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Histopathological discrepancies between colposcopy-directed biopsy and LEEP-conization observed during SARS-CoV-2 pandemic

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ABSTRACT

Objectives: Long-term exposure to the human papillomavirus (HPV) is a known cause of squamous intraepithelial lesions that lead to cervical cancer. The loop electrosurgical excision procedure (LEEP) conization is an established treatment method. According to the latest recommendations, we present a paper to evaluate the effectiveness of various diagnostic methods of squamous intraepithelial lesions.

Material and methods: We analyzed 229 patients who reported to District Public Hospital in Poznan to undergo LEEP conization in 2019–2021 during the SARS-CoV-2 Pandemic. The analysis included Pap smear/liquid-based cytology, HPV genotyping, colposcopy with targeted biopsy and LEEP-conization. We offered post-treatment HPV vaccination and, as a follow-up, performed HPV re-genotyping after six months.

Results: In total, 89.1% of patients were HPV-positive. The coloscopy-directed biopsy (CDB) results show that almost 70% of the patients had high-grade intraepithelial lesions (HSIL). The diagnosis obtained by LEEP-conization showed that half of the women were diagnosed with HSIL and one-third with the low-grade squamous intraepithelial lesion (LSIL). The sensitivity of Pap smear/LBC accounted for 93.7% and was lower than for CDB, which reached 95.1%. Both diagnostic methods tend to underestimate the final diagnosis.

Conclusions: The inclusion of a colposcopic examination in an in-depth diagnostic process in women with abnormal Pap smear results facilitates the identification of patients requiring therapeutic intervention. LEEP-conization may be used without the primary biopsy. It applies to multiparous women in the perimenopausal period, extensive abnormalities, discrepancies in test results, extensive visible abnormalities, and suspicion of invasive cervical cancer in the colposcopic examination.

Key words: cervical cancer; CDB; squamous intraepithelial lesion

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INTRODUCTION

Cervical cancer stays the fourth most frequent cancer in women worldwide [1] unless it appears that it is theoretically preventable. It is estimated that in 2018, 570 000 women heard a diagnosis of cervical cancer, and 311 000 died from this. Most cervical intraepithelial neoplasia and invasive cervical cancers are caused by persistent infection with high-risk human papillomavirus (HR HPV). We observe a decrease in the incidence of cervical cancer for several decades thanks to preventive measures and screening.

New diagnostic methods enable the early detection of pre-cancerous lesions. Early treatment of squamous intraepithelial lesions, especially high-grade SIL, is essential to preventing cervical cancer. Established treatment methods comprise cold knife conization, loop electrical excision procedure (LEEP) and a large loop of the excision transformation

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zone (LLETZ). To our knowledge, randomized trials show similar efficacy, with rates ranging from 90% to 95% [2].

It is worthwhile noting that in May 2020, WHO called all institutions for global epidemiological eradication of cervical cancer. The WHO's goal is to reduce the incidence of cervical cancer at the level of a rare disease. The assumed timeframe for Europe is the year 2059. The minimum goals that WHO wants to achieve by 2030 are abbreviated as 90–70–90. These are: 1) covering 90% of the female population of girls up to 15 years of age with HPV vaccination, 2) covering 70% of the female population with a highly effective screening at least twice in a lifetime, *i.e.*, at 35 and 45 years of age, 3) coverage of 90% women with pre-cancerous lesions and cervical cancer with appropriate care [3–5]. The European response to the WHO's call is the initiative of the European CanCer Organization (ECCO), the European Society of Gynaecological Oncology (ESGO) and the European Federation for Colposcopy (EFC). In Poland, on the other hand, the Colposcopy 2020 initiative was established, creating new guidelines for secondary prevention of cervical cancer [6–8]. Further, temporary recommendations are introduced to the worldwide SARS-CoV-2 pandemic. So far, 293 047 852 cases have been registered globally and over four million in Poland. The Polish Association of Gynecologists and Obstetricians and the Polish Society of Colposcopy and Cervical Pathophysiology aimed new recommendations to ensure a balance between women's safety in terms of oncology and infectious diseases, respecting the limitations in interpersonal contacts. The developed recommendations allowed for the postponement of diagnostic and therapeutic procedures in patients with abnormal results of screening tests towards pre-neoplastic and neoplastic cervical conditions. Polish data for 2021 in the secondary prevention of cervical cancer financed from public funds are worrying — only 12.82% of the female population underwent screening [9]. The overriding goal of these recommendations is to achieve the highest possible population covered by screening in Poland. Optimal screening is related to the recommended temporary screening models, with the most effective diagnostic possible selection of patients requiring referral to colposcopy.

It may be noticed that previous studies have reported discrepancies between colposcopy-directed biopsy (CDB) and LEEP results, with overall concordance or agreement rates ranging from 43% to 86% [10–12]. However, study populations and designs, as well as statistical methods, differed among the studies.

This study investigates pathologic discrepancies between the CDB and LEEP to liquid-based cytology (LBC). We provide a survey to assess the ability of a Pap-smear, HR HPV testing, and colposcopy-directed biopsy to identify the final diagnosis. The study's second goal is to answer whether the gold diagnostic and therapeutic standard, LEEP-conization, is not overtreatment.

MATERIAL AND METHODS

This study included 229 patients treated with LEEP — conization between 2019 and 2021 at Provincial Hospital in Poznań during the COVID-19 Pandemic. The inclusion criteria were diagnosis of squamous intraepithelial lesion or carcinoma via colposcopy-directed biopsy or clinically suspicious image of the cervix. We excluded pregnant and breastfeeding patients or those with unsatisfactory colposcopy images. In the beginning, we obtained material from all patients for Pap-smear and molecular test detecting DNA of 37 HPV genotypes. Afterwards, an experienced gynecologic oncologist performed a colposcopy and parallel biopsy. Then, the oncologist performed LEEP-conization in patients with histopathologically diagnosed dysplasia. After a 6-months follow-up, we performed subsequent hrHPV testing and genotyping in each patient. All patients gave informed consent to participate in our study. The Bioethics Committee approved the study of the Medical Chamber of Wielkopolska- 95/2021.

Pap-smear/LBC and HPV genotyping test

We collected either Pap-smear or liquid-based cytology (LBC) and molecular assessment samples with an endocervical Cyto-Brush preserved in PreservCyt® (Hologic Corp) and SurePath® (BD Diagnostics-TriPath). Then we passed probes to the independent, standardized laboratory. PCR followed by DNA enzyme immunoassay and genotyping with a reverse hybridization line probe assay for HPV detection. Lab technicians performed sequence analysis to characterize HPV- positive samples with unknown HPV genotypes. The molecular test detected DNA of 37 HPV genotypes.

Colposcopy

A specialist in gynecologic oncology with 10-year experience performed colposcopy with SmartOPTIC colposcope. In all cases, a trial with a 5% aqueous solution of acetic acid was performed, as well as Schiller's test with Lugol's iodine. The colposcopic images were evaluated according to Reid's Colposcopic Index, which assesses the colour, lesion boundaries and surface, blood vessels and iodine test (scale range 0–8 points). All colposcopic images were archived. We used the International Federation of Cervical Pathology and Colposcopy classification recommended by the Polish Society of Colposcopy and Cervical Pathophysiology. Each time the gynaecologist performed a biopsy from clinically suspect sites and curettage of the endocervix.

LEEP — conization

Excisions were done with colposcopic guidance after application of acetic acid 5%. The sizes of the loops were

adequate to the size of the lesions, and each time, the lesion's margin was taken. After that, to obtain endocervix cells, the curettage of the cervical canal was performed. 12 to 16 paraffin blocks were created from each cervical specimen, and four to five sections were examined from each block. Experienced pathologists in an independent laboratory conducted a histopathological analysis.

The follow-up schedule for all women included Pap-smear and high risk — HPV genotyping test at six months.

Statistical methods

We used descriptive statistics to describe the clinicopathologic characteristics of the study population. Using Excel, we performed calculations using the statistical package Statistica (ver. 13.1) and graphs. Statistical hypotheses were verified at the level of significance of 0.05. Diagnostic test rates and the 95% confidence interval (CI) for LBC and punch biopsy were calculated compared to the golden standard. Pearson's chi-squared test was used to calculate the incidence of specific HPV genotypes in the final diagnosis.

RESULTS

The mean age of the entire population was 34. Most patients had less than three children, and more than half lived in the town or city with less than 100,000 inhabitants. Almost 90% of women were HPV-positive. About one-third of the studied population had comorbidities. Table 1 presents the descriptive characteristics of the study group. The obtained Pap-smear results are shown in Figure 1. Most of the patients had LSIL and HSIL. One patient was pre-diagnosed with adenocarcinoma (AC) and four with squamous cell carcinoma (SCC). The most frequent HPV genotypes in HPV positive patients were: 16 (55.6%), 31 (13.2%), 56 (8.3%), 51 (6.8%), 53 (6.8%), 18 (6.3%). The coloscopy-directed biopsy results show that almost 70% of the patients had high-grade intraepithelial lesions. Less than one-fourth of women were diagnosed with LSIL. The biopsy revealed one adenocarcinoma and one squamous cell carcinoma. The exact dependencies are shown in Figure 2. The diagnosis obtained by LEEP-conization showed that half of the women were diagnosed with HSIL and one-third with the low-grade squamous intraepithelial lesion. LEEP-conization revealed two adenocarcinomas and one SCC, which presents Figure 3. Figure 4 shows histopathological results, including the highest result from CDB and LEEP- conization, which means gold standard results. The most frequent diagnosis in our study group is HSIL.

The examples of diagnosis discrepancies are presented in Table 2. Neither in the case of CDB nor LEEP did we observe any overdiagnosis concerning gold-standard. However, a group of patients heard a lower diagnosis than it finally turned out. Patients with diagnosed invasive cervical cancer attract attention. Eventually, three cases of adenocarcinoma and two cases of squamous cell carcinoma were diagnosed in our study group. In women with SCC, one was finally diagnosed based on LEEP-conization (CDB- HSIL), and the other one - after hysterectomy (CDB- NILM, LEEP- HSIL). For women with adenocarcinoma, two were diagnosed based on the LEEP result (CDB- SCC and AC respectively) and one after hysterectomy (biopsy- NILM, LEEP- NILM).

Table 1. Descriptive characteristics of the study groups, means or N (%)

N	229
Age [years]	34
Living status	
City > 100,000 inh.	97 (42.4%)
Town or city < 100,000 inh.	132 (57.6%)
HPV status	
Positive	205 (89.1%)
Negative	24 (10.1%)
Comorbidities	75 (32.8%)
Parity	
0	98 (42.8%)
1–2	115 (50.2%)
≥ 3	16 (7.0%)

HPV — human papilloma virus; inh — inhabitants

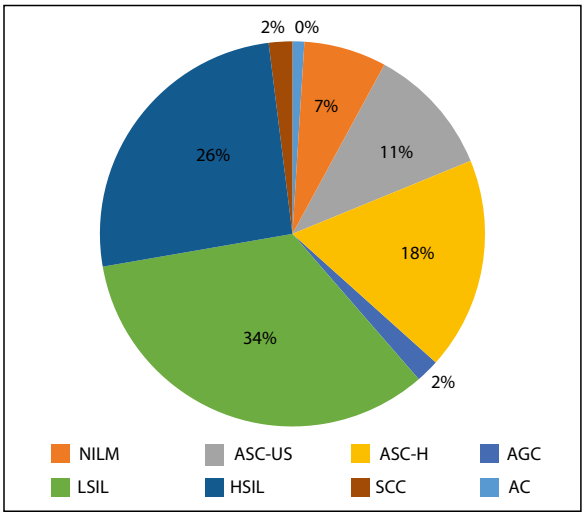

Figure 1. Liquid-based cytology results; NILM — negative for intraepithelial lesion or malignancy; ASC-US — atypical squamous cells of undetermined significance; ASC-H — atypical squamous cells cannot exclude HSIL; AGC — atypical glandular cells; LSIL — low--grade squamous intraepithelial lesion; HSIL — high-grade squamous intraepithelial lesion; SCC — squamous cell carcinoma; AC — adenocarcinoma

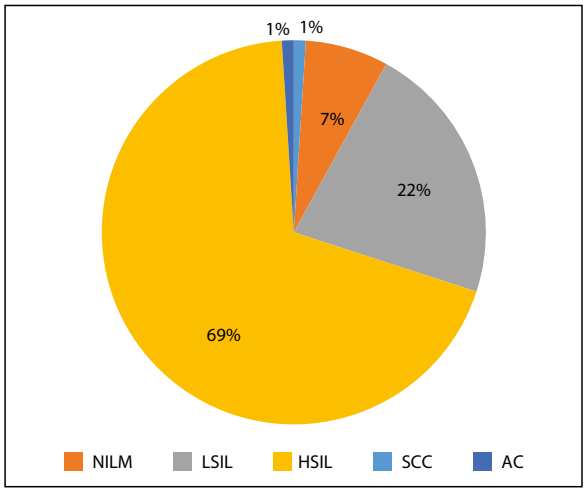

Figure 2. Histopathological results after colposcopy-directed biopsy; NILM — negative for intraepithelial lesion or malignancy; LSIL — low-grade squamous intraepithelial lesion; HSIL — high-grade squamous intraepithelial lesion; SCC — squamous cell carcinoma; AC — adenocarcinoma

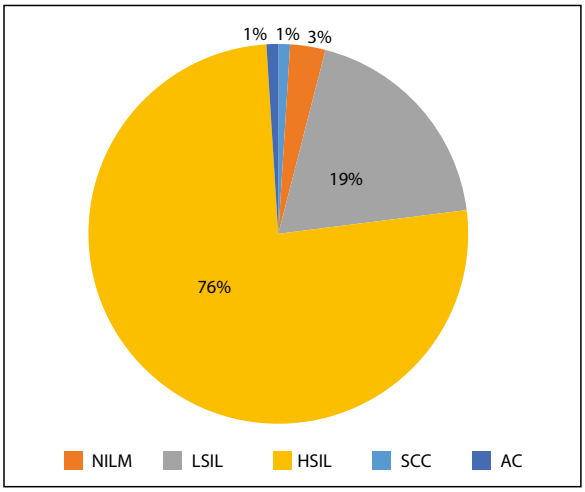

Figure 4. Histopathological results including highest result from colposcopy-directed biopsy and loop electrosurgical excision procedure conization — the gold standard; NILM — negative for intraepithelial lesion or malignancy; LSIL — low-grade squamous intraepithelial lesion; HSIL — high-grade squamous intraepithelial lesion; SCC — squamous cell carcinoma; AC — adenocarcinoma

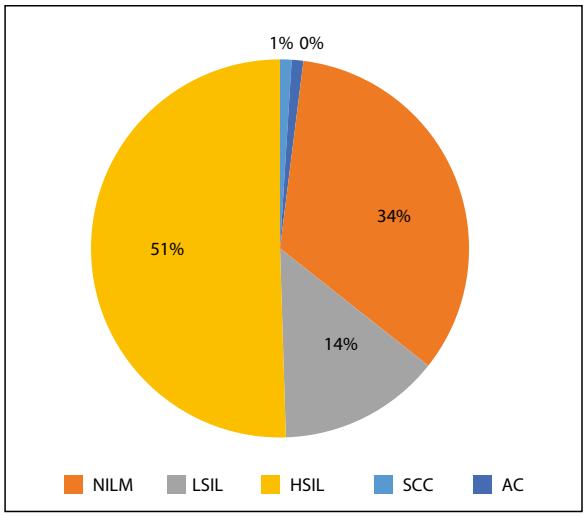

Figure 3. Histopathological results after loop electrosurgical excision procedure conization; NILM — negative for intraepithelial lesion or malignancy; LSIL — low-grade squamous intraepithelial lesion; HSIL — high-grade squamous intraepithelial lesion; SCC — squamous cell carcinoma; AC — adenocarcinoma

Another analyzed aspect was the assessment of the usefulness of diagnostic tests. The sensitivity of Pap smear/ LBC accounted for 93.7% and was lower than for colposcopy-directed biopsy, which reached 95.1%. The specificity of CDB reached the level of 100% and was twice as high as in the case of cytology. The most common HPV genotypes we observed were: 16 (50.2%), 31 (12.2%), 33 (6.6%) and 18 (6.1%). Table 3 shows the significant relationships between specific HPV genotypes and diagnoses obtained in various diagnostic tests. The comparison of both liquid-based cytology and colposcopy-directed biopsy results was statistically significant. There are discrepancies in both studies, and both diagnostic methods tend to underestimate the final diagnosis ($p < 0.001$).

DISCUSSION

The presented study aims to assess pathologic discrepancies between the CDB and LEEP to liquid-based cytology (LBC). Additionally, the second goal of this manuscript is to answer whether the gold diagnostic and therapeutic standard, LEEP-conization, is not overtreatment.

The gold standard is developed based on both CDB and material analysis from LEEP-conization. In the case of higher abnormalities in the LEEP-conization, the final diagnosis results from this procedure. In the case of normal or lower results from the conization, the final diagnosis is made after re-analysis of the colpograms. Squamous intraepithelial lesions such as LSIL and HSIL may be characterized by focal occurrence and be radically removed during a colposcopy-directed biopsy. A gynaecologist confirmed each situation after re-analysis of the colpograms.

In 2020 Shrestha [12] conducted a study in which researchers performed colposcopy with aqueous AA and delayed histopathological verification in 144 women. Achieved sensitivity, specificity, PPV and NPV accounted for 81%, 65%, 61% and 83%, respectively. In comparison, those parameters obtained for LBC were higher and amounted to 100%, 91%, 89% and 95%. The study confirmed the superiority of liquid diagnostics over the colposcopic evaluation of the cervix. However, the survey concerned a small group of patients [12].

Table 2. Comparison of pathological results between colposcopy-directed biopsy and loop electrosurgical excision procedure

CDB	Gold standard					
	NILM	LSIL	HSIL	SCC	AC	Total
NILM	6	3	6	1	1	17
LSIL	–	41	10	–	–	51
HSIL	–	–	158	1	–	159
SCC	–	–	–	–	1	1
AC	–	–	–	–	1	1
LEEP	**Gold standard**					
	NILM	LSIL	HSIL	SCC	AC	Total
NILM	6	24	46	–	1	77
LSIL	–	20	11	–	–	31
HSIL	–	–	117	1	–	118
SCC	–	–	–	1	–	1
AC	–	–	–	–	2	2

LEEP — loop electrical excision procedure; CDB — colposcopy-directed biopsy; NILM — negative for intraepithelial lesion or malignancy; LSIL — low-grade squamous intraepithelial lesion; HSIL — high-grade squamous intraepithelial lesion; SCC — squamous cell carcinoma; AC — adenocarcinoma

Table 3. Human papillomavirus genotyping in results of the gold standard

Chi^2 Pearson	Chi-squared	df	p value
HPV 16	17.53	4	0.002
Chi^2 Pearson	Chi-squared	df	p-value
HPV 18	18.06	4	0.001
HPV genotyping in results of CDB			
Chi^2 Pearson	**Chi-squared**	**df**	**p value**
HPV 16	14.31	4	0.006
Chi^2 Pearson	Chi-squared	df	p-value
HPV 31	10.51	4	0.033
HPV genotyping in results of Pap smear/LBC			
Chi^2 Pearson	**Chi-squared**	**df**	**p value**
HPV 18	18.30	6	0.006

HPV — human papillomavirus; CDB — colposcopy-directed biopsy; LBC — liquid-based cytology

The meta-analysis by Khan et al. [13] confirmed the high value of colposcopy in pre- and neoplastic lesions of the cervix. Achieved sensitivity, specificity, PPV and NPV accounted for 94%, 96%, 76% and 99%, respectively. The study covered a population of 500 women. It is worth emphasizing that both the colposcopic examination and the assessment of Pap smears are subjective diagnostic methods. They depend on the operator's experience, the usage of colposcopic protocols, the quality of the liquid media, and controls of the units performing them [13].

In Poland, the experts led by Professor R. Jach created the project named Colposcopy 2020. They recommend performing screening on a liquid medium (LBS) if possible. LBC allows performing several diagnostic tests from one swab. Moreover, it enables faster possible qualification for colposcopy with targeted biopsy of suspicious places. All colposcopy examinations containing both biopsy and curettage of the endocervix should follow the protocol established by Project Colposcopy 2020. Experts recommend diagnostic tests registered by the FDA or validated with the VALGENT and Meijer protocols [7]. Increasing the number of taken targeted sections and performing a random biopsy of the transformation zone in the case of higher screening irregularities significantly lifts sensitivity from 84% to 100% [14].

A higher diagnostic value characterizes both LEEP and LEETZ conization. It is not much more of a surgical procedure than a biopsy but may, in specific clinical situations, be used without the primary biopsy. Such cases mainly apply to multiparous women in the perimenopausal period, extensive abnormalities, or discrepancies in test results. These relate to cytology, molecular tests for the presence of hrHPV, p16 and Ki 67 tests. Moreover, LEEP-conization should be primarily used in the case of extensive visible abnormalities or even suspicion of invasive cervical cancer in the colposcopic examination.

The LEEP and LEETZ procedure is also a see and treat procedure more frequently performed in the developing countries of South America, Africa, Asia, and Oceania. It does not require admission to the hospital, shortens the time from access to diagnosis, similar to the optoelectronic method using the Truscreen device, the electronic method using the Zedscan device, the mobile Dysis system or the mobile EVA system [15]. The use of artificial intelligence systems may in

the future assist the colposcopist in deciding on a targeted cervical biopsy [16].

Simple outpatient excisional methods such as LEEP-conization have the potential to be used as a see-and-treat approach. In means the ability to perform both evaluation and treatment at the same visit [17]. See-and-treat has many advantages, especially for women diagnosed with HSIL in Pap-smear. Most of them will eventually undergo treatment irrespective of the results of colposcopy. Performing a loop excision at the initial colposcopic examination reduces the number of visits.

Additionally, it minimizes the potential for losing women in follow-up before treatment and eases patients' anxiety [18]. However, it might result in some cases of overtreatment in women without CIN 2+. One can minimize the overtreatment by performing see-and-treat only in patients obtaining HSIL in Pap-smear [19]. One see-and-treat study found that 84% of women with cytologic HSIL had histologically identified CIN 2 or 3 in LEEP-conization samples [20].

The study conducted by Kim et al. from 2020 confirmed the higher diagnostic value of the LEEP- conization over CDB in patients over 50 years of age. In the study group of 297 patients, the sensitivity of targeted biopsy for detecting HSIL+ lesions was 88%, and the specificity, positive and negative predictive values were 59%, 96% and 32%, respectively. Significant statistical discrepancies in diagnostic compliance occurred in postmenopausal patients [21]. The team's meta-analysis from China from 2015 confirmed the validity of more extended observation of CIN 2 lesions in the population of young and non-giving birth patients. The rate of spontaneous regression of CIN 2 lesions was approximately 26% and increased in the population of young patients with the extension of the follow-up and LEEP-conization procedure [22]. Another study reported that 94% of loop excisions specimens obtained using a see-and-treat approach in women referred with HSIL had histologically identified CIN 2,3 [23].

A relatively small research group limited our methodological choices. However, we will be able to increase the study group in the future. We count on the fact that with patients' vaccinations against COVID and the gradual easing of the restrictions, patients will report more frequently for routine gynaecological check-ups and access to surgical diagnostics might not be delayed.

CONCLUSIONS

The inclusion of a colposcopic examination in an in-depth diagnostic process in women with abnormal Pap smear results facilitates the identification of patients requiring therapeutic intervention. LEEP-conization is not much more of a surgical procedure than a biopsy but may be used without the primary biopsy. Such cases mainly apply to multiparous women in the perimenopausal period, extensive abnormalities, or discrepancies in test results. Moreover, LEEP-conization should be primarily used in the case of extensive visible abnormalities or even suspicion of invasive cervical cancer in the colposcopic examination. Furthermore, according to current cervical cancer prophylactic rules, minor abnormalities found in the Pap-smear allow for the temporary postponement of in-depth diagnostic steps. It seems that these changes did not affect the quality of diagnosis and the therapeutic process concerning the period before the pandemic.

Conflict of interest

All authors declare no conflict of interest.

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