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Prediction of cervical epithelial lesions level in patients with positive cytologic findings using colposcopic classification Rio De Janeiro 2011

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Summary

Purpose of Investigation: Standard procedure for diagnosis of premalignant cervical changes includes cytological, colposcopic, and histopathological examination. Comparison of the results depends on classifications differences that may influence diagnosis. The aim of this study was to determine efficacy and accuracy of Rio de Janeiro classification in colposcopic prediction of cervical intraepithelial neoplasia (CIN) degree. *Materials and Methods:* The authors conducted a prospective study over a one-year period. Colposcopic findings were compared with histopathological results. Tumors were classified according to the WHO 2014 criteria. *Results:* The accuracy of colposcopy is higher for high-grade squamous intraepithelial lesion (HSIL). For major changes and height grade CIN 76% compatibility was found, but in patients without intraepithelial lesion, the compatibility was only 14%. Squamous cell cervical cancer was recognized in 67% of patients and in 33% of patients with cervical planocellular cancer was classified as colposcopic G2 change, which in terms of clinical use can be a satisfactory result. *Conclusion:* Combination of cytology screening and colposcopy is a good method in the detection of epithelial premalignant and early stages of malignant changes of the cervix.

Key words: Cervical intraepithelial neoplasia; Colposcopy; Papanicolaou smear; Cervical cancer screening; Sensitivity; Specificity.

Introduction

Standard procedure for diagnosis of premalignant cervical changes includes cytological, colposcopic, and histopathological examination. The gold standard is histopathology. Comparison of the results is somewhat confusing and depends on classifications differences that may influence diagnosis. Rio de Janeiro colposcopic classification has clear numerical degrees of cervical changes. This makes it very suitable for comparison with cytological and histopathological classifications [1-4].

In 2011 there were 321 new cases of cervical cancer in Croatia (14.5/100,000) and 493 (22.3/100,000) cases of cervical carcinoma in situ (CIS). The highest incidence of CIS was recorded in the 30- to 34-year-old group [5].

Colposcopy was introduced by Hinselmann in 1925 and used for description of various cervical conditions. It enables six- to 40-times enlargement of cervical changes and illumination. The primary goal is early diagnosis of cervical cancer [6]. Hinselmann used colposcopy as a screening method for cervical cancer but it was not widely accepted [7, 8]. Colposcopy preceded test of exfoliative cytology that was introduced in 1941 by Papanicolaou and Traut [9]. Meta-analysis of eight longitudinal studies comparing colposcopy and colposcopy-guided biopsy found sensitivity to be 87-99% and specificity 26-87% [10]. Although some countries use colposcopy as a screening method for cervical cancer, due to its low specificity, it should only be used for screening in cases with abnormalities in cytological screening [11].

Efficiency of colposcopy depends on skill. Colposcopy skills should be constantly improved and evaluated in clinical practice [12,13]. Pap smear has been a method of secondary prevention of cervical cancer for 50 years now. It is not only used as a screening test but also for differential diagnosis and prediction for histopathology. It is considered one of the most effective screening tests and reason for decrease of cervical cancer incidence and mortality [14, 15]. The issues with this complex cytology screening system include initial smear standards, cytology interpretation errors, terminology adjustment between cytologist and gynaecologist, and patient cooperation [16]. However most important objection is low sensitivity [17]. Over one-third of screened patients with cervical cancer had normal Pap smears [18, 19]. Use of colposcopy as a complementary method assures the best prevention and early detection of cervical cancer [20-22]. All colposcopic classifications differentiate minor and major changes, enabling comparison with cytology and histopathology [1, 6,

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8, 23-25]. The newest Rio de Janeiro colposcopic classification provides clear numerical grade of cervical changes, thereby providing reproducible, accurate, objective, and clinically meaningful prediction severity of cervical intraepithelial neoplasia (CIN) [1, 26-29]. Colposcopic–histologic correlation should be at least 80%. If not so, colposcopist is required to receive additional training in colposcopic assessment of cervical changes [30]. Cytological Bethesda 2002 classification for intraepithelial lesions of cervix enables good accuracy and reproducibility [31-35]. Structure and degrees of this classification are very similar to those of Rio de Janeiro colposcopic classification. The present authors have compared these grades with histopathological 2014 WHO tumor classification [2].

Table 1 contains comparison of cervical changes using common characteristics of different methods. The aims are: 1) to compare success rate of colposcopic *vs*. histopathological classification as the best one for diagnosis of cervical intraepithelial neoplasia, 2) to clarify disparities of classifications through follow up, and 3) to avoid overtreatment in patients with positive cytological screening in case of good correlation between colposcopy and histology.

Table 1. — *Comparison of three classifications: cytological, colposcopical, and histopathological.*

Cytological form "Zagreb 2002"	NCI Bethesda 2001.	Colposcopic form "Rio de Janeiro/ Zagreb2011" [4]	Histopathological classification WHO 2014
ASCUS	ASCUS	G1	LG
ASC-H	ASC-H	G2	HG
CIN I	LSIL	G1	LG (CIN I)
CIN II	HSIL	G2	HG (CIN II)
CIN III	HSIL	G2	HG (CIN III)
CIS	HSIL	G2	HG (CIS)
Squamous Cell Carcinoma	Squamous Cell Carcinoma	Suspected malignant invasion	Squamous Cell Carcinoma

ASCUS: atypical squamous cells of undetermined significance.; ASC-H: atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion; CIN I: cervical intraepithelial neoplasia grade 1; CIN II: cervical intraepithelial neoplasia grade 2; CIN III: cervical intraepithelial neoplasia grade 3; CIS: carcinoma in situ; LSIL: low grade squamous intraepithelial lesion-Bethesda classification 2001.guideline; HSIL: high grade squamous intraepithelial lesion – Bethesda classification 2001 guideline; G1 (minor changes "low grade" colposcopy); G2 (major changes "high grade" colposcopy); LG: low grade (CIN I); HG: high grade (CIN 2, CIN 3, CIS).

Table 2. — *Distribution of participants regarding age.*

Age group (years)	Number of patients (N)	Percentage of patients (%)
> 20	3	3%
21-30	27	28%
31-40	34	36%
41-50	23	24%
51-60	4	4%
< 60	4	4%

Materials and Methods

A prospective study in 95 patients was conducted during one-year period from August 1, 2012 to July 31, 2013 in University Hospital Centre "Sestre milosrdnice" in Zagreb. The study included patients referred from their primary gynaecologist for further diagnosis and treatment after diagnosed cervical dysplasia or cervical carcinoma during routine cytological screening (Pap smear). Pregnant patients, patients with other genital tract disease, with other malignant or immune system disease, and corticosteroid therapy were excluded from the study.

Biopsy of the most expressed lesion during routine colposcopy exam was performed in the studied group. The specimens were sent for further histopathological exam. In cases of cytology, colposcopy and histopathological results' disparity, the patients were re-examined after three months. All patients signed informed consent for participation in the study. The study was also approved from The Ethics Committee of the University Hospital Center "Sestre milosrdnice".

Cells collected from the cervix using spatula and cytobrush were placed on a glass slide and stored in the fixative (96% alcohol). The result is presented on internationally approved form (Zagreb 2002) classifying CINs according to the algorithm proposed from National Cancer Institute Bethesda 2001 [3].

Colposcopy exam was performed using Leisegang-Model 3MLW with ×7.5/15/30 enlargement. Cervix was soaked with 5% chloroacetic acid and Lugol [36-38]. Colposcopy results were expressed according to the "Rio de Janeiro 2011" classification, also accepted for semiquantitative evaluation of colposcopic changes from Croatian Society for colposcopy and cervical diseases [4]. Colposcopy and biopsy was performed by licenced gynaecological oncologist with colposcopy licence from Croatian Society for Colposcopy and Cervical Diseases.

Tissue samples obtained during colposcopy and biopsy were processed by standard histological method involving tissue fixation in 10% buffered formalin inclusion in paraffin blocks, cutting the blocks to 5-mm thickness, and dyeing with haematoxylin eosin (HE). Classification of premalignant lesions and invasive cervical squamous epithelium was determined according to the WHO tumor classification [2].

The age of the patients is expressed with median value and the remaining numeric results are expressed in share. For determination of specificity and sensitivity, Clinical Calculator 1 was used.

Results

Comparison of all three classifications, cytology, colposcopy and pathohistology in presented in Table 1. The average age of women in this study was 36.5 years (19-76). Table 2 shows the distribution of participants regarding age. Table 3 shows the distribution of patients considering the number of deliveries. Table 4 shows the distribution of cytology results in the studied group according to Bethesda classification 2001. Table 5 shows the distribution of colposcopy results in the studied group according to "Rio de Janeiro /Zagreb 2011" classification. Table 6 shows the distribution of histopathological results in the studied group. Compatibility between cytology and histopathological results in the studied group is shown in Table 7. Chronic cervicitis in histopathological examination was found in four

Table 3. — *Distribution of patients considering the number of deliveries.*

Number of deliveries (N)	Number of patients (N)	Percentage (%)
0	43	45%
1	21	22%
2	25	26%
3	6	6%

Table 4. — *Distribution of cytology results in the studied group according to Bethesda classification 2001.*

	Number of patients (N)	%
LSIL	14	15
HSIL	77	81
Squamous cell carcinoma	4	4
Total	95	100

Table 5. — *Distribution of colposcopical results in the studied group according to "Rio de Janeiro/Zagreb 2011" classification.*

Colposcopy classification of lesion	Number of patients	%
No dysplasia	4	4
G1	32	34
G2	53	56
Suspected malignant invasion	6	6
Total	95	100

Table 6. — *Distribution of histopathological results in the studied group.*

Histopathological results	Number of patients	%
No dysplasia	22	23
LG	17	18
HG	50	53
Squamous cell carcinoma	6	6
Total	95	100

patients. Three of four cytological examination were classified as HSIL and colposcopic as G2. Compatibility between colposcopy and histopathological result in the studied group is shown in Table 8.

Methods sensitivity and specificity of colposcopic analysis was compared with histopathological method. Diagnostic sensitivity of colposcopic method was 0.986 (95% CI: 0.916−0.999) and diagnostic specificity 0.136 (95% CI: 0.036−0.360). The authors also tested sensitivity and specificity of colposcopic analysis in the group without dysplasia or low grade dysplasia with group that included high grade dysplasia and cancer. In this case the diagnostic sensitivity of colposcopic method was 0.804 (95% CI: 0.672−0.893) and diagnostic specificity was 0.641 (95% CI: 0.472−0.783).

Table 7. — *Compatibility between cytological and histopathological results in the studied group.*

PAP smear	PHD			
	No dysplasia	LG	HG	Ca
LSIL	4	5	4	1
HSIL	18	12	46	1
Squamous cell carcinoma	0	0	0	4
Total	22	17	50	6

Table 8. — *Compatibility between colposcopical and histopathological results in the studied group.*

Colposcopy	Histopathological results			
	No dysplasia	LG	HG	Ca
0	3	0	1	0
G1	11	11	10	0
G2	7	6	38	2
Squamous cell carcinoma	1	0	1	4
Total	22	17	50	6

Discussion

For further diagnosis and treatment, patients with CINs revealed by Pap smear test were referred to Clinical Hospital Centre "Sestre milosrdnice". This is the reason for the high percentage of patients with HSIL in the study (80%). According to the recommendations of Croatian Society of Gynaecology and Obstetrics Colposcopy, a screening technique for further diagnostics exam was performed in all patients with CINs [39]. Depending on the colposcopy findings, further histopathological confirmation was performed, or no action was taken in cases of low grade intraepithelial lesions. Colposcopy also enables good biopsy and therefore more accurate diagnosis. [40]. The addition of a Pap smear at the time of colposcopy has the potential role of recognizing high-grade cervical dysplasia [41]. Colposcopy and cytological correlation is reported to be 80% (30). In the present study it was 59% in all colposcopic grades. In G2/HG group, correlation was 76% and in G1/LG group it was 65%. This result implicates overtreatment. Lowest correlation was for normal findings (3/22, 14%), making colposcopy inappropriate for normal finding confirmation after cytology screening. Squamous cell cancer of the cervix was found in 4/6 (67%) and G2/HG was found in 2/6 (33%). This could be considered as a clinically satisfactory result. It is also clear that colposcopy is better in recognising higher grades of cervical premalignant changes.

In four of the 22 cases of histopathology, no dysplasia group had chronical cervicitis. Three cases were graded as HSIL/G2 and one as LSIL/G1 by cytology and colposcopy,

respectively. Therefore, both cytology and colposcopy recognise chronic cervicitis as a higher grade of CIN. In one case, the authors found a discrepancy between colposcopic possible cervical cancer and normal histopathology. This case was thoroughly investigated. Cytology screening grade was HSIL (CIS) and HPV 16 and HPV 18 positive. Colposcopy showed atypical capillary pattern. Repeated colposcopy-guided biopsy after three months confirmed normal histopathology. In this particular case, further follow up is mandatory in order to elucidate discrepancy.

Seven patients with normal histopathology finding had G2 changes at colposcopy and CIN 2 or higher score at cytology screening and four of them had HPV HR. Three months after initial biopsy, cytology screening and colposcopy were repeated and in six patients colposcopy-guided biopsy was performed. HSIL was found in four patients at cytology screening. Three of them had G2 and one G1 at colposcopy. Histopathology in all four was HG (CIN 2 or higher).

Eleven patients graded as G1 or lower at colposcopy had HG at histopathology. According to Croatian Gynaecology and Obstetrics Society guidelines, histopathological verification in G1 group is not recommended [39]. After three months, repeated histopathological evaluation was performed and 36% (4/11) had HG, while the other seven had lower graded changes. Some of the lower graded results might have been caused by previous biopsy of the small surface changes that were also therapeutic.

In all investigated cases, specificity was very high but sensitivity was low as in other published studies [42]. Very high sensitivity of the colposcopy enables detection of premalignant changes of the cervix. Discrepancies between results of cytology, colposcopy, and histopathology should be re-examined because they can hide methods faults. The present results confirm that premalignant changes of the cervix should be diagnosed with use of cytologic screening, colposcopy, and confirmed by histopathology as a gold standard. Yet, it is important to remember that individuals and organs have varying sizes and morphology [43]. Colposcopy enables prediction of histopathology grade in selected groups.

Conclusion

Rio de Janeiro 2011 colposcopic classification enables distinction of CINs. It also improves comparison with cytology and histopathology. Compatibility of the classification grades are better in higher grades. Combination of cytology screening and colposcopy is a good method for detection of epithelial premalignant and early stages of malignant changes of the cervix. All patients with higher grades of intraepithelial cervical changes discovered by cytology or colposcopy should be verified by histopathology. All discrepancies should be thoroughly investigated.

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