	89	21.0
Advanced and metastatic	17	4.0

Abbreviation: N= Number, %= Percent, ASC-US= Atipical Squamous Cells-Undetermined Significance, ASC-H= Atipical Squamous Cells-Cannot Exclude High Grade Squamous Intraepithelial Lesions, HSIL= High-Grade Squamous Intraepithelial Lesion, AGC-FN= Atypical Glandular Cells - Favor Neoplasia, AGC-NOS= Atypical Glandular Cells – Not Other Specified, AEC-NOS= Atypical Endocervical Cells – Not Other Specified. MI= Myometrial Invasion, LVSI= Lymphovascular Space Invasion, * = Analysis was performed in 366 patients, † = The prognostic risk groups based on data from ESGO (European Society of Gynaecological Oncology) / ESTRO (European Society for Radiotherapy and Oncology) / ESP (European Society of Pathology) guideline for endometrial cancer (2020).

Table 2. Clinico-pathologic characteristics according to cervical cytology results (N= 423)

	Cervical Cytology		
	Negative (N= 372) n (%)	**Positive (N= 51) n (%)**	**P Value**
Age (mean years ± S.E)	56.3 ± 0.5	58.1 ± 1.5	0.198 ‡
Histopathology			**0.001**
Endometrioid	314 (90.5)	33 (9.5)	
Non-endometrioid	58 (76.3)	18 (23.7)	
Tumor Size (mean mm ± S.E)	37.5 ± 1.4	42.9 ± 4.3	0.188 ‡
MI			0.157
< 50 %	269 (89.4)	32 (10.6)	
≥ 50 %	103 (84.4)	19 (15.6)	
Cervical Involvement			0.052
No	328 (89.1)	40 (10.9)	
Yes	44 (80.0)	11 (20.0)	
Adnexal Involvement			**0.007** §
No	350 (89.3)	42 (10.7)	
Yes	22 (71.0)	9 (29.0)	
LVSI			0.070
No	265 (89.8)	30 (10.2)	
Yes	107 (83.6)	21 (16.4)	
Peritoneal Cytology			0.110 §
Negative	352 (88.7)	45 (11.3)	
Positive	20 (76.9)	6 (23.1)	
Lymph Node Involvement *			0.616
No	286 (87.5)	41 (12.5)	
Yes	33 (84.6)	6 (15.4)	
FIGO Stage			0.113 §
I	292 (89.6)	34 (10.4)	
II	25 (80.6)	6 (19.4)	
III	40 (87.0)	6 (13.0)	
IV	15 (75.0)	5 (25.0)	
Prognostic Risk Groups †			**0.017**
Low	192 (92.8)	15 (7.2)	
Intermediate	32 (84.2)	6 (15.8)	
High-Intermediate	63 (86.3)	10 (13.7)	
High	74 (83.1)	15 (16.9)	
Advanced and metastatic	12 (70.6)	5 (29.4)	

Abbreviation: N= Number, %= Percent, S.E= Standart Error, mm= Millimeter, MI= Myometrial Invasion, LVSI= Lymphovascular Space Invasion, * = Analysis was performed in 366 patients, † = The prognostic risk groups based on data from ESGO (European Society of Gynaecological Oncology) / ESTRO (European Society for Radiotherapy and Oncology) / ESP (European Society of Pathology) guideline for endometrial cancer (2020). Statistical analysis obtained by Pearson Chi-square test. ‡= based on Independent Samples T-Test. §= based on Fisher's Exact Test.

In the additional analysis of patients (n=347) whose pathology result was endometrioid type endometrial adenocarcinoma, factors other than FIGO grade did not differ between the normal and abnormal cytology groups. In patients with FIGO grades 1, 2 and 3 endometrioid type endometrial adenocarcinoma, abnormal cytology rates were calculated as 7.1%, 10.2%, and 22.9%, respectively (p= 0.014) (Fig. 3).

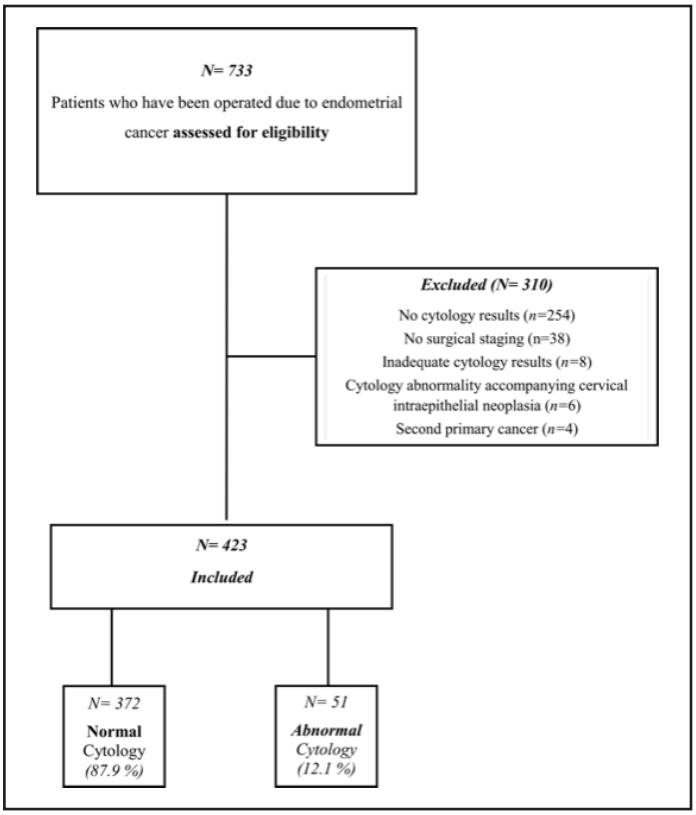

Figure 1. Flow diagram of the study.

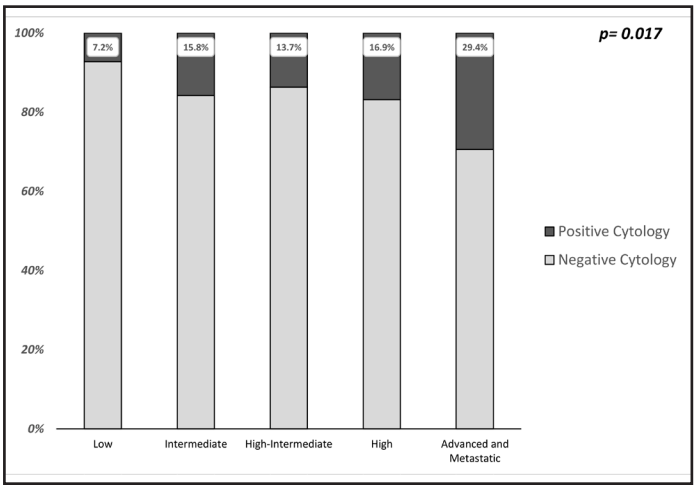

Figure 2. Percentage of positive cytology in prognostic risk groups.

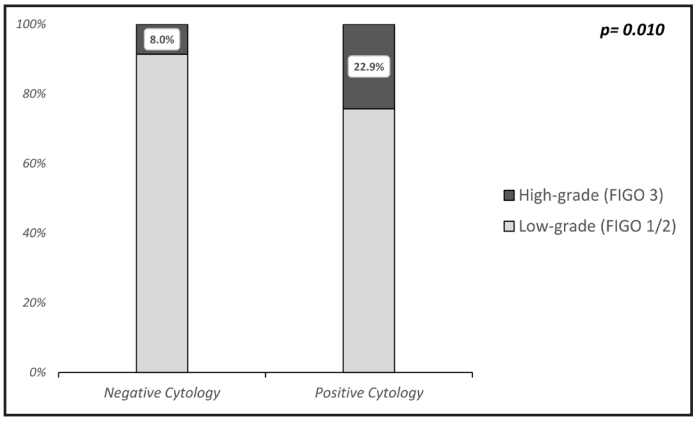

Figure 3. Percentage of high grade tumor according to negative and positive cytology groups.

DISCUSSION

Endometrial cancer is the most common gynecological cancer in the world and it's incidence has increased in recent years [6]. The intraoperative approach is total hysterectomy and bilateral salpingoopherectomy after the removal of the abdominal washing fluid. In order not to increase morbidity, surgical staging including lymph node dissection is performed in patients with high risk of lymph node involvement and debulking procedure is performed in patients with distant metastasis [7]. Therefore, surgical management is highly dependent on tumor histology and grade. However, preoperative and postoperative findings are generally inconsistent in high grade tumors [8]. Patient selection and prognostic factors have been the subject of research in many studies. It is thought that Pap smear test can contribute to the preoperative management and give an idea about the surgical approach [9,10]. So, we examined the relationship between preoperative Pap tests and clinico-pathological factors of patients with endometrial cancer. Our results independently suggested that Pap test abnormality may contribute to patient perioperative and postoperative management. According to analysis of the results of our data, preoperative abnormality of Pap tests were related with ESGO/ESTRO/ESP prognostic risk groups (molecular classification unknown). So, preoperative abnormality of Pap tests may predict the need of adjuvant treatment.

There is no accepted screening method for endometrial cancer. Although the rate of abnormal cytology in endometrial cancer in traditional Pap smear applications varies between 30-60%, it was reported as 45% in a recent large meta-analysis [2]. In our study, this rate was determined as 12%. Khumthong et al. [11] found that only 21% of 238 patients, 30% of whom had type 2

endometrial cancer, showed preoperative cytology abnormality, and this abnormality was an independent risk factor for cervical stromal invasion. In our study, a total of 12.1% cytological abnormalities were found in 423 patients, 18% of whom were non-endometrioid type tumors, and a borderline significance was found between cervical stromal involvement and smear abnormality. Mehta et al. [12] found preoperative abnormal cytology in 49% of 380 patients. Gu M et al. [13] evaluated 76 patients in their study, while abnormal Pap smear was associated with FIGO stage, they found no association with age, MI, and LVSI. In our study, we could not find relation between abnormal cytology results and FIGO stage. It has also been reported in the literature that abnormal pap smear tests require more staging and may be associated with more lymph node metastases [14,15]. On the contrary, there are studies reporting that Pap smear result will not affect this decision and it is not powerful in predicting lymph node metastasis [16]. In our study, lymph node involvement rates were not associated with abnormal Pap test.

Roelofsen et al. [9] found preoperative abnormal Pap test with a rate of 87.5% in patients with serous endometrial carcinoma and found the frequency of extra uterine disease to be significantly higher in this group. Similarly, abnormal results of Pap tests was found significantly more frequently in non-endometrioid type tumors in our study. We found the rate of abnormal cervical cytology to be 46.4% in patients with serous type carcinoma. This may be suggestive for the investigation of extra uterine metastases in the preoperative evaluation. This can be explained by the fact that non-endometrioid tumors are more brittle and shed easily.

Abu-Zaid et al. [17] evaluated only patients with endometrioid type endometrial adenocarcinoma and found preoperative abnormal cytology at a rate of 39% and showed that these abnormalities were not associated with FIGO stage, depth of MI, LVSI. In order to eliminate the bias that might be caused by analyzing endometrioid and non-endometrioid tumors in the same group, subgroup analysis was performed only in endometrioid type tumors. We found the rate of cytological abnormality as 9.5% in this group and increment of FIGO grade was positively correlated with increasing rate of abnormal cytology. The rate of abnormal cytology was found as 8% and 22.9% in low and high FIGO grade tumors, respectively. This may be due to the tendency of high-grade tumors to spill into vagina, as they are more aggressive and exhibit weaker cell connections.

The biggest shortcoming of our study is that it was retrospective and disease-free and overall survival rates could not be evaluated. It strengths are the inclusion of heterogeneous histological types and grades of tumors, the relatively large sample size, and the fact that it was performed in a single-center reference branch hospital. All pathology results were reported by expert gynecopathologists blinded to the diagnosis of endometrial cancer. Categorizing our patients according to prognostic risk groups gave us the opportunity to investigate the effect of Pap smear findings on prognosis. The histological classification of Endometrial Cancers of the World Health Organization and the International Society of Gynecological Pathology was updated in 2020 [18]. Again in 2020, an updated guideline for the diagnosis and treatment of patients with endometrial cancer was published by ESMO, ESGO and ESP associations. According to this guideline, prognostic risk groups are defined for cases where the molecular classification is known or unknown in the management of endometrial cancer, and adjuvant decision is applied according to these groups [4]. In our study, which was planned in this direction, we found that the rates of abnormal cervical cytology were significantly higher in non-endometrioid histology, high FIGO grade, adnexal involvement and high prognostic risk groups.

As a conclusion, we found that preoperative abnormal cervical cytology can predict the need for intraoperative systematic staging and postoperative adjuvant therapy in endometrial cancer.

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