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Colposcopically Directed Biopsy Before Ablative Treatment *Versus* Direct Ablative Treatment in Patients With Cervical Oncogenic HPV

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Abstract. *Background/Aim: In the past, the standard of care for women with abnormal cervical cytology has been the performance of colposcopically guided biopsy, followed by conization or large loop excision of the transition zone (LLETZ) where biopsy revealed pre-cancerous or cancerous areas. More straightforward protocols are emerging which advocate performing LLETZ in all women with highly suspicious cytology, suspicious colposcopic impression, or the presence of high-risk oncogenic human papilloma virus (HPV) strains in their cervical swabs. This, theoretically, would reduce the rate of false-negative diagnoses, but at the price of overtreating a significant number of healthy women. Patients and Methods: We retrospectively analyzed cervical cancer screening protocols in two large cohorts of women with high-risk HPV. The study compared outcomes between patients undergoing a colposcopically directed biopsy before LLETZ (n=683) and those proceeding directly to LLETZ without a biopsy (n=136). The primary focus was to assess whether intervening biopsies would reduce unnecessary ablative procedures without compromising the detection of high-grade lesions. Results: The biopsy group had a high false-negative rate, with several high-grade lesions (CIN3) and a case of invasive cancer initially underdiagnosed. Conversely, the direct-to-LLETZ approach, while ensuring no high-grade lesions were missed, led to overtreatment of lower grade lesions. Conclusion: These findings raise concern about the reliance on biopsy results for treatment decisions. Neither protocol was entirely satisfactory, although the more aggressive one avoided the potentially life-threatening consequence of false-negative results. Further research is mandatory to accurately diagnose all cases requiring aggressive treatment, without subjecting healthy women to ablative treatments they do not need.*

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Cervical cancer is one of the very few cancer types in which secondary prevention is effective, due to the fact that most cases develop over a relatively long time span from identifiable precursor lesions (cervical intraepithelial neoplasia, CIN) which can be identified and treated by means of local ablative therapy (1). Despite the accepted fact that cervical cancer screening is effective and results in a verified, significant reduction in cervical cancer mortality, there is no internationally agreed protocol on how best to screen the target population [using cytology, human papillomavirus (HPV), or both] nor on the best pathway leading from identifying women at highest risk to their treatment (2-5). This results in the absence of stringent protocols at most referral centers, the decision of how to proceed from colposcopy to eventual excisional therapy being often left in the hands of each individual colposcopist. Two main lines of thought collide here with each other: the first, more traditional one, holds that colposcopy must be followed by colposcopically guided biopsy of suspicious areas, with subsequent steps tailored by the pathological results of the biopsy. In general, this means that excisional therapy is only reserved for histologically verified CIN2 and CIN3 (CIN2+) lesions, thus avoiding unnecessary overtreatment of women harboring lower-grade lesions, or no lesion at all. The price of this is the occasional high-grade lesion slipping through this diagnostic sequence (6). On the other hand, there is the view that all women with a

Table I. *Clinical features of patients having undergone large loop excision of the transition zone with an intervening colposcopically directed biopsy (n=683, Group 1), or directly after colposcopy (n=136, Group 2).*

Variable		Group 1	Group 2	*p*-Value
Age, years	Mean±SD	41.83±10.7	47.41±11.9	**<0.001**
Pregnancies	Median (range)	1.5 (0-8)	1.8 (0-6)	0.6
Abortions	Median (range)	0.5 (0-6)	0.5 (0-4)	0.992
Vaginal deliveries	Median (range)	0.9 (0-5)	1.2 (0-6)	**<0.05**
Cesarean section	Median (range)	0.0 (0-3)	0.2 (0-3)	0.17
Active smoker, n (%)	Yes	40.1%	34.3%	0.23
HPV 16/18, n (%)	Yes	380 (55.6%)	73 (53.6%)	0.67

HPV: Human papillomavirus. Statistically significant *p*-values are shown in bold.

'high-grade impression' colposcopy should be subject to ablative therapy (generally known as the 'see and treat' strategy), most usually by means of large loop excision of the transformation zone (LLETZ), in order to exclude any possibility of a false-negative result, even at the price of an admittedly high rate of overtreatment. An even more radical attitude (known as the 'screen and treat' strategy) is to submit all women carrying a high-risk HPV to an ablative procedure, based on studies showing a low degree of correlation between the colposcopic impression, cytology, and the presence of a high-risk, CIN2+ lesion [reviewed in (7)].

We retrospectively compared two distinct populations, one proceeding directly to LLETZ from colposcopy, the other with an intervening biopsy (or multiple biopsies), in order to elucidate whether having followed the colposcopical impression, without considering the results of the intervening biopsy to indicate LLETZ if this had been done, would have avoided unnecessary ablative procedures, without compromising the ultimate target, which is to identify and treat the maximum number of high-grade lesions.

Patients and Methods

Our center provisionally adopted the 'screen and treat' policy in 2016. All cases with evidence of oncogenic HPV infection, irrespective of the associated cytological result, are referred for further treatment from the associated primary health care centers. To the present day, however, an intervening colposcopy is carried out in all of cases, as an internal control of the track leading directly from virological suspicion to ablation, before making this protocol official. It is left to the personal criteria of the colposcopist to additionally take directed biopsies of colposcopically suspicious areas.

Between January 2016 and September 2022, having been referred after detection of cervical high-risk HPV at the associated primary care centers to the colposcopy unit of Hospital Universitario Valdecilla, Santander, Spain, 819 women were submitted to LLETZ, irrespective of the corresponding cytology result or the colposcopical impression. In one group of patients (n=683), an intervening biopsy of colposcopically suspicious areas was performed, whereas the rest (n=136) proceeded directly to LLETZ. Following either pathway to LLETZ was completely random, in that it depended on which particular colposcopist was assigned to them, based on free slots in the schedules of the physicians, and not on patient choice. All colposcopists were certified, residency-trained gynecologists, and no procedure was undertaken by trainee residents. Colposcopist experience was thus comparable. Furthermore, the biopsy technique was homogeneous, in that it involved the complete excision of the transformation zone in a circular, donut-like fashion. In all instances, a 20 mm diathermic loop, with 60 W monopolar energy, was used (Medtronic®; Minneapolis, MN, USA).

Table II. *Pathological end results after large loop excision of the transition zone (LLETZ) in the group with an intervening colposcopically directed biopsy (Group 1) and the group proceeding directly to LLETZ after a diagnosis of the presence of high-risk human papillomavirus (Group 2).*

Pathological result	Group 1 (n=683)	Group 2 (n=137)	*p*-Value
CIN1	174 (25.4%)	60 (43.8%)	**<0.001**
CIN2	169 (25.0%)	27 (19.7%)	0.19
CIN3	332 (48.4%)	48 (35%)	**0.004**
Invasive carcinoma	8 (1.3%)	2 (1.5%)	0.77

CIN: Cervical intraepithelial neoplasia. Statistically significant *p*-values are shown in bold.

There were slight differences in the mean age and number of vaginal deliveries between the groups but the clinical features of patients composing them were otherwise comparable (Table I). All patients had an HPV test performed, looking for oncogenic variants of the virus. Specifically, HPV variants 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68A-68B were sought for by means of reverse transcriptase–polymerase chain reaction.

Statistics. Mean values±standard deviation were compared by means of analysis of variance. Proportions were compared by means of the chi-square test. Differences were considered significant when the *p*-value was less than 0.05.

Ethics. The study was approved by the Ethics Committee of Instituto de Investigación Sanitaria Valdecilla (IDIVAL) with code no. 2021.405 on 11.02.2022.

Table III. *Concordance between final pathological results after ablative therapy and previous colposcopically directed biopsy results*

	Biopsy result, n (%)				
Final pathological result	Insufficient tissue (n=31)	Normal tissue (n=15)	CIN1 (n=91)	CIN2 (n=245)	CIN3 (n=301)
Normal cervical tissue	0	0	0	0	0
CIN1	20 (63.3%)	11 (71.4%)	62 (68.2%)	52 (21%)	29 (9.7%)
CIN2	6 (20%)	0	15 (16.5%)	105 (43%)	43 (14.4%)
CIN3	5 (16.7%)	4 (28.6%)	13 (14.3%)	88 (36%)	222 (73.6%)
Infiltrating carcinoma	0	0	1 (1%)	0	7 (2.3%)

CIN: Cervical intraepithelial neoplasia.

Results

The pathological end results after LLETZ differed between groups and is shown in Table II.

In the group of patients with an intervening directed biopsy of colposcopically suspicious areas, the results were as follows: in 31 cases (4.5%), the obtained material was insufficient for pathological workup; 15 additional cases (2.1%) yielded normal cervical tissue; 47 were CIN1 (6.9%); 245 were CIN2 (35.9%) and 301 were CIN3 (44.1%). However, the final pathological result of the excised material after LLETZ corresponded only partially with the previous biopsy result. Particularly worrying was the fact that out of the 31 cases with insufficient biopsy material, five (16.7%) were CIN3 on LLETZ, as were 4/15 cases with normal cervical biopsy tissue, and 13/91 (14.3%) of those with a previous CIN1 biopsy. In this latter group, LLETZ ultimately revealed one case of invasive cancer. For those patients with a CIN2 biopsy, CIN3 was underdiagnosed in 88/245 (36%) of instances, although this would not have been highly relevant, since the usual protocol worldwide is to submit all patients with a so-called CIN2+ biopsy to an ablative procedure. Nevertheless, the resulting gross false-negative rate of an intervening biopsy with a result of up to CIN2 between colposcopy and LLETZ for detecting CIN3 or invasive cancer was an unacceptable 22.5% (Table III).

Discussion

The findings of this study underscore critical insights and challenges in the current approach to cervical cancer screening and management, particularly in women with high-risk HPV. The comparison between two distinct protocols – one involving an intervening biopsy and the other proceeding directly to LLETZ – reveals significant implications for clinical practice. Firstly, the notable discrepancy in pathological outcomes between the two groups raises concerns about the reliability of colposcopically directed biopsies in accurately diagnosing the severity of cervical lesions. The high false-negative rate observed in the biopsy group, where a substantial number of high-grade lesions (CIN3) and even a case of invasive cancer were initially underdiagnosed, is alarming. This suggests that reliance on biopsy results alone may lead to under-treatment of potentially serious lesions. It also raises questions about the sensitivity of colposcopy and biopsy in detecting high-grade cervical intraepithelial neoplasia, especially considering the gradual and often asymptomatic progression of cervical cancer (1).

The study's findings also bring to light the potential overtreatment in the group proceeding directly to LLETZ. While this approach ensures that high-grade lesions are not missed, it also means that patients with lower-grade lesions, which might regress spontaneously, are subjected to unnecessary surgical intervention. This is not a trivial concern, as LLETZ and similar procedures can have long-term reproductive consequences, such as cervical stenosis, preterm labor, and other pregnancy-related complications (3). The variation in treatment pathways, based on the colposcopist's discretion, also points to a lack of standardized guidelines in managing high-risk HPV cases. This inconsistency can lead to varied patient outcomes and may contribute to both overtreatment and undertreatment of cases, depending on the individual practitioner's judgment and experience (2). Our initial working hypothesis was that the performance of an intervening biopsy would significantly diminish the need for further ablative treatment if the biopsy yielded a normal cervix or CIN1 result, without compromising the final target of identifying all CIN3 and invasive cancer cases. In the face of the high false-negative rate, this hypothesis has been refuted, much to our dismay. We are not the only ones, however, to have come up with such a result. Colposcopy seems not to be as reliable as previously thought even when performed by experienced or very experienced colposcopists. In one of the largest studies conducted on this issue to date in Sweden (8), considering over 82,000 colposcopic assessments, the best accuracy reached in distinguishing low-grade from high-grade lesions was a mere 76%, very similar to our own figures. More importantly still, accuracy was not related to the experience of the intervening colposcopists. The obvious conclusion is that colposcopy per se is insufficicient for individually tailoring the best treatment of cervical cancer precursors, even in the most experienced of

hands. A further argument in this direction is provided by a report from Huh *et al*. (9), who showed that the performance of random cervical biopsies after a negative colposcopy disclosed the presence of almost 20% of unsuspected CIN3+ cases, again much in line with our own results.

Among other things, this study seems to corroborate the superiority of HPV-testing over traditional cytology for cervical cancer screening, something already pointed out by a large Canadian study (10). In it, the likelihood of CIN3 or invasive cancer at 48 months was less than half following HPV-based screening, compared to traditional, cytology-based screening. What is still open to debate is the strategy to follow after a positive screening result. In the aforementioned study, colposcopy was still the cornerstone of management. Our study aimed precisely at defining whether the use of colposcopy after a positive screening result improves the final outcome in terms of less overtreatment, without compromising the end result of identifying all cases of histologically verified CIN3+, and the answer is no, as discussed above. The validity of the 'see and treat' strategy is therefore put into doubt, in favor of the 'screen and treat' one, something already anticipated by the results of the study by Ebisch *et al*. (7).

Furthermore, the study highlights the complexity of managing cervical cancer precursors in the era of HPV vaccination and changing epidemiological patterns (4). With the advent of HPV vaccination, the prevalence of certain high-risk HPV types is decreasing, which may eventually lead to changes in the natural history of cervical cancer and its precursors. This evolving landscape necessitates continuous re-evaluation of screening, treatment, and, especially, vaccinating protocols (5).

In conclusion, this study shows that the use of an intervening biopsy after colposcopy is insufficient for tailoring the treatment of cervical cancer precursors. Although it is certainly able to diminish the rate of overtreatment of low-grade lesions, when compared to ablative treatment in all cases of oncogenic HPV infection, this is achieved at the price of an unacceptably high rate of false-negative diagnoses. Future research should focus on refining screening and treatment algorithms, possibly integrating novel diagnostic tools and biomarkers to enhance the accuracy of cervical cancer precursor detection and risk stratification (7).

Conflicts of Interest

None.

Authors' Contributions

Diego Erasun supervised the collection of data and performed the statistical analyses; Ana Vazquez Del Campo, Alazne De Castro and Alberto Munoz-Solano collected data from the medical charts; José Schneider devised and supervised the study and wrote the final article. All Authors critically read the article and discussed it.

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