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Does Secondary Cervical Biopsy Increase the Detection of Cervical Intraepithelial Neoplasia?

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Colposcopically directed biopsy is the standard method for the diagnosis of cervical intraepithelial neoplasia (CIN); however, it is burdened by significant subjectivity, which may lead to incorrect selection of the biopsy site and underestimation of lesion severity.

The aim of the study was to evaluate whether a secondary cervical biopsy increases the accuracy of CIN grade detection.

This prospective study included 32 patients with abnormal cytological findings (ASCUS, LSIL, HSIL) and satisfactory colposcopy (TZ1). Under colposcopic guidance, two biopsies were obtained: a primary biopsy from the site with the most severe colposcopic impression and a secondary biopsy from another affected area.

The results showed that the secondary biopsy detected a higher CIN grade (CIN II/III) in 25% of cases compared with the primary biopsy. Increased detection was more pronounced in younger patients and was not related to the extent of the colposcopic lesion.

Secondary biopsy significantly increases the sensitivity and reliability of CIN diagnosis, particularly in younger women, regardless of the size of the colposcopic lesion.

Key words**:** colposcopy, uterine cervical neoplasms, cervical intraepithelial neoplasia, biopsy, early detection of cancer

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Da li sekundarna biopsija grlića materice povećava detekciju cervikalne intraepitelne neoplazije?

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Rezime: Kolposkopski ciljana biopsija predstavlja standardnu metodu za dijagnostiku cervikalne intraepitelne neoplazije (CIN), ali je opterećena značajnom subjektivnošću, što može dovesti do pogrešnog izbora mesta biopsije i potcenjivanja težine lezije.

Cilj ispitivanja je Ispitati da li sekundarna biopsija grlića materice povećava tačnost detekcije gradusa CIN.

Prospektivna studija obuhvatila je 32 pacijentkinje sa patološkim citološkim nalazom (ASCUS, LSIL, HSIL) i zadovoljavajućom kolposkopijom (TRZ1). Pod kontrolom kolposkopa uzete su dve biopsije: primarna sa mesta najteže kolposkopske slike i sekundarna sa drugog zahvaćenog područja.

Rezultati studije su pokazali da sekundarna biopsija je u 25% slučajeva detektovala viši gradus CIN (CIN II/III) u odnosu na primarnu biopsiju. Povećana detekcija bila je izraženija kod mlađih pacijentkinja i nije zavisila od proširenosti kolposkopske promene.

Uzimanje sekundarne biopsije značajno povećava senzitivnost i pouzdanost dijagnostike CIN, posebno kod mlađih žena, nezavisno od veličine kolposkopske lezije.

Ključne reči: kolposkopija neoplazme grlića materice, cervikalna intraepitelna neoplazija, biopsija, rano otkrivanje karcinoma

Introduction

Colposcopy is a method used to select the site with the most severe lesion from which a tissue sample should be obtained for histopathological examination. The assessment of the severity of the colposcopic image is a subjective category and depends on multiple factors. Hormonal status, epithelial thickness, patient age, as well as the colposcopist's level of training and individual approach, represent only some of the factors that may lead to an incorrect choice of the biopsy site. Thus, epithelial thickness and density may produce a misleading impression of a milder lesion when the epithelial thickness is approximately 184 μm, or a more severe lesion in cases of thicker epithelium exceeding 321 μm (1).

The subjectivity of colposcopy is best illustrated by the fact that two colposcopists agree on the biopsy site in only 52.4% of cases, and that agreement with their own previous findings is achieved in merely 66.7% of cases (2). An incorrect selection of the biopsy site may result in inaccurate diagnosis and inappropriate treatment.

Colposcopy-directed biopsy remains the standard diagnostic method and is still routinely used for establishing the diagnosis of cervical intraepithelial neoplasia (CIN). However, an increasing number of studies, as well as clinical experience, indicate discrepancies between the histopathological (HP) findings of biopsy specimens and the final HP findings of surgical specimens.

Combining endocervical curettage with biopsy increases the detection rate of CIN only in a small proportion of carefully selected and clinically indicated cases. Loop excision using the "see and treat" approach also improves diagnostic accuracy, but it is associated with iatrogenic effects, particularly an increased risk of preterm birth and infertility. The use of new technological solutions that eliminate colposcopist subjectivity also improves biopsy sensitivity; however, due to financial constraints, such technologies (e.g., the Dynamic Spectral Imaging System – DySIS) are not widely available in routine clinical practice.

Aim of the Study

The aim of this study was to evaluate the extent to which a second biopsy increases the accuracy of detecting the grade of cervical intraepithelial neoplasia.

Patients and Methods

This prospective study included 32 patients with abnormal cytological findings suggestive of squamous intraepithelial lesions of the cervix (ASC-US, LSIL, HSIL). All patients had a satisfactory colposcopic examination with a type 1 transformation zone (TZ). The cervix was divided into four quadrants by imaginary longitudinal and transverse axes intersecting at right angles.

All patients had abnormal colposcopic findings, with lesion extent defined according to the involved quadrants. Histopathological samples were obtained under colposcopic guidance and labeled as sample 1 and sample 2. Sample 1 was taken from the site that gave the impression of the most severe colposcopic abnormality.

Results

Table 1. Distribution of patients according to age

Table 1 shows that the highest proportion of patients belonged to the younger age group, under 32 years of age (37.5%). This distribution was expected, as the study population consisted of patients with intraepithelial lesions, multifocal HPV changes, and satisfactory colposcopic findings.

Table 2. Distribution of patients according to concordance and discordance of HP findings between primary and secondary biopsy

Table 3. Overall concordance of HP findings between primary and secondary biopsy

Tables 2 and 3 demonstrate that secondary cervical biopsy detected CIN II and CIN III lesions that were not identified by the primary biopsy in 25% of cases.

Table 4. Distribution of patients with a higher disease stage on secondary biopsy according to age

Table 4 indicates that the highest proportion of patients in whom CIN II or CIN III was diagnosed by secondary biopsy belonged to the youngest age group. This distribution corresponds to the overall age

distribution shown in Table 1. In younger patients, various stages of HPV infection evolution may be found on the exocervix, ranging from koilocytosis and condylomas to CIN I, CIN II, and CIN III lesions.

Table 5. Distribution of colposcopic lesion extent in relation to identical or higher HP findings on secondary biopsy

Table 5 shows that the extent of the colposcopic lesion does not influence the increased detection of CIN by secondary biopsy. In 75% of patients in whom a higher-grade diagnosis was established by secondary biopsy, the colposcopic lesion involved fewer than two quadrants. These findings were unexpected, as it was anticipated that a larger colposcopic lesion would increase diagnostic reliability through multiple biopsies. A possible explanation for this distribution lies in the fact that intraepithelial lesions often begin unifocally, within a small clone of altered cells in which deregulated HPV infection processes are initiated. Multifocal lesions, presenting as satellite multiple HPV-infected fields, are more often associated with benign viral types, koilocytosis, condylomas, and CIN I lesions. Therefore, when performing biopsy, not only lesion size but also lesion intensity should be taken into consideration.

Discussion

Numerous studies report that colposcopy-directed cervical biopsy may miss CIN II+ lesions in 30–55% of cases. Taking a second biopsy increases the sensitivity of biopsy for CIN detection from 51.7% to 60.4% (3).

The Canadian guidelines for the management of abnormal cervical cytology emphasize that, in patients with LSIL cytology, obtaining a second biopsy increases the sensitivity for detecting CIN II+ lesions from 68.3% to 81.8% (4).

A study evaluating the significance of multiple biopsies, random biopsies, and endocervical curettage in CIN detection highlights that a greater number of biopsies, including random biopsies, increases the sensitivity for detecting CIN II+ lesions by 25%, and that a single targeted biopsy may miss up to one third of CIN lesions (5).

Obtaining more than two biopsies, particularly in patients with HSIL cytology who are positive for high-risk oncogenic HPV types (HPV 16 and 18), may increase biopsy sensitivity for detecting HSIL lesions

from 60.6% to 85.6% with two biopsies, and up to 95.6% with three biopsies. Additionally, taking an extra biopsy from an area of the cervix without visible colposcopic abnormalities may detect HSIL lesions in 2% of cases (6).

Pretorius et al. reported that random biopsy in patients with positive cytology and negative colposcopy detected CIN II+ lesions in 37.4% of cases, whereas endocervical curettage detected only 5.5% (7). Biopsy sensitivity in improving CIN diagnosis does not depend significantly on improved colposcopist training alone, as this increases sensitivity only from 67.3% to 76.4%, whereas obtaining a second biopsy raises sensitivity to 83.3% (8).

These discrepancies in biopsy sensitivity and biopsy site selection stem from the fact that colposcopy is a subjective method, with an overall sensitivity of 89%, specificity of 52%, positive predictive value of 80%, and negative predictive value of 68%. Overall colposcopic compatibility with CIN grade, using the Reid Colposcopic Index (RCI), ranges from 37% to 75% (9).

In our study, secondary biopsy increased the sensitivity of biopsy in detecting CIN II+ lesions by 25%. Secondary biopsy proved to be particularly important in improving diagnostic accuracy in younger patients, regardless of the extent of the colposcopic lesion.

Conclusion

In cases of complex colposcopic lesions, involving a larger surface area, performing a secondary cervical biopsy increases the detection rate of CIN lesions by 25%.

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* Table 1. Distribution of patients according to age

Age	Number of patients	Percentage
28–32 years	12	37,5%
33-37 years	8	25%
38-42 years	6	18,75%
>42 years	6	18,75%
total	32	100%

* Table 2. Distribution of patients according to concordance and discordance of histopathological (HP) findings between primary and secondary biopsy

H.P. finding on primary biopsy	CINI	CINII	CINIII	Total
CIN I	16 (72,12%)	2(9,09%)	4(18,18%)	22(100%)
CIN II		6(75%)	2(25%)	8(100%)
CIN III			2(100)	2(100%)
Total	16(50%)	8(25%)	8(25%)	32(100%)

* Table 3. Overall concordance of histopathological findings between primary and secondary biopsy

Secondary biopsy finding	Number	Percentage
Identical HP finding	24	75%
Higher-grade lesion	8	25%
Total	32	100 %

* Table 4. Distribution of patients with a higher-grade lesion on secondary biopsy according to age

Age (years)	Number of patients	Percentage
28-32 years	4	50%
33-37 years	2	25%
38-42 years	0	0%
>42 years	2	25%
Total	8	100 %

* Table 5. Distribution of colposcopic lesion extent in relation to identical or higher histopathological findings on secondary biopsy

Secondary biopsy finding	1-2 quadrants	>2 quadrants	Total
Identical	16 (66,5%)	8 (33,33%)	24 (100%)
Higher-grade	6 (75%)	2 (25%)	8 (100%)
Total	22 (68,75%)	10 (31,25%)	32 (100%)