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Original Article

# Mandatory colposcopic findings of severe cervical dysplasia. Are there key-signs that need our special attention?

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ABSTRACT

*Introduction.* – To test for colposcopic differences between CIN2+ and non CIN2+ lesions of the "major changes" of the RIO 2011 nomenclature of the International Federation of Cervical Pathology (IFCPC).
*Material and methods.* – Retrospective cohort analysis of colposcopic examinations of patients with histologically confirmed CIN2+ ($n = 99$) and non CIN2+ ($n = 102$) lesions during a four years period. Main outcome measures: leukoplakia, coarse mosaic and punctuation, dense acetowhitening, sharp boarders, ridge sign, atypical vessels.
*Results.* – Only coarse punctuation ($P \leq 0.001$; OR 9.64; 95% CI 2.15–43.13), coarse mosaic ($P \leq 0.001$; OR 4.00; 95% CI 1.83–8.73) and dense acetowhitening ($P \leq 0.05$; OR 1.86; 95% CI 1.06–3.26) occurred more frequently in CIN2+ lesions which were confirmed as predictors by a regression analysis.
*Conclusions.* – Only coarse punctuation and coarse mosaic followed by dense acetowhitening as part of the "major changes" of the IFCPC Rio 2011 nomenclature achieve predictive values for CIN2+ lesions and should be therefore emphasized in colposcopy.



## Introduction

According to the World Health Organization, more than 270,000 women die from cervical cancer per year [1]. Prevention and early detection of cervical carcinoma and its precursor lesions is still a major issue in world health policy. These dysplastic lesions are situated at the transformation zone of the cervix uteri. The severity of dysplasia and the time of its detection determine the chance of invasive growth. Before acquiring the ability for malignant invasion dysplastic lesions may rest for up to ten years [2]. Chronic infection of the cervix uteri with high-risk human papilloma viruses (HPV) is necessary for development of precursor lesions of the cervix carcinoma [3]. Besides HPV vaccination, Pap smear analyses and early HPV-detection, colposcopy is one of the four major tools for detection and evaluation of dysplastic lesions.

For description and evaluation of colposcopic findings, the nomenclature of the International Federation of Cervical Pathology (IFCPC) Rio 2011 is a world wide standard [4].

After general assessment, which addresses quality of the examination (adequate or inadequate), the colposcopist defines the evaluated area of the cervix uteri as normal or abnormal, suspicious for invasion or might detect miscellaneous findings.

For abnormal colposcopic findings, the nomenclature of the IFCPC Rio 2011 distinguishes between minor, major and non-specific findings. All signs are supposed to "mirror" histopathology: "minor" change lesions correlate with CIN 1 lesions whereas "major" change lesions mainly correlate with CIN2+ in histopathology according to the IFCPC [4].

On the other hand, previous studies have shown conflicting results regarding validity of some of the "major signs" and suggested modifications of the colposcopic evaluation to improve correlation with the histopathological result [5,6].

Therefore, aim of this study is to investigate the colposcopic "major signs" of the IFCPC Rio 2011 nomenclature in a

*Abbreviations:* CIN, cervical intraepithelial neoplasia; ES, estimated size; IFCPC, International Federation of Cervical Pathology; i.a., inter alia; NPV, negative predictive value; SD, Standard deviation; PPV, positive predictive value; SEN, sensitivity; SPEC, specificity.

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setting of patients with histologically confirmed CIN2+ and non CIN2+ lesions for differences in correlation with histopathology.

## Material and methods

This study was approved by the ethical board of the University of Luebeck, Germany (registration number 12-234). Data of all patients ($n = 517$) who were referred to the Department of Obstetrics and Gynecology at University hospital of Luebeck, Germany because of suspected cervical dysplasia in a period of four years were screened retrospectively.

Inclusion criteria were defined as colposcopy performed by a specially trained colposcoper, current Pap smear test, histological confirmed cervical dysplasia. Patients with transformation zone type 3 on colposcopic examen ($n = 97$), incomplete set of data or negative informed consent were excluded. In total, $n = 201$ patients could be included.

The Department of Obstetrics and Gynaecology at University hospital of Luebeck is certified and registered for treating patients with dysplasia according to national guidelines by the "*Arbeitsge*-Arbeitsgemeinschaft Zervixpathologie und Kolposkopie e.V.". Examinations were performed by an experienced senior gynaecologist and by a supervised advanced resident. Both colposcopers were trained for colposcopy following the IFCPC guidelines. In Germany, this training consists of at least a basic course (8 hours) and an advanced course (14 hours) and ends with a colposcopic exam. Cervical biopsy was performed under colposcopic surveillance using Eppendorf cervical biopsy forceps. Examinations were performed with a Leisegang 3MVS LED colposcope (45.000–52.000 Lux; 300 mm free working distance) with integrated camera. Portio-examinations were performed: natively, after aceto acid 5% and iodine stained. The most severe colposcopic sign determined the overall diagnosis.

### *Outcome measure*

The outcome measure was defined according to IFCPC Rio 2011 nomenclature: leukoplakia, coarse mosaic and coarse punctuation, dense acetowhitening, sharp boarders, ridge sign, atypical vessels. The computer software ORBIS, Agfa HealthCare GmbH, Bonn, Germany was standardised used for acquisition of patient data. Dichotome signs were recorded yes/no.

The colposcopy of the first patient contact was used for analysis for this study. The histological diagnosis was received afterwards. Thereby, an observer bias resulting from histological diagnosis should be avoided.

### *Histological diagnosis*

Histological analysis was done by the Institute of Pathology of the University of Luebeck. Biopsies or resected cones were embedded in formalin and later stained by Haematoxylin-Eosin staining for microscopic evaluation.

A histological result from a biopsy was available for all patients. Additionally, $n = 81$ patients received a surgical therapy which consisted in $n = 75$ cases of loop electrosurgical excision procedures. Two patients had a hysterectomy and four patients different surgical interventions (e.g. cold knife conization, etc.).

### *Power calculation*

A statistical power analysis was performed for sample size estimation which was based on data from Pino et al., 2010 [7] and Hammes et al., 2007 [8]. The effect size (ES) was estimated with $d = 0.5$ (medium) using Cohen's (1988) criteria [9]. With an alpha 0.05 and a power of 0.80, the projected sample size needed with this ES is approximately $n = 64$ for group comparison. Thus, the proposed sample size of 201 will be more than adequate for the main objective of this study.

### *Statistical analysis*

Analysis included Mann–Whitney test for continuous data, $Chi^2$ test for categorical data and Fisher's exact T-test.

Multivariate regression analysis was used to investigate the association between the dependent variable CIN2+ lesion of the cervix and the independent predictor variables coarse leukoplakia, mosaic and punctuation, dense acetowhitening, sharp boarders, ridge sign, atypical vessels. The predictor variables were entered in a regression model using the backward stepwise elimination method. Concerning the inclusion of the variables into the regression model dichotomized dummy variables were built. A $P$-value of $\leq 0.05$ was considered statistical significant. Statistical analysis was performed using SPSS statistical package version 17.0 for windows.

## Results

Two hundred-one patients have met the inclusion criteria and were separated into two groups: CIN2+ lesion ($n = 99$) and non CIN2+ lesion ($n = 102$). A flowchart of patients is depicted by Fig. 1. Mean patients age was $31.2 \pm 7.3$ years. Comparison of basic patient demography shows a difference for smoking only (CIN2+ versus non CIN2+: 66% versus 44%; $P \leq 0.05$, Table 1).

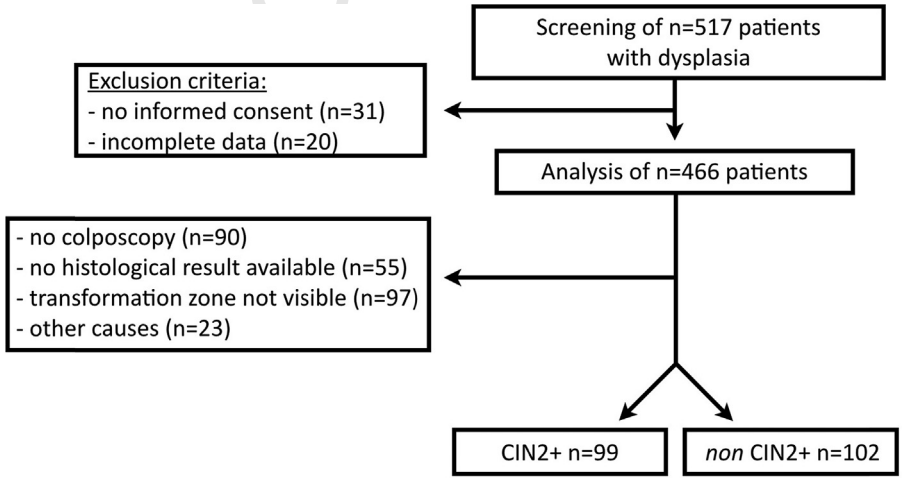


**Fig. 1.** Flowchart of patient.

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