



Accuracy of colposcopy-directed biopsy in detecting early cervical neoplasia: a retrospective study

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Abstract

Purpose Colposcopy-directed biopsy is a cornerstone method for diagnosing cervical intraepithelial neoplasia. The aim of this study was to evaluate the accuracy of colposcopy-directed biopsy in comparison with definitive surgery.

Methods The accuracy of colposcopy-directed biopsy was compared with the final histology in relation to different types of transformation zone (TZ), the patient's age, and the examiner's level of training.

Results The overall accuracy of biopsy in comparison with definitive surgery was 71.9% for all entities—benign lesions, low-grade squamous intraepithelial lesions, high-grade squamous intraepithelial lesions (HSILs), and cervical carcinoma—with an underdiagnosis rate of 11.8% and an overdiagnosis rate of 16.5%. The accuracy for detecting HSIL was 88% (401/455), with an underdiagnosis rate of 10.5% and overdiagnosis rate of 1.3%. The accuracy rates for detecting HSIL in women with TZ 1, TZ 2, or TZ 3 were 92.2, 90.5, and 76.5%, respectively. The accuracy rates for detecting HSIL in the different age groups were 93.1% (age 0–34), 83.6% (age 34–55), and 80% (age 55 or older).

Conclusions A combination of the colposcopic findings, cytology, human papillomavirus testing, and colposcopy-directed biopsy is necessary for the correct diagnosis of HSIL. The accuracy rate depends on the TZ and the patient's age. The examiner's level of training does not have any substantial influence on the accuracy.

Keywords Cervical intraepithelial neoplasia (CIN) · Colposcopy-directed biopsy · Conization · High-grade squamous intraepithelial lesion (HSIL) · Cervical cancer

Introduction

Cervical cancer is the fourth most common cause of gynecological cancer-related death among women in Germany [1]. Nationwide screening programs in the developed countries have been reducing the incidence of cervical cancer over the past 5 decades [2–5]. Since high-grade squamous intraepithelial lesions (HSILs) are able to progress to become invasive cervical cancer, the detection of HSIL plays a crucial role in preventing cervical cancer [6]. Abnormal cytological findings are, in many cases, one of the first signs of HSIL or carcinoma; women with abnormal cytology are referred to certified gynecological cancer centers [7]. The gold standard for diagnosing HSIL and cervical cancer is a combination of colposcopy, cytology, and colposcopy-directed biopsy [8]. Using colposcopy enables experienced examiners to detect suspicious lesions [9]. To perform a complete examination, the colposcopist carries out a Pap test, a human papillomavirus (HPV) test, and applies acetic acid to the cervix. The

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Pap test and visual inspection with acetic acid have a sensitivity of up to 93% for detecting cervical cancer, and both tests are mandatory for every examination of the cervix in a certified dysplasia unit [10]. However, a colposcopy-directed biopsy has to be performed to confirm a diagnosis of HSIL or cervical cancer [11, 12]. If HSIL is diagnosed, surgery is necessary in most cases, as the lesion has a little potential for regression [13].

On one hand, colposcopy-directed biopsy is crucial for diagnosing HSIL, since up to 30% of HSILs are missed with colposcopy alone [14, 15]. On the other hand, it is necessary to avoid unnecessary treatments and the morbidity associated with them, such as perinatal mortality (relative risk 2.87), preterm delivery (<32/34 weeks; relative risk 2.59–2.78), or low birth weight (<2000 g; relative risk 2.53–2.86) [16–19]. Colposcopy-directed biopsy also plays a major role in the management of women undergoing ablative therapy for HSIL, since microinvasion needs to be excluded before ablative therapy is carried out [20, 21].

In the literature, the reported accuracy of colposcopy-directed biopsy is in the range of 60–95% for HSIL and 26–31% for invasive carcinoma [22–25]. This has raised concerns about the possibility that HSIL lesions may be missed, leading to invasive cervical cancer. Various explanations have been proposed for the low sensitivity of colposcopy-directed biopsy, including inexperienced colposcopists, inadequate conditions at the time of colposcopy (e.g., menstruation), an inability to obtain a biopsy from the abnormal lesion with the biopsy forceps, and the lesion not being visible to the colposcopist [18]. The aim of the present study was to determine the accuracy of colposcopy-directed punch biopsy in comparison with the final histological diagnosis obtained with a cone biopsy or hysterectomy.

Materials and methods

Between January 2014 and June 2017, 4132 colposcopies were performed at the nationally certified dysplasia unit at Erlangen University Hospital. Abnormal cervical cytology was the most common reason for women being referred to the dysplasia unit.

In our department, colposcopies are performed in standardized conditions using a Zeiss KSK 150 FC colposcope. The general assessment was carried out in accordance with the 2011 International Federation for Cervical Pathology and Colposcopy (IFCPC) colposcopic terminology for the cervix: “adequate” or “inadequate” for the reason (e.g., inflammation, bleeding, and scar); squamocolumnar junction visibility (completely visible, partially visible, and not visible); and transformation zone types 1, 2, or 3 [26–28]. A conventional Pap smear of the cervix, a test for human papillomavirus (hybrid capture test 2), and application of 5%

acetic acid to the cervix represent the standard of care in our unit, and this procedure is carried out for every woman who is referred with abnormal cytology. In addition, to examine the cervix and vagina more specifically, Lugol’s iodine is applied in some cases to visualize “precancerous lesions” in the vagina that were not visible beforehand.

The colposcopic findings were classified in accordance with the IFCPC into “normal,” “minor,” “major,” and “suspicious for invasion/cancer.” Normal findings included, for example, metaplasia, viral warts, or polyps. Minor findings are defined by delicate puncturing, thin acetowhite epithelium, and irregular and geographic borders. Typical major lesions are represented by sharp borders, an inner border, ridge sign, dense acetowhite epithelium, a coarse mosaic pattern, and coarse puncturing. Atypical vessels, fragile vessels, irregular surface, exophytic lesions, necrosis, and ulceration are suspicious for invasion [26]. If there is a major finding or a lesion that is suspicious for invasion, a colposcopy-directed biopsy has to be taken from the most suspicious part of the lesion, using biopsy forceps (Seidl Biopsy Forceps ER076R; Aesculap AG, Tuttlingen, Germany). In some patients with multifocal lesions, more than one biopsy is necessary. Decisions regarding surgical treatment are based on the cytology results, HPV testing, and the histological findings.

During the period of this retrospective analysis, the team in the dysplasia unit consisted of seven colposcopists with various degrees of clinical experience and training. They were divided into three groups: those with 0–5 years’ experience, those with 5–10 years’ experience, and those with over 10 years’ experience.

All data such as colposcopic findings, Pap smear and HPV test results, histological outcomes, number of biopsies, type of transformation zone, and epidemiological outcomes were recorded prospectively in a database for further research.

The aim of this retrospective analysis was to compare the precision of the histological findings obtained using colposcopy-directed biopsy with the final histological outcome assessed using the surgical specimen. The accordance rate is the percentage of patients with the same histological findings in the biopsy and in the final operation. Overdiagnosis was considered to be present if the final histology showed a less advanced lesion than histological examination of the biopsy, and underdiagnosis was present if the final histology showed a more advanced lesion than the biopsy. All patients ($n = 641$) who underwent excisional surgical treatment—large loop excision of the transformation zone (LLETZ), loop electrosurgical excision procedure (LEEP) with laser coagulation of the periphery, laser conization, or hysterectomy—were included. Patients in whom ablation was performed were excluded from the analysis due to the lack of final histology. All patients in whom a biopsy had not been obtained before surgery were also excluded.

Women with normal or minor changes were referred back for regular check-up examinations. If the biopsy revealed HSIL, a decision in favor of surgery was made. Depending on the size of the lesion, the transformation zone, and the patient's age, different types of conization were possible. Postmenopausal women, those with intracervical lesions, or those with a type 3 transformation zone underwent LLETZ. Women aged below 25 with a diagnosis of HSIL were selected for observation due to the strong chances of regression [29]. These women were scheduled for intensified follow-up examinations with cytology and colposcopy. Surgical excisional treatment was carried out if HSIL persisted or invasion was confirmed. In these cases, LEEP with laser coagulation of the periphery or laser conization was carried out. In women in whom the colposcopy-directed biopsy excluded invasion, ablative treatment was an option to minimize the damage done to the cervix. All of the operations were performed by experienced and highly qualified staff at Erlangen University Hospital.

Statistical analysis

Differences between underdiagnosis, accordance rates, and overdiagnosis between subgroups of all the patients were examined using Chi-squared tests or generalized Fisher's exact tests, where appropriate. Spearman's rho was calculated to quantify the correlation between the histological findings at biopsy and at the final operation. To account for multiple testing, the Bonferroni-corrected significance level was set to 0.004. All statistical analyses were performed using the statistical programming language R (version 3.4.3; R Development Core Team, Vienna, Austria, 2017).

Results

A total of 4132 colposcopies were performed at the dysplasia unit in Erlangen. A biopsy was not obtained in 1855 cases, and surgery was not necessary after biopsy in 1177 cases. Ablative treatment or staging laparoscopy without the final histology was performed in 445 patients. Repeated pre-operative examinations were carried out in 14 cases. A total of 641 cases of colposcopy-directed biopsy before final treatment thus remained. Laser conization was performed in 325 patients, LLETZ in 53, and LEEP in 216. Hysterectomy was performed in 35 patients. Twelve women were treated with the other surgical techniques, such as cervicectomy (Fig. 1 shows the flow chart for the patients).

The mean age of this group of women at the time of colposcopy was 37 (standard deviation 9.7 years); 600 of the women were premenopausal, and 41 were postmenopausal (Table 1). The histology of the biopsy showed benign results in 30 cases (4.7%), LSIL in 76 cases (11.9%), HSIL in 505 cases (78.9%), and carcinoma of the cervix in 30 cases (4.7%). The final histology showed benign results in 44 cases (6.8%) and LSIL in 100 (15.6%). The majority of the final histology findings showed HSIL ($n = 455$; 70.9%). In 42 women (6.6%), the final operation revealed carcinoma of the cervix. The overall accuracy of colposcopy-directed biopsy in comparison with the final histological findings was 71.9%. The accuracy rates for punch biopsy in comparison with the final histological findings were: benign, 15.9% (seven of 44); LSIL, 31% (31 of 100); HSIL, 88.1% (401 of 455); cervical cancer, 52.4% (22 of 42). Overall, 11.8% of the patients had more advanced lesions diagnosed and 16.2% had less advanced lesions

Fig. 1 Flowchart showing exclusion of ineligible patients. *LEEP* loop electrosurgical excision procedure, *LLETZ* large loop excision of the transformation zone, *LSK* staging laparoscopy

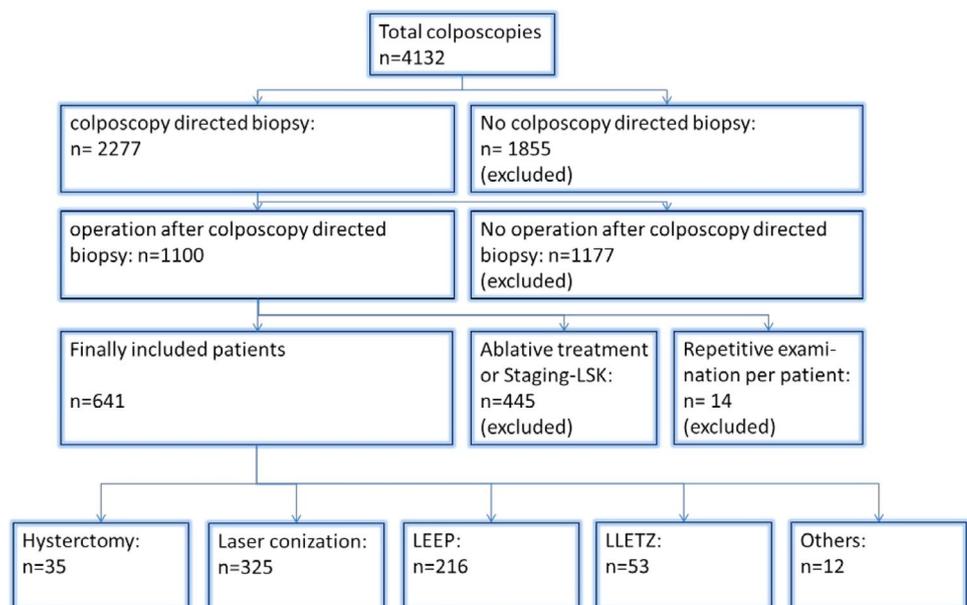


Table 1 Demographic characteristics of the study population

Characteristics	<i>n</i>
Total colposcopies (<i>n</i>)	4132
Total patients (<i>n</i>)	641
Exclusion criteria	
No colposcopy-directed biopsy	1855
No surgery after colposcopy-directed biopsy	1177
Ablative treatment or staging laparoscopy	445
Repeated examinations per patient	14
HPV HR status	
HR-positive	547
HR-negative	93
Unknown	1
Age (years)	
Mean	37
0–34	295
35–54	313
> 55	33
Menopausal status	
Premenopausal	600
Postmenopausal	41
Transformation zone type	
TZ 1	213
TZ 2	266
TZ 3	155
Unknown	7
Histology at biopsy	
Benign	30
LSIL	76
HSIL	505
Carcinoma	30
Histology at final operation	
Benign	44
LSIL	100
HSIL	455
Carcinoma	42

HPV human papilloma virus, HR high-risk, HSIL high-grade squamous intraepithelial lesion, LSIL low-grade squamous intraepithelial lesion, TZ transformation zone

diagnosed than had been indicated by the biopsy. In 10.5% of the patients (48 of 455), HSIL at the final histology was underestimated by the punch biopsy, and in 1.3% (six of 455), it was overestimated. LSIL was underestimated in 8% (eight of 100) and overestimated in 61% (61 of 100).

In almost half of the patients who had cervical cancer in the surgical specimen (20 of 42), the preoperative biopsy failed to detect the carcinoma; punch biopsy showed HSIL in 16 cases, LSIL in two cases, and normal results in two cases (Fig. 2).

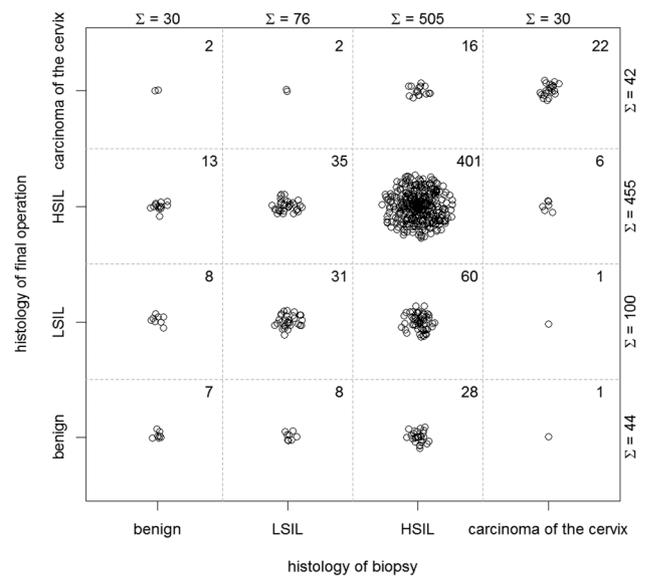


Fig. 2 Numbers of lesions identified by histological examination of the biopsy in comparison with histology after the final operation; Spearman's $\rho=0.372$ ($P<0.001$). LSIL low-grade squamous intraepithelial lesion, HSIL high-grade squamous intraepithelial lesion

Tables 2, 3, 4 show the results for subgroup analysis (transformation zone, age of the women at the time of examination, and examiner's level of experience). The accuracy for detecting HSIL in women with TZ 1, TZ 2, or TZ 3 was 92.3, 90.5, and 76.5% ($P=0.01$), respectively (Table 2). The rate of underdiagnosis was worse in women with TZ 3 (22.4%), whereas women with TZ 1 or TZ 2 had underdiagnosis rates of 7.1% and 7.5%, respectively (Table 2). The likelihood of diagnosing HSIL correctly also decreased with increasing age: 93.2% for age 0–34, 83.6% for age 34–55, and 80% for age 55 or older (Table 3). At the same time, the chances of underdiagnosing an HSIL lesion increase as the women get older. Practitioners with a little experience (less than 2 years) were correct with the final diagnosis of HSIL in 87% of cases; experienced practitioners (with 2–10 years' experience) had an accuracy rate of 85.3%; and 90.2% of women with the final histology showing HSIL were correctly diagnosed by the most experienced colposcopists (with more than 10 years' experience; $P=0.559$) (Table 4). The latter were also the group of examiners who were least likely to underdiagnose an HSIL (8.4%). The other two groups underdiagnosed HSIL in approximately 12% of cases.

LSILs were overdiagnosed in more than half of the cases, regardless of the type of transformation zone. LSILs were most likely to be missed in women with TZ 3. The accuracy rates increased across the different age groups (0–34, 15%; 35–54, 40.7%; > 55, 50%).

Table 2 Accordance rate, overdiagnosis, and underdiagnosis of high-grade squamous intraepithelial lesions (HSILs) relative to the type of transformation zone ($P=0.01$; in one case, the type of transformation zone was unknown)

	TZ 1 ($n=155$)	TZ 2 ($n=201$)	TZ 3 ($n=98$)	Total ($n=454$)
Overdiagnosis	1 (0.6%)	4 (2%)	1 (1%)	6
Accordance	143 (92.3%)	182 (90.5%)	75 (76.5%)	400
Underdiagnosis	11 (7.1%)	15 (7.5%)	22 (22.4%)	48

Table 3 Accordance rate, overdiagnosis, and underdiagnosis of high-grade squamous intraepithelial lesions (HSILs) relative to the patient's age ($P=0.013$)

	0–34 years ($n=220$)	35–54 years ($n=220$)	≥ 55 years ($n=15$)	Total ($n=455$)
Overdiagnosis	2 (0.9%)	4 (1.8%)	0 (0%)	6
Accordance	205 (93.2%)	184 (83.6%)	12 (80%)	401
Underdiagnosis	13 (5.9%)	32 (14.5%)	3 (20%)	48

Table 4 Accordance rate, overdiagnosis, and underdiagnosis of high-grade squamous intraepithelial lesions (HSILs) relative to the examiner's level of experience ($P=0.559$)

	Little experience ($n=138$)	Experienced ($n=102$)	Highly experienced ($n=215$)	Total ($n=455$)
Overdiagnosis	1 (0.7%)	2 (2%)	3 (1.4%)	6
Accordance	120 (87%)	87 (85.3%)	194 (90.2%)	401
Underdiagnosis	17 (12.3%)	13 (12.7%)	18 (8.4%)	48

Discussion

A total of 641 women in whom cervical biopsies were obtained before surgery were seen in the dysplasia unit at Erlangen University Hospital from January 2014 to June 2017. Histological analysis of the biopsy revealed HSIL in most cases (78.9%), followed by LSIL (11.9%), cervical cancer, and benign results (both 4.7%). The overall accuracy of the biopsies for all entities was 71.9%. The highest rate of accordance was seen for HSIL at 88.1%, followed by cervical cancer at 52.4%, LSIL at 31%, and benign findings 15.9%. HSIL at the final histological examination was underestimated by punch biopsy in 10.5% of cases (48 of 455), while it was overestimated in 1.3% (six of 455). LSIL was underestimated in 8% of cases (eight of 100) and overestimated in 61% (61 of 100).

Colposcopy-directed biopsy is a cornerstone method for diagnosing HSIL and cervical cancer. However, there have been numerous reports in the literature describing poor accuracy and a high rate of false-negative results with colposcopically guided biopsy [30–32]. The present retrospective study was performed to assess the accuracy of colposcopy-directed biopsy in comparison with the final diagnosis in relation to different subgroups. The overall accuracy in this study was higher than in other studies, at almost 80% [33–35]. In a meta-analysis, Underwood et al.

reported an accuracy rate of 91% for HSIL [18]. This is in line with the present results, with an agreement rate of 88% for HSIL.

The accuracy of colposcopy-directed biopsy is lower for detecting LSIL in comparison with HSIL. LSIL had been correctly diagnosed by biopsy in only 31% of all patients who were found to have LSIL in the surgical specimen. These poor levels of accuracy are confirmed in the literature [33, 34]; only Baldauf et al. reported an accuracy rate of over 80% for LSIL [24]. Sixty-one percent of all cases of LSIL were overdiagnosed at biopsy. This might be due to the fact that the most severe point in the lesion was removed by the biopsy, leaving only LSIL for conization. Underdiagnosis of LSIL was seen only in 8% of all the cases.

For HSIL, the accuracy rates decreased from TZ 1 to TZ 3 (TZ 1, 92.2%; TZ 2, 90.5%; TZ 3, 76.5%). It was more difficult to diagnose HSIL in women with TZ 3, as most of the lesions were not visible to the examiner and, therefore, could not be diagnosed by biopsy. The 22.4% rate of underdiagnosis for HSIL in women with TZ 3 was much higher than in women with TZ 1 or TZ 2 (7.1% and 7.5%, respectively). Fan et al. reported similar results in a study including 513 women, with accuracy rates of 96.43% for TZ 1, 94.68% for TZ 2, and 85.71% for women with TZ 3 [36].

The correlation between the histological findings at biopsy and after surgical treatment is influenced by women's age. Women aged under 34 had an accuracy

rate of 93% for HSIL, but women older than 55 had an accuracy rate of only 80%. Other studies have described similar results, with a poorer rate of accordance in women aged over 50 [24, 37]. Women over 50 are more likely to be postmenopausal and have a TZ 3 [38]. Interestingly, Zuchna et al. noted increasing sensitivity for HSIL, the older the patients were [34].

The accordance rate between colposcopy-directed biopsy and the final surgical specimen does not depend on the examiner's level of experience and training. This was shown in the ASC-US/LSIL Triage Study by Gage et al. The authors enrolled 408 women with HSIL or cancer and evaluated factors that influenced the sensitivity of colposcopy. It was not influenced by the colposcopist's level of experience [39]. In another study, it was shown that the second-year residents had an accuracy rate of 77%, third-year residents 75%, fourth-year residents 73%, and nurse-practitioners 92% in comparisons between colposcopic impression and colposcopy-directed biopsy. The authors suggested that nurse-practitioners' vast experience was a reason for their high rate of accordance [40]. However, the present study showed a higher accordance rate for diagnosing HSIL and cervical cancer among examiners with more than 10 years' training in comparison with the other two groups. The difference is greatest for cervical cancer, with an accordance of only 30.8% for the least experienced examiners and over 60% for the most experienced examiners. Interestingly, the rate is different for LSIL, where the least experienced examiners have the highest rate of accordance. This might be due to the structure of the dysplasia unit. Patients most likely to have HSIL or cervical cancer are seen by the examiners with the most experience. By contrast, candidates for LSIL or normal histology are seen by residents in their first years. The second group of examiners is thus much more aware of LSILs. Another reason might be the fact that the first set of examiners is more skilled in performing colposcopy-directed biopsies and, consequently, remove the most severe part of the lesion.

The rate of accuracy depends on the numbers of biopsies taken [39, 41]. The sensitivity for detecting HSIL increases from 60.6% with a single biopsy to 85.6% with two biopsies, and further to 95.6% for three biopsies [42]. In the present study, detection of HSIL increased from 87.6% with one biopsy to 92% with two biopsies. Three biopsies were taken in only eight cases, a number that is not large enough for an appropriate judgment to be made. In many cases, more than one biopsy is normally taken when the colposcopist expects the lesion to be more severe. This could be another reason why multiple biopsies lead to a higher accuracy rate.

Biopsies taken from the cervix can cause pain and anxiety for women. Women who undergo a biopsy experience more pain than those who do not [43]. Only as many biopsies as are needed should, therefore, be taken.

In the present study, the false-negative rate for invasive cervical cancer was very poor, at almost 50%, but 16 of the 42 patients (38%) were diagnosed with HSIL in the colposcopy-directed biopsy, so that 88% were diagnosed with at least HSIL, which led to further treatment.

One reason for the poor rate of diagnosis using colposcopy-directed biopsy might be that the diagnosis of cervical cancer is often quite obvious to the examiner, and further procedures are planned without a biopsy being performed. Another reason is that many women diagnosed with cervical cancer are not seen in the dysplasia unit. Some are diagnosed in the other hospitals and are referred to our oncological center for treatment, while others are diagnosed in the other units within the hospital.

In three out of four cases in which biopsy revealed minor lesions or normal histological findings and the final diagnosis was invasive cancer, the examiner had thought the colposcopic findings represented at least a major lesion or were suspicious for cancer.

Strengths and limitations

This study has certain limitations. First, it is a retrospective study, and this may limit the availability of some information. Second, interobserver variability cannot be ruled out. At the time of the retrospective analysis, the team consisted of seven different examiners. In addition, the biopsies and surgical specimens were examined by different pathologists. Third, the biopsies were taken from suspicious lesions in most cases, and there are no control samples. The dysplasia unit in Erlangen is specialized for neoplasia and carcinoma in the lower genital tract. The probability of women having a neoplasia or carcinoma is, therefore, higher than in the normal population, and this may have increased the accordance rate.

Conclusion

With a sensitivity of over 80%, colposcopy-directed biopsy plays an important role in detecting cervical neoplasia, but a diagnosis of cervical intraepithelial neoplasia (CIN) should be based on a combination of the colposcopic findings, HPV test results, and Pap smear. Reports in the literature show that multiple biopsies improve the rate of correct diagnosis. HSILs are easier to detect and are detected more accurately in young women (under age 34) with TZ 1. The sensitivity for detecting CIN does not depend to any relevant extent on the examiner's level of training and experience.

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Author contributions FAS, MCK, and MWB: protocol/project development and manuscript writing/editing. FAS, MCK, CES, GM, PG, and SKR: data collection or management. FAS, MCK, MWB, GM, SKR, SPR, WA, AH, SK, and CG: data analysis.

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Compliance with ethical standards

Conflict of interest P Gass has received honoraria from Novartis, financial support for symposia from Novartis, Roche, and PharmaMar, and reimbursement of travel expenses from the discovering hands® company. None of the other authors have any conflicts of interest. Completed disclosure of conflict of interest forms are available for viewing online as supporting information.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments, or comparable ethical standards.

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