

Endocervical Brush Cytology After Cervical Conization as a Predictor of Treatment Failure: A Prospective Cohort Study

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Objective: Endocervical curettage (ECC) is the gold standard for predicting the persistence of high-grade squamous intraepithelial lesions (HSIL) after cervical conization. However, ECC has a high rate of unsatisfactory samples and may be uncomfortable for women. Endocervical sampling with brush (ECB) has been proposed as an alternative to ECC, which, in addition to the cytological evaluation, allows performing HPV testing using the same sample. We compared ECC and ECB performed immediately after conization to identify women with persistent HSIL.

Materials and Methods: This is a prospective single-center study, including 518 patients who underwent conization over a 10-year period (2012–2021). Immediately after treatment conization, we performed ECB sampling followed by ECC to all patients. We evaluated the accuracy of the 2 techniques for diagnosing persistent HSIL during follow-up.

Results: Persistent HSIL was identified in 8.9% of women. Eighteen percent of the ECC samples and only 7% of ECB cytology were unsatisfactory ($p < .001$). The accuracy of detecting persistent HSIL was similar for ECB and ECC (89.0%, 95% CI = 85.9–91.5 vs 90.8%, 95% CI = 87.7–93.2; $p = .797$). Adding HPV testing to ECB cytological evaluation increased the accuracy to 91.5% (95% CI = 88.8–93.6).

Conclusions: ECB can be reliably used to identify women with persistent HSIL after conization, as its accuracy is similar to ECC, with a lower rate of unsatisfactory results. The technique allows adding HPV testing to cytological evaluation, improving the accuracy of the test.

Key Words: endocervical cytology, HPV, conization

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After conization, the standard treatment for women with high-grade squamous intraepithelial lesion (HSIL) of the uterine cervix, 7%–17% of patients show persistent lesions, which can be detected during follow-up.^{1–4} Early detection of persistent HSIL is key for tailoring management after treatment by scheduling closer follow-up in women at higher risk of persistent disease and avoiding delays in re-excision.^{5–7}

Endocervical evaluation performed immediately after treatment is considered a key predictor of status of persistent disease.^{8–10} The gold standard procedure for this endocervical evaluation is endocervical curettage (ECC). Indeed, some studies have shown that ECC predicts persistent disease better than the status of the surgical margins.¹¹ ECC performed immediately after excisional treatment provides histological information on the remaining endocervix. However, in up to 25% of cases, the quality of the sample obtained by ECC is unsatisfactory to achieve an accurate diagnosis.⁹ In addition, the procedure is uncomfortable for the women.^{12,13}

Endocervical sampling with brush (ECB) provides adequate material for cytological evaluation of the endocervical canal and has been proposed as an alternative to ECC for endocervical evaluation during diagnostic procedures. Moreover, ECB may overcome the percentage of unsatisfactory samples of ECC and reduce the discomfort of curettage. The few existing studies comparing ECB and ECC in women referred to colposcopy due to positive human papillomavirus (HPV) testing or abnormal cytology reported a similar sensitivity and specificity for the identification of endocervical HSIL, with lower rates of unsatisfactory samples, and less discomfort for the patients when endocervical evaluation was done with ECB.^{12,13}

An additional benefit of ECB is that, when a liquid-based cytology fixative is used, the same sample allows the performance of HPV testing. In previous studies, HPV testing performed immediately after excisional treatment in the ECB sample has shown to be a sensitive test to identify women at risk of persistent disease.¹⁴ However, the benefit of combining HPV testing with the cytological evaluation in the ECB sample to detect persistent HSIL after treatment has not been evaluated.

The aim of this study was to compare the accuracy of ECC and ECB performed immediately after treatment, including cytological evaluation and HPV testing in the latter sample, to identify women at risk of persistent HSIL.

METHODOLOGY

We conducted a prospective cohort study. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the institutional ethics committee (HCB/2020/0126). Written informed consent was obtained from participating patients.

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IRB status: the present study was approved by the institutional review board from Hospital Clínic de Barcelona on May 10, 2012 (HCB 2012/7618 - HCB/2020/0126)

The results of the present study were presented at the Eurogin 2024 conference as an oral communication titled ‘Endocervical brush after cervical conization as an alternative to endocervical curettage for predicting high-grade squamous intraepithelial lesion persistence’ on March 14, 2024, in Stockholm, Sweden. The abstract can be accessed here: Eurogin. Abstracts. Free Communications Sessions at <https://prod65.eurogin.com/en/abstracts-posters/abstracts.html>.

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Case Selection

Women undergoing cervical conization at our center between 2012 and 2021 were prospectively included. Following the recommendations of the American Society for Colposcopy and Cervical Pathology¹⁵ and the Spanish Society of Cervical Pathology and Colposcopy,⁸ the criteria for treatment were as follows: (1) histological diagnosis of HSIL or (2) repeated cytological result of HSIL in at least 2 Pap smears separated by 12 months in patients without histological confirmation (cytological discordance). The exclusion criteria were as follows: (1) pregnancy, (2) previous unsuccessful excision (i.e., absence of negative cytology and HPV testing results) after treatment, (3) diagnosis of invasive disease in the surgical specimen, (4) ECB and/or ECC not performed after conization, and (5) follow-up of less than 12 months.

Cervical Conization

Conizations are generally performed in the outpatient clinic under local anesthesia. Only in a few cases in which the cervix or the lesions are particularly wide and the procedure is anticipated to be difficult under local anesthesia is the conization performed in the operating room. According to the quality standards recommended in our national guidelines, the percentage of women undergoing conization in the operation room should not exceed 30%.¹⁶ Cervical conization using a large-loop excision procedure was performed under colposcopy vision.¹⁷ When endocervical extension of the lesion was suspected (extension of the abnormal area to the endocervix or cases with transformation zone not completely visible), a second selective endocervical sweep was performed (top hat). If the exocervical lesion was too large to be accommodated by a single sweep, the excision was exceptionally achieved with 2 systematic sweeps.

Postconization Endocervical Sampling

Immediately after conization, ECB of the remaining cervix was collected by inserting the cytobrush (Medscand cytobrush Plus GR) ~1–2 cm into the endocervix and rotating it 360° clockwise five times. ECB samples were kept in PreservCyt (Hologic Corp, Marlborough, MA) for liquid-based cytology and HPV testing.¹⁴ Afterward, an ECC was performed systematically introducing a Kervokian curette into the cervical canal and debriding the 4 quadrants with the aim of obtaining strips of epithelium representative of the complete endocervical surface. ECC samples were fixed in 10% formalin. The ECB and ECC samples were submitted separately to the department of pathology for analysis.

Histological Diagnosis of the Conization Specimen

Surgical specimens were fixed in 10% neutral buffered formalin. Four μm sections were stained with hematoxylin and eosin and examined *in toto*. Immunohistochemistry for p16 was performed in at least one of the suspicious sections. The histological diagnosis was established based on the combination of the hematoxylin and eosin findings and the p16-stained sections. Only cases showing continuous “block” staining of the basal and parabasal layers were considered positive for p16.¹⁸ Surgical specimens were classified as negative for squamous intraepithelial lesion (SIL), low-grade squamous intraepithelial lesion (LSIL), or HSIL according to World Health Organization criteria.¹⁹ p16-positive staining was considered a mandatory criterion for the diagnosis of HSIL. Surgical margins were identified with ink and carefully examined and were considered positive when SIL of any grade was present. Margins were considered negative if no SIL was detected.

Endocervical Sampling With Brush and ECC Processing

A ThinPrep T2000 slide processor (Hologic) was used to prepare thin-layer slides for cytological evaluation of the ECB samples, which were stained using the Papanicolaou method. The slides were evaluated following the Bethesda criteria.²⁰ The cytological samples were defined as unsatisfactory for diagnosis when less than 60 glandular or metaplastic cells were available for evaluation in the slide. After the slide for cytological evaluation had been obtained, HPV testing was performed in the ECB sample remaining in the PreservCyt container. The Cobas HPV test (Cobas 4800; Roche Molecular Diagnostics) was used for HPV testing. This method is based on a real-time polymerase chain reaction system and detects 14 high-risk HPV types providing specific genotyping for HPV16 and HPV18.

ECC samples were fixed in 10% neutral buffered formalin. Sample processing and criteria for histological diagnoses were the same as for the conization specimen. ECC were defined as unsatisfactory for diagnosis when no continuous strips of metaplastic/glandular epithelium were identified and only isolated cells were detected in a single 3- μm section.

Posttreatment Follow-up

The first follow-up control was scheduled at 4 months after treatment for women with positive margins and at 6 months for women with negative margins.^{8,21,22} Liquid-based cytology and HPV testing were performed in the first follow-up visit. If all tests were negative, a second visit with cervical cytology and HPV testing was scheduled 12 months after the first control, in which liquid-based cytology and HPV testing was, again, obtained. If one of these tests was positive (abnormal cytology or positive HPV testing), a new colposcopy was performed with a colposcopy-directed biopsy and/or ECC, if indicated. Women diagnosed with histological HSIL in any of the follow-up visits, were referred for a second excision treatment.

Outcome Definitions and Data Analysis

The main outcome of the study was the diagnosis of persistent HSIL, which was defined by the following criteria: 1) presence of histologically confirmed HSIL in the first posttreatment control or 2) cytological HSIL in the first control with a repeated HSIL result in the Pap smear performed at the 12-month follow-up control, together with positive HPV testing result, and no vaginal lesions after careful examination.

The follow-up time was defined as the time lapse from cervical conization to the diagnosis of persistence or to the last follow-up.

StataIC/v15.0.591 was used for data analysis. Categorical variables are presented as absolute numbers and percentages and continuous variables as mean and SD.

For data analysis, cytological results of atypical squamous cells (ASC) cannot exclude a high-grade lesion (ASC-H) were grouped with HSIL due to the significant risk of histological HSIL in these cases.^{8,15} ASC of uncertain significance (ASC-US) were grouped with LSIL.

Univariate analysis was calculated using the risk estimation as hazard ratio (HR) with 95% CIs to evaluate the role of cytological examination of the ECB sample, the ECC and other prognostic variables described in the literature for persistent HSIL (HPV testing result performed in the ECB sample, diagnosis of the conization specimen, surgical margins of the conization specimen, immunosuppression).¹⁴ Multivariate regression models were applied to evaluate interaction effects with regard to persistent HSIL calculating the adjusted HR with the 95% CI. Two different models were analyzed. The first model included the results obtained with the ECB sample (cytological evaluation and HPV

testing) and the status of the surgical margins as covariables. The second model included ECC and the status of the surgical margins as covariables. In this second model, HPV testing was not included because it is performed with the ECB sample.

Sensitivity, specificity, positive and negative predictive values (PPV, NPV), and accuracy of ECB and ECC to predict persistent HSIL were calculated. *p* values less than .05 were considered statistically significant.

RESULTS

Between 2012 and 2021, 690 women underwent cervical conization in our center. After applying exclusion criteria, 518 patients were finally included in the analysis. Figure 1 shows a flowchart of the included patients. The mean age at conization was 39.8 ± 9.8 years. Four hundred seventy-six women (476/518; 91.9%) underwent treatment because of histological HSIL and 42 patients (8.1%) because of cytohistological discordance. Eighty-two percent (425/518) of patients underwent conization in the outpatient clinic under local anesthesia, while 18% (93/518) had the conization performed the operating room as an outpatient surgery.

Pathological Characteristics of the Surgical Specimens

The pathological features of the cervical conization specimens are shown in Table 1. Histological HSIL was confirmed in 414/518 (79.9%) surgical specimens. In total, 97/518 cases included (18.7%) showed a positive endocervical margin (either alone or together with a positive exocervical margin).

Results of the ECB and ECC

Table 2 shows the results of the ECB and the ECC performed after conization. The cytological sample of the ECB was unsatisfactory

TABLE 1. Pathological Features of the Cervical Conization Specimens

Pathological feature of the surgical specimen	<i>n</i> Total = 518	(%) (100%)
Histological diagnosis		
No lesion	54	(10.4%)
LSIL	50	(9.7%)
HSIL	414	(79.9%)
Surgical margins		
Not specified	42	(8.1%)
Negative	285	(55.0%)
Positive (any)	191	(36.9%)
Endocervical margin only	81	(42.4%)
Exocervical margin only	94	(49.2%)
Both margins	16	(8.1%)

in 37 cases (7.1%), and the ECC was reported as unsatisfactory in 93 cases (18.0%) (*p* < .001). There was a correlation between a diagnosis of HSIL in the ECB or the ECC and a positive endocervical margin, but not with the involvement of the exocervical margin: 24.7% (24/97) of women with positive endocervical margin and 5.5% (21/379) of the women with negative endocervical margin showed a HSIL in the ECB (*p* < .001). Similarly, 18.6% (18/97) and 2.4% (9/379) of women with a positive and negative endocervical margin had a histological HSIL in the ECC (*p* < .001).

HPV testing was positive in 199 ECB samples (38.4%): 74.5% (35/47), 35.5% (154/434) and 27.0% (10/37) of the women with a cytological result of HSIL, no HSIL and unsatisfactory, respectively (*p* < .001).

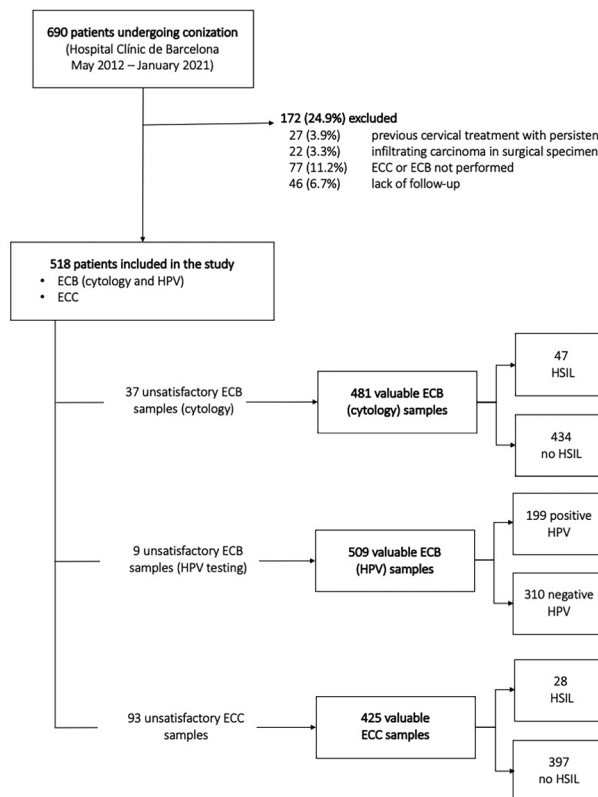


FIGURE 1. Flowchart of the study patients.

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TABLE 2. Results of the Cytological Evaluation of the ECB, the HPV Testing Performed in the ECB Sample, and the Histological Evaluation of the ECC Performed Immediately After Excisional Treatment

Endocervical study test and result	<i>n</i> Total = 158	(%) (100%)
ECB (cytology)		
Unsatisfactory	37	(7.1%)
No HSIL	434	(83.8%)
HSIL	47	(9.1%)
ECB (HPV testing)		
Unsatisfactory	9	(1.7%)
Negative	310	(59.9%)
Positive	199	(38.4%)
HPV16	90	(45.2%)
HPV18	4	(2.0%)
Other HPV genotypes	83	(41.7%)
HPV16+ other genotypes	21	(10.6%)
HPV18+ other genotypes	1	(0.5%)
ECC		
Unsatisfactory	93	(18.0%)
No HSIL	397	(76.7%)
HSIL	28	(5.4%)

Predictors of Persistent HSIL During Follow-up: Univariate and Multivariate Analysis

The mean follow-up time was 24.8 ± 13.6 months. In total, 46 (8.9%) patients developed persistent HSIL, with a mean time to the diagnosis of persistence of 10.0 ± 11.8 months.

Table 3 shows the univariate and multivariate analysis for persistent HSIL. In the univariate analysis, HSIL in both the cytological evaluation of the ECB sample and in the ECC significantly increased the risk of persistent HSIL (HR = 9.0, $p < .001$ and HR = 12.1, $p < .001$, respectively). A positive HPV testing result in the ECB sample and a positive endocervical surgical margin were also correlated with a higher risk of persistent HSIL. In contrast, a positive exocervical margin did not increase the risk of persistent HSIL. In the multivariate ECB model analysis, both the cytological result and positive HPV testing in the ECB sample, but not the status of the margins of the conization specimen, were associated with persistent HSIL. In the multivariate ECC model analysis, ECC diagnosis and positive margins were also associated with persistent HSIL.

Sensitivity, Specificity, and Accuracy Analysis

The cytological result of the ECB and ECC samples showed a similar sensitivity (42.9% vs 35.1%; $p = .988$), specificity (93.4% vs 96.1%; $p = .121$), and accuracy (89.0% vs 90.8%; $p = .797$) for persistent HSIL. Positive HPV testing in the ECB sample showed a higher sensitivity (86.4%; $p < .001$) but lower specificity (65.4%; $p < .001$) for persistent HSIL. The best accuracy was obtained when combining the HSIL result in cytology and positive HPV testing in the ECB sample (Table 4).

DISCUSSION

The main result of the present study, including more than 500 women who underwent cervical conization, is that cytological evaluation of the ECB sample performed immediately after excision has a similar accuracy as that of ECC for predicting persistent

HSIL during follow-up, with a lower rate of inadequate samples. In addition, ECB allows performing HPV testing in the same sample, which provides useful information for identifying women at risk of persistent HSIL.

In the follow-up controls after cervical conization, cervical cytology and HPV testing are considered the cornerstone for identifying persistent HSIL.⁸ However, ECC performed in the remaining cervix immediately after conization is the gold standard to predict early treatment failure,⁸ and an abnormal result has been shown to be associated with an increased risk of persistent HSIL.^{8–10} The role of ECB sampling obtained immediately after conization to predict treatment failure has been poorly explored. A recent systematic review reported that cytological evaluation of the ECB sample and ECC have a similar accuracy for endocervical evaluation in women with suspected cervical neoplasia,¹³ and a few previous studies including women undergoing excisional treatment for HSIL also showed a strong association between an abnormal cytological result in the ECB performed immediately after treatment and persistent disease.^{12,14}

An important advantage of ECB after cervical conization is that HPV testing can be performed using the same sample if liquid-based cytology is used. Persistent HPV infection is considered the main risk factor for persistent HSIL after cervical treatment.^{4–7,23,24} Indeed, positive HPV testing in these cases has shown to increase the risk of persistent HSIL more than other classical factors such as positive margins.^{5,13,23} In this study, a positive HPV testing result performed in the ECB sample increased the risk of persistent HSIL seven-fold. This finding is in keeping with a previous study by our group which evaluated the role of HPV testing performed immediately after conization as a predictor of persistent disease, including both HSIL and LSIL.¹⁴

In our series, the sensitivity, specificity, and accuracy of the cytological evaluation of the ECB sample and ECC to identify persistent HSIL were similar. Despite the absence of studies comparing the sensitivity, specificity and accuracy of the 2 tests performed immediately after treatment to predict persistent HSIL, several studies have analyzed the 2 tests in women with an abnormal screening test.¹³ A pooled sensitivity of 81% and 70% for ECB and ECC, respectively, and a pooled specificity of 81%, and 73% have been reported in a recent review.¹³ These results show a slightly higher sensitivity but a lower specificity for the detection of HSIL compared to our cohort in which both tests are performed immediately after treatment. Interestingly, in the present series, the addition of HPV testing to ECB liquid-based cytology significantly improved the sensitivity to detect persistent HSIL, rising from 43% to 89%, which is in keeping with previous studies.^{12,14} Indeed, almost half of the women with a positive result of the 2 tests showed persistent HSIL.

An additional benefit of ECB over ECC is the lower rate of unsatisfactory results. While 17% of the ECC samples were considered unsatisfactory for evaluation, only 7% of the ECB samples were. This confirms that ECB could be a useful predictor of persistent HSIL after treatment. Finally, another reported advantage of ECB is that it is less uncomfortable for the patients. Many clinical guidelines have already stated that the role of ECC for endocervical evaluation in women with an abnormal screening test result is controversial due to the discomfort and pain produced in patients, as well as its limitations in relation to sample quality.¹⁶ Although conization is usually performed under local anesthesia, which improves the tolerance of ECC, it might still be uncomfortable for women. Thus, the better tolerability of ECB is a nonnegligible reason to recommend the use of this technique in the study of the endocervical canal.

Involvement of the endocervical margin of the conization specimen, one of the classical variables reported as a predictor of persistent HSIL after treatment,^{6,23} was significantly correlated

TABLE 3. Univariate and Multivariate Analysis of Predictors of Recurrent HSIL

	Univariate analysis			Multivariate model with ECB ^a			Multivariate model with ECC ^b		
	HR	(95% CI)	p	HR	(95% CI)	p	HR	(95% CI)	p
ECB (cytology)									
No HSIL (negative or LSIL)	1			1					
HSIL	9.0	(4.9–16.7)	<0.001	4.2	(2.4–8.7)	<0.001			
ECB (HPV testing)									
Negative	1			1					
Positive	10.6	(4.5–25.2)	<0.001	6.3	(2.4–16.7)	<0.001			
ECC									
No HSIL (negative or LSIL)	1						1		
HSIL	12.1	(6.1–24.1)	<0.001				9.2	(4.1–21.0)	<0.001
Surgical margins									
Negative	1			1					
Positive (any)	3.8	(2.0–7.3)	<0.001	-			-		
Endocervical margin	4.8	(2.3–10.1)	<0.001	1.7	(0.7–4.0)	0.125	2.6	(1.0–6.3)	0.042
Exocervical margin	2.2	(0.9–5.0)	0.078	1.4	(0.6–3.4)	0.502	2.7	(1.1–6.7)	0.030
Both margins	10.3	(3.9–27.1)	<0.001	2.7	(0.9–8.0)	0.067	5.5	(1.6–21.0)	0.009
Diagnosis of the conization specimen									
Negative	1								
LSIL	1.7	(0.3–10.0)	0.571						
HSIL	2.9	(0.7–12.2)	0.173						
Immunosuppression									
No	1								
Yes	2.1	(0.7–6.0)	0.157						

^aVariables included in multivariate model with ECB: ECB (Cytology), ECB (HPV testing), surgical margins.

^bVariables included in multivariate model with ECC: ECC, surgical margins.

with the risk of persistent HSIL in our series. These findings are consistent with previous reports concluding that the status of the endocervical margin provides better information about the risk of disease after conization than the status of the exocervical margins.^{8,11,25} Interestingly, although there was a good correlation between the results of the three tests, a positive result of the cytological study of the ECB sample and the diagnosis of the ECC were better predictors of persistent HSIL than a positive endocervical margin. Endocervical margin status was a specific marker of persistent disease, but showed a poor positive predictive value. Although it is well known that the presence of positive margins increases the risk of posttreatment disease, the presence of affected margins is not synonymous of residual lesion. It has been reported

that the status of the margins as a single factor has a low predictive capacity since approximately 60% of the patients with positive margins do not develop SIL during follow-up.^{8,26} This fact might be explained by the artifactual oblique sectioning during the preparation of the surgical specimen for histological evaluation, or because the excision is performed close to the margin but removes the whole lesion, or because cauterization of the surgical margins destroys the few dysplastic cells remaining in the canal after excision.^{11,27,28} Indeed, in our series only positive endocervical margin increased the risk of persistent HSIL.

This is the first study comparing ECB after cervical conization and ECC to predict persistent HSIL. Strengths include the large number of women included in the clinical setting and its

TABLE 4. Sensitivity, Specificity, Positive and Negative Predictive Values, and Accuracy of ECB, ECC, HPV Testing in the ECB Sample, Both ECB Cytology and HPV Testing Positive, Either ECB Cytology or HPV Testing Positive, and Positive Endocervical Margin of the Excisional Specimen Involved by SIL

	ECB (cytology)	ECB (HPV testing)	ECC	ECB (cytology and HPV testing)	ECB (cytology or HPV testing)	Endocervical margin
Sensitivity	42.9 (19.1–57.8)	86.4 (73.3–93.6)	35.1% (21.8–51.2)	40.5 (17.0–55.5)	88.6 (76.0–95.0)	47.7% (33.8–62.1)
Specificity	93.4 (90.7–95.4)	65.4 (60.9–69.6)	96.1% (93.7–97.6)	96.1 (94.0–97.5)	60.8 (56.2–65.3)	82.4% (78.5–85.7)
Positive predictive value	38.3 (25.8–52.6)	19.1 (14.2–25.1)	46.4% (29.5–64.2)	48.6 (33.0–64.4)	18.5 (13.8–24.3)	21.6% (14.6–30.8)
Negative predictive value	94.5 (85.9–91.5)	98.1 (95.8–99.1)	94.0% (91.2–95.9)	94.7 (92.3–96.4)	98.2 (95.8–99.2)	93.9% (91.1–95.9)
Accuracy	89.0 (85.9–91.5)	67.2 (63.0–71.1)	90.8 (87.7–93.2)	91.5 (88.8–93.6)	63.4 (59.0–67.5)	79.2% (75.3–82.6)

Values are shown in percentage and 95% CIs.

prospective design with adequate follow-up. Limitations of our study include its nonrandomized nature, which prevents a full assessment of whether ECC could be replaced by ECB and whether the former could be omitted in clinical practice. Moreover, performing ECC after ECB could have impacted the quality of the ECC sample. However, the accuracy of both tests aligns with the data reported in the literature in nontreated patients, suggesting that the possible impact of this on the results can be disregarded. On the other hand, HPV typing to distinguish persistent HSIL from new HPV infection after treatment was not considered in this study.

In conclusion, the present study shows that the accuracy of ECB performed after conization is similar to that of ECC for detecting patients at risk of persistent HSIL who might benefit from a closer follow-up, reducing the number of inadequate samples. These results suggest that ECB can be considered in addition to ECC, if not as a potential replacement. Further randomized studies comparing ECB and ECC groups are needed to confirm these findings.

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