Correlations between colposcopy and histologic results from colposcopically directed biopsy in cervical precancerous lesions

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Abstract

Introduction: Cervical cancer develops from well-defined precursor lesions in a varied period of time. Detected in early or pre-invasive stages, cervical cancer is preventable and curable, so detection of precancerous lesions is very important. Colposcopy with directed biopsy is used in the evaluation and management of patients with cervical lesions, and described as the ‘gold standard’ for the diagnosis of cervical precancer. Aim: The aim of this study is to assess the accuracy of colposcopic examination and cervical punch biopsy, to determine the correlation between these two methods. Materials and Methods: We examined 245 patients who present malignant findings at colposcopy and biopsy. Colposcopic findings in our study group: 28 (11.4%) cases were CIN I, 50 (20.4%) cases were CIN II, 150 (61.2%) cases were CIN III, 13 (5.3%) cases were micro-invasive carcinoma and four (1.6%) cases were CIS. Histological results in the 245 examined cases were: four (1.6%) cases normal, 26 (10.6%) cases CIN I, 55 (22.4%) cases CIN II, 138 (56.3%) cases CIN III, 15 (6.1%) cases micro-invasive carcinoma and seven (2.8%) cases of CIS. Results: The correlation was 78.5% in the CIN I category, 84% in the CIN II category, 88.6% (133 out of 150 patients) in the CIN III category, 46.1% for micro-invasive carcinoma and 50% for CIS. The colposcopy method incurred fewer false negatives (four patients), giving a general accuracy rate of 98.3%. Sensitivity of colposcopic examination was 83.6%. Conclusions: This study demonstrated high accuracy and correlation between colposcopy and histology, comparable with results from similar studies in the literature. Sensitivity is lower, probably because biopsies were done in all cases, during diagnostic work-up. We also demonstrated the usefulness of these two diagnostic procedures as screening tests in preclinical cervical cancer. In our study, there were cases of under or over diagnose; the benefit of colposcopy and directed biopsy is to avoid over treatment of low-grade lesion, and under treatment of high-grade lesion.

Keywords: colposcopy, precancerous lesions.

Abbreviations: CIN – Cervical intraepithelial neoplasia; CIS – Carcinoma “in situ”; ASCUS – Atypical squamous cell of undetermined significance; LSIL – Low-grade intraepithelial squamous lesions; ALTS – ASCUS/LSIL Triage Study.

Introduction

Cervical cancer is very frequent, being the second most common cancer at women worldwide, and the first cause of women’s death in Romania. Because recent studies clearly substantiate the view that cervical cancer develops from well-defined precursor lesions in a variable period of time, and that cervical cancer is preventable and curable if detected in early or pre-invasive stages, the detection of this precancerous lesions is of outmost importance. Premalignant lesions are characterized by abnormal cellular or epithelial architecture in the areas surrounding the junction between the squamous and columnar epithelium (transformation zone) of the uterine cervix [1] and are microscopically characterized as a spectrum of events progressing from cellular atypia to various grades of dysplasia or cervical intraepithelial neoplasia (CIN), before progression to invasive carcinoma [2].

The term dysplasia designates the cervical epithelial atypia that is intermediate between the normal epithelium and CIN [3]. Dysplasia was further categorized into three groups – mild, moderate and severe – depending on the degree of involvement of the epithelial thickness by the atypical cells. The term CIN denotes the whole range of cellular atypia confined to the epithelium. CIN was divided into grades I, II and III [4]: CIN I corresponded to mild dysplasia, CIN II to moderate dysplasia, and CIN III corresponded to both severe dysplasia and CIS. Thus, in 1990, a histopathological terminology based on two grades of disease was proposed: low-grade CIN comprising the abnormalities consistent with koilocytic atypia and CIN I lesions and high-grade CIN comprising CIN II and III. The high-grade lesions were considered true precursors of invasive cancer [5].

The detection of precancerous lesions is made with
the help of screening tests – most important include the Papanicolaou (Pap) smear, colposcopy and histology.

In the presence of an abnormal cytological smear, a tissue diagnosis is essential before proceeding with definitive treatment. The most common indication for colposcopic investigation of cervix is abnormal cytological smears [6], followed by clinical suspected cervical lesions biopsy. Colposcopy is more than a simple intermediate link between cytologic screening and histologic diagnosis [7].

The colposcopic diagnosis of cervical neoplasia requires an understanding and recognition of four main features: color tone and intensity of aceto-whitening, margins and surface contour of aceto-white areas, vascular pattern and iodine staining. Variations in quality and quantity of these atypical appearances help in differentiating CIN from other lesions or between types of CIN.

Low-grade lesions tend to be thin, less dense, and less extensive, with well-demarcated but irregular, feathery, geographic or angular margins. Vascular features, such as fine punctation and/or fine mosaics in aceto-white areas, may be associated with low-grade CIN. Sometimes, low-grade lesions may be detached from the squamo-columnar junction, and atypical vessels are seldom observed in low-grade lesions.

On the other hand, high-grade lesions are associated with dense, opaque, grey white, aceto-white areas with coarse punctation and/or mosaic and with regular and well demarcated borders. Visualization of one or more borders within an aceto-white lesion or an aceto-white lesion with varying color intensity is associated with high-grade lesions. These lesions often involve both lips and may occasionally harbor atypical vessels. CIN III lesions tend to be complex, extending into the endocervical canal. CIN lesions do not contain glycogen and thus do not stain with iodine and remain mustard or saffron yellow areas [2].

Colposcopy performs better in differentiation of high-grade from low-grade disease than in differentiation of low-grade disease from normal cervix [8], and correlated with directed biopsy is described as the reference investigation or ‘gold standard’ for the diagnosis of cervical precancer [9].

Study of bibliography revealed that the positive predictive rate of the colposcopic impression is better as the cervical lesion is more severe. When directed biopsies are taken, the positive predictive rate of colposcopy increases considerably. For micro-invasive disease, the positive predictive rate is quite poor, probably because of the absence of characteristic features. The choice of whether and where to biopsy is more important than assigning a colposcopic impression. ALTS quality-control colposcopists demonstrated only mediocre agreement among them and compared with clinical center colposcopists [10].

The sensitivity of enrollment colposcopy was shown to increase steadily with additional biopsy specimens in another recent ALTS analysis, regardless of any other variable [11].

The aim of this study is to assess the accuracy of colposcopic examination and cervical punch biopsy, to determine the correlation between these two methods, and to compare the data obtained with ones from bibliography.

Materials and Methods

We performed a study for precancerous lesions and cervical cancer over a period of five years, between 2006 and 2010, on 500 cases chosen from patients who sought consultation for various gynecological disorders or for prescription contraceptives, in two gynecology clinics from Craiova. Parity was from 0 to 6 with a medium of 3, and age was between 20 and 69 years.

Colposcopy was performed by the same physician on each patient, using Zeiss coloscope on an outpatient basis and, the clinical methods and criteria used were recommended by Coppleson M [6]. The colposcopically directed biopsies were taken from all examined patients, by punch biopsy forceps from the most advanced part of lesion. Biopsy fragments were processed by the usual technique for inclusion in paraffin, Hematoxylin–Eosin stained and interpreted in the Pathology Laboratory of Emergency County Hospital of Craiova.

Colposcopic examinations included:

- Direct examination of cervix with green filter and saline application;
- Examination of the cervix after test with 3% acetic acid, seeing the junction of squamous cell, erosion, papillary lesions, aceto-white areas and vascular design;
- Examination of the cervix after Lugol test in which normal squamous epithelium, which contains glycogen, it turns brown.

The colposcopic findings were classified into non-malignant and malignant categories. The non-malignant category included normal findings or viral wart changes, and the malignant category was divided into five groups: CIN I, CIN II, CIN III, micro-invasive carcinoma and CIS. Histological diagnosis was also classified into five groups: CINI, CIN II, CIN III, micro-invasive carcinoma and CIS.

Results

From all 500 patients examined, 255 patients (51%) presented non-malignant findings that do not require biopsy for histopathological examination, but required a full monitoring: bacteriological, cytological and colposcopic at different time intervals, and where not included in our study. 245 patients (49%) presented malignant findings and underwent colposcopic examination to further investigate a cytological abnormality on their pap smears – 174 cases (71.02%) or an abnormal appearance of the cervix – 71 patients (28.98%). These 245 patients represent our study group. We noticed that lesions were diagnosed in patients aged between 20 and 69 years, most cases encountered in the interval 30–49 years (Tables 1 and 2).

Table 1 – Distribution of cases by age

<table>
<thead>
<tr>
<th>Age [years]</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–29</td>
<td>33</td>
<td>13.4</td>
</tr>
<tr>
<td>30–39</td>
<td>80</td>
<td>32.6</td>
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<td>40–49</td>
<td>95</td>
<td>38.7</td>
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<td>50–59</td>
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<td>8.9</td>
</tr>
<tr>
<td>60–69</td>
<td>15</td>
<td>6.1</td>
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</table>
Table 2 – Distribution of cases by clinical and morphological parameters

<table>
<thead>
<tr>
<th>Clinical and morphological parameters</th>
<th>No. of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colposcopic findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN I</td>
<td>28</td>
<td>11.4</td>
</tr>
<tr>
<td>CIN II</td>
<td>50</td>
<td>20.4</td>
</tr>
<tr>
<td>CIN III</td>
<td>150</td>
<td>61.2</td>
</tr>
<tr>
<td>Micro-invasive carcinoma</td>
<td>13</td>
<td>5.3</td>
</tr>
<tr>
<td>CIS</td>
<td>9</td>
<td>1.6</td>
</tr>
<tr>
<td>Normal</td>
<td>4</td>
<td>1.6</td>
</tr>
<tr>
<td>CIN I</td>
<td>26</td>
<td>10.6</td>
</tr>
<tr>
<td>CIN II</td>
<td>55</td>
<td>22.4</td>
</tr>
<tr>
<td>CIN III</td>
<td>138</td>
<td>56.3</td>
</tr>
<tr>
<td>Micro-invasive carcinoma</td>
<td>15</td>
<td>6.1</td>
</tr>
<tr>
<td>CIS</td>
<td>7</td>
<td>2.8</td>
</tr>
<tr>
<td>Total</td>
<td>245</td>
<td>100</td>
</tr>
</tbody>
</table>

Colposcopic findings in our study group were: 28 (11.4%) cases were CIN I, 50 (20.4%) cases were CIN II, 150 (61.2%) cases were CIN III, 13 (5.3%) cases were micro-invasive carcinoma and four (1.6%) cases were CIS (Figure 1).

Figure 1 – Colposcopic findings in percents in our study group.

Colposcopic aspects of the selected cases showed a variety of issues that can be found isolated or associated:

- Mosaic: areas looking like pavement, composed of rectangular fields, square or polygonal, separated by dotted or red lines (Figures 2 and 3).
- Punctuation: thick aceto-white epithelium, with vascular spots on surface with variable distribution and size. Correspond to simple dysplasia, CIN I (Figures 4 and 5).
- Leukoplakia: simple shape, hypertrophic or warty. Colposcopic appearance is given by pearly white appearance, irregular surface, single or multiple plates. Correspond to CIN I, II, or III (Figures 6–8).

Histopathologic findings

Histological results in the 245 examined cases were: four (1.6%) cases normal, 26 (10.6%) cases CIN I, 55 (22.4%) cases CIN II, 138 (56.3%) cases CIN III, 15 (6.1%) cases micro-invasive carcinoma and seven (2.8%) cases CIS (Figure 9).

CIN may be suspected after colposcopic examination. The final diagnosis of CIN presence and the respective degree is made on cervical tissue specimen, dependent on the histological features concerned with differentiation, maturation and stratification of cells and nuclear abnormalities [2].

In CIN I, there is good maturation with minimal nuclear abnormalities and few mitotic figures. Undifferentiated cells are confined to the deeper layers (lower third) of the epithelium. Mitotic figures are present, but not very numerous [2] (Figures 10–12).

CIN II is characterized by dysplastic cellular changes mostly restricted to the lower half or the lower two thirds of the epithelium, with more marked nuclear abnormalities than in CIN I. Mitotic figures may be seen throughout the lower half of the epithelium [2] (Figures 13 and 14).

In CIN III, differentiation and stratification may be totally absent or present only in the superficial quarter of the epithelium with numerous mitotic figures. Nuclear abnormalities extend throughout the thickness of the epithelium. Many mitotic figures have abnormal forms [2] (Figure 15).
Figure 8 – Atypical vessels – CIN II.

Figure 9 – Histological results in percents in our study group.

Figure 10 – CIN I: Dysplastic squamous cells in the lower one-third of the epithelium with histological signs of HPV infection (HE stain, ob. ×10).

Figure 11 – CIN I: Dysplastic squamous cells in the lower one-third of the epithelium with histological signs of HPV infection (HE stain, ob. ×10).

Figure 12 – CIN I: Dysplastic squamous cells in the lower one-third of the epithelium with histological signs of HPV infection (HE stain, ob. ×10).

Figure 13 – CIN II: Dysplastic squamous cells in the basal two-thirds of the epithelium with histological signs of HPV infection; the upper half of the epithelium shows some differentiation and maturation with nuclear atypia. Nuclear abnormalities are more marked than in CIN I (HE stain, ob. ×10).

Figure 14 – CIN II: dysplastic squamous cells in the basal two-thirds of the epithelium with histological signs of HPV infection; the upper half of the epithelium shows some differentiation and maturation with nuclear atypia. Nuclear abnormalities are more marked than in CIN I (HE stain, ob. ×10).

Figure 15 – CIN III: dysplastic squamous cells throughout the full thickness of the epithelium. HPV changes, if present, are confined to the superficial layer (HE stain, ob. ×10).
To determine the overall accuracy of the colposcopic impression and to compare our results with other studies published, we used the cervical biopsy result as standard values because all probes were histologically analyzed. The colposcopic aspects of the lesions were compared with histologic results from colposcopic directed biopsy to assess a correlation between these two diagnostic methods.

The correlation was calculated reporting the number of cases histologically confirmed to the number of cases colposcopic diagnosis for each lesion group separately. Table 3 shows the correlation between colposcopic findings and histological diagnosis. The correlation was 78.5% (22 out of 28 patients) in the CIN I category, 84% (42 out of 50 patients) in the CIN II category, 88.6% (133 out of 150 patients) in the CIN III category, 46.1% (six out of 13 patients) for micro-invasive carcinoma and 50% (two out of four patients) for CIS.

Table 3 – Correlation between colposcopy and histology

<table>
<thead>
<tr>
<th>Colposcopic diagnosis</th>
<th>Normal</th>
<th>CIN I</th>
<th>CIN II</th>
<th>CIN III</th>
<th>Micro-invasive carcinoma</th>
<th>CIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CIN I</td>
<td>3</td>
<td>22 (78.5%)</td>
<td>2</td>
<td>1</td>
<td>–</td>
<td>– 28</td>
</tr>
<tr>
<td>CIN II</td>
<td>1</td>
<td>3</td>
<td>42 (84%)</td>
<td>2</td>
<td>2</td>
<td>– 50</td>
</tr>
<tr>
<td>CIN III</td>
<td>–</td>
<td>1</td>
<td>9</td>
<td>133 (88.6%)</td>
<td>5</td>
<td>2 150</td>
</tr>
<tr>
<td>Micro-invasive carcinoma</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>2</td>
<td>6 (46.1%)</td>
<td>3 13</td>
</tr>
<tr>
<td>CIS</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>2 (50%) 4</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>26</td>
<td>55</td>
<td>138</td>
<td>15</td>
<td>7 245</td>
</tr>
</tbody>
</table>

Discussion

As shown in Table 3, data obtained confirm what we noted in the beginning of this paper, that colposcopy performed better in differentiation of high-grade from low-grade lesions and that the positive predictive rate of the colposcopic impression is better as the cervical lesion is more severe: 133 cases confirmed as CIN III from 42 cases CIN II and 22 cases CIN I. The 14.2% (four out of 28 cases) error rate in distinguishing between normal and LSIL, confirming it is difficult to distinguish between normal and abnormal.

The colposcopy method incurred fewer false negatives (four patients), giving a general accuracy rate of 98.3% (241 out of 245 biopsied patients). Sensitivity of colposcopic examination was 83.6% (205 out of 245 cases).

As with cytology, some patients were under classified from CIN I to normal (three from 28 cases), from CIN II to CIN I (three out of 50 patients) and from CIN III to CIN II (nine out of 150 patients) using colposcopic examination.

Evaluation of the colposcopic results yielded the following prevalence percentages based on the histologic diagnoses: 8.9% for CIN I, 17.1% for CIN II, 54.2% for CIN III, 2.4% for micro-invasive carcinoma and 0.8% for CIS.

The ASCUS LSIL Triage Study (ALTS) Group, a large, randomized, multcenter trial designed to compare management strategies for women with ASCUS or LSIL cytology results, obtained the following data published in 2001: colposcopic findings for CIN I lesions were found in 51.4% of cases, and only 7% of examinations were considered to be CIN II or more severe. Among participants, the underlying prevalence of histologically confirmed CIN III was 5.1%. Compare to this data, in our study we found colposcopic findings for CIN I lesion in 78.5% of cases, 10.7% of examinations were CIN II or more severe. Among LSIL participants, the underlying prevalence of histologically confirmed CIN III was 3.5%. The data obtain from our study are appropriate as value noting that in ALTS study values were lower because directed biopsy was performed if any CIN lesion was suspected by colposcopic examination, so a lower number of biopsies reported to a lower number of colposcopies [12].

Adams AL et al. noticed in their study that the true sensitivity of the whole diagnostic process of colposcopy plus biopsy is lower because biopsies were not performed for all women, and some of the biopsy specimens may not have been taken from the most severe lesion. This results in an overestimate of sensitivity [13].

In a study meant to track the management outcomes of abnormal cervical cytology and hence confer credence to the value of colposcopy in management of abnormal cervical cytology, published in 2007, colposcopic detection rates were: 68% for CIN I, 73.3% for CIN II, 81.4% for CIN III and 88.9% for invasive carcinoma [14]. Sensitivity and specificity of the colposcopically directed histological abnormality detection rates was acceptably high: 58% for CIN I, 73.3% for CIN II, 81.4% for CIN III, 89% for invasive carcinoma. Overall detection rate was 70%. Despite the fact that the results of this study are closed to ours, the high percent of micro-invasive carcinoma, which is in concordance with higher number of cases of cervical cancer, can be explained by lack of screening programs for early detection of cancer, in poor countries. Compared to ours, those results highlight again the value of screening test for cervical cancer.

Maziah AM et al., in 1991, in a comparative study of cytologic and colposcopic findings in preclinical cervical cancer, obtained an accuracy rate of 94% for colposcopy. The colposcopic findings rates were: 10% for CIN I, 34% for CIN II, 34% for CIN III and 12% for invasive carcinoma. Histology findings were: 10% were CIN I, 20% were CIN II, 60% were CIN III and 10% were micro-invasive carcinoma. In this study, the overall results were similar to ours, except that the diagnosis of micro-invasive carcinoma was not made on colposcopy. According to authors, poor results obtained were very likely because specific diagnosis in these
Similar data also obtained Díaz-Amézquita EL et al., in 2006, in a study of establishing cytologic, histologic and colposcopic correlations of low and high grade cervical lesions found a 69.61% rate (142 of 204) [16].

Olaniyan OB et al., in 2002, conducted a meta-analysis to quantify the validity of colposcopy in the diagnosis of early cervical neoplasia. Eight longitudinal studies were selected, which compared correlation of colposcopic impression with colposcopically directed biopsy results. The prevalence of cervical disease in the studies ranged from 40 to 89%. Colposcopic accuracy was 89%, which agreed exactly with histology in 61% of cases. The sensitivity and specificity of colposcopy for low-grade lesions are 87–99% and 62–87% respectively. For the threshold of normal and low-grade SIL vs. high-grade SIL, the values were 30–90% and 67–97% [17].

Brotzman GL et al., in 2004, in a study made on 564 patients observed that the colposcopic impression correctly predicted the presence of LSIL, compared with gold standard biopsy results, in 64.3% of the time. The colposcopic impression of HSIL, compared with biopsy results correctly predicted the presence of HSIL 70% of the time. There was a 12.7% error rate in discriminating normal from LSIL [18].

Moss EL et al., in 2009, in a study on 469 patients to determine whether colposcopy is reliable in diagnosing cervical intraepithelial neoplasia in women who have undergone a previous cervical excision biopsy: the sensitivity and specificity of colposcopy for any cervical disease were 93.9% respectively 51.9% [19].

Boonlikit S, in 2011, in a 100 patients study the correlation between Reid’s Colposcopic Index and histologic results from biopsy. Overall, predictive accuracy was 89% and had good correlation with histology [8].

Pimple SA et al., in 2010, made an evaluation of colposcopy vs. cytology as secondary test to triage women found positive on visual inspection test. The colposcopic impression was CIN I changes in 33.8% of cases, CIN II–III in 8.6% of cases, and invasive carcinoma in 2.7% of cases. Histopathology findings were reported as benign in 81.6%, CIN I in 5.8% of cases, CIN II in 2.9% of cases, CIN III in 2.6% of cases, and invasive carcinoma in 2.9% of cases. The estimates of sensitivity for low- and high-threshold colposcopy were 58% and 74.5%, respectively, and those of specificity were 57.5% and 92.9%, respectively [20].

When interpreting values from different studies we might take into consideration that the performance and accuracy of colposcopy depends largely on the training, experience, and skills of the colposcopist, and accuracy of cytology requires laboratory services and skilled cytologists.

Staffa A and Mattingly RF prospectively evaluated the colposcopic impression in 282 patients and compared them to the histology. They subsequently recommended a minimal proficiency level of 80% for colposcopic accuracy to show proof of colposcopic competency [21].

When deciding which test to use for screening, specificity must be taken into account because tests with low specificity applied to a healthy population with a very low prevalence of disease will result in a high proportion of false-positive test results [22].

The most important role of these tests is to identify the women with HSIL lesions that require treatment, because the low-grade lesions are frequently regressive [23].

Conclusions

This study demonstrated high accuracy and correlation between colposcopy and histology, comparable with results from similar studies in the literature. Sensitivity is lower in our study, probably because biopsies were performed in all cases, during diagnostic work-up.

We also demonstrated the usefulness of these two diagnostic procedures as screening tests in preclinical cervical cancer.

The main goal of cervical screening is to identify women with high-grade intraepithelial lesions, which were considered to be the true precursors of invasive cancer and require treatment.

In our study, there were cases of under or over diagnose; the benefit of colposcopy and directed biopsy is to avoid over treatment of low-grade lesion, and under treatment of high-grade lesion.

References


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