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Research article

The role of performing a routine four-quadrant cervical biopsy in patients with negative colposcopic findings in increasing the identification rate of cervical intraepithelial neoplasms

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ABSTRACT

Aim: In patients with high-risk human papilloma virus (HPV), there is no consensus on the inclusion of cervical biopsy for diagnostic purposes in cases whereas there is no pathological finding in colposcopy. In this study, we aimed to investigate the effect of simultaneous routine cervical biopsy in patients with normal colposcopic findings on the rate of cervical intraepithelial neoplasia diagnosis.
Methods: This retrospective study included 119 patients with colposcopy indications who had no cervical pathology between January 2015 and March 2017 and the histopathological results were evaluated.
Results: The mean age of the population was 45.75±9.52 years. The histopathological results obtained in our study patients are as follows; 38.7% (n=46) LSIL, 28.7% (n=33) chronic cervicitis, 15, 3 % (n=19) coilositosis, 9.2% (n=11) HSIL, 2.5% (n=5) adenocarcinoma, 1.7% (n=2) carcinoma in situ and 2.1% (n=3) squamous carcinoma. LSIL 33 (27.5%), HSIL and advanced lesion 11 (9.2%) were detected in patients with normal cervical cytology before colposcopy. LSIL 26 (21.7%), HSIL and advanced lesion were found to be 13 (10.8%) in patients with abnormal cervical cytology. There was no significant difference in terms of biopsy pathology results between normal and abnormal cervical cytology results.
Conclusions: In patients with HPV positive and normal colposcopic findings, adding simultaneous routine four-quadrant cervical biopsy to the colposcopy might increase the detection rate of cervical intraepithelial lesions.
Keywords: Cervical intraepithelial neoplasia, colposcopy, biopsy, human papilloma virus.

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Introduction

Cervix cancer is the second most frequent cancer among women cancers in developing countries after breast cancer [1,2]. "National Standards of Cervical Cancer Screening" was published by the Ministry of Health in Turkey

in 2007. In a community-based screening program to be conducted in Turkey, it is recommended to sample smear on all women between the ages 35-40 years old at least once and to repeat in every five years and terminate at the age of 65 years old if the previous two test results are negative [3]. The development of cervical cancer on a background of dysplasia and the possibility of the early diagnosis of these lesions during the dysplasia stage with screening tests is an essential advantage for the early diagnosis of this fatal malignancy [4]. According to the statistical analysis of the data verified from the Turkey Ministry of Health Cancer Department, the prevalence of cervical cancer is 0,004%, which was previously reported as 0,0045% at 2000 [5]. According to these data, the adequate conduction of the screening programs on the selected population decreases the prevalence of the malignancy by 25% and the mortality by 35% [6]. Cervical cancer is the overall second most common cancer among women and 50.000 new cases per year are reported, and 250.000 women die every year from this cause [7]. According to ALTS (ASCUS-LSIL Triage Study), colposcopy and colposcopic biopsy are recommended on patients with LGSIL and HGSIL smear result [8]. The data about the dysplasia ratios on the follow up of ASCUS cases and cases with benign (inflammation, etc.) smear results are limited in our country [8]. According to the Guide of American Cancer Society, published in 2012, in addition to cytology (Pap test), HPV DNA test has prioritized [9]. 50% of women diagnosed with cervical cancer have never been screened previously, and only 10% have been screened for cervical cancer in the last five years [9]. Colposcopy is used for clarification of the cytological diagnosis by identification of the lesions localization and size and treatment management [10]. Although the treatment options are specified when High-grade lesions are detected, management of low-grade lesions is still controversial [11]. While the effect of treatment of low-grade lesions on the incidence of cervical cancer has not yet been decisive, the necessity of invasive methods such as colposcopy and biopsy used in the management of these lesions and the cost-effectiveness are still controversial [12,13]. There are also publications in the literature reporting that colposcopy could miss 30-55% of the high-grade lesions like CIN II and above [14,15,16]. Therefore, it is argued that random cervical biopsies in patients with high-grade Pap smear results may reveal CIN II and higher graded lesions that may be unnoticed via colposcopy [11,12].

This study aimed to investigate the efficiency of routine four quadrants cervical punch biopsy in the diagnosis of cervical intraepithelial neoplasms in patients with normal colposcopic findings.

Methods

This study is designed as a retrospective case study. This study was carried out with the approval of the ethics committee of the Bolu Abant Izzet Baysal University clinical researches (Decision no: 2017/72). Among gynecology outpatient patients between January 2015 – March 2017, who had a colposcopic examination, those with no abnormal colposcopic findings were included in the study. Colposcopy indications include HPV 16 or 18 positivity independent of smear result, ASCUS with any type of HPV positivity, all kinds of epithelial cell abnormalities from ASCUS, recurrent inadequate cytology and gross lesion in the cervix. A total of 119 patients aged between 26-67 years were evaluated.

Patients' files were scanned retrospectively, and for the missing information, the patients were reached by phone. Colposcopy indications include HPV 16 or 18 positivity independent of smear result, ASCUS with any type of HPV positivity, all kinds of epithelial cell abnormalities from ASCUS, recurrent inadequate cytology and gross lesion in the cervix.

Patients with a history of previous cervical surgery and cervical pre-invasive/ invasive lesion, pregnant, and hysterectomy were excluded from the study.

At least two days of sexual absence were required for all the patients included in the study. The colposcopic evaluation was performed in the follicular phase. Colposcopic examinations were performed with a 40X zoom, green filtered, Carl Zeiss brand binocular colposcope. The colposcopic examination was assessed as adequate when the cervix was fully observed, the squamocolumnar junction was completely visible, and there were no severe inflammation or atrophy. During the colposcopic examination, the presence of any suspicious areas on the cervix was assessed by 5% acetic acid staining, and subsequently by Lugol staining (Schiller test). The green light examination was used to assess the presence of any abnormal vascularity. Abnormal colposcopic findings such as aceto-white epithelium, punctuation, mosaicism, leukoplakia, and atypical vascular structures were evaluated. In our study, patients with adequate colposcopy and none of these abnormal findings were included. In patients with normal colposcopic findings, routine random punch biopsies were taken from four quadrants of the cervix, and the specimens were sent for histopathological examination. In our clinic, it is routine to obtain four quadrants cervical biopsy even if there is no abnormal finding, and this is also in accordance with ASCCP.

Biopsy samples were dehydrated with ethanol solution after being kept in 10% formaldehyde solution overnight. Then the biopsy specimens were washed with xylene and buried in paraffin blocks. 4 mm thick section cuts were taken. With the help of a light microscope, a histopathologic examination was performed under the magnification of 20 x and 40 x. Cervical smear and biopsy findings were compared. Pathology reports were grouped as abnormal (CIN I, CINII-III, invasive carcinoma) and normal (cervicitis, metaplasia, cervical, and others) findings. Cervical smear results and histopathological results were evaluated retrospectively.

Statistical analysis

SPSS (Statistical Package for Social Sciences) version 18.0 (SPSS Inc. USA) is used for statistical analysis. One - sample test and Chi-Square tests are used for interpreting data. Test results are assessed within 95% confidence interval and statistical significance is considered if $p<0.05$.

Results

The cervical cytology and histopathology results of 119 patients with normal colposcopic findings were retrospectively examined. This study initially included 119 patients. All of patients' colposcopy examinations were adequate.

When the demographic characteristics of the patients were examined, the mean age was 45.75±9.52 years (44.04 - 47.47, 95% CI), mean gravida was 2.44±1.79 (2.12 - 2.77, 95% CI), mean parity was 2.06±1.44 (1.80 - 2.32, 95% CI).

According to HPV-DNA results of the cases (Table 1); 35.5% (n=42) of the cases had HPV-16 positivity, 8.4% (n=10) had HPV-18 positivity, 32.8% (n=39) had other types of HPV positivity, 4.2% (n=5) had both HPV 16 and18 positivity, 7.6% (n=9) had HPV 16 and other types, 1.7% (n=2) had HPV16-18 and other types positivity , 1.7% (n=2) had negative for HPV, 7.6% (n=9) had unknown HPV types and 0.8(n=1) had HPV18 and other types positive.

Table 1. Types of HPV-DNA.

Types	Number (n)	Percentage (%)
HPV 16	42	35,5
HPV others	39	32,8
HPV 18	10	8,4
HPV 16 and others	9	7,6
HPV 16-18	5	4,2
HPV 16-18 and others	2	1,7
HPV 18 and others	1	0,9
HPV negative	2	1,7
Unknown HPV	9	7,6

Distribution of pathology results according to HPV results were shown in table 2. The pathology results of HPV 16 positive patients were as follows; 10% (n=12) LSIL, 12, 6% (n=15) chronic cervicitis, 6,8% (n = 8) HSIL, 0,9% (n=1) invasive squamous carcinoma and 5% (n=6) coilositosis. When the HPV18 positive patients were evaluated 7,6% (n=9) had LSIL and 0,9% (n=1) had carcinoma in situ and HPV 16-18 positive patients were evaluated 3,4% (n=4) had LSIL and 0,9% (n=1) had carcinoma in situ, The pathology results of HPV other types positive 6,8% (n=8) had LSIL, 2,5% (n=3) had HSIL, 2,5% (n=3) had adenocarcinoma, 5% (n=6) coilositosis, 11,8 (n=14) chronic cervicitis and 0,9% (n=1) invasive squamous carcinoma. HPV 16 and other positive patients were evaluated 6,8% (n=8) had LSIL, 1% (n=1) had chronic cervicitis. HPV 18 and other positive patients were evaluated 0, 9% (n=1) invasive squamous carcinoma and HPV 16-18 and others positivity histopathological results were 1, 7% (n=2) adenocarcinoma and unknown HPV results were 0, 9% (n=1) LSIL, 6 % (n=7) coilositosis and 0.9% (n=1) chronic cervicitis, HPV negative results were 1.7% (n=2) chronic cervicitis.

Table 2. Distribution of pathology results according to HPV results.

Types	LSIL	HSIL	CIS	Invasive Squamous Carcinoma	Adeno Carcinoma	Coilositosis	Chronic Cervicitis
HPV 16	12	8	0	1	0	6	15
HPV 18	9	0	1	0	0	0	0
HPV 16-18	4	0	1	0	0	0	0
HPV others	8	3	0	1	3	6	14
HPV 16 and Others	8	0	0	0	0	0	1
HPV 18 and others	0	0	0	1	0	0	0
HPV 16-18 and others	0	0	0	0	2	0	0
Unknown HPV	1	0	0	0	0	7	1
HPV negative	0	0	0	0	0	0	2

According to the cervical cytology results of the examined cases (Table 3), 29.4% (n = 35) had normal findings, 17.6% (n=21) had infection, 16% (n=19) had ASCUS, 3.4% (n=4) had ASC-H, 8.4% (n=10) had insufficient, 18,4%(n=22) had LSIL, 5.04%

(n=6) unknown smear results, 0.9% (n=1) had AGUS, and 0.9% (n=1) had AGS.

Table 3. Distribution of cytology results.

	Number (n)	Percentage (%)
Normal	35	29,4
LSIL	22	18,4
Infection	21	17,6
ASCUS	19	16
Insufficient material	10	8.4
Unknown smear	6	5.04
ASC-H	4	3,4
AGUS	1	0,9
AGS	1	0,9

Thirty three patients (27.5%) had CIN-I, and five patients (4.2%) had CIN II-III at histopathology. Smear results of the five patients with CIN II and III were reported as infection. When the HPV DNA results of these patients were compared, 1.7% (n = 2) had HPV 16 positivity, 2.4% (n=3) had HPV 16 and 18 positivity.

Distribution of smear results according to pathology results were shown in table 4. When the pathology result of the patients who presented LSIL as results of smear had 4,2% (n=5) LSIL, 1,7% (n=2) had HSIL, 0,9% (n=1) had squamous carcinoma, 5% (n=6) had chronic cervicitis, 6,8% (n=8) had coilositosis, ASCUS as results of smear had 6,8% (n=8) LSIL, 1,7% (n=2) had HSIL, 0,9% (n=1) had adenocarcinoma, 0,9%(n=1) had carcinoma in situ, 0,9% (n=1) had squamous carcinoma 3,4 % (n=4) had chronic cervicitis, 1,7%(n=2) had coilositosis and the pathology result of the patients who presented ASH as results of smears had 1,7% (n=2) LSIL, had 1,7% (n=2) chronic cervicitis. Smear results were normally distributed in 11,8% (n=14) had LSIL, 2,1% (n=3) had HSIL, 0,9% (n=1) had carcinoma in situ, 0,9% (n=1) had adenocarcinoma,10% (n=12) had chronic cervicitis, 3,4% (n=4) had coilositosis. Then smear results were infection distributed in 10% (n=12) had LSIL, 0,9% (n=1) had HSIL, 0,9% (n=1) had adenocarcinoma, 5% (n=6) had chronic cervicitis, 0,9% (n=1) coilositosis. The pathology of the patient with smear result AGC 0, 9 (n=1) had LSIL and results of AGUS had 0, 9% (n=1) had adenocarcinoma.

The result of the unknown smear results were 0, 9% (n=1) LSIL, 0, 9% (n=1) HSIL, 0, 9% (n=1) chronic cervicitis, 1,7% (n=2) coilositosis. Insufficient material of smear results according to pathology result were 2, 1% (n=3) LSIL, 1, 7% (n=2) HSIL, 0,9% (n=1) adenocarcinoma, 0,9% (n=1) squamous carcinoma and 1,7% (n=2) chronic cervicitis, 1,7% (n=2) coilositosis.

Table 4. Distribution of smear results according to pathology results.

	LSIL	HSIL	CIS	Invasive Squamous Ca.	Adeno Ca.	Chronic Cervicitis	Coilositosis
LSIL	5	2	0	1	0	6	8
ASCUS	8	2	1	1	1	4	2
ASC-H	2	0	0	0	0	2	0
Normal	14	3	1	0	1	12	4
Infection	12	1	0	0	1	6	1
AGC	1	0	0	0	0	0	0
AGUS	0	0	0	0	1	0	0
Unknown Smear	1	1	0	0	0	1	2
Insufficient material	3	2	0	1	1	2	2

The histopathological results obtained in our study patients are as follows; 38.7% (n=46) LSIL, 28.7% (n=33) chronic cervicitis, 15, 3%

(n=19) coilositosis, 9.2% (n=11) HSIL, 4,2% (n=5) adenocarcinoma, 1.7% (n=2) carcinoma in situ and 2.1% (n=3) squamous carcinoma (Table 5).

Table 5. Distribution of four-quadrant cervical biopsy results.

	Number (n)	Percentage (%)
LSIL	46	38,7
Chronic cervicitis	33	28,7
Coilositosis	19	15,3
HSIL	11	9,2
Adenocarcinoma	5	4,2
Invasive squamous carcinoma	3	2,1
Carcinoma in-situ	2	1,7

When the pathological diagnosis were examined according to age groups, the highest frequency was in between the ages of 46-55 years. The most common pathology encountered in this age group was LSIL and chronic cervicitis. In the 46-55 age group population, LSIL was 13.4% (n=16), and chronic cervicitis was 9.2% (n=11). In 25-35 age group, 5.9% (n=7) had chronic cervicitis, 9.2% (n=11) had LSIL, 1.7% (n=2) had HSIL and 1.7% (n=2) had carcinoma in situ. In the 36-45 age group, 11.8% (n=14) had chronic cervicitis, 15.1% (n=18) had LSIL, 1.7% (n=2) had HSIL, 1.7% (n=2) had invasive squamous carcinoma.

In the 46-55 year age group, 4.2% (n=5) had chronic cervicitis, 13.4% (n=16) had LSIL, 3.4% (4) had HSIL. When the group of 56 years of age and above was examined, 4.2% (n=5) had chronic cervicitis, 9.2% (n=11) had LSIL, 1.7% (n=2), 2.5% (n=3) had HSIL. The diagnosis of carcinoma did not increase with the increased age and no significant differences were found.

The cytology results were evaluated as non-pathological when the findings were normal or infectious. 35 of the smear results were normal, 10 were insufficient material and 21 were infections. When the cytology and histopathology results were compared (Table 7), we saw that, of the 65 (54.2%) patients with normal smear results. 54 (45.8%) smear results were pathologic-abnormal smear results. LSIL 33 (27.5%), HSIL and advanced lesion 11 (9.2%) were detected in patients with normal cervical cytology before colposcopy. LSIL 26 (21.7%), HSIL and advanced lesion were found to be 13 (10.8%) in patients with abnormal cervical cytology. There was no significant difference in terms of biopsy pathology results between normal and non-normal cervical cytology results ($p=0.655$).

Table 6. Comparison of biopsy pathology results between normal and pathological smear results.

Pathology	Normal smear N (%)	Pathologic Smear N (%)	Total N (%)	*P (Chi-Square test)*
LSIL (coilositosis + CIN 1)	33 (27.5)	26 (21.7)	59 (49.2)	0.655
HSIL and advanced lesion (CIN 3 +insitu Ca +invasive Ca)	11 (9.2)	13 (10.8)	24 (20.0)	0.656
Chronic cervicitis (+ insufficient material)	21 (17.7)	15 (12.6)	36 (30.3)	0.936
Total	65 (54.2)	54 (45.8)	119 (100)	0.655

Discussion

In this article, the histopathological diagnoses of patients who were referred to colposcopy

due to various indications are examined by concerning both smear and colposcopy results, and it was found that four quadrant biopsy can increase the sensitivity of colposcopy. Our study is shown that in patients with high-risk HPV DNA positivity, the diagnose rate of pre-invasive and invasive cancer could be increased 20, 2% with 4-quadrant cervical biopsy application in addition to colposcopy. According to the ASCCP guide, CIN was detected in 17,2% of patients with a routine four-quadrant cervical biopsy, with the addition of a normal to a biopsy of the patient without any pathological findings to be diagnosed with colposcopy. Gage et al. among the analytical group of 2675 women with adequate enrollment colposcopically guided biopsy results, the 2-year cumulative risk for Pathology Quality Control Group histology diagnosis of CIN 3 at any time during ALTS was 15.3% [17].

Community-based screening programs have high importance in preventing cervical neoplasia. The diagnosis of asymptomatic pre-invasive lesions resulted in a significant decrease in the mortality and morbidity of the disease as a result of early intervention [6,18]. Most of the low-grade cytological abnormalities are known to regress spontaneously; however, one-third of the patients with a biopsy result of high-grade cervical intraepithelial neoplasia (CIN) is known to be reported as ASCUS in cytology [19,20]. In this study, the rate of patients who had ASCUS in cytology and subsequently CIN II-III in pathological biopsy was found as 10%. These ratios were consistent with the results of the ALTS (ASCUS/LSIL Triage Study) study (11.4 %) [8].

Dogan et al. [21] analyzed the prognostic value of HPV genotypes in cervical cancer in their large retrospective study. They reported that HPV-18-associated tumors frequently had earlier relapse than HPV-16, and adenocarcinoma was preferentially related to HPV-18 and therefore HPV 18 was more aggressive than HPV 16. Our study revealed HPV 16 positive patients had the following pathological diagnoses; 6.2% (n=8) HSIL, 0.9% (n=1) invasive squamous carcinoma. When HPV 18 positive patients were evaluated; 7,6% (n=9) had LSIL and 0.9% (n=1) had carcinoma in-situ. Our findings are inadequate either to support or refuse the findings of this study.

In the study by Tasdemir et al. [22] random biopsies were performed on 49 patients whose colposcopy revealed no lesions, and results showed that one patient had CIN 3, and two patients had CIN2. Those three patients consisted of %6,1 of the negative colposcopy patients.

In the present study, CIN II-III was diagnosed with four-quadrant cervical biopsy in 11 patients (9.6%). This rate is consistent with the study of Tasdemir et al. [22] when their relatively smaller cohort size is taken into consideration. Therefore, in various studies, it is argued that random biopsies in patients with normal colposcopic findings can capture the lesions of CIN II and above, particularly in those with a high-grade Pap smear result [16,19].

In a study with 2825 patients conducted by Massad et al. [14], the specificity of colposcopy for CIN II -III was found as 52%. The sensitivity for the CIN II-III was found to be higher, like 58%. The specificity of colposcopy was below 60%, which came with high false positivity rates. False negativity ranged from 20-40%. However, colposcopy is known to have high sensitivity in HGSIL detection [15,16]. In this study, the sensitivity of colposcopy was not evaluated because

colposcopy positive patients were not included in the study. Intraepithelial lesion was identified in 10% of the patients with normal colposcopy results by adding a routine simultaneous cervical biopsy. According to these preliminary results, we believe that colposcopy may have a lower sensitivity without a routine cervical biopsy.

Since the aim of the screening programs is to identify CIN II and above lesions, we think that performing a cervical biopsy on patients with high-risk HPV will increase the sensitivity of colposcopy in the diagnosis of cervical cancers.

When we categorize our patients according to age groups, we have reached the data that most of the patients were between 46-55 years of age. We think that this was due to the routine application of cervicovaginal smears for the last ten years in patients over 30 years of age which also resulted in a higher diagnoses rate in patients over 40 years of age. However, due to the low positive predictive value of screening tests, unnecessary interventions can be performed. Also, the high false negativity rates of screening tests affect the reliability of these tests adversely; those rates are very valuable because they are the simplest and the most commonly used tests that can be applied in a large number of patients. In a large study, 353 patients were evaluated according to the general colposcopic findings, and no random biopsies were performed from the four quadrants when there were no detectable abnormal findings [23]. They found the sensitivity and specificity of the general colposcopic findings as 63.8% and 88.8%, respectively. This study supports our work. In the case of general colposcopy examination, there may not be any correlation between morphology and biopsy results.

The study, including 195 patients who had colposcopy due to the atypical squamous cell by Patton et al. [24] found the risk of CIN II-III as 6% after the age of 40 years. Consistently, our study found that 6, 2% of the patients aged over 40 years who underwent colposcopic examination due to various indications were diagnosed with CIN II-III.

The non-inclusion of cases with positive colposcopic findings and the relatively low number of cases included in the study were the limitations of this study. However, this study was initially designed as a theoretical study. Assessing the sensitivity and specificity of colposcopy-guided biopsy results of our clinic was not primarily aimed. Since all patients in a given period were included in the study, it is assumed that the low number of patients can reflect the regional population.

Conclusion

Adding simultaneous routine four-quadrant cervical biopsy to the colposcopy might increase the detection rate of cervical intraepithelial lesions should be assessed in large randomized controlled trials.

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Research Ethics Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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