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Screening and Diagnosis of High-Grade Cervical Lesions – Preliminary Results

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ABSTRACT

Introduction: In Bulgaria, the incidence of invasive cervical cancer is one of the highest in Europe. The underlying issue is the lack of well-organized and functioning screening in general, but especially the lack of primary HPV screening.
Objective: To determine an adequate screening approach for the selection of patients with high-grade cervical lesions (HSIL/CIN 2-3) and the potential of colposcopic examination for the diagnosis of HSIL/CIN 2-3
Materials and Methods: From September 2022 to June 2023, 55 patients underwent screening and diagnosing for all types of precancerous lesions at Prof. Kornovski Medical Centre. The age of patients with LSIL and HSIL was 20–49 (mean 35.6) and 18–72 (mean 36.1) respectively. The methods we used were: Alinity HR HPV test; PAP test; colposcopy; histological diagnosis made by targeted biopsy under colposcopic control or by LLETZ for cases in which HSIL in the cervical canal could not be excluded.
Results: Patients with HSIL were HPV (-) in 10% and HPV (+) in 84%. Of the latter, 53.8% were HPV 16+. Cytological screening in HSIL patients revealed normal cytology in 19%, of which 83% were HPV (+) and of these, 80% were HPV 16(+), and 20% were (+) for HPV, including 31 and 33 strains. In 84% of histologically confirmed HSIL cases, colposcopy showed evidence of HSIL and in 13% (4 patients) – LSIL. In the latter, the diagnosis was made by excisional biopsy procedure (LLETZ). The indication and reason for loop excision was the HPV status of these patients –HPV16(+) in 67% and HPV18(+) in 33%. Cytology in these 4 patients was normal in 50% of cases.
Conclusion: The Alinity HR HPV test adequately stratified oncogenic strains according to their risk for HSIL. Patients who are HPV 45+, as well as the HPV (31, 33, 52, 58) (+) group, should be referred for colposcopy without an additional triage method or should be subject to closer follow-up (repeat test in 6 –12 months) before referral for colposcopy. Patients who are HPV 16+ and HPV 18+ should undergo mandatory expert colposcopy and biopsy, including excisional biopsy (LLETZ), in the absence of HSIL from the colposcopy-directed targeted punch biopsy. Patients who are positive for any of the HPV strains (35, 39, 51, 56, 59, 66, 68) may be referred for cytology and those with abnormal cytology – for expert colposcopy.
Key words: HPV screening, colposcopy, HSIL

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INTRODUCTION

Cervical cancer prevention is possible through screening as progression from infection to cancer is usually slow, on the order of decades (1). Cervical screening is cytology, HPV screening (high-risk cancer strains) and combined (cytology and HPV) (2). According to Cuzack et al. (2006), cytology screening has 53% sensitivity and 96.3% specificity, while HPV screening shows 96.1% sensitivity and 90.1% specificity (2). The Pap test has a history of over 50 years in medicine, and this is the main reason why we have seen a significant reduction in cervical cancer mortality in most countries with organized screening systems. Despite its success, the Pap test is far from perfect. This is mainly because Pap cytology is based on a highly subjective interpretation of morphological changes and depends on correct sample collection. Currently, there is considerable interest in the use of HPV DNA testing as a cervical cancer screening tool. An essential advantage of this method is that it is amenable to automation, making it less susceptible to human error. This allows for high reproducibility; over time, large-scale testing can reduce its cost (3). Two categories of HPV tests can be used for cervical cancer screening. The generic assays test for the presence of 13–14 high-risk HPV as a group provides "positive/negative" type results. Partial genotyping assays provide results separately for types 16 and 18 and as a group for the other high-risk types (3). Overall, studies have shown that HPV testing results are more reproducible than Pap test results; most HPV testing systems are more sensitive and have a higher negative predictive value than Pap testing. HPV testing has also been shown to result in a more significant reduction in the incidence and mortality of cervical cancer and the proportion of carcinomas diagnosed at an advanced stage compared with Pap testing. However, HPV testing has lower specificity when used as a stand-alone test (4,5). In women with cervical cancer, HPV-16 is also the most common type, followed by HPV 18. Together, they account for 70% of cervical cancer cases worldwide. When HPV 31, 33, 35, 45, 52, and 58 are added, these 8 most common HPV types account for 90% of cervical cancers worldwide.

In women with HSIL, HPV-16 remains by far the most common, but the importance of HPV 18, 31, 33, and 58 types varies considerably by region (1,6). With regard to the diagnosis of high-grade cervical precancers, colposcopy is the gold standard. Patients with abnormal screening results should undergo colposcopy. Colposcopy is used to determine the site from which to take a biopsy. Colposcopy-directed punch biopsies provide tissue from the most suspicious area of the cervix, which is sent for histological examination. The histological examination diagnoses the precancerous lesion (CIN 1, 2 or 3). The biopsy results determine the course of treatment (7,8).

MATERIALS AND METHODS

Study design

This is a prospective, single-centre study performed at Prof. Kornovski Medical Centre in which 150 patients with cervical precancerous lesions, are intended to be included. The study will be held for a period from September 2022 to December 2024. We present the preliminary results of 55 patients treated in period of ten months (September 2022 to June 2023).

Objective of the study

To determine the adequate screening approach for selecting patients suspected of high-grade cervical lesions (HSIL/CIN 2-3) and the potential of colposcopic examination for diagnosing HSIL/CIN 2-3.

Clinical cohort

For the period from September 2022 to June 2023, 55 patients underwent screening and diagnosing for all types of precancerous lesions at Prof. Kornovski Medical Centre. The age of patients with LSIL and HSIL was 20-49 years (mean 35.6 years) and 18-72 years (mean 36.1 years), respectively. Diagnosed as LSIL were 24 patients and az HSIL 31.

Methodology

Alinity HR HPV test was used; colposcopy was performed by one gynaecologic oncologist using a Leisegang colposcope, 2020, an original system with HD monitor and archiving software; the histological diagnosis was made by colposcopically directed targeted biopsies or by LLETZ for cases in which HSIL lesions in the cervical canal could not be excluded. The samples for cytological examination (PAP test), as well as the HR HPV test, were taken by the same gynaecologic oncologist who performed the colposcopic examination. The same highly qualified histopathologist performed histological diagnosis and cytological examination. The Alinity HR HPV test provides an estimate of the carriage of 3 high-risk strains and two groups of HPV strains according to their risk for HSIL.

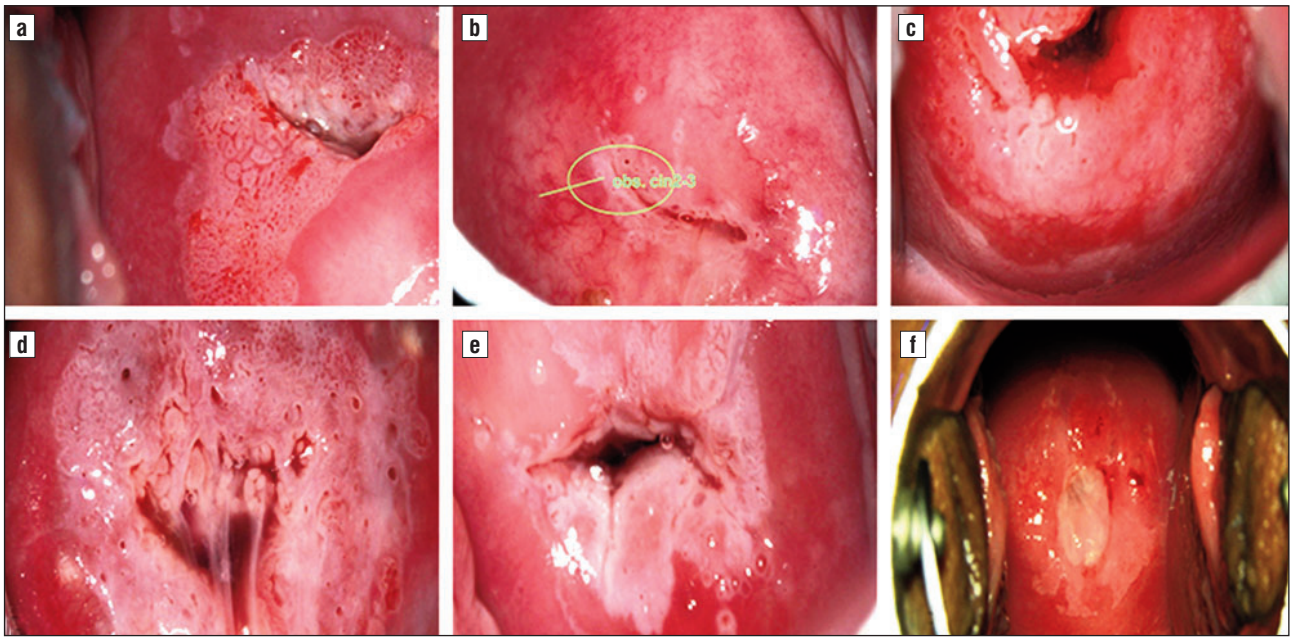


Figure 1 - Colposcopic findings

Colposcopic findings (*fig. 1*): (a) the colposcopy of 38-year-old nullipara, HPV 16 (+), with normal cytology. The colposcopy shows features of HSIL – coarse mosaic and punctuation and a sharp border with normal epithelium. Biopsy confirms the diagnosis of CIN 3; (b) a discrete area with dense acetowhitening and cuffed gland opening. The patient is 27-year-old, nullipara, HPV 16 (+), with normal cytology, and the biopsy result is CIN 2; (c) colposcopy of an 18-year-old nullipara, HPV 16 (+), with normal cytology. Areas of dense acetowhitening are seen in the background of ectopia. The biopsy result is CIN 2; (d) colposcopic features for HSIL – an extensive area of colposcopic atypia, coarse mosaic and punctuation, dense aceto-whitening and sharp border. The patient is 34-year-old, nullipara, HPV 31, 33, 52, 58 (+), with normal cytology. Biopsy shows CIN 3 with glandular involvement; (e) colposcopic evidence of HSIL – an extensive area of dense acetowhitening with a sharp border. The patient is 28-year-old, primiparous, HPV 16 (+), with normal cytology. The decision was made to 'see and treat' strategy, and LLETZ was performed. The result showed CIN 3; (f) colposcopy revealed LSIL; biopsy confirmed it, but the histological result after LLETZ was CIN 3 with glandular involvement. The patient was 31-year-old, nullipara, HPV 16 (+), with normal cytology. If we had not performed LLETZ, the patient would have been monitored while CIN 3 and possibly carcinoma continued to develop in the cervical canal. This case demonstrates that LLETZ is advisable for HPV 16 (+) regardless of the colposcopic findings.

RESULTS

Baseline results are based on the first 55 patients enrolled in the study. HPV and cytology screening were examined in patients with LSIL and HSIL, respectively.

In the LSIL group, 75% of patients were HPV (-), and 25% were HPV (+) (*fig. 2*).

When examining the distribution of positive strains, we established that the most frequent HPV group included strains 35 to 68 (15%), followed by the group including strains 31, 33 (12%) and the least frequent –

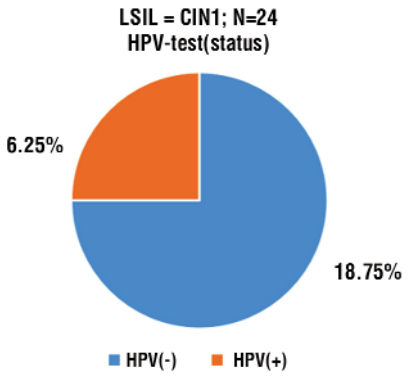


Figure 2 - Distribution of the patients by HPV results in LSIL group

HPV 16, in one case. The percentage exceeds 100 as some patients carried more than 1 strain (*fig. 3*).

Cytological screening of the LSIL group detected III A / LSIL in 67% of cases (*fig. 4*). In the HSIL group, 10% were HPV (-), and 84% were HPV (+) (*fig. 4*).

The distribution of positive strains showed the highest frequency of HPV 16 – 53.8%, followed by the HPV group, including strains 31, 33 – 34.6%. HPV 18 and 45 strains are less frequent in the Bulgarian population (*fig. 5*).

Cytological screening of patients in the HSIL group found normal cytology in 19% (*fig. 6*).

Notably, 83% of patients with normal cytology were HPV (+). Of the latter, 80% were HPV 16 (+), and 20% were (+) for HPV, including 31 and 33 strains (*figs. 7, 8*).

The diagnostic capability of colposcopy in our study is reflected in *fig. 9*.

In 84% of histologically confirmed HSIL cases, colposcopy showed evidence of HSIL and in 13% of LSIL. In the latter, the diagnosis was made by excisional

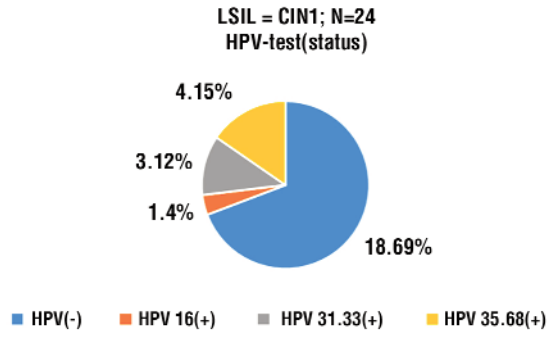


Figure 3 - Distribution of the patients by HPV test results in LSIL group

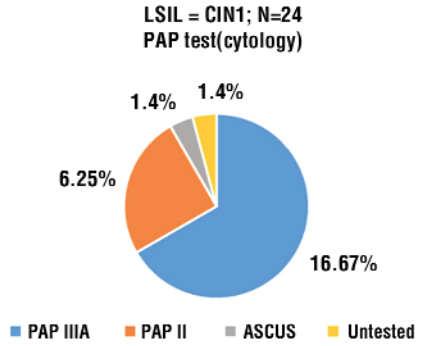
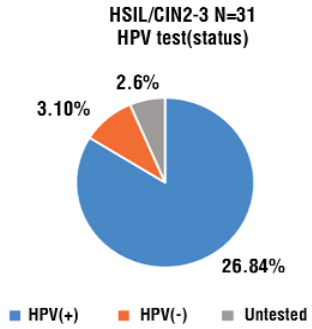


Figure 4



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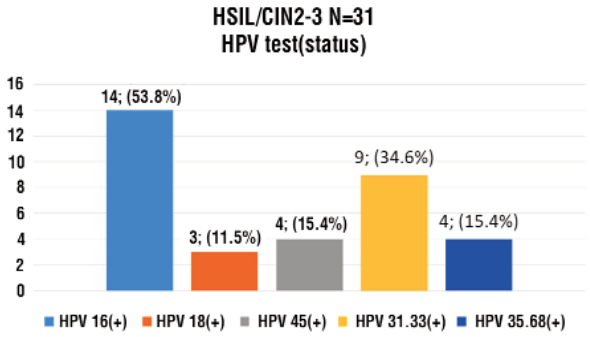

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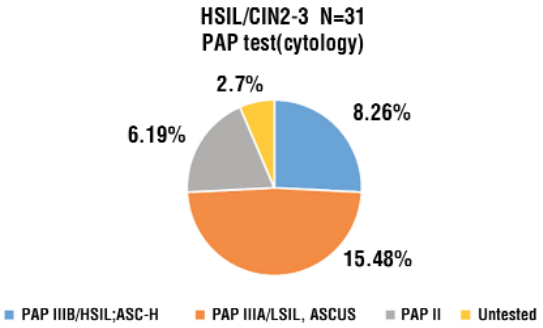

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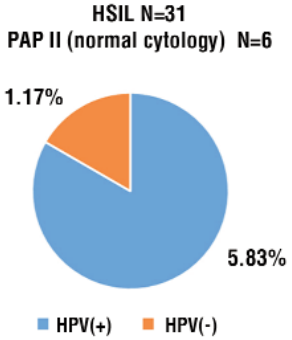

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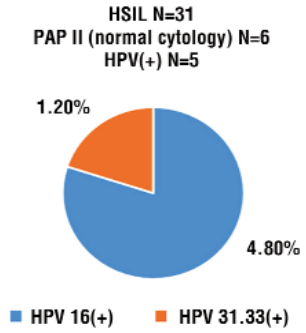

Figure 9

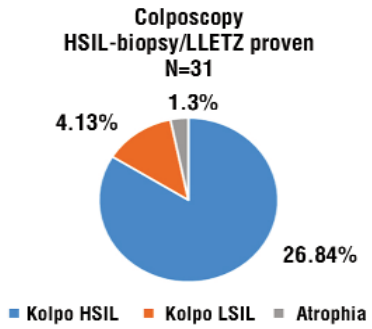

Figure 10

biopsy procedure (LLETZ). The indication and reason for loop excision was the HPV status of these patients (*fig. 10*).

Despite the low-grade colposcopic finding, the high oncogenic strains 16 and 18 correlate with HSIL from the histological examination.

On the other hand, *fig. 11* illustrates the low sensitivity of the cytological screening (PAP test), with cytology not signalling abnormality in 50% of these cases.

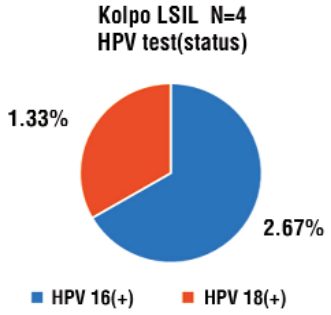

Figure 11

DISCUSSION

In Bulgaria, the incidence of invasive cervical cancer is one of the highest in Europe. This is due to the lack of well-organized and functioning screening in general, but especially the lack of primary HPV screening.

The establishment of the association between persistent HPV infection with high-risk strains and the development of cervical cancer (CRC) has led to the introduction of screening programmes in which HPV screening plays a significant role, either as a stand-alone test or in co-testing with cytology screening (9,10).

Several randomized trials comparing HPV with cytology screening have found the former more effective in detecting CIN 3 (11-15). In addition, a follow-up analysis of 4 randomized European trials found that HPV screening provided 60–70% better prevention of invasive cancer than cytology screening (16).

Screening systems aim to detect HSIL (CIN 2/3) on the one hand and to reduce the workload in colposcopy centres (to reduce false positive screening results) on the other hand, i.e. to increase the specificity of the screening method. In a number of European countries, HPV testing of high-risk strains as primary screening has been introduced in recent years. In Germany, HPV co-testing and cytology screening every 3 years for women over 35 years of age was introduced in 2020. For women with normal cytology but HPV (+), screening is repeated after 12 months. If persistent HPV infection with high-risk strains is present, the patient is referred for colposcopy to diagnose HSIL (CIN 2/3) (17).

HPV typing is important in identifying women at higher risk for HSIL (CIN 2+). There is growing evidence suggesting that cervical carcinoma develops in relation to carriage and persistent infection with specific HPV strains, with HPV 16 being associated with the highest risk, followed by HPV 18, 31, 33 (18-24).

Regarding the prevalence of individual HR HPV strains, HPV 16 is the most common worldwide, but the next most common strain, especially in patients with normal cytology, varies by geographic region. In northern and western Europe, it is HPV 18; in Eastern Europe, it is HPV 31 (25).

Our study of HSIL patients found high-risk HPV strains in 84%, with HPV 16 occurring in 53.8%, HPV 18 – in 11.5%, HPV 45 – in 15.4%, and HPV (31, 33, 52, 58) – in 34.6%. These results are almost identical to those reported in a Polish study: 88.9% of CIN 3 patients had

HR HPV (+), and 55.5% were HPV 16(+) (26). Other studies have also shown that HPV 16 is the starting point for the diagnosis of HSIL or cervical carcinoma (27–29). The frequency distribution of HR HPV (+) strains in a German study showed that HPV 16 was the most common strain (26%), followed by HPV 31 (15%), while HPV 45, 51, and 39 (6%) were the least common strains (17). Another study reported the following frequency and distribution of HR HPV strains: HPV 16 – 24.2%; HPV 31 – 20.5%; HPV 52 – 20.5%; HPV 51 – 14.4%; HPV 33 – 13.4%; HPV 39 – 11.3%; HPV 45 – 11%; HPV 56 – 10%; HPV 18 – 9.5%) (19). Similar results were found by Sand et al. (30). In the above-mentioned Polish study, HPV 16 was found in 23.2% of the study population, HPV 31 – in 18.2%, and HPV 33 – in 11.1% (26). This study confirms the data that the second (after HPV 16) most common oncogenic strain in Eastern Europe is HPV 31. Conversely, HPV 45 has not been detected; other studies also confirm its low frequency (31-34).

The main purpose of the screening is to diagnose HSIL/CIN 2+ cervical lesions. Diagnosis of CIN 3 among HR HPV+ patients ranges between 11% and 14% (17, 35–37). In women with negative cytology but HPV (+), CIN 3 was found in 11% of HPV 16 carriers, 33% of those with HPV 18, 33% of HPV 33, 27% of HPV 31, and 33% of HPV 52 on biopsy after colposcopic examination (17). CIN 3 was found in 14% of women with HPV16 and HPV 18 combined, whereas in those with HR HPV (+) combined, CIN 3 was documented in 9%. Overall, for the entire population examined in this study (n=89) who were HPV (+) but cytologically negative, the authors diagnosed CIN 3 in 12%, with biopsy performed only in colposcopic atypia and type 3 transformation zone (TZ) (17). Peace et al. reported 12% CIN 3 in such patients (cytologically negative but HPV+) after biopsy from colposcopically atypical sites (35). The authors followed the American Society of Colposcopy and Cervical Pathology (ASCCP) consensus guidelines for immediate referral for colposcopy in HPV 16⁄18(+) patients and repeated co-testing (HPV and cytology) for the remaining HPV (+) strains. The authors found CIN 3 in 14.7% of HPV 16+ and 1.4% of HPV 18+ patients (35). Luyten et al. found CIN 3 in 12.9% of the cases with normal cytology and HPV (+) strains (36). Similar to Peace's study, the authors performed a biopsy only in the presence of colposcopic atypia.

The question of whether the absence of colposcopic atypia can be used to rule out pathology is debatable, given the subjectivity of the study and the investigator's qualifications and experience. Kabaca et al. found CIN 3 in 8.3% of HPV 33+, 7.8% of HPV 31+ and 5.1% of HPV 39+ patients (37). These studies did not present data on the incidence of CIN 2. Perhaps the patients with CIN 2 together with CIN 3 patients would give the actual incidence of HSIL among the HR HPV positive patients and, more specifically, HPV16+. Another critical point is whether the absence of colposcopic atypia in HPV16+ patients means the absence of HSIL lesions in the cervical canal and whether excisional biopsy (LLETZ) should be performed on them for diagnostic purposes. The hypothesis is reinforced by evidence of the HPV16 carriage frequency in histologically proven HSIL cases. In the data, we have presented and the Polish study cited above (26), this incidence is above 50%, the latter considering only CIN 3 cases but without those with CIN 2.

Another interesting topic is the possibility of developing CIN 3 in HPV (+) women over time. A large Danish prospective study with up to 11.5 years of follow-up found that CIN 3 developed in 23.3% of HPV 16 carriers, followed by those with HPV 33 (17.9%), HPV 31 (11.3%), and HPV 18 (10.8%) (38). These results are of great importance for adapting and targeting screening programs for at-risk patient populations. On the one hand, they are important for extending the testing periods for the remaining patients and streamlining the financial strain on the respective national screening program.

One of the controversial issues in primary HPV screening is whether and which test should be performed in patients referred for screening (so-called triage), with cervical cytology being the most commonly used test for triage. The need for triage is driven by the fact that HPV tests have a higher sensitivity than specificity (26). Their sensitivity ranges from 78% to 93% and specificity – from 63 to 81% (39-43). The main advantage of HPV screening is the ability to extend the interval between tests in HPV (-) patients (41,42,44-47). Some screening systems separate HPV16⁄18+ from the other high-risk HPV strains, as these two strains are considered to have higher specificity than the others, and triage is not required in these cases. This is the US primary screening system (35). Giray et al. (48) reviewed the importance of HPV 16⁄18 on women with normal cytology for the early diagnosis of invasive carcinoma. The authors found no statistical difference in the incidence of invasive carcinoma (0.5% vs. 1.5%) in 1 647 patients with normal and abnormal cytology who were HPV 16⁄18 (+) and concluded that cytology does not contribute to the early detection of cervical cancer in such patients. In our study, 19% of HSIL cases had negative cytology, while HPV16 was

detected in 80% of these cases. Therefore, we believe that cytology is not necessary or irrelevant in such cases.

Colposcopy is a specialized test to which screening-referred patients are referred (most commonly after abnormal cervical cytology) (7). The assessment of colposcopic findings is primarily subjective. Hence, colposcopic findings are known as colposcopic impressions and are a function of knowledge, skill, experience, and maintaining competence with continuous and case-rich practice (8).

The sensitivity of colposcopy for CIN 2+ ranges from 30 to 60% (49-51). A higher sensitivity for HSIL has been reported in two other publications, 85.2% and 85%, respectively (26,52). To increase sensitivity (diagnostic accuracy), some authors recommend multiple biopsies and biopsies from normal-appearing colposcopic areas (53-58). Endocervical curettage (ECC) is not recommended if the squamocolumnar junction (SCJ) is visible (59).

A study by Kabaca et al. confirmed that ECC does not benefit the diagnosis of both LSIL and HSIL (37).

We believe that the most critical factor in increasing both the sensitivity and specificity of colposcopic examination is good expertise, extensive experience of the colposcopist, the use of freshly prepared 3% – 5% acetic acid and good optics with up to 30X magnification.

With regard to the specificity of colposcopy for HSIL diagnosis, literature data also range widely. A team from Germany reported a 38% PPV of colposcopy (41). Three other studies found 69%, 72.9%, and 80% specificity of the method for CIN 2+ detection, respectively (52, 26, 49).

The high specificity of colposcopic examination for HSIL – 84%, distinguishes our study. The still relatively small number of patients enrolled should be considered.

The introduction of colposcopic indices is a way to quantify, a criterion and an opportunity to reduce subjectivism in the interpretation of colposcopic findings and thus increase the specificity of the method. One colposcopic index is the Swede Colposcopic Index (SCI) introduced by a Swedish group of scientists. Despite its efficacy, this index has some inconveniences related to measuring the cervical lesion size in millimetres and assessing the response to Lugol's solution (60). In a paper in the Journal of Gynecologic Oncology, Rodpenpear et Pataradool proposed a modified SCI (MSCI), replacing the response to Lugol's solution with another sign-localization of the lesion relative to the squamocolumnar junction (SCJ). They suggested that the lesion size be assessed by quadrants of the cervix rather than in millimetres (61). MSCI includes 5 colposcopic features: acetic acid reaction; margins and surface; vessels (mosaic, punctuation); lesion size (1/4, 2/4, > 3/4 in a single lesion, or 2 quadrants or 3-4 quadrants in multiple lesions); lesion localization (outer 1/2 of TZ, outer and inner 1/2 of TZ, enters the cervical canal). Each of these factors (criteria) is scored 1 to 3 points.

The authors found that the MSCI of 11 pts provided 84.2% sensitivity and 96.2% specificity for HSIL. The MSCI has a high specificity; thus, the overdiagnosis, respectively – overtreatment was only 4%. According to the Cochrane Colposcopy and Cervical Cytopathology Collaborative Group, an acceptable value for overtreatment should not exceed 10% (62).

The following figures demonstrate colposcopy's potential for diagnosing HSIL (CIN 2/3) in cytologically negative patients who are carriers of high-risk oncogenic strains, especially HPV 16.

CONCLUSION

Unlike most European countries, primary HPV screening has yet to be introduced in Bulgaria. The type of HPV test and the method of triage prior to colposcopy of patients referred for screening are debated. Although the results of our study are initial and on a limited number of patients, we believe that the Alinity HR HPV test adequately stratifies oncogenic strains according to their risk for HSIL. For patients who are HPV 45+, as well as the HPV (31,33, 52,58) (+) group, it is advisable to be referred for colposcopy without an additional triage method or to be closely monitored (repeat test in 6-12 months) before referral for colposcopy. In the absence of HSIL from the colposcopy-directed targeted punch biopsy, patients who are HPV 16+ and HPV 18+ should undergo mandatory expert colposcopy and biopsy, including excisional biopsy procedure (LLETZ). Patients who are positive for any of the HPV strains (35,39,51,56,59,66,68) should be referred for cytology, and those with abnormal cytology should be referred for colposcopy performed by an expert colposcopist.

Conflict of interest

Authors state no conflict of interest.

Ethical statement

Informed consents were signed antemortem by all participating in the study.

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