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Use of electrical impedance spectroscopy as an adjunct to colposcopy in a pathway of cervical intraepithelial neoplasia diagnostics

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ABSTRACT

Objectives: Screening with cytology decreases cervical cancer burden, but new methods have emerged. We assessed the diagnostic value of electrical impedance spectroscopy (EIS) in the real-world gynecological setting. The study aimed to determine the diagnostic usefulness of EIS used as an adjunct to colposcopies in the diagnosis of high-grade squamous intraepithelial lesions in women with abnormal cytology findings.

Material and methods: A cross-sectional, single center, observational study considered 143 women. All were subjected to a colposcopy and EIS with ZedScan. ZedScan-guided or colposcopically-guided biopsies were carried out.

Results: Data from 118 women were analyzed. The average age of the included women was 38.29 ± 12.52 years (range: 22–86 years). Overall, 27 had a diagnosis of CIN2+ and above on histopathological examination, 99 had low-grade colposcopy results, 18 had high-grade colposcopy results, and 80 had positive ZedScan examination. No adverse events related to the examination with ZedScan were observed. EIS used as an adjunct to colposcopies showed sensitivity of 96.30% (95% CI: 81.03–99.91) and specificity of 39.56% (95% CI: 29.46–50.36), and accuracy of 52.54% (95% CI: 43.15–61.81). The procedure allowed to detect 11 additional cases with positive histo-pathological result in comparison to colposcopies alone.

Conclusions: Colposcopies performed with ZedScan as an adjunct were effective in detecting high-grade cervical lesions. Advantages of ZedScan include real-time result display, no additional diagnostic burden posed on the patient, and good safety profile. Studies on large patient cohorts are needed for further evaluations of this diagnostic procedure and factors which may affect its diagnostic accuracy.

Key words: electrical impedance spectroscopy; colposcopy; squamous intraepithelial lesions; sensitivity; specificity; predictive value

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INTRODUCTION

Cervical cancer is one of the most important health problems in women. This cancer ranks as the fourth most commonly diagnosed cancer and the fourth leading cause of cancer-related death in women worldwide. In 2018, the total estimated number of cases reached 570,000 while deaths 311,000 [1]. In 2016, the Polish National Cancer Registry reported 2,622 new cases of cervical cancer and 1,550 cancer-related deaths [2].

The incidence and mortality rates due to cervical cancer have been decreasing in many countries, mainly due to the elimination of risk factors and the introduction of screening. The rates are lower in well-developed countries than in developing countries [1]. Factors associated with this drop include the overall improvement in socioeconomic status and genital hygiene, reduced parity, and a decreasing incidence of sexually transmitted diseases [1, 3]. Cervical cancer screenings include cytology, high-risk human papillomavirus (hrHPV) testing, and other approaches to identification of preinvasive disease [4]. Although screening programs based on cytology contribute to decreasing cervical cancer burden, their efficiency is still insufficient. The study conducted on 687 women with histologically confirmed cervical intraepithelial neoplasia (CIN) from the Polish population revealed that cytology had a sensitivity of 58.02% and specificity of 63.28% in the diagnosis of CIN. A colposcopy, which is recommended if cervical screening gives abnormal findings, was more accurate in this group of patients with

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a sensitivity of 89.21% and % specificity of 98.87 [5]. Authors from other centers report lower diagnostic parameters of this method. The meta-analysis based on pooled data from 6,281 patients showed the weighted sensitivity and specificity of coloscopies were 85% and 69% respectively [6]. Relatively low sensitivity and specificity of those methods often associated with prolonged waiting times for the result have led to the development of new diagnostic techniques. The measurements of electrical impedance spectra are the most promising, cheap and fast method of detection of abnormal cell arrangements in cervical tissue [7].

The use of electrical impedance measurements has been evaluated in a wide range of cancers. In vivo, this method is used to help identify superficial tissues with an altered structure as a result of a neoplastic transformation. Reports from the literature show that electrical impedance spectroscopy was found to be useful in differentiation between normal and abnormal skin lesions, especially in detecting malignant melanoma [8]. In gynecology, preliminary reports on the use of electrical impedance spectroscopy (EIS) as an adjunct to colposcopies in the diagnosis of CIN showed increased accuracy [9]. An introduction of intraoperative evaluation of electrical impedance spectroscopy-on-a-needle may serve as an additional tool to diminish the risk of positive surgical margins while maximizing tissue sparing [10]. The altered electrical impedance of excised cancer tissue and metastases awaits a determination of its clinical significance [11].

Increasing interest in EIS and growing evidence showing benefits for both patients and physicians encourage further research. We attempted to assess the diagnostic value of EIS in gynecological practice. The aim of the study was to determine the diagnostic accuracy of EIS when used as an adjunct to colposcopies in the diagnosis of high grade squamous intraepithelial lesions in women with abnormal cytology findings.

MATERIAL AND METHODS

This is a cross-sectional, single center, observational study conducted in the real-world settings. All eligible women were referred to colposcopies to our institution due to abnormal cytology results, following conization, and for follow-up of previously diagnosed LSIL and inflammatory changes. On the qualification visit, women with diagnosed cancer of the cervix, vaginal bleeding or active menstruation, and those who had used vaginal contraceptives and vaginal medications up to 2 days before the visit were excluded. Included females were subjected to colposcopies, EIS and histopathology examination when needed. All diagnostic procedures were conducted by two experienced gynecologists. All biopsies were evaluated by a histopathologist with experience in assessment of cervical pathology. In total, 143 women were recruited to participate in the study, but complete data were available for 118 women. The study was conducted after obtaining the written informed consent for participation in the study and undergoing diagnostic procedures. The study was approved by the Commission of Bioethics at Wroclaw Medical University.

All women were subjected to the same diagnostic procedure. Colposcopies using Videocolposcope HD-1000 with IRIS software (Medicom, Wroclaw, Poland) was conducted according to our local procedures. Colposcopic examinations were video recorded for comparison with the results of other procedures. Video recording was done twice, first without and next after application of 3% acetic acid. Colposcopic examinations were video recorded for comparison with the results of other procedures. Next, EIS was performed with ZedScan (Zilico Limited, Manchester, UK). The device consisted of a hand-held unit with a single use sensor on the tip of the unit. Electrical impedance was measured by 4 electrodes when the tip of the device was placed on the cervical epithelium. With each patient after the application of 5% acetic acid, 12 measurements were taken from the cervical transformation zone. Measurements were displayed on the screen of the hand-held unit and recorded. Three colors were used to identify areas of the highest probability of HSIL occurrence: red (the highest probability), amber (lower probability), and green (the lowest probability) and helped select potential areas for biopsy. In cases in which red light was displayed, single point mode was used to help select areas for diagnostic biopsy. A diagnostic procedure was completed by the application of Lugol's solution (potassium iodide) to the surface of the cervix to help identify abnormalities on the cervical epithelium without staining.

For each examination, 1 of the 3 recommendations were made based on the results given by coloscopy and ZedScan:

1. ZedScan-guided biopsy in the case of low-grade lesions identified in colposcopies and red light in ZedScan,
2. Colposcopically guided biopsy in the case of a scanty high-grade lesion in colposcopies and green light in ZedScan.

Punch biopsies for histological examination were sampled from the most abnormal areas indicated by the combined assessment carried out with colposcopies and EIS.

Data were analyzed for the three groups. Each of the patients received only one ZedScan and histopathology examination result regardless of the number of impedance measurements and biopsies. In addition, the colposcopy, results were compared to those of ZedScan carried out as an adjunct to the colposcopy.

The patient was considered to be negative for High Grade Squamous Intraepithelial Lesions (HG-SIL) when the result of the colposcopies were normal without any visible lesions, and the ZedScan results were normal (green light). The cases of a negative result in colposcopies and positive

in ZedScan were considered false negative for colposcopies. The result of the histopathological examination was used as a measure of the performance of both colposcopies and colposcopies with ZedScan. Biopsy samples were considered positive for HG-SIL when presenting with the diagnosis of CIN II and above.

Statistical analysis

Data were presented as numbers and percentages. Fisher's exact test was used to compare the distribution of results between the 2 diagnostic methods: classical colposcopies or colposcopies with ZedScan as an adjunct. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) were calculated.

RESULTS

The mean age of the 118 women included was 38.29 ± 12.52 years with a range from 22 to 86 years. All women were referred to our institution with abnormal cytology results (Tab. 1).

Of the 118 women included, 27 had CIN2 and above on histopathological examination, 99 had low-grade colposcopy results, 18 had high-grade colposcopy results, and 80 had positive ZedScan examination. ZedScan-guided biopsy (LG + ZedScan red) was carried out in 62 patients. One colposcopically guided biopsy (HG + ZedScan green) was performed. None of the patients reported adverse events that could be related to the examination with ZedScan. Histological examination was available for 118 cases. The results of histopathological examination of included patients are presented in Table 2.

To perform diagnostic test evaluation results of the 3 tests used were juxtaposed. For further analysis, samples with a histology result were considered (118 cases). ZedScan guided biopsy was performed in 47 patients. In this group, positive histopathological examination was found in 11 patients. All patients had negative colposcopy results and positive ZedScan results.

Table 1. Results of cytology results at referral

	Cytology diagnosis	No of patients
1.	Atypical glandular cells (AGC)	9
2.	Atypical squamous cells cannot exclude HSIL (ASC-H)	16
3.	Atypical squamous cells of undetermined significance (ASC-US)	14
4.	High-grade squamous intraepithelial lesion (HSIL)	23
5.	AIS	1
6.	Low-grade squamous intraepithelial lesions (LSIL)	43
7.	Negative for intraepithelial lesion or malignancy (NILM)	12

The results of colposcopy and ZedScan examinations were juxtaposed with results of histopathology (Tab. 3) allowing for calculation of sensitivity, specificity, positive predictive value, negative predictive value, and accuracy (Tab. 4).

The use of adjunct ZedScan allowed detecting of 11 additional cases with positive histo-pathological result in comparison to colposcopy alone.

DISCUSSION

EIS is a novel option in diagnosing high-grade SIL of the cervix. Currently, it is used in conjunction with colposcopies. Our study revealed that ZedScan used as an adjunct to colposcopies is a sensitive diagnostic procedure. In our cohort of 118 women with abnormal cervical cytology, common use of colposcopies and EIS allowed for detecting an additional 11 cases of high-grade CIN. ZedScan used as an adjunct to colposcopies showed sensitivity of 96.30% (95% CI: 81.03– 99.91) and specificity of 39.56% (95% CI: 29.46–50.36). Accuracy of this procedure was 52.54% (95% CI: 43.15–61.81).

The strength of this study is that it is the first report from the study conducted on the Polish population and

Table 2. Results of histopathological examination of included patients

Lp.	Histological diagnosis	No of patients
1.	Carcinowa planoepitheliale akeratodes (G1)	1
2.	High-grade squamous intraepithelial lesion (HSIL)	26
4.	Low-grade squamous intraepithelial lesion (LSIL)	12
5.	Chronic inflammation	6
6.	Acute inflammation	1
7.	Normal	72

Table 3. Test calculations

Results of the test		Histopathology results	
		Positive	Negative
Colposcopy + Zed Scan	Positive	N = 26	N = 55
	Negative	N = 1	N = 36

Table 4. Results of test evaluation

	Colposcopy + ZedScan
Sensitivity	96.30% (95% CI: 81.03–99.91)
Specificity	39.56% (95% CI: 29.46–50.36)
Positive Predictive Value	32.10% (95% CI: 28.27–36.19)
Negative Predictive Value	97.30% (95% CI: 83.80–99.60)
Accuracy	52.54% (95% CI: 43.15–61.81)

CI — confidence interval

one of the first reports on this joint diagnostic procedure worldwide. Although the study includes a relatively low number of women, the experience with using EIS in the diagnosis of cervical pathologies increases. As EIS is a new procedure, colposcopists need to develop new skills to diagnose pathological lesions correctly. Tidy et al. noted that gaining sufficient experience with EIS requires the conduct of up to 20 examinations [12], yet our experience suggests that a learning curve may be longer. In our institution, ZedScan has been used since the middle of 2017, allowing colposcopists participating in the study and gaining sufficient experience with the device and study protocol.

Our study was conducted in a real-world setting which has an important consequences. Patients were undergoing normal diagnostic procedures which reflects the reality of clinical practice and showed the feasibility of diagnosing cases of high-grade CIN, which otherwise would have been missed.

ZedScan is a relatively expensive diagnostic tool so it is currently not a part of the routine diagnostic process. Due to low evidence available, it is used as adjuncts to conventional colposcopies. This combination increases the cost of the overall diagnostic procedure, but pose no additional burden on patients. The examination is painless and free from other unpleasant experiences. A cost-effectiveness analysis performed by Peron et al. aimed to compare classical colposcopies with two methods designed to increase sensitivity of colposcopies: Dynamic Spectral Imaging System (DySIS) map and ZedScan, both used as an adjunct to colposcopies [13]. Both procedures were found to increase diagnostic accuracy when compared with colposcopies alone. ZedScan proved to be more effective, but also more costly than colposcopies alone and DySIS. Peron et al. highlighted the fact that the evidence on the use of ZedScan is limited. For this reason, a comparison between ZedScan and DySIS was not feasible [13].

Clinical reports on the diagnostic accuracy of ZedScan used as adjunct to colposcopies is limited to several publications. In the first-ever work on the clinical usefulness of EIS in gynecology practice reported by Brown et al. [7], 124 women with abnormal cervical cytology were examined. They reported a clear difference in EIS results between measurements taken from normal squamous tissues and those taken from precancerous tissues. They reported a sensitivity of 92% and a specificity of 92% in differentiating patients with normal epithelium from those with cervical intraepithelial neoplasia. Muszyński et al. [14] recruited 91 women aged 33 years on average, with a range between 23 to 61 years. They found that using ZedScan as an additional diagnostic procedure with colposcopies in comparison to colposcopies alone increases sensitivity from 61.3% to 93.3% for detecting high-grade SIL but reduces specificity from 80% to 34.4%. Balasubramani et al. [9] analyzed data from 104 women with any cervical smear abnormality or a clinical indication for colposcopies. They reported 18 cases with colposcopic impression and EIS indicating high-grade disease along with an agreement with histological diagnosis of high-grade CIN which suggest a 100% sensitivity and specificity; however, the reported sample was small. Macdonald et al. [15] evaluated the impact of hrHPV infection on the accuracy of a diagnostic procedure carried out with colposcopies and EIS as an adjunct. Their study included the largest cohort of 839 women. The researchers concluded that using EIS contributed to a significant increase in detecting CIN II and above from 85.6% to 96% regardless of hrHPV genotype status ($p < 0.0001$). Tidy et al. [12] recruited 474 women in their study. The study showed that using EIS as an adjunct to colposcopies increased specificity from 83.5% to 95.4%, but significantly reduced sensitivity from 73.6% to 62.1% in detecting high-grade CIN. The most recent study conducted by Tidy et al. [16] on a cohort of 1,237 women with abnormal cervical cytology showed additional 53 (12.8%) cases of high-grade CIN detected by a diagnostic procedure based on the joint use of colposcopies and EIS. The use of acetic acid did not affect the diagnostic accuracy of ZedScan [9, 12].

ZedScan has a good safety profile. In our study, none of the patients reported any adverse events related to measurement impedance spectra. The occurrence of adverse events in relation to diagnosing cervical abnormalities was reported only Tidy et al. [12] who reported two adverse events and one serious adverse event. The first (patient felt unwell) is not linked directly to any procedure, while the other two (bleeding) are linked to biopsies. In the present study, no adverse events were observed.

It is worth noting that ZedScan offers obtaining results in the real-time, which contributes to a reduction in the emotional burden associated with diagnostic procedures. The device is easy to use for colposcopists. Currently, it is included in the diagnostics guidance on adjunctive colposcopy technologies for assessing suspected cervical abnormalities published by NICE [17]. ZedScan has been identified as a promising diagnostic modality, yet due to insufficient evidence, further research on the effects of using the technology on clinical and patient outcomes was recommended.

Currently, ZedScan is one of the options that increase accuracy of diagnosing high-grade CIN, but other techniques emerge on the market as well. Two techniques are worth mentioning. Automated visual evaluation (AVE) uses a deep learning algorithm for cervical cancer screening during colposcopies. Evaluations are made after straining with 3–5% acetic acid. The images are recorded during colposcopies and then compared to cervical images taken during a National Cancer Institute (NCI) prospective epide-

miologic study. Studies on an algorithm that can identify cervical precancer were conducted for 7 years and involved 9,406 women. The results are promising. They indicate that AVE has higher accuracy in detection of precancer lesion in comparison to traditional method of assessment of cervical images and cytology [area under the curve (AUC) = 0.91; 95% confidence interval (CI) = 0.89–0.93 for AVE in comparison to AUC = 0.69; 95% CI = 0.63–0.74 for cervigram; $p < 0.001$ and AUC = 0.71; 95% CI = 0.65–0.77 for conventional Pap smears; $p < 0.001$] [18]. Another method is carried out based on the assessment of staining with folate-receptor-mediated (FRD). Studies have shown that folate receptor subtype α are overexpressed on the surface of cells of gynecological malignant lesions. A reduced methylene blue (MB)-folic acid complex binds with folate receptor subtype α on the neoplastic epithelial cells triggering endocytosis. Next, colorless reduced MB is converted to blue oxidized MB by the intracellular reactive oxygen species and becomes detectable [19]. The study on over 14,000 women showed the sensitivity of this method in detecting CIN2 + of 85.7%, specificity of 76.4%, the positive predictive value of 61.3% and negative predictive value of 92.5% [20]. Other studies confirmed the effectiveness of FRD emphasizing the simplicity of staining and the possibility of getting immediate result [21, 22].

CONCLUSIONS

Colposcopies performed with ZedScan as an adjunct demonstrated effectiveness in the diagnosing of high-grade cervical lesions. Advantages of ZedScan include real-time result display, no additional diagnostic burden posed on the patient, and good safety profile. The high cost of the procedure may limit its widespread use. Studies on large patient cohorts are needed for further evaluations of this diagnostic procedure and factors which may affect its diagnostic accuracy.

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