The correspondence between abnormal transformation zone Grade 1 and Grade 2 colposcopic parameters and histology. Clinical implications.

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Summary

Objective: To analyse the correlation between the colposcopic parameters of Grade 1 and Grade 2 abnormal transformation zone (ANTZ G1 – ANTZ G2) and histological examination of the cone. *Materials and Methods:* A retrospective analysis of medical records of 600 women who underwent colposcopy and conisation (large loop excision of the transformation zone - LLETZ) between January 1, 2009 and July 31, 2012. The correlation between colposcopic and histological parameters was analysed using the Spearman non-parametric test. *Results:* In ANTZG1 there was no correlation (r= - 0.03; $p = 0.55$); in ANTZG2 however, a low degree of correlation (r = 0.21; $p = 0.03$) was found. Sensitivity, specificity, and positive and negative predictive values of an ANTZ G2 colposcopic picture were 33.45% (confidence interval [CI] 95% 28.0% to 39.2%), 95.48% (CI 95% 92.5% to 97.5%), 87.4% (CI 95% 79.7% to 92.9%), and 60.5% (CI 95% 56% to 64.9%), respectively. *Conclusions:* The decisive factor in the diagnosis of the cervical oncologic pathologies is the histological examination of the cone, and not the colposcopy which should be seen as a "guiding" investigation in predicting conisation and application of the most appropriate treatment.

Key words: Colposcopy; CIN; Biopsy; Conisation; LLETZ; HPV.

Introduction

Every year about ten million high-grade squamous intraepithelial lesions (HSIL) and over 500,000 cases of cervical carcinomas are diagnosed, of which about 80% occur in developing countries [1, 2]. About 3,500 new cases of cervical carcinoma and 1,500 deaths occur in Italy every year [3]. Cervical cancer is the third most common cancer affecting women worldwide [4]. Infection with human papillomavirus (HPV) is an inevitable cause of cervical cancer [5].

Over the last 50 years, screening has reduced the mortality rate for cervical cancer from 50% to 70% in industrialised countries and is, thus one of the most important methods for the secondary prevention of this disease [6, 7].

More specifically, the prevention and early detection of the cervical carcinoma are based on the interpretation of three analyses: cytology, colposcopy, and the histological results of a possible biopsy or cone biopsy.

Where a smear is abnormal, a colposcopy must be performed before starting therapy, to locate the exact spot from which the abnormal cells originate, to evaluate its extension and, above all, to ascertain its relation with the squamocolumnar (SJ).

Colposcopy can detect alterations not only on the surface and deep below it but also, in the composition of the epithelium and, in the vascularisation of the connective tissue, thus giving images of aceto-white and iodonegative areas, both isolated or associated, like more or less irregular epithelium, fine or coarse punctation, glandular openings inspissation and atypical blood vessels. Other features contributing to the evaluation of the abnormal colposcopic picture are the characteristics of the peripheral edges of the lesions, both clear and blurred, and the absence or presence of glandular openings [8-10], particularly if inspissated [11].

In addition, a good colposcopic test is meant to allow targeted biopsy of the lesions and proper post-therapeutic follow-up as well as to ascertain the horizontal and vertical extension of the lesion in line with preventive criteria.

Colposcopy nonetheless has some diagnostic limitations. The main limitation is that it is impossible to evaluate the characteristics of the endocervical lining, either when the endocervical lesion reaches up through the cervical canal or when the lesion is exclusively localised in the endocervical seat.

The reliability of a good biopsy sample from four mm of chorion cannot be overlooked; samples must also have an overall surface dimension of at least five to seven mm.

In the literature, the comparison between the histological results of the biopsy and the histological results of a larger surgical sample (cone), show variable underestimate (5.8% to 47%) and overestimate (4.6% to 42.4%) values of the lesion that can probably ascribed to the lack of homogeneity of the protocols adopted in various centres [12-14],

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to a sampling physician's less than perfect professional background, to less than perfect or incomplete sampling of the lesion, or to all of these variables at the same time..

The accuracy of colposcopy has been increasingly questioned. Studies of loop excision after colposcopy have identified women with CIN2+ and cancer who were not detected by colposcopy [14]. Biopsy of colposcopic normal areas may reveal unsuspected CIN2+ [15]. Colposcopic lesion grade may predict histology poorly [16, 17].

Women with negative colposcopy remain at substantial risk for subsequent detection of CIN2+, suggesting that lesions were missed [18].

In the Atypical Squamous Cells of Undetermined Significance/Low Grade Squamous Intraepithelial Lesion Triage Study (ALTS), only 53% of women found to have CIN3 over two years of follow-up were identified at colposcopy intake, though most missed lesions were small and presumably early in their natural history and so at low risk of imminent progression to invasive cancer [19].

Unfortunately, colposcopy does not have optimal sensitivity for CIN2+. The National Health Service Cervical Screening Programme (NHSCSP) Guidelines for Colposcopy and Programme Management, which guides British practice, require evidence of 65% colposcopic accuracy [20].

Zuchna *et al.* reported 66.2% sensitivity of CIN2+ when up to three guided cervical biopsies were taken as a diagnostic test with the cone specimen as the reference standard [21].

Using digitised cervical images from 919 women referred for equivocal or minor cytological abnormalities to the ASCUS-LSIL Triage Study, Massad *et al.* reported 39% sensitivity for CIN2+ [22].

The present study aims to analyse the correlation – if there is any correlation – between the component colposcopic parameters of abnormal transformation zone grade 1 and grade 2 (ANTZ G1 – ANTZ G2) and histological examination of the cone.

In the abnormal colposcopic picture, two grades can be identified: ANTZ G1 that is characterised by a thin white epithelium, fine mosaic and fine punctation, and ANTZ G2 that is characterised by a thick white epithelium, coarse mosaic, coarse punctuation, thickened glandular openings, and atypical blood vessels leading to the suspected invasive neoplasia.

Materials and Methods

The present study took into consideration a sample of 600 patients who were attending two Prevention Centres and taking part in the Abruzzi Region Screening Program: these were the Colposcopy and Cervicovaginal Center of L'Aquila, in collaboration with the Colposcopy and Cervicovaginal Center of the Avezzano Hospital. The study covered the period spanning from January 1, 2009 to July 31, 2012.

The first phase of the study was a meticulous case history survey to gather information about the presence of preexisting cytological and/or colposcopic alterations and to check whether any biopsies and/or conisations had already been carried out on the patients.

Each patient underwent a new colposcopy and conisation procedure on the basis of the previous positive colposcopic tests carried out in both the above mentioned centres and in other centres outside the region.

For reporting and colposcopic terminology, the authors used the model approved by the International Federation for Cervical Pathology and Colposcopy (IFCPC) International Congress of Barcelona (2002).

To compensate for underestimates or overestimates in targeted biopsies, the authors performed the conisations directly, avoiding "aggressive" behavior as much as possible and always taking account of the SJ, the lesion, any bending inward of the lesion, and the constitutive parameters of the transformation zone (thick white epithelium, mosaic, punctation, glandular openings, atypical blood vessels, etc.).

The conisations were carried out in an outpatient regimen through large loop excision of the transformation zone (LLETZ). The patients were put under local anaesthesia with paracervical block, with about 15 ml of two percent mepivacaina injected into the vaginal fornices through a 20 G curved tip needle.

The size of the cones varied according to the topography of the lesion, the morphology of the cervix, and the ecto-endocervical extension of the lesion.

After immediate fixation with 10% buffered formalin, the cone samples were sent to the anatomopathologist with the insertion of a marker wire which allowed the correct orientation of the surgical samples.

The excisional treatment caused no relevant painful symptomatology; in some instances, it caused light bleeding at most.

The authors adopted the WHO classification and used the SNOMED code (Systematized Nomenclature in Medicine) for the histological specimens.

The patients were properly informed by the gynecologist about the modality, characteristics, and purposes of the colposcopic test and conisation was dealt with by means of informed consent.

To begin with the descriptive statistical analysis of the main anamnestic and clinical variables (age, parity, ethnicity, biopsies, and/or previous conisations) was carried out; subsequently, the analysis of the Spearman non-parametric correlation was performed to assess the correlation between colposcopic parameters and histological examination.

The authors also found the colposcopic index cut-off value with higher degrees of sensitivity and specificity.

The statistical analysis was carried out using the statistical software SAS Version 9.2 (2002-2008) and the statistical software MedCalc Version 12.0.4 (1993-2011).

Results

The characteristics of the women (n = 600) who took part to the study are listed in Table 1. The average age is 37.2 years (range 18-75) and the standard deviation was 11.23 years. It turned out that the patients who underwent a previous conisation for CIN 2+ were 2.3% (n = 14). The remaining population under examination stated they had never undergone colposcopy, even if positive to colposcopy.

The colposcopic test carried out in the population under examination showed an ANTZ G1 clinical picture in 489 patients (81.5%) and an ANTZ G2 picture in 111 patients (18.5%) (Table 2). The conisation results are listed in Table 3. The excisional therapy caused light bleeding in 20 patients.

Table 1. — *Characteristics of 600 women who underwent colposcopy.*

	Frequency	Percentage ±
Age (years)		
< 20	6	1
20-29	154	26
30-39	205	34
>39	235	39
Parity		
0	307	51
1-2	199	33
>2	89	15
Unknown	5	1
Etnicity		
White-Hispanic	531	89
White- Non Hispanic	44	7
African	8	1
Asian	2	1
Other - Unknown	15	2
Study site		
L'Aquila	114	19
Avezzano	486	81
Previous conizations and/or cervical biopsies		
Yes	14	2
No	586	98

± Some percentage columns do not add to 100% because of rounding.

Table 2. — *Colposcopic pictures of the abnormal transformation zone (ANTZ) Grade 1 and Grade 2.*

ANTZG 1	N	%
White epithelium	318	53
Fine mosaic	112	18,7
Fine puntaction	59	9,8
Total	489	81,5

ANTZG 2	N	%
Thick white epithelium	38	6,3
Coarse mosaic	28	4,7
Coarse puntaction	12	2
Thickened glandular openings	18	3
Atypical vessels	11	1,8
Suspect invasive neoplasia	4	0,7
Total	111	18,5

Table 3. — *LLETZ findings after colposcopy.*

HISTOLOGY	N	%
Negative	312	52
CIN 1	56	9,3
CIN2	67	11,2
CIN3	150	25
Cancer	15	2,5

CIN: Cervical intraepithelial neoplasia

The analysis of the correlation between colposcopy and histological examination was carried out separately in ANTZ G1 and ANTZ G2 colposcopic grading. In the former case it did not show any correlation between colposcopic picture and histological examination ($r = - 0.03$; $p = 0.55$); in the latter case it showed a low degree of correlation ($r = 0.21$; $p = 0.03$).

An ANTZ G2 colposcopic picture had a sensitivity of 33.45% (CI 95% 28.0% to 39.2%) and a specificity of 95.48% (CI 95% 92.5% to 97.5%). These results suggested high probabilities of false negative results. The high rate of specificity instead implied a low probability of false positive results.

Concerning the prevalence ratio of positive results in histological examination (disease prevalence: 48.3%), the positive predictive value (PPV) of an ANTZ G2 colposcopic picture was 87.4% (CI 95% 79.7% to 92.9%). This meant that the probabilities for an ANTZ G2 colposcopic picture to produce a cone positive to histological examination were 87.4%, while only 12.6% turned out as false positives. Instead, the negative predictive value (NPV) of an ANTZ G2 colposcopic picture was 60.5% (CI 95% 56% to 64.9%), thus implying high probabilities of false negatives (39.5%).

Discussion

Given the results obtained both clinically and statistically, some conclusions can be drawn:

a) The analysis of ANTZ G1 colposcopic parameters and histological examination of the cone did not show any correlations ($r = - 0.03$; $p = 0.55$). More precisely, the correlation between punctuate and histological examination and, to a greater extent, the correlation between thin epithelium and fine mosaic did not correspond perfectly to the degree of the histological lesion supposed by colposcopy (CIN 1-LOW SIL).
b) ANTZ G2 constitutive parameters (thick white epithelium, coarse mosaic, coarse punctation, thickened glandular openings, atypical blood vessels) seem to be more indicative in the study of the correlation between colposcopy and histology ($r = 0.21$; $p = 0.03$). Colposcopically, the most reliable parameters proved to be the atypical blood vessel and the thick white epithelium.
c) The present study clearly shows that in clinical practice, the colposcopic report cannot and should not be considered fundamental as concerns the prediction of the degree of gravity of cervical lesions. The correlation between colposcopy and histological grading, also studied by other authors [17] even taking a different course, is not always a certainty.

In conclusion, the decisive factor in the diagnosis of the cervical oncologic pathologies is the histological examination of the cone, and not the colposcopy which should be considered as a "guiding" investigation in prediction of the conisation and of the application of the most appropriate treatment.

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