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Original Research

Diagnostic value of colposcopy for cervical intraepithelial neoplasia 2–3/carcinoma *in situ* and microinvasive cervical cancer

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Objective: The aim of this study was to assess the diagnostic value of colposcopy for the diagnosis of cervical intraepithelial neoplasia 2–3/carcinoma *in situ* and microinvasive cervical cancer. *Methods*: Sensitivity, positive predictive value, and rate of false negative results of colposcopy were calculated in 718 patients with verified cervical intraepithelial neoplasia 2–3/carcinoma *in situ* and microinvasive cervical cancer. Assessment was made after final histological verification referring to the estimated diagnosis at colposcopic examination based on International Federation for Cervical Pathology and Colposcopy criteria. *Results*: A full agreement of colposcopic and morphological diagnosis was observed in 329 of 718 cases, resulting in a colposcopy sensitivity of 45.8% for the diagnosis of cervical intraepithelial neoplasia 2–3/carcinoma *in situ* and microinvasive cervical cancer. A type 3 transformation zone, dominant in patients with cervical intraepithelial neoplasia 2–3/carcinoma *in situ* and microinvasive cervical cancer, regardless of age and neoplasia grade (observed in 81.3% of patients included in the study), and a high rate of acetowhite lesions that were not visible (36.6% of patients) limited the sensitivity of colposcopy and colposcopy-guided biopsy, resulting in underdiagnosis, even in young patients. The risk of underdiagnosis grew significantly in women older than 30 years because of the growing incidence of non-visible acetowhite lesions ($p = 0.01$). This study suggests that large loop excision of the transformation zone may be recommended as an optimal diagnostic procedure in women with high grade squamous intraepithelial lesion (HSIL)+ cytology, even in the absence of lesions at colposcopy. *Conclusion*: Colposcopy and colposcopy-guided biopsies are not always sensitive enough to assess maximal degree and even the presence of cervical neoplasia. This study suggests that large loop excision of the transformation zone may be recommended as an optimal diagnostic procedure in women with HSIL+ cytology, even in the absence of lesions at colposcopy.

Keywords

Colposcopy; Cervical intraepithelial neoplasia 2–3/carcinoma *in situ*; Microinvasive cervical cancer; Type of transformation zone; False negative result

1. Introduction

Cervical cancer can be prevented by detecting and treating pre-cancerous lesions in the cervix before the development of invasive cervical cancer [1, 2]. This is related to various factors, such as the possibility of disease visualization, slow neoplastic lesion development (over 8–10 years or even several decades), well-defined clinical forms of precancerous lesions, known pathogenesis associated with high risk human papillomavirus (HPV), infection and adequately sensitive and specific diagnostic tests, such as HPV-testing and cytology [1, 2].

The subsequent diagnostic stage after the abovementioned screening and triage tests is colposcopy referral. Colposcopy is considered a definitive diagnostic tool for high-grade cervical intraepithelial neoplasia 2–3/carcinoma *in situ* and microinvasive cervical cancer in patients with cytological abnormalities (the threshold often starts from equivocal cytology results, such as atypical squamous cells of undetermined significance, with atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion and high grade squamous intraepithelial lesion (HSIL) as an immutable indication for colposcopy and biopsy to exclude high-grade lesions) [2].

Colposcopy is also essential for revealing biopsy sites; histopathological diagnosis of biopsy traditionally defines further treatment.

Some data, however, suggest inadequate sensitivity, specificity, and positive predictive value of colposcopy for the diagnosis of cervical intraepithelial neoplasia 2 and higher-grade lesions (cervical intraepithelial neoplasia 2+), mostly in women with cytological abnormalities revealed in organized screening programs.

In the ASCUS-LSIL Triage Study the sensitivity for CIN2+ of an online colpophotographic assessment of high-grade disease was 39%. The sensitivity for CIN2+ of a high-grade diagnosis by Reid Index scoring was 30%. All acetowhite lesions should be assessed with biopsy to maximize sensitivity of colposcopic diagnosis with good specificity [3].

Brown *et al.* [4] show a wide variety of colposcopy diagnostic value rates depending on biopsy indications: colposcopic diagnostics of cervical intraepithelial neoplasia 2+ or any atypical picture. The mean method sensitivity is 68.5%

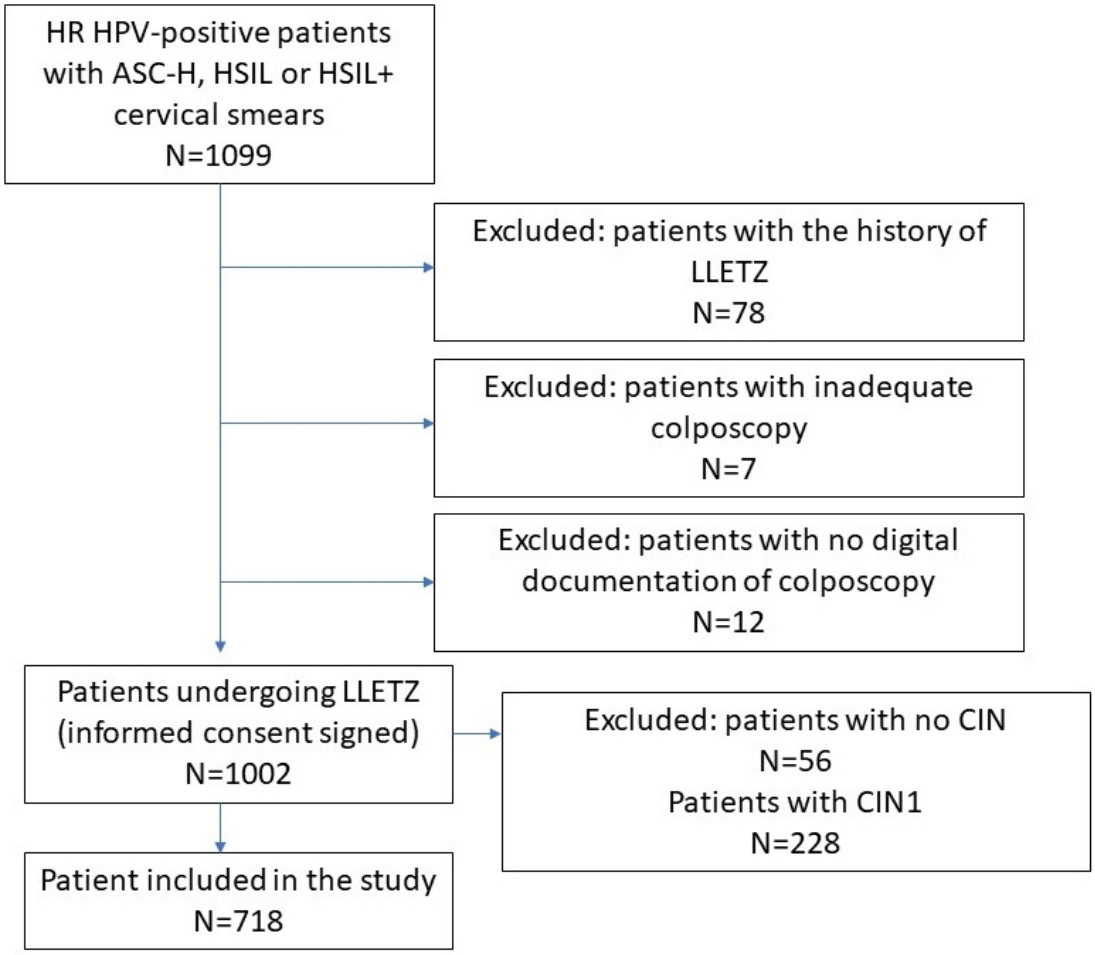

Fig. 1. Flow-chart of patient selection for the study.

(95% CI 59.9–77.1) in the first case and 95.7% (95% CI 93.4–98.0) in the last case, with specificity varying from 75.9% (95% CI 69.3–82.5) to 34.2% (95% CI 27.0–41.4), respectively [4]. Thus, the absence of acetowhite cervical lesions might not exclude cervical intraepithelial neoplasia 2+ in HPV-positive patients with cytological abnormalities.

To solve this problem, random multifocal biopsies are suggested in cervix quadrants with no visible lesions in this patient category [5, 6]. Regardless of skill, performing more biopsies increases the sensitivity of colposcopy [7]. Zuchna *et al.* [8] reported 66.2% sensitivity of CIN2+ when up to three guided cervical biopsies were taken regarded as a diagnostic test with the cone specimen as reference standard.

Pretorius *et al.* [6] reveal the location of lesions exclusively in the cervical canal with negative results of random biopsies in 9.3% of cases with cervical intraepithelial neoplasia 2+ and 18.5% of cervical intraepithelial neoplasia 3+. According to S. Sorbye *et al.* [9] in the follow-up of 520 women with a negative cervical biopsy after ASC-H or HSIL cytology, the risk of CIN2+ was 23.8% (124/520) including six cases of invasive cervical cancer. Hence, all women with negative cervical biopsy require follow-up before resumption of routine screening.

This suggests that the probability of false negative colposcopy results in women with a high risk of cervical cancer is relatively high. There are a limited number of studies on diagnostic pitfalls associated with colposcopically non-visualized cervical lesions (including invasive cervical cancer) and underdiagnoses in focal biopsies. Detailed analysis of colposcopic and morphological hypodiagnostics is crucial to reveal the predictors of false-negative colposcopy results and prevent dramatic consequences of misdiagnosis.

The aim of this study was to assess the colposcopy diagnostic value for the diagnosis of cervical intraepithelial neoplasia 2–3/carcinoma *in situ* and microinvasive cervical cancer and to identify risk factors for false-negative colposcopy results.

2. Materials and methods

The study comprised 718 patients with CIN2+ (116 patients with CIN2, 490 with CIN3, and 112 with microinvasive cervical cancer, among which 100 patients were in stage 1A1 and 12 were in stage 1A2). The age ranged from 19–63 years (mean age, 34.0 $\pm$ 7.1 years). The patients were examined in the N.N. Blokhin National Medical Research Center of Oncology from 2010–2019 after receiving positive HPV-

testing and abnormal cervical cytology results (atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion/HSIL/HSIL+) with no visible lesion at visual inspection.

Inclusion criteria included histologically confirmed final diagnosis of cervical intraepithelial neoplasia 2–3/carcinoma *in situ* or microinvasive cervical cancer, and adequate colposcopy with documented digital registration (Fig. 1).

Exclusion criteria included patients with a history of previous large loop excision of the transformation zone or conization. These patients were excluded because the transformation zone was completely removed, which affected the representability of colposcopy.

All patients were colposcopically assessed with digital documentation of cervical pictures using LeiseCap software (1.0, Leisegang, Germany) in the Leisegang 3MV colposcopic system (Leisegang, Germany). All colposcopies were performed by one practitioner with more than 30 years of experience. Colposcopy sensitivity was assessed after final histological verification in large loop excision of the transformation zone specimens (excisions were performed even if no colposcopic changes were seen because of the high risk of cervical cancer in HPV-positive women with atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion/HSIL/HSIL+ cytology results). All patients signed an informed consent form that explained the reasons for performing large loop excision of the transformation zone, as well as the risks and adverse effects of the procedure.

Colposcopic features assessed in the study included the presence of acetowhite epithelium and its characteristics (density, mosaics, punctation, layers, papillae, iodine-negative areas, and atypical vessels). Diagnosis of atypical colposcopic pictures grade 1 and 2 and suspected invasion was based on the International Federation for Cervical Pathology and Colposcopy criteria (2011, Rio-de-Janeiro) [10].

The relative square rate (%) of a lesion and general ectocervix surface was assessed using LeiseCap software tools, as a direct comparison of a lesion square is inappropriate in patients with various cervix sizes. Transformation zone visibility criteria were as follows: all transformation zones were visible on the ectocervix, including the squamous-columnar junction, which corresponds to a type I transformation zone according to International Federation for Cervical Pathology and Colposcopy nomenclature; the transformation zone has an endocervical component, but the squamous-columnar junction may be visualized by instrument-assisted inspection corresponding to a type 2 transformation zone; the transformation zone is partially or fully located in the endocervix with no visible squamous-columnar junction corresponding to type 3 [10, 11].

Statistical analysis was performed with standard parametric and non-parametric methods using Statistica 13.0 software (Tibco Software, Palo Alto, CA, USA). One-sided Fisher's Exact Test and chi-square test were used to reveal correlations between colposcopy conclusions and neoplasia grade identified in large loop excision of the transformation zone specimens, patient age, and transformation zone type. $p < 0.05$ (95% confidence interval) indicated a significant difference. Colposcopy sensitivity and positive predictive value were calculated, as well as the rate of false-negative colposcopy results.

3. Results

There was no significant difference between the ages of patients with various grades of neoplasia. The mean age of patients with cervical intraepithelial neoplasia 2, cervical intraepithelial neoplasia 3/carcinoma *in situ*, and microinvasive cervical cancer was 32.8 ± 8.4 years, 34.1 ± 6.8 years and 35.7 ± 7.6 years, respectively ($p = 0.25$). The vast majority of patients were of fertile age: 697 patients were younger than 49 years, 657 were younger than 44.

This study showed that transformation zone type 3 was the most prevalent in patients with high-grade cervical intraepithelial neoplasia and microinvasive cervical cancer. A type 1 transformation zone was observed in 93 (13.0%) patients, type 2 in 41 (5.7%) patients, and type 3 in 584 (81.3%) patients.

Rates of transformation zone type 1 and 3 correlated with patient age (Table 1). The rate of type 1 significantly decreased, while type 3 increased with age ($p = 0.01$).

Table 1. Rate of transformation zone types in various groups of patients (age, neoplasia grade, and relative lesion square) with cervical intraepithelial neoplasia 2–3/carcinoma *in situ* and microinvasive cervical cancer.

Transformation zone type	Type 1	Type 2	Type 3	Totals
Age, years				
19–29	54 (27.1%)	15 (7.5%)	130 (65.4%)	199
30–39	36 (9.6%)	21 (5.6%)	319 (84.8%)	376
40–49	1 (0.8%)	4 (3.3%)	117 (95.9%)	122
Older than 50	0	0	21 (100%)	21
Neoplasia grade				
CIN2	26 (22.4%)	5 (4.3%)	85 (73.3%)	116
CIN3	59 (12.1%)	31 (6.3%)	400 (81.6%)	490
Microinvasive cervical cancer	8 (7.1%)	5 (4.5%)	99 (88.4%)	112
Relative lesion square, %				
<1	6 (2.3%)	8 (3.0%)	249 (94.7%)	263
1–5	19 (12.8%)	8 (5.4%)	122 (81.9%)	149
6–20	26 (20.2%)	13 (10.1%)	90 (69.8%)	129
21–50	20 (24.0%)	4 (4.8%)	60 (71.2%)	84
>50	22 (23.7%)	8 (8.6%)	63 (67.7%)	93
Totals	93	41	584	718

Even in patients <29 years, a type 3 transformation zone was observed in 65.4% of cervical intraepithelial neoplasia 2–3/carcinoma *in situ* and microinvasive cervical cancer cases. Further age-related increase resulted in an 84.8% rate at 30–39 years and 95.9% in those aged 40–49 years. In patients with cervical intraepithelial neoplasia 2–3/carcinoma *in situ*

Table 2. The accuracy of colposcopic diagnostics of cervical intraepithelial neoplasia 2–3/carcinoma *in situ* and microinvasive cervical cancer in various age groups, transformation zone types, and neoplasia grades.

Diagnostic accuracy	Full agreement	Colposcopic overdiagnosis	Colposcopic underdiagnosis/no lesion	Totals
Age, years				
19–29	99 (49.7%)	20 (10.1%)	80 (40.2%)/54 (27.1%)	199
30–39	184 (48.9%)	27 (7.2%)	165 (43.9%)/133 (35.4%)	376
40–49	41 (33.6%)	9 (7.4%)	72 (59.0%)/61 (50%)	122
>50	5 (23.8%)	2 (9.5%)	14 (66.7%)/10 (47.6%)	21
Transformation zone type				
Type 1	61 (65.6%)	9 (9.7%)	23 (24.7%)/9 (9.7%)	93
Type 2	25 (61.0%)	1 (2.4%)	15 (36.6%)/7 (17.1%)	41
Type 3	242 (41.4%)	48 (8.3%)	294 (50.3%)/227 (38.9%)	584
Neoplasia grade				
Cervical intraepithelial neoplasia 2	50 (43.1%)	33 (28.4%)	33 (28.4%)/30 (25.9%)	116
Cervical intraepithelial neoplasia 3/carcinoma *in situ*	244 (49.8%)	25 (5.1%)	221 (45.1%)/170 (34.7%)	490
МРШМ	34 (30.4%)	0 (0)	78 (69.6%)/43 (38.4%)	112
Totals	329	58	331	718

and microinvasive cervical cancer older than 50 years, all had a type 3 transformation zone.

A type 2 transformation zone was observed as equally rare in all age groups. Vallikad *et al.* (2017) [12] show that reproducibility of a "type 2 transformation zone" conclusion is poor, even in experienced colposcopists and it is often defined as type 3 [8]. It may be associated with rapid endocervical displacement of the squamous-columnar junction in the course of cervical neoplasia development, which makes it difficult to reveal squamous cell carcinoma instrumentally close to the external orifice.

Polymorphic high-grade cervical neoplastic lesions have been shown to be located in occult squamous cell carcinoma and underlying crypts [13–15]. Thus, an age-related increase in the type 3 transformation zone led to a decrease in the diagnostic value of colposcopy in some cases, resulting in the absence of visible lesions on the ectocervix. Only 9.6% of women aged 30–39 years had a type 1 transformation zone, making the colposcopy conclusion reliable in only 1 out of 10 patients. The difference between the type 3 transformation zone rates was significant between the 19–29 and 30–39 year-old age groups. These data confirmed the risk of neoplasia underdiagnosis and the absence of visible colposcopic lesions to be clinically relevant in patients >30 years with cervical intraepithelial neoplasia 2–3/carcinoma *in situ* and microinvasive cervical cancer.

There was no correlation between the rate of transformation zone type and neoplasia grade. The microinvasive cervical cancer group had a higher prevalence of type 3 and less type 1 than that of patients with cervical intraepithelial neoplasia 2 (Table 1), but the type 3 transformation zone was dominant in all neoplasia grades.

The relative square of visible colposcopic lesions was as follows: no visible lesions in 263 (36.6%), 1–5% in 149 (20.8%), 6–20% in 129 (18.0%), 21–50% in 84 (11.7%), >50% in 93 (13.0%) patients. Thus, more than one-third of patients showed no visible lesion on the ectocervix and no reason for biopsy. In 42.6% of type 3 transformation zone cases, there were either no visible lesions or the square of a lesion located very close to or in the cervical canal was too small to interpret (Fig. 2).

Table 1 and Fig. 3 illustrate the relative square lesion in patients with various transformation zone types. Cervical lesions of various sizes may be well visualized, even in patients with type 3 transformation zones [11], which do not contradict these findings, but at the same time, almost half of patients with a type 3 transformation zone have no visible or interpretable lesions. This may be explained by the absence of cervical ectopy at HPV inoculation and neoplasia development resulting in cervical intraepithelial neoplasia foci formation in the occult part of the transformation zone in the cervical canal.

The absence of visible acetowhite lesions in 36.6% of patients with confirmed cervical intraepithelial neoplasia 2–3/carcinoma *in situ* and microinvasive cervical cancer demonstrated the insufficient reliability of colposcopy for morphological assessment of lesions in patients with cytological anomalies, as the absence of atypical colposcopic pictures did not exclude cervical intraepithelial neoplasia 2+ in the occult part of the transformation zone and endocervical crypts. Random 4-quadrant cervical biopsies and endocervical curettage in women with positive screening, but negative colposcopy may be a way to overcome this issue [5, 6]. A pooled multicenter study by Hu *et al.* [5], however, shows that in random biopsies without endocervical curettage, 9.3% of cervical intraepithelial neoplasia 2+ and 18.5% of cervical intraepithelial neoplasia 3+ are missed.

A type 3 transformation zone was the most prevalent, even in patients with a high relative square of lesions (involving more than half of the ectocervix). Having an obvious location for biopsy, these patients still presented a certain risk for neoplasia grade underdiagnosis, as the most severe neoplastic changes might be located inside the cervical canal. The risk for underdiagnosis was minimal in patients with a type

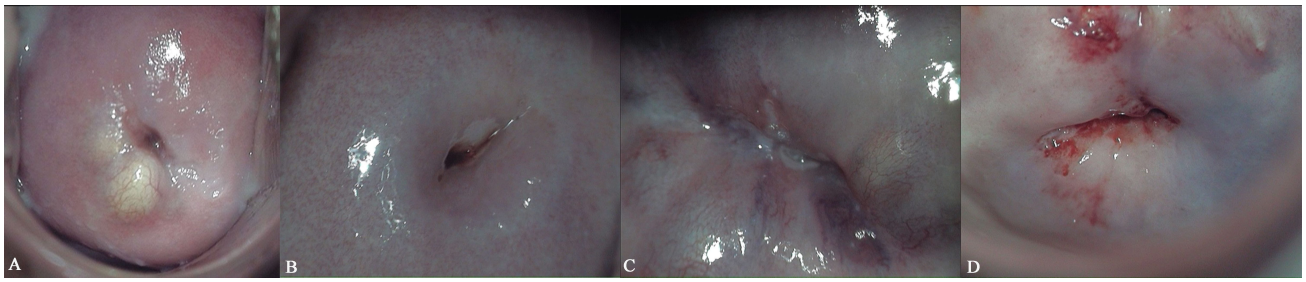

Fig. 2. Cases of colposcopy low diagnostic value due to non-visible lesions or lesions difficult to interpret in patients with confirmed cervical intraepithelial neoplasia 3/carcinoma *in situ* and microinvasive cervical cancer. All photos are taken after 5% acetic acid is applied. (A) Colposcopy (7× amplification) of patient V., age 34 years with a history of high grade squamous intraepithelial lesion (HSIL) cytology and type 16 human papillomavirus (HPV). Adequate colposcopy conditions, a type 3 transformation zone, and a non-visible squamous-columnar junction or acetowhite lesion. Large loop excision of the transformation zone verified cervical intraepithelial neoplasia 3/carcinoma *in situ*. (B) Colposcopy (15× amplification) of patient U., age 42 years, with a history of HSIL cytology and type 16 HPV. Adequate colposcopy conditions, a type 3 transformation zone, and a non-visible squamous-columnar junction. Note very limited acetowhite lesions at the canal orifice occupying less than 1% of the cervix. Large loop excision of the transformation zone verified cervical intraepithelial neoplasia 3/carcinoma *in situ*. (C) Colposcopy (30× amplification) of patient D., age 49 years with a history of HSIL cytology and type 16 HPV. Adequate colposcopy conditions, a type 3 transformation zone, and a non-visible squamous-columnar junction. Note several limited acetowhite lesions at the canal orifice occupying less than 1% of the cervix. Large loop excision of the transformation zone verified cervical intraepithelial neoplasia 3/carcinoma *in situ* in cervical crypts. (D) Colposcopy (15× amplification) of patient L., age 46 years with a history of HSIL cytology and type 16 HPV. Adequate colposcopy conditions (some insignificant bleeding occurred after taking cytology), a type 3 transformation zone, and a non-visible squamous-columnar junction. Note an equivocal lesion in the canal. Large loop excision of the transformation zone verified microinvasive cervical cancer with 5 mm invasion and cervical intraepithelial neoplasia 3/carcinoma *in situ* in the endocervical curettage.

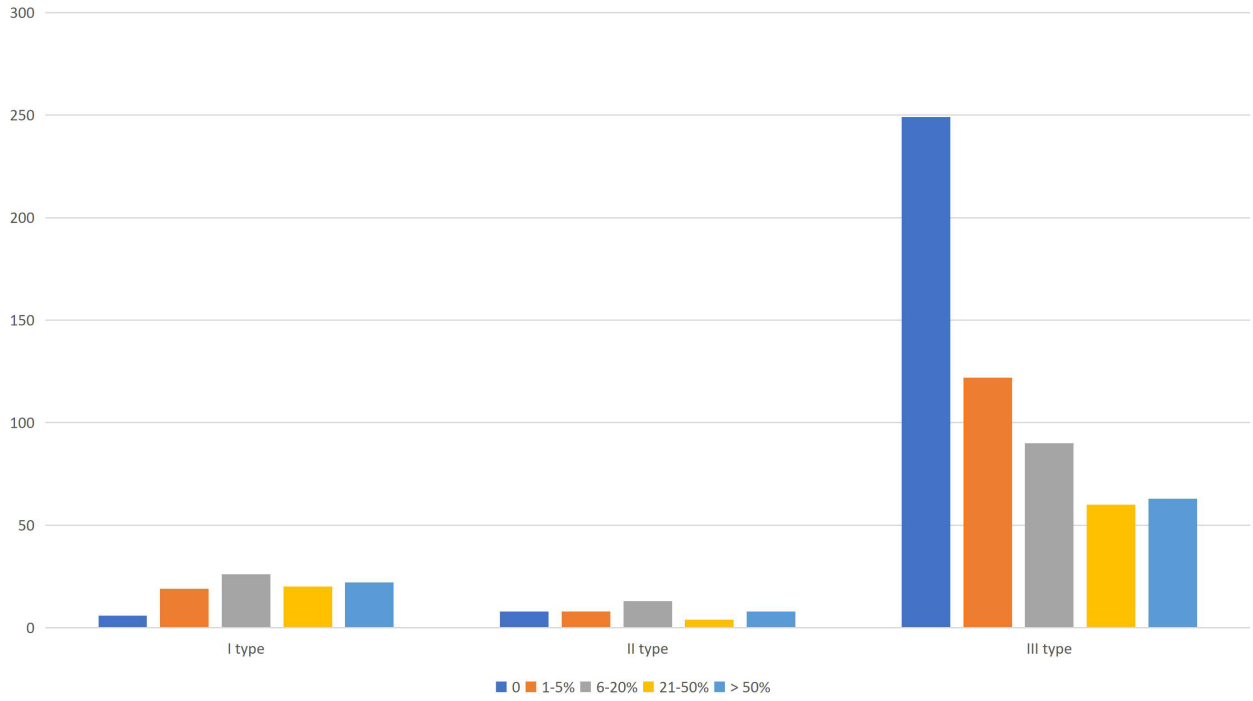

Fig. 3. Relative square lesions in various transformation zone types.

1 transformation zone and high relative lesion size, but a favorable combination was only observed in 22 (3.1%) patients.

There was no significant correlation between the relative square of ectocervical lesions and neoplasia grade.

A full agreement of colposcopic and histological diagnosis was observed in 329 (45.8%) cases. The colposcopy sensitivity was higher in patients with at least some acetowhite lesions on the ectocervix, reaching 69.4%.

Overdiagnosis of neoplasia grade was revealed in 58 patients (8.2%). It was mostly the case of patients with microinvasive cervical cancer diagnosis in cervical intraepithelial neoplasia 3/carcinoma *in situ*. Overdiagnosis is not a

problem in the women with CIN2+ because all women with CIN2+ should be treated. Large loop excision of the transformation zone would be an appropriate diagnostic and treatment procedure in either case.

Underdiagnosis, however, was the most critical colposcopy failure, and was observed in 330 (45.9%) cases, from which, in 244 (34.0%) there were no signs of acetowhite lesions on the ectocervix!

The diagnostic value of colposcopy significantly decreased with age (Table 2), which was negatively correlated with the growing prevalence of the absence of acetowhite lesions on the ectocervix and the underdiagnosis rate ($p = 0.01$). The correlation was especially strong in 40–50 year olds when compared to that of 20–30 year olds.

Colposcopy sensitivity was significantly lower in the type 3 transformation zone group than that in the type 1 group ($p = 0.001$). The underdiagnosis rate was two times higher in the type 3 group than that in the type 1 group (50.3% vs. 24.7%, respectively). Colposcopy sensitivity in patients with a type 3 transformation zone was 41.4% (Table 2).

Table 2 shows colposcopy accuracy for detection of various neoplasia grades.

The real hazard was associated with underdiagnosis of neoplasia grade, especially in cervical intraepithelial neoplasia 3/carcinoma *in situ* and microinvasive cervical cancer. In cervical intraepithelial neoplasia 2, underdiagnosis was detected in 28.4% of cases, mostly because of the absence of any acetowhite epithelium during colposcopy (in 30 of 33 cases).

There was a significant difference between the colposcopic diagnosis accuracy of cervical intraepithelial neoplasia 3/carcinoma *in situ* and microinvasive cervical cancer ($p < 0.05$) due to the high rate of microinvasion detection failure (in 69.6% of cases) (Table 2). Microinvasion underdiagnosis, both during colposcopy and random biopsies, is an obvious problem; according to Xiao *et al.* [16], colposcopy-guided biopsy sensitivity for microinvasion is only 4.4%, with a 95.6% rate of false negative results.

This is not surprising considering that histologic microinvasive cervical cancer criteria start from <1 mm invasion in the background of cervical intraepithelial neoplasia 3/carcinoma *in situ*. These minimal histological changes, as well as the usual invasion of 1–2 mm do not have specific colposcopic signs.

4. Discussion

Random biopsies rarely reveal microinvasion foci, resulting in cervical intraepithelial neoplasia 3/carcinoma *in situ* diagnosis with microinvasive cervical cancer as an incidental finding of cone specimens; in such cases, treatment is not changed by underdiagnosis. However, in 36.5% of patients with microinvasive cervical cancer, cervical intraepithelial neoplasia 1–2 areas are present alongside microinvasive cervical cancer and cervical intraepithelial neoplasia 3 [13]. Thus, in cases of random biopsies, especially in the absence of visible acetowhite changes during colposcopy, there is a potential for cervical intraepithelial neoplasia 1–2 diagnosis leading to inappropriate follow-up or destruction treatment. Missed invasion foci typically may not be eliminated by rather shallow destruction, resulting in occult progression to advanced cancer stages. These results suggest that large loop excision of the transformation zone is optimal for histological verification of neoplastic lesions in women with HSIL cytology results.

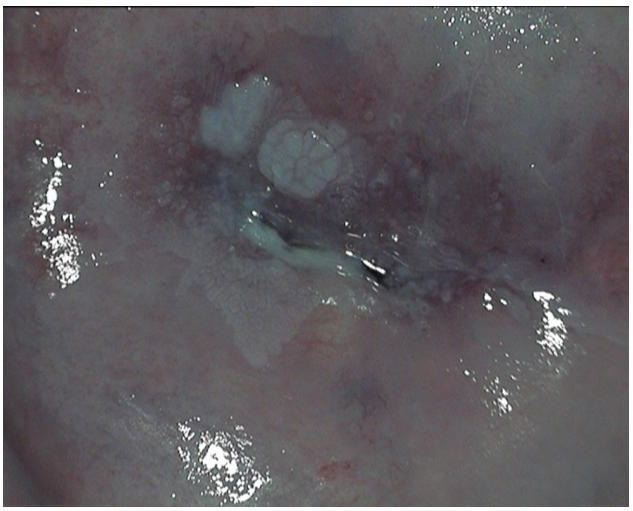

Fig. 4. A case illustrating the coexistence of various neoplasia grades in one patient. Colposcopy (15× amplification) of patient K., age 44 years, with a history of high grade squamous intraepithelial lesion (HSIL) cytology and type 16 human papillomavirus (HPV). Adequate colposcopy conditions, a type 3 transformation zone, and a non-visible squamous-columnar junction. An ectocervical lesion is observed consisting of alternating areas of acetowhite epithelium with various thicknesses forming from light to highly opaque mosaics. A very thick acetowhite epithelium ridge goes into the cervical canal. A morphological study confirms coexistence of cervical intraepithelial neoplasia 1, 2 and 3.

Endocervical curettage with multifocal biopsies may be seen as a diagnostic alternative to large loop excision of the transformation zone [17]. The yield on the endocervical curettage increases in the setting of unsatisfactory colposcopy [18]. Some studies showed the procedure to be of limited value for evaluating endocervical lesions and the reproducibility of curettage-rendered diagnosis is a concern [19–21]. Thus, Mueller K *et al.* [19] found the agreement between endocervical curettage findings and the results of conization to be only 49.1% irrespective of patient age, transformation zone or the patient's menopausal status.

Modern morphological conception of cervical intraepithelial neoplasia 2–3/carcinoma *in situ* and early cervical cancer development indicates lesion origin from reserve cells of the transformation zone, squamous-columnar junction, and underlying endocervical crypts, as well as lesion polymorphism with the possibility of the simultaneous presence of various neoplasia grades [12–14]. The coexistence of various neoplasia grades in one patient might be the reason for un-

derdiagnosis, even in colposcopy-guided biopsies, as a lesion with maximal neoplasia grade might not be visualized when located inside a cervical canal and endocervical crypts, and thus, might be missed by biopsy [22–25].

In some of these cases, visible signs of neoplasia polymorphism were observed colposcopically simultaneously with acetowhite epithelium with various characteristics (thin, moderate, and thick epithelium corresponding to atypical colposcopic pictures grade 1, 2, and suspect of invasion, Fig. 4).

5. Conclusions

A type 3 transformation zone, dominant in patients with cervical intraepithelial neoplasia 2–3/carcinoma *in situ* and microinvasive cervical cancer, regardless of age and neoplasia grade (observed in 81.3% of the included patients), and a high rate of non-visible acetowhite lesions (36.6% of patients) limited the sensitivity of colposcopy and colposcopy-guided biopsy, resulting in underdiagnosis, even in young patients. The risk of underdiagnosis grew significantly in women >30 years because of the growing incidence of non-visible acetowhite lesions (p = 0.01). This study suggested that large loop excision of the transformation zone might be recommended as an optimal diagnostic procedure in women with HSIL+ cytology, even in the absence of lesions during colposcopy.

Author contributions

LIK—conception, study design, data collection, manuscript writing; ISS—study design; INL—data collection, statistics.

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of N.N. Blokhin National Medical Research Center of Oncology (approval number: 2/2010).

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Conflict of interest

The authors declare no conflict of interest.

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