Gynecologic Cytopathology

ACTA CYTOLOGICA

Acta Cytologica 2011;55:158–162
DOI: 10.1159/000320911

Received: April 27, 2010
Accepted: August 12, 2010
Published online: February 15, 2011

Discordance between Cytology and Biopsy Histology of the Cervix: What to Consider and What to Do

Fernando Anschau[a] Manoel Afonso Guimarães Gonçalves[b]

[a]Instituto de Cardiologia do Rio Grande do Sul, Fundação Universitária de Cardiologia (IC, FUC), y
[b]Faculdade de Medicina Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, Brazil

Key Words
Cervical cytology · Cervical histology · Cervical intraepithelial neoplasia · Pre-malignant lesions of the cervix

Abstract
Objective: Since cytology is the examination utilized for the screening of cervical cancer, it is important to determine its correlation with histologic examination, the gold standard in the diagnosis of cervical disease. ***Study Design:*** A retrospective evaluation was made of 431 patients who presented with colposcopic indication for cervical biopsy between 2003 and 2007. ***Results:*** In 90.8% (289/318) of the patients, cytology showing cervical intraepithelial neoplasia (CIN) was confirmed as CIN in the histology of the cervix, while 62.8% (71/113) of patients with normal cytology had a confirmation of a normal histology ($\kappa = 0.558$). ***Conclusion:*** Cytology demonstrated a sensitivity and specificity of 87.3 and 71.0%, respectively. The agreement between cervical cytology and histology, considering the presence of CIN, was moderate. Correlations between accuracy and errors of cytology are discussed with therapeutic emphasis.

Introduction

In our knowledge of oncology and of methods for the screening and prevention of cancer, malignant neoplasia of the cervix is the model in which there is the greatest power of early detection and treatment. The knowledge accumulated over the years has enlightened us about the natural history of this cancer, to the point of knowing even the situations that precede its appearance [1].

It is well established that cancer of the cervix has precursor stages in which there is still no invasion of the stroma. In these stages, we can observe cellular alterations in the cervix which compromise the epithelium of the region and translate into cervical intraepithelial neoplasia (CIN), divided into grades I, II and III (carcinoma in situ). As a rule, decades pass between the time of infection, by the sexual route, of the basal cells of the cervical epithelium by human papillomavirus, the etiologic agent of cervical cancer, and the development of invasive neoplasia [1, 2].

The introduction of colposcopy by Hinslemann in the 1920s and of cervical cytology by Papanicolaou in the 1940s, together with histologic examination by means of a biopsy of the cervix, brought about the basis for the diagnosis of cervical disease. Such a foundation guarantees today that pre-malignant aberrations of the cervix are closely followed. The understanding of the molecular biology of human papillomavirus by Zur Hausen was essential for understanding the natural history of these cervical alterations, which were classified earlier by Richard

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0001–5547/11/0552–0158$38.00/0

Accessible online at:
www.karger.com/acy

Correspondence to: Prof. Fernando Anschau
Instituto de Cardiologia do Rio Grande do Sul
Fundação Universitária de Cardiologia (IC, FUC)
Av. Princesa Isabel 370, Santana, Porto Alegre, RS 90620-000 (Brazil)
Tel. +55 51 3230 3757, Fax +55 51 3219 2802, E-Mail editoracao-pc@cardiologia.org.br

into cervical intraepithelial neoplasias (grades I, II and III) and currently by the Bethesda system as squamous intraepithelial lesions (SIL) of high and low grades [3–5].

Therefore, it is expected that in some circumstances diagnostic tests will be in disagreement. The rate of discrepancy between cervical cytology and biopsy histology is reported as being between 11 and 28% [6–8]. Thus, it is important to be aware of the correct management of patients who show such discordance. Considering that cytology is the examination utilized for the screening of cancer of the cervix, it is important for us to determine its correlation with histologic examination, the gold standard in the diagnosis of cervical disease.

The aim of the current study is to evaluate cytology accuracy in patients with colposcopic indication for biopsy, and also to describe the profile of discordance between cytotologic and histologic examinations of the cervix. Another purpose of this study is to discuss management of cytology/histology discrepancy.

Patients and Methods

A total of 431 patients participated in this study. They were seen at the gynecology outpatient clinic (colposcopy clinic) of the Hospital São Lucas in the period of January 2003 to January 2007 and had a colposcopic indication for biopsy of the cervix, besides having complete data in their medical charts for analysis.

Cervical samples were taken using a Cervex Brush and Ayre Spatula collection device from patients referred to the colposcopy clinic. A conventional smear was prepared on 2 glass slides. An experienced cytopathologist whose diagnostic experience exceeds 20 years and a senior cytotechnologist examined all samples.

All women underwent colposcopic and cervical biopsy assessment. The indications for colposcopic biopsy followed the recommendations usually proposed for such procedures [9, 10]. Biopsies were taken in all cases of suspected low- or high-grade abnormalities by an experienced colposcopist (in practice for more than 10 years) and reviewed by a senior colposcopist as part of the routine.

The 3-tiered CIN and the low- and high-grade SIL Bethesda system were used for histological diagnosis. All cases were diagnosed by an experienced pathologist (more than 10 years experience).

The sampling was sequential, and the patients were divided based on the cytology results into normal cytology and cytology with SIL when there was any grade of CIN. Patients with glandular lesions in the cervix (12 cases) and those with atypical squamous cervical lesions (14 cases) were excluded from the present study. This division focused on the calculation of sensitivity, specificity and positive and negative predictive values of cytology when compared with histology, considered to be the gold standard.

For statistical analysis, the Kappa test was used to determine the correlations between the cytologic and histologic diagnoses, assessing the accuracy of the cytology in this group of patients with colposcopic abnormalities. Sensitivity, specificity and positive and negative predictive values of cytology were calculated just for the cytology with or without CIN (normal) because of the small number of patients per group when grading and comparing CIN in cytology with histology.

The present study is part of an investigation of factors involved in the development of cancer of the cervix and was previously approved by the Committee on Ethics in Research of the Pontifícia Universidade Católica do Rio Grande do Sul.

Table 1. Cytology versus histology

	Histology		Total
	CIN	normal	
Cytology			
CIN	289 (87.3)	29 (29.0)	318 (73.8)
Normal	42 (12.7)	71 (71.0)	113 (26.2)
Total	331 (100.0)	100 (100.0)	431 (100.0)

Data are numbers with percentages in parentheses.

$\kappa = 0.558$; sensitivity = 87.3%; specificity = 71.0%; positive predictive value = 90.9%; negative predictive value = 62.8%.

Results

In the period studied (2003–2007), we found 318 patients showing cytologic alterations with pre-malignant lesions in the gynecology outpatient department of the Hospital São Lucas. A total of 113 patients with normal cytology had colposcopic indication for biopsy of the cervix, and of these patients 83% underwent colposcopy because they showed a positive Schiller test, and the other 17% due to post-coital bleeding. Of the patients with cytology showing CIN, 90.8% (289/318) had confirmation by histology of the cervix, while 62.8% (71/113) of those with normal cytology were confirmed as having normal histology ($\kappa = 0.558$).

These values, shown in table 1, translated into a sensitivity and specificity for cytology of 87.3% and 71.0%, respectively. We found positive and negative predictive values of 90.9% and 62.8%, respectively.

Table 2 shows the distribution of CIN grading in cytology and the corresponding diagnosis in histology. In 54% (235/431) of cases there was concordance between cytology and histology, in normality as well as grading of the pre-malignant lesions. In 34.5% (149/431) of cases, cytology pointed to a less severe diagnosis compared to histology. However, in 10.9% (47/431) of cases cytology indicated a more severe diagnosis ($\kappa = 0.391$).

Table 2. Cytology (with CIN grading) versus histology

	Histology				Total
	CIN III	CIN II	CIN I	normal	
Cytology					
CIN III	96 (48.7)	7 (12.1)	2 (2.6)	6 (6.0)	111 (25.8)
CIN II	59 (29.9)	32 (55.2)	9 (11.8)	5 (5.0)	105 (24.4)
CIN I	33 (16.8)	15 (25.9)	36 (47.7)	18 (18.0)	102 (23.7)
Normal	9 (4.6)	4 (6.9)	29 (38.2)	71 (71.0)	113 (26.2)
Total	197 (100.0)	58 (100.0)	76 (100.0)	100 (100.0)	431 (100.0)

Data are numbers with percentages in parentheses. κ = 0.391 (considering the accuracy of cytology).

Table 3. Cytology (Bethesda classification) versus histology

	Histology			Total
	HSIL	LSIL	normal	
Cytology				
HSIL	194 (76.0)	11 (14.5)	11 (11.0)	216 (50.1)
LSIL	48 (18.8)	36 (47.3)	18 (18.0)	102 (23.7)
Normal	13 (5.0)	29 (38.2)	71 (71.0)	113 (26.2)
Total	255 (100.0)	76 (100.0)	100 (100.0)	431 (100.0)

Data are numbers with percentages in parentheses. κ = 0.498 (considering the accuracy of cytology).

If we consider the classification of Bethesda and group the pre-malignant lesions into squamous intraepithelial lesions of low (LSIL) and high grades (HSIL), we will have concordance between cytology and histology in 69.8% (301/431) of cases (κ = 0.498; table 3). In this classification, we observe some interesting types of discordance: (1) patients with normal cytology and histology with HSIL or LSIL (42 cases); (2) patients with cytology with HSIL or LSIL, but with normal histology (29 cases); (3) patients with cytology with LSIL and histology with HSIL (48 cases), and (4) patients with cytology with HSIL and histology with LSIL (11 cases).

Discussion

The efficacy and efficiency of Papanicolaou cytology, already proven, depend on the engagement of women in cervical cancer screening programs, adequate sampling and critical analysis of examinations [11]. In screening programs, false-negative examinations are problems that should be overcome. Inadequate sampling is responsible for about two-thirds of examinations with false-negative results [12, 13]. Therefore, we can find false-negative results in about 1.5–50% of examinations, depending on the work studied [14, 15]. In the present study, 37.2% (42/113) of the cytology results considered normal showed CIN in histology. We should point out, however, that these patients displayed some colposcopic abnormalities that led them to a histologic examination through a biopsy of the cervix. Thus, we cannot extrapolate this result for the population in general, without colposcopic abnormalities, diminishing the external applicability of this specific finding. It is interesting to also point out that the number of biopsies performed in patients with normal cytology is due mainly to the characteristics of the university service where the study was conducted. Because a colposcopic study is recommended in any patient with a positive Schiller test, as well as with post-coital bleeding, we obtained a considerable percentage of patients in this group (26.2%).

False-positive results are exactly related to histologic proof of normality based on cytologic alteration with the later need of biopsy of the cervix. Our findings are similar to those in the literature, with 9.1% in the present study versus 8.3–12.5% in another series of cases [16].

The results for the sensitivity and specificity of cytology in the literature, regardless of the type of examination analyzed (conventional or liquid-based cytology), are about 70–80 and 80–99%, respectively. In the present study, we demonstrated a sensitivity of 87.3% and a specificity of 71.0%, probably due to the colposcopy being utilized together with cytology in determining the diagnosis [13, 17–19].

When we considered the cytology finding as a dichotomous variable with CIN or normal, we found a moderate correlation between this examination and histology (κ =

0.558). On proceeding to grading of CIN or diagnosis of HSIL and LSIL, we found slight to moderate correlations between cytology and histology ($\kappa = 0.391$ and 0.498, respectively). The positive predictive value found (90.9%) is very high, and the low negative predictive value (62.8%) can be compensated by repeating the cytologic examination, which guarantees greater accuracy of the examination, and with the help of colposcopy in particular cases.

The combination of examinations in the gynecology clinic in the diagnosis of cervical disease leads to situations in which discrepancies in results occur. Cytology and histology, for example, will show discrepancies to which we should be ready to respond as to what to consider and what course of action to take. The frequency of these discrepancies in the literature varies between 11 and 28%, but some studies indicate frequencies around 3 and 31% [8, 20–24].

In 42 cases we found discordance between cytology with normal results and histology demonstrating some SIL. We should consider 2 possibilities: (1) false-negative cytology and (2) false-positive histology. These possibilities were approached by a study with 166 cervical SIL in histology with negative cytology, obtained in a period of less than 30 months. That work demonstrated, through the review of cytology slides, that 123 (74%) cases did not demonstrate any lesion, as a result of failure in the sampling for cytology, according to the gold standard (histology of the cervix). The other 43 (26%) cases demonstrated displastic cells, demonstrating failure in cytologic interpretation. We believe it prudent, when faced with this type of discordance, to initiate a review of the processes of sampling in the examinations, of performance of colposcopy, and of the clinical alterations of the patients, such as the period of the menstrual cycle in which the examination was performed, the presence of leukorrhea or bleeding and even the presence of comorbitidies which can influence the sampling. We also believe it is important to review cytology and histology slides for the purpose of guaranteeing greater diagnostic accuracy in the laboratory. In this type of discrepancy, histology (gold standard) should guide the course taken.

Another disagreement between cytology and histology was found in 29 patients with cytologic SIL, but with normal histology. The first question that arises is: are we looking at false-positive results of cytology or false-negative results of histology? We need to also remember that the biopsy can be taken at a site different from that of the cervical lesion, or with an erroneous technique (not guided by colposcopy or with an inappropriate instrument). We must also ask ourselves if there was a gap of time between cytology and histology, since in that case there may have been a regression of the lesions or a lesion in the vagina that could explain such discrepancy.

In this study, there was no gap of time between cytology and histology that could explain the results at least for histology, ruling out the possibility of lesion regression. Therefore, we are looking at possible false-positive results of cytology, with an incidence similar to that in the literature (9.1%) [16]. In a situation such as this, we should review the cytology slides, which can demonstrate results contrary to the first diagnosis [25]. We believe that the review of the processes as described above as well as the review of the histologic specimens are important in the elucidation of the diagnosis. In this type of discrepancy, it is important to investigate the endocervical canal and to eventually repeat the biopsy as well as cytology. When the cytologic review confirms HSIL and when there is a normal histology, it is important to refer the patient for a new colposcopy, observing the squamocolumnar junction, endocervix and vagina. In the absence of lesions, except in cytology with HSIL, conization with endocervical curettage emerges as a diagnostic and therapeutic possibility [26, 27].

A third type of discrepancy is the presence of cytology with LSIL and histology with HSIL. In 48 patients we found that such discrepancy indicates the first conclusion: there is a cervical SIL. The course of reviewing the slides will serve to improve the diagnostic accuracy of the pathology laboratory, but the clinical course should be guided by the histology.

The last discrepancy pointed out is the presence of cytology with HSIL, but with a histologic diagnosis of LSIL, observed in 11 cases. We should recall that we are dealing with a cervical SIL, and we should scale correctly to determine the course of action. The review of cytology and histology slides is an interesting approach to diminish the possibility of errors in interpretation. The biopsy of the cervix might have been obtained at a site other than that of the most serious lesion, or there are multiple lesions in the uterus, or there might have been a time gap between cytology and histology where regression of the lesions might have occurred.

The most conservative course described above, with review of the processes as well as of cytology and histology, appears to be very adequate. The modification of orientation of sections in the tissue specimen is recommended to improve the accuracy of histology in these cases [8, 28]. Another option is to perform a new colposcopy and possibly a new biopsy of the cervix, as well as a more critical evaluation of the endocervical canal.

Errington et al. [20] found that the positive predictive value of cytology with SIL was 75.4% for HSIL and 91.7% for any SIL. In our study, the positive predictive value of cytology with SIL was 89.8% (194/216 cases) for HSIL and 94.9% for any SIL (205/216 cases). In view of the high positive predictive values for cytology with HSIL, conization as a diagnostic method can be an alternative when all others are discarded without response to discrepancy.

However, before recommending a diagnostic conization or loop electric excision procedure in the transformation zone, the cytology sampling should be repeated and the original slide reviewed. When there are cytologic changes, we should refer the patient for a new colposcopy, examining the squamocolumnar junction and the vagina. In the absence of lesion, we should investigate the endocervix, and if no lesion is identified, we should excise the transformation zone and perform endocervical curettage [29].

With cytology suggesting HSIL, the greater problem is eliminating the possibility of HSIL or invasion in histology. Ideally, all cases with discrepancy in high-grade cytology, colposcopy and histologic lesions should be discussed in a multidisciplinary meeting [29].

References

1 Behtash N, Mehrdad N: Cervical cancer: screening and prevention. Asian Pac J Cancer Prev 2006;7:683–686.
2 Östor AG: Natural history of cervical intraepithelial neoplasia: the critical review. Int J Gynecol Pathol 1993;12:186–192.
3 Zur Hausen H: Condylomata acuminata and human genital cancer. Cancer Res 1976;36:794.
4 Bosch FX, Lorincz A, Muñoz N, et al: The causal relation between human papilomavírus and cervical cancer. J Clin Pathol 2002;55:244–265.
5 Smith JH: Bethesda 2001. Cytopathology 2002;13:4–10.
6 Ibrahim SN, Krigman HR, Coogan AC, et al: Prospective correlation of cervicovaginal cytologic and histologic specimens. Am J Clin Pathol 1996;106:319–324.
7 Tritz DM, Weeks JA, Spires SE, et al: Etiologies for non-correlating cervical cytologies and biopsies. Am J Clin Pathol 1995;103:594–597.
8 Bewtra C, Pathan M, Hashish H: Abnormal Pap smears with negative follow-up biopsies: improving cytohistological correlations. Diagn Cytopathol 2003;29:200–202.
9 Nooh A, Babburi P, Howell R: Achieving quality assurance standards in colposcopy practice: a teaching hospital experience. Aust NZ J Obstet Gynaecol 2007;47:61–64.
10 Lindeque BG: Management of cervical premalignant lesions. Best Pract Res Clin Obstet Gynaecol 2005;19:545–561.
11 Silverberg E, Boring CC, Squires TS: Cancer statistics, 1990. CA Cancer J Clin 1990;40:9–26.
12 Koss LG: Cytology: accuracy of diagnosis. Cancer 1989;64(suppl 1):249–252.
13 Vooijs GP, Elias A, van der Graaf Y, Poelen-van de Berg M: The influence of sample takers on the cellular composition of cervical smears. Acta Cytol 1989;30:251–257.
14 Sprenger E, Schwarzmann P, Kirkpatrick M, Fox W, Heinzerling RH, Geyer JW, Knesel EA: The false negative rate in cervical cytology: comparison of monolayers to conventional smears. Acta Cytol 1996;40:81–89.
15 Abulafia O, Sherer DM: Automated cervical cytology: meta-analyses of the performance of the AutoPap 300 QC System. Obstet Gynecol Surv 1999;54:469–476.
16 Mount S, Harmon M, Eltabbakh G, Uyar D, Leiman G: False positive diagnosis in conventional and liquid-based cervical specimens. Acta Cytol 2004;48:363–371.
17 Abulafia O, Pezzullo JC, Sherer DM: Performance of ThinPrep liquid-based cervical cytology in comparison with conventionally prepared Papanicolaou smears: a quantitative survey. Gynecol Oncol 2003;90:137–144.
18 Soost HJ, Lange HJ, Lehmacher W, Ruffing-Kullmann B: The validation of cervical cytology: sensitivity, specificity, and predictive values. Acta Cytol 1992;35:8–14.
19 Coste J, Cochand-Priollet B, de Cremoux P, Le Galès C, Cartier I, Molinié V, Labbé S, Vacher-Lavenu MC, Vielh P: Cross sectional study of conventional cervical smear, monolayer cytology, and human papillomavirus DNA testing for cervical cancer screening. BMJ 2003;326:733–736.
20 Errington CA, Roberts M, Tindle P, Michael E, Bulmer JN, Wadehra V: Colposcopic management of high-grade referral smears: a retrospective audit supporting 'see and treat'? Cytopathology 2006;17:339–347.
21 Jostle NE, Crum CP, Cibas ES: Cytologic/histologic correlation for quality control in cervicovaginal cytology: experience with 1,582 paired cases. Am J Clin Pathol 1995;103:32–34.
22 Jones BA, Novis DA: Cervical biopsy-cytology correlation: a College of American Pathologists Q-Probes study of 22,439 correlations in 348 laboratories. Arch Pathol Lab Med 1996;120:523–531.
23 Joste NE, Wolz M, Pai RK, Lathrop SL: Noncorrelating Pap tests and cervical biopsies: histologic predictors of subsequent correlation. Diagn Cytopathol 2005;32:310–314.
24 Petry KU, Böhmer G, Iftner T, Davies P, Brummer O, Kühnle H: Factors associated with an increased risk of prevalent and incident grade III cervical intraepithelial neoplasia and invasive cervical cancer among women with Papanicolaou tests classified as grades I or II cervical intraepithelial neoplasia. Am J Obstet Gynecol 2002;186:28–34.
25 Stoler MH, Schiffman M; Atypical Squamous Cells of Undetermined Significance-Low-grade Squamous Intraepithelial Lesion Triage Study (ALTS) Group: Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LSIL triage study. JAMA 2001;285:1500–1505.
26 Milne DS, Wadehra V, Mennim D, Wagstaff TI: A prospective follow up study of women with colposcopically unconfirmed positive cervical smears. Br J Obstet Gynecol 1999;106:38–41.
27 Hellberg D, Nilsson S: 20-year experience of follow-up of the abnormal smear with colposcopy and histology and treatment by conization or cryosurgery. Gynecol Oncol 1990;38:166–169.
28 Cioc AM, Julius CJ, Proca DM, Tranovich VL, Keyhani-Rofagha S: Cervical biopsy/cytology correlation data can be collected prospectively and shared clinically. Diagn Cytopathol 2002;26:49–52.
29 Jordan J, Martin-Hirsch P, Arbyn M, Schenck U, Baldauf JJ, Da Silva D, Anttila A, Nieminen P, Prendiville W: European guidelines for clinical management of abnormal cervical cytology, part 2. Cytopathology 2009;20:5–16.