

# Performance of Conventional Cytology and Colposcopy for the Diagnosis of Cervical Squamous and Glandular Neoplasias

## *Desempenho da citologia convencional e da colposcopia para o diagnóstico de neoplasias cervicais escamosas e glandulares*

Giselle Fachetti-Machado<sup>1</sup> Rosane Ribeiro Figueiredo-Alves<sup>1</sup> Marise Amaral Rebouças Moreira<sup>1</sup>

<sup>1</sup>Health Sciences Postgraduate Program, Universidade Federal de Goiás, Goiânia, GO, Brazil

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Address for correspondence Giselle Fachetti-Machado, MD, MSc, Universidade Federal de Goiás, Av. T4, esq. com T13, 1478, Salas 91B e 92B, Setor Bueno, Goiânia, GO, 74230-030, Brazil (e-mail: gfachettimachado@uol.com.br).

### Abstract

**Objective** To estimate the cytological and colposcopic performances for the diagnosis of cervical neoplasias.

**Methods** Cross-sectional retrospective study with data from patients' charts. The participants underwent colposcopy, guided biopsies, and excision when needed. The cytological and colposcopic categorization followed the Bethesda System and the international colposcopic terminologies. The cytology and colposcopy performances were evaluated by sensitivity (SE), specificity (SP), positive predictive value (PPV), and negative predictive value (NPV) analyses with 95% confidence interval (95% CI).

**Results** From 1,571 participants, a total of 1,154 (73.4%) were diagnosed with cervical squamous intraepithelial neoplasia grade 2 or worse (CIN 2<sup>+</sup>), 114 (7.2%) with adenocarcinoma in situ or worse (AIS<sup>+</sup>), 615 (39.2%) presented atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion or worse (ASC-H<sup>+</sup>) cytology, and 934 (59.4%) presented major or suspicious for invasion colposcopic abnormalities. The SE, SP, PPV, and NPV of ASC-H<sup>+</sup> for diagnoses of CIN 2<sup>+</sup> and AIS<sup>+</sup> were, respectively: 44% (95% CI: 41–47) and 72% (95% CI: 67–76), 79% (95% CI: 77–81) and 79% (95% CI: 75–83), 88% (95% CI: 87–90) and 55% (95% CI: 50–60), and 28% (95% CI: 26–31) and 88% (95% CI: 85–91). The SE, SP, PPV, and NPV of major or suspicious for invasion colposcopic abnormalities for diagnoses of CIN 2<sup>+</sup> and AIS<sup>+</sup> were, respectively: 62% (95% CI: 60–65) and 86% (95% CI: 83–89), 59% (95% CI: 57–62) and 59% (95% CI: 55–64), 85% (95% CI: 83–87) and 44% (95% CI: 40–49), and 29% (95% CI: 27–32) and 92% (95% CI: 89–94).

**Conclusion** The SE analyses results of ASC-H<sup>+</sup> and major or suspicious for invasion colposcopic abnormalities were higher for diagnoses of glandular neoplasias. These results confirm the role of cytology in identifying women at risk who will have their final diagnoses settled by colposcopy and histology.

### Keywords

- ▶ uterine cervical neoplasms
- ▶ cervical intraepithelial neoplasia
- ▶ squamous intraepithelial lesions of the cervix
- ▶ adenocarcinoma in situ
- ▶ papanicolaou test
- ▶ colposcopy
- ▶ sensitivity and specificity

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**Resumo**

**Objetivo** Estimar o desempenho da citologia e colposcopia no diagnóstico das neoplasias cervicais.

**Métodos** Estudo retrospectivo de corte transversal com dados coletados em prontuários. Foram incluídas participantes que foram submetidas a colposcopia, biópsia e excisão quando necessário. A categorização da citologia e da colposcopia seguiram a terminologia de Bethesda e a classificação colposcópica internacional. Os desempenhos da citologia e colposcopia foram avaliados por análises de sensibilidade (S), especificidade (E), valor preditivo positivo (VPP) e valor preditivo negativo (VPN), com intervalos de confiança de 95% (IC 95%).

**Resultados** Das 1.571 participantes, um total de 1.154 (73,4%) foram diagnosticadas com neoplasia intraepitelial escamosa cervical de grau 2 ou mais grave (NIC 2<sup>+</sup>), 114 (7,2%) com adenocarcinoma in situ ou mais grave (AIS<sup>+</sup>), 615 (39,2%) apresentaram células escamosas atípicas de significado indeterminado, quando não se pode excluir lesão intraepitelial de alto grau ou mais grave (ASC-H<sup>+</sup>) e 934 (59,4%) tiveram achados colposcópicos maiores ou suspeitos de invasão. Os valores de S, E, VPP e VPN das ASC-H<sup>+</sup> para o diagnóstico de NIC 2<sup>+</sup> e AIS<sup>+</sup> foram, respectivamente: 44% (IC 95%: 41–47) e 72% (IC 95%: 67–76), 79% (IC 95%: 77–81) e 79% (IC 95%: 75–83), 88% (IC 95%: 87–90) e 55% (IC 95%: 50–60) e 28% (IC 95%: 26–31) e 88% (IC 95%: 85–91). Os valores de S, E, VPP e VPN dos achados colposcópicos maiores ou suspeitos de invasão para o diagnóstico de NIC 2<sup>+</sup> e AIS<sup>+</sup> foram, respectivamente: 62% (IC 95%: 60–65) e 86% (IC 95%: 83–89), 59% (IC 95%: 57–62) e 59% (IC 95%: 55–64), 85% (IC 95%: 83–87) e 44% (IC 95%: 40–49) e 29% (IC 95%: 27–32) e 92% (IC 95%: 89–94).

**Conclusão** Os resultados das análises de S de ASC-H<sup>+</sup> e achados colposcópicos maiores ou suspeitos de invasão foram mais elevados para o diagnóstico das neoplasias glandulares. Esses resultados confirmam o papel da citologia na identificação de mulheres em risco que terão seus diagnósticos definidos por colposcopia e histologia.

**Palavras-chave**

- ▶ neoplasias do colo do útero
- ▶ neoplasia intraepitelial cervical
- ▶ lesões intraepiteliais escamosas cervicais
- ▶ adenocarcinoma in situ
- ▶ exame colpocitológico
- ▶ colposcopia
- ▶ sensibilidade e especificidade

**Introduction**

Well organized invasive cervical cancer (ICC) screening programs based on cytology, colposcopically-guided biopsies, and treatment of precursor neoplasias have led to an important decrease in the ICC incidence and mortality. However, none of these programs could eradicate cervical cancer in any part of the globe.<sup>1</sup> In fact, evidences have shown that in the last decades, the incidence of cervical adenocarcinoma (AC) has risen, especially in younger women, denoting the lack of impact of these programs for this particular histological type.<sup>2</sup>

Although the triage of patients at risk for ICC precursor lesions is based on cytological abnormalities, these do not have adequate specificity to indicate treatment to all women with such findings.<sup>3</sup> Therefore, colposcopically-guided biopsy was added to the system aiming to select which women with abnormal cytology would actually need treatment.<sup>4</sup>

Recently, as expected, a decrease in the prevalence of cervical intraepithelial neoplasias has been observed in developed countries due to high human papillomavirus (HPV) vaccination coverage.<sup>5</sup> It is possible that in vaccinated populations, the neoplasias that will still be found will show more subtle appearance and smaller sizes.<sup>6</sup> At the same time, a better diagnostic performance has been reached with the introduction of new screening programs with high sensitiv-

ity, which added DNA detection methods to cytology, resulting in a decrease in false-negatives,<sup>6</sup> and an improvement in cytological detection rates, even for more discrete neoplasias. Nonetheless, knowledge about colposcopy performance is still needed, especially regarding the recognition of subtle neoplasias,<sup>6</sup> which could be missed since colposcopic criterion has not been updated to the new scenario.

The histopathological diagnosis of specimens obtained using colposcopically-guided biopsy has been traditionally considered the gold standard for cytological and colposcopic analyses. However, this assumption has an intrinsic flaw.<sup>4</sup> Any mistakes made when choosing the site to take the biopsies, due to a misinterpretation of the colposcopic images, would necessarily lead to a bias, compromising the results of these analyses.

This study estimated cytological and colposcopic performance to predict the final diagnosis of squamous and glandular neoplasias and determine the performance of these diagnostic tests used in clinicians' daily practice, considering that the final diagnosis was based on excisional specimens.

**Methods**

This cross-sectional epidemiological study was based on data collected over a period of 24 years, from April 16, 1991 to November 26, 2015, in a private colposcopy health unit in

Goiânia, GO, Brazil. The project was approved by the Research Ethics Committee of the Hospital das Clínicas of the Universidade Federal de Goiás (CAAE no. 58228016.1.0000.5078).

A total of 11,999 medical records of patients referred to colposcopy were reviewed. Among them, 1,527 participants were selected for having their final diagnoses settled by histopathological analyses of transformation zone excision (TZE) pieces, 7 by analysis of cold knife conization (CKC) pieces, and 37 with invasive cervical neoplasias diagnosed in the initial biopsy fragment. Therefore, the final sample was composed of 1,571 participants.

All the patients without a histopathological analysis of an excisional specimen were excluded from the study, even if they had cytological abnormalities, and regardless of whether they had normal or abnormal histopathology. Exceptions were made only in the cases with stromal invasion observed in the initial biopsy fragment, because once invasion is found, no worst diagnosis is possible, making a subsequent excisional procedure unnecessary in most cases.

The data obtained from patients' charts, colposcopic reports, and computer software Diagnose Pro 6, Ginecologia e Obstetrícia, prontuário eletrônico e captura de imagens. (LPT4 sistemas de informação, Curitiba, Paraná, Brazil) and Zscan 7 Gineco, version 7.4 (Zscan Software, 2001-2016, Goiânia, Goiás, Brazil) image files were coded and kept on a 2013 Excel spreadsheet (Microsoft Corp., Redmond, WA, USA). The cytological, colposcopic, and histopathological data included referral cytology, colposcopic findings, visualization of squamocolumnar junction (SCJ), the histopathological diagnosis of an excision piece or a hysterectomy piece, and the histopathological report of biopsy fragments.

The cytological abnormalities were classified as proposed by the Bethesda terminology, updated in 2014:<sup>7</sup> atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H), high-grade squamous intraepithelial lesion (HSIL), squamous cell carcinoma (SCC), atypical glandular cells (AGC), adenocarcinoma in situ (AIS), and adenocarcinoma (AC).

The ASC-H<sup>+</sup> group had a cut-off point settled in the cytological results of ASC-H or worse, a threshold in which the patients' management changes to immediate referral to colposcopy rather than the mere cytological follow-up.<sup>8</sup> This group included all patients with cytological abnormalities classified as ASC-H, HSIL, SCC, AIS, and AC.

A single colposcopist performed the exams using at first a 5-fold DFV videocolposcope (D. F. Vasconcellos, Valença, RJ, Brazil) and afterward a Medpej PE 7000 MDL videocolposcope also with five levels of magnification (6x, 10x, 16x, 25x and 40x). Initially 5% and 10% acetic acid solutions were applied followed by the spraying of Schiller's solution, at this point, the needed biopsies were taken with Gaylor-Medina forceps. Endocervical curettages with a Kevorkian curette were performed whenever necessary.

The colposcopic images were reviewed by the examiner and the 2011 International Federation of Cervical Pathology and Colposcopy (IFCPC)<sup>9</sup> terminology was used to group them as follows: normal, minor findings, major findings, or

suspicious for invasion. Minor findings elementary images included: fine mosaic, fine punctuation, and thin acetowhite epithelium with geographic borders. Major findings included: coarse mosaic, coarse punctuation, and dense acetowhite epithelium with sharp border, with or without ridge and inner border sign, and also cuffed crypt openings. The images considered suspicious for invasion included: atypical or fragile vessels, irregular surface, exophytic lesion, necrosis, necrotic ulceration, and gross neoplasm.<sup>9</sup>

Moreover, new colposcopic images similar to those described by Wright et al<sup>10</sup> were added to the major findings category. It is necessary to emphasize that these images are not accredited by IFCPC terminology.

The cut-off point of colposcopic images was settled at images worse than minor findings, since taking biopsies from this type of findings is considered needless by many colposcopists. Thus, the colposcopic findings were sorted into two groups: 1) normal and minor findings; 2) major findings and suspicious for invasion findings.

A Wavetronic 5000 Digital Hf Surgical Unit (Loktal Medical Electronics Ind. Com. Ltda, São Paulo, SP, Brazil) was employed to perform TZE under colposcopic guidance and local anesthesia, using its handswitch pencil and cord with loop electrodes, at 50% of the coagulation power and the shear power regulated to output 8. A single-fragment resection was performed unless a large transformation zone was present.

A single examiner performed all histopathological analyses and categorized the findings following the World Health Organization International Tumors Classification<sup>11</sup> and the Richart Classification for cervical intraepithelial neoplasias.<sup>12</sup> The final diagnosis was defined as the most severe histopathological diagnosis among specimens of excision or hysterectomy, except when invasion was already found in fragments of initial biopsies.

The data analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows version 21.0 (IBM Corp., Armonk, NY, USA). Descriptive analyses of the sociodemographic, behavioral, and clinical features as well as cytological abnormalities, colposcopic findings, and histopathological diagnosis were performed.

Diagnostic performance of cytological abnormalities and colposcopic findings to predict the final diagnosis were evaluated by analysis of sensitivity (SE), specificity (SP), positive predictive value (PPV), and negative predictive value (NPV), with the respective 95% confidence interval (95% CI). Values of SE, SP, PPV, and NPV between 0.00 and 0.40 were considered as poor, between 0.40 and 0.60 as low, between 0.60 and 0.80 as moderate, and between 0.80 and 1 as high.

## Results

The sociodemographic and behavioral characteristics of the participants in this survey are shown in **Table 1**. The mean age of the participants was 31.7 years and at the first intercourse, it was 18.9 years. A total of 615 (39.6%) patients out of 1,571 were referred to colposcopy due to cytological findings of atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion or worse (ASC-H<sup>+</sup>).

**Table 1** Sociodemographic and behavioral profile of 1,571 participants

Variables		
Age	Years	
Range	15–85	
Mean (sd)	31.7 ± 10.8	
Marital status <sup>a</sup>	n	%
Single	817	52.0
Married	752	47.9
Age at first intercourse <sup>b</sup>	Years	
Range	9–47	
Mean (sd)	18.9 ± 3.7	
Lifetime sexual partners <sup>c</sup>	n	%
≤ 2	624	39.7
> 2	756	48.1
Full-term pregnancy <sup>d</sup>	n	%
≤ 1	1,107	70.5
> 1	453	28.8
Tobacco use <sup>e</sup>	n	%
Past and current smoker	148	9.4
Never smoker	1,073	68.3

Abbreviation: SD, standard deviation. missing data: <sup>a</sup>2; <sup>b</sup>128; <sup>c</sup>192; <sup>d</sup>11; <sup>e</sup>350.

Colposcopic images categorized as major or suspicious for invasion were found in 934 (59.4%) patients (► **Table 2**). Concerning the final diagnosis, 1,154 (73.4%) participants had cervical squamous intraepithelial neoplasia grade 2 or worse (CIN 2<sup>+</sup>) and 114 (7.2%) had adenocarcinoma in situ or worse (AIS<sup>+</sup>) (► **Table 2**).

The SE, SP, PPV, and NPV results of ASC-H<sup>+</sup> for the prediction of CIN 2<sup>+</sup> were, respectively: 44% (95% CI 41–47), 79% (95% CI: 77–81), 88% (95% CI: 87–90), and 28% (95% CI: 26–31). The SE, SP, PPV, and NPV results of ASC-H<sup>+</sup> for the prediction of AIS<sup>+</sup> were, respectively: 72% (95% CI: 67–76), 79% (95% CI: 75–83), 55% (95% CI: 50–60), and 88% (95% CI: 85–91) (► **Table 3**).

The SE, SP, PPV, and NPV results of major or suspicious for invasion colposcopic findings for the diagnosis of CIN 2<sup>+</sup> were, respectively, 62% (95% CI: 60–65), 59% (95% CI: 57–62), 85% (95% CI: 83–87), and 29% (95% CI: 27–32), whereas to detect AIS<sup>+</sup> they were, respectively, 86% (95% CI: 83–89), 59% (95% CI: 55–64), 44% (95% CI: 40–49), and 92% (95% CI: 89–94) (► **Table 4**).

## Discussion

In the present study, the performances of cytological abnormalities ASC-H<sup>+</sup> and colposcopic major or suspicious for invasion findings were evaluated to separately predict the final diagnoses of CIN 2<sup>+</sup> and AIS<sup>+</sup> in a sample of 1,571 participants. The final diagnosis was defined as the most severe report obtained among all biological specimens of

**Table 2** Cytological, colposcopic, and final diagnoses in 1,571 participants

Colposcopy referral	n	%
ASC-US/LSIL	796	50.7
ASC-H/HSIL	532	34.0
AGC	29	1.8
Adenocarcinoma in situ	22	1.4
Squamous cell carcinoma	16	1.0
Adenocarcinoma	16	1.0
Others <sup>a</sup>	153	9.7
Colposcopy findings <sup>b</sup>	n	%
Normal	9	0.5
Minor	618	39.3
Major	908	57.8
Suspicious for invasion	26	1.6
Final diagnosis	n	%
≤ CIN 1	303	19.3
CIN 2/CIN 3	1,124	71.6
Microinvasive squamous carcinoma	13	0.8
Squamous carcinoma	17	1.1
Adenocarcinoma in situ	78	5.0
Microinvasive adenocarcinoma	8	0.5
Adenocarcinoma	28	1.8

Abbreviations: AGC, atypical glandular cells; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion. <sup>a</sup>cervical polip, cervical bleeding, unknown cytological finding, etc. <sup>b</sup>missing data:10.

patients who underwent excisional procedure, except when invasion was initially found in biopsy fragments.

The SE of ASC-H<sup>+</sup> (44%) to identify squamous neoplasias was low; in contrast, SP (79%) and PPV (88%) were moderate and high, respectively. Regarding glandular neoplasias, SE (72%) and SP (79%) of ASC-H<sup>+</sup> were moderate, whereas PPV (55%) was low. To the best of our knowledge, to date, no studies have simultaneously measured the performance of cytological and colposcopic diagnoses of squamous and glandular neoplasias.

The sensitivity of a test represents its ability to correctly identify unhealthy individuals, while its specificity shows the ability to identify the healthy ones.<sup>13</sup> Therefore, the low sensitivity found implies that ASC-H<sup>+</sup> may not sort out a reasonable number of patients with CIN 2<sup>+</sup>, since the false-negative rate was high (56%). Similarly, the SP of 79% obtained means that absence of ASC-H<sup>+</sup> identifies a high number of patients that do not actually have CIN 2<sup>+</sup>.

Moderate SE (72%) and SP (79%) of ASC-H<sup>+</sup> to identify glandular neoplasias mean that ASC-H<sup>+</sup> involves lower rates of false-positives (28%) and false-negatives (21%). Analyzed individually, SE of cytology for the detection of glandular

**Table 3** Performance of cytological findings of atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion or worse (ASC-H<sup>+</sup>) to predict final diagnosis of squamous and glandular cervical neoplasias

Cytological findings	Final diagnosis		Estimated performance (%) (95% CI)	
	Positive	Negative		
ASC-H <sup>+</sup>	CIN 2 <sup>+</sup> (n = 1,376)			
	Positive	Negative		
Positive	474	63	Sensitivity	44 (41–47)
			Specificity	79 (77–81)
Negative	603	236	PPV	88 (87–90)
			NPV	28 (26–31)
ASC-H <sup>+</sup>	AIS <sup>+</sup> (n = 408)		Estimated performance (%) (95% CI)	
	Positive	Negative		
Positive	78	63	Sensitivity	72 (67–76)
			Specificity	79 (75–83)
Negative	31	236	PPV	55 (50–60)
			NPV	88 (85–91)

Abbreviations: AIS<sup>+</sup>, adenocarcinoma in situ or worse; ASC-H<sup>+</sup>, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion or worse (including ASC-H, HSIL, AIS, SCC, and AC); CIN 2<sup>+</sup>, cervical squamous intraepithelial neoplasia grade 2 or worse; 95% CI, 95% confidence interval; NPV, negative predictive value; PPV, positive predictive value.

neoplasias has been reported in a wide range of values, such as 43.1%<sup>14</sup> and 91.2%.<sup>15</sup> Those results contrast with the findings of this study, since most patients with glandular neoplasias were found using ASC-H<sup>+</sup> (72%) cytology, and most patients without cytological reports of ASC-H<sup>+</sup> (NPV 88%) were truly free of glandular neoplasias. For this reason, when ASC-H<sup>+</sup> is found, whether squamous neoplasias have already been identified or not, it would be safer to exclude the possibility of coexistent glandular neoplasias.

Sensitivity and SP are inherent properties of a test and do not change. However, the predictive values depend on the prevalence of the disease in the study sample.<sup>13</sup> Therefore, the PPV will proportionally increase according to the prevalence of the disease in the studied group. In the present study, on one hand, the high prevalence of squamous neoplasias implied a high PPV of ASC-H<sup>+</sup> for CIN 2<sup>+</sup> detection, because most participants with ASC-H<sup>+</sup> actually had CIN 2<sup>+</sup>. On the other hand, the low prevalence of glandular neoplasias implied a low PPV of ASC-H<sup>+</sup> ability to predict AIS<sup>+</sup>. Hence, most positive results of ASC-H<sup>+</sup> do not correspond to patients with glandular neoplasias, but rather to patients with squamous neoplasias.

Evidences involving the performance of cytological abnormalities for predicting intraepithelial and invasive cervical neoplasias, whether squamous or glandular, were found with SE ranging from 30 to 100%, and SP from 86.8 to 99.3%.<sup>16–29</sup> This large divergence may be due to the diversity of cut-off points chosen to consider the tests as positive or negative, as well as to the use of different morphological criteria to interpret cytological smears and classify abnormal

**Table 4** Performance of major or suspicious for invasion colposcopic findings to predict final diagnosis of squamous and glandular cervical neoplasias

Colposcopic report	Final diagnosis		Estimated performance (%) (95% CI)	
	Positive	Negative		
Major or suspicious for invasion	CIN 2 <sup>+</sup> (n = 1,447)			
	Positive	Negative		
Positive	713	123	Sensitivity	62 (60–65)
			Specificity	59 (57–62)
Negative	432	179	PPV	85 (83–87)
			NPV	29 (27–32)
Major or suspicious for invasion	AIS <sup>+</sup> (n = 416)		Estimated performance (%) (95% CI)	
	Positive	Negative		
Positive	98	123	Sensitivity	86 (83–89)
			Specificity	59 (55–64)
Negative	16	179	PPV	44 (40–49)
			NPV	92 (89–94)

Abbreviations: AIS<sup>+</sup>, adenocarcinoma in situ or worse; CIN 2<sup>+</sup>, cervical squamous intraepithelial neoplasia grade 2 or worse; 95% CI, 95% confidence interval; NPV, negative predictive value; PPV, positive predictive value.

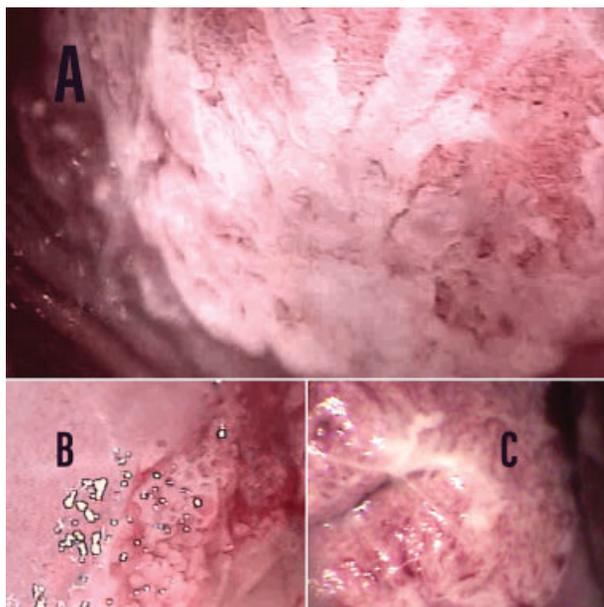
findings. Conversely, a study that used ASC-H<sup>+</sup> as a cut-off point to ascertain the performance for the detection of CIN 2<sup>+</sup> reported SE of 67.9% and SP of 87%.<sup>30</sup>

In this study, SE of major or suspicious for invasion colposcopic findings for the detection of CIN 2<sup>+</sup> was moderate (62%), while SP was low (59%). Although these values were different from each other, this difference was not statistically significant, since their confidence interval overlapped. The major or suspicious for invasion colposcopic findings failed to identify a substantial number of patients with CIN 2<sup>+</sup>. Consequently, the absence of colposcopic images showing major or suspicious for invasion findings does not rule out a large number of healthy participants.

These results are in line with a previous study,<sup>3</sup> and suggest that guided biopsies are needed by women with cytological abnormalities, even if they present subtle colposcopic findings, that is, those colposcopic images classified as minor findings by the IFCPC. Taking multiple biopsies would also be an acceptable strategy to improve the SE of colposcopy.<sup>31</sup>

The SE of major or suspicious for invasion colposcopic findings for the detection of AIS<sup>+</sup> was high (86%), while the SP and PPV were low (59% and 44%, respectively). This high SE value found for the detection of AIS<sup>+</sup> implies that the major or suspicious for invasion colposcopic findings express low rates of false-negatives for this singular histopathological type of neoplasia. In view of these colposcopic images, whether squamous neoplasias are suspected or not, the need to exclude a possible coexistent glandular neoplasia still persists.

These results show that the SE values of colposcopic findings were higher for the detection of squamous (62%)



**Fig. 1** New colposcopic images are herein named: (A) fused acetowhite villi with invaginated borders; (B) obstructed dilated grouped glands; (C) atypical vessels in cylindrical epithelium area.

and glandular (86%) neoplasias than the cytological findings of ASC-H<sup>+</sup> (44% and 72% for squamous and glandular neoplasias, respectively). However, SP values of ASC-H<sup>+</sup> (79% and 79%) were higher than those of colposcopic findings (59% and 59%) for the detection of these two main histopathological types of neoplasia. Moreover, the SE of major or suspicious for invasion colposcopic findings and ASC-H<sup>+</sup> cytological findings were higher for glandular (86% and 72%) than for squamous neoplasias (62% and 44%).

The high SE of colposcopy for the detection of glandular neoplasias found in this study was probably due to the inclusion of new subtle images in the major colposcopic finding category. Such new images are similar to those identified by Wright et al<sup>10</sup> as suggestive of glandular neoplasias and are not described in the International Colposcopic Classification of the IFCPC.<sup>9</sup> They are herein named: obstructed dilated grouped glands, fused acetowhite villi with invaginated borders, and atypical vessels in cylindrical epithelium area (► Fig. 1).

Considering that the PPV of ASC-H<sup>+</sup> (88%) and major or suspicious for invasion colposcopic findings (85%) for the detection of CIN 2<sup>+</sup> were high, the see and treat protocol, already endorsed by previous published evidences,<sup>32</sup> is here corroborated as a secure option. The sequential use of two tests with high PPV prior to the see and treat protocol substantially decreases the probability of performing unnecessary excisional procedures in disease-free patients, mainly because both cytological and colposcopic findings must simultaneously be abnormal to indicate such management.

The possibility of finding an unexpected glandular neoplasia in a see and treat excision piece, estimated to happen in 52% of the patients with final diagnosis of AIS<sup>+</sup>,<sup>33</sup> would not contraindicate this approach. As a matter of fact, evidences

have shown that outpatient excisional procedures are also suitable for the management of glandular neoplasias.<sup>33,34</sup>

## Conclusion

The performance of cytological abnormalities is somehow different from that of colposcopic findings to predict the diagnoses of AIS<sup>+</sup> and CIN 2<sup>+</sup>. Sensitivity of major or suspicious for invasion colposcopic findings for the diagnoses of CIN 2<sup>+</sup> was moderate. The high PPV values found for ASC-H<sup>+</sup> and major or suspicious for invasion colposcopic findings for the detection of CIN 2<sup>+</sup> endorse the see and treat protocol. Sensitivity results of ASC-H<sup>+</sup> and major or suspicious for invasion were higher for the diagnosis of glandular than squamous neoplasias. These results reinforce the role of cytology in sorting out women at risk who should have their diagnosis settled by colposcopy and histopathology.

## Contributions

Fachetti-Machado G., Figueiredo-Alves R. R. and Moreira M. A. R. contributed with the project and interpretation of data, writing of the article, critical review of the intellectual content and final approval of the version to be published.

## Conflicts of Interest

The authors have no conflicts of interest to declare.

## References

- 1 Koss LG. The Papanicolaou test for cervical cancer detection. A triumph and a tragedy. *JAMA* 1989;261(05):737-743. Doi:10.1001/jama.1989.03420050087046
- 2 Chan PG, Sung HY, Sawaya GF. Changes in cervical cancer incidence after three decades of screening US women less than 30 years old. *Obstet Gynecol* 2003;102(04):765-773. Doi:10.1016/S0029-7844(03)00696-3
- 3 Massad LS, Jeronimo J, Katki HA, Schiffman M; National Institutes of Health/American Society for Colposcopy and Cervical Pathology Research Group. The accuracy of colposcopic grading for detection of high-grade cervical intraepithelial neoplasia. *J Low Genit Tract Dis* 2009;13(03):137-144. Doi:10.1097/LGT.0b013e31819308d4
- 4 Jordan J, Arbyn M, Martin-Hirsch P, et al. European guidelines for quality assurance in cervical cancer screening: recommendations for clinical management of abnormal cervical cytology, part 1. *Cytopathology* 2008;19(06):342-354. Doi:10.1111/j.1365-2303.2008.00623.x
- 5 Drolet M, Bénard É, Boily MC, et al. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. *Lancet Infect Dis* 2015;15(05):565-580. Doi:10.1016/S1473-3099(14)71073-4
- 6 Jeronimo J, Schiffman M. Colposcopy at a crossroads. *Am J Obstet Gynecol* 2006;195(02):349-353. Doi:10.1016/j.ajog.2006.01.091
- 7 Nayar R, Wilbur DC. The Pap Test and Bethesda 2014. "The reports of my demise have been greatly exaggerated." (after a quotation from Mark Twain). *Acta Cytol* 2015;59(02):121-132. Doi:10.1159/000381842
- 8 Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva. Coordenação de Prevenção e Vigilância. Divisão de Detecção Precoce e Apoio à Organização de Rede. *Diretrizes Brasileiras para o Rastreamento do Câncer do Colo do Útero*. 2a ed. Rio de Janeiro, RJ: INCA; 2016. [http://www1.inca.gov.br/inca/Arquivos/DDiretrizes\\_para\\_o\\_Rastreamento\\_do\\_cancer\\_do\\_colo\\_do\\_uterio\\_2016\\_corrigido.pdf](http://www1.inca.gov.br/inca/Arquivos/DDiretrizes_para_o_Rastreamento_do_cancer_do_colo_do_uterio_2016_corrigido.pdf). Accessed March 26, 2018

- 9 Bornstein J, Bentley J, Bösze P, et al. 2011 colposcopic terminology of the International Federation for Cervical Pathology and Colposcopy. *Obstet Gynecol* 2012;120(01):166–172. Doi:10.1097/AOG.0b013e318254f90c
- 10 Wright VC, Dubuc-Lissoir J, Ehlen T, Heywood M, Plante M. Guidelines on adenocarcinoma in situ of the cervix: clinical features and review of management. *J Obstet Gynaecol Can* 1999;21(07):699–706. Doi:10.1016/S0849-5831(16)30106-9
- 11 Scully RE, Bonfiglio TA, Kurman RJ, Silverberg SG, Wilkinson EJ. *Histological Typing of Female Genital Tract Tumors*. 2nd ed. Berlin: Springer Verlag; 1994
- 12 Buckley CH, Butler EB, Fox H. Cervical intraepithelial neoplasia. *J Clin Pathol* 1982;35(01):1–13. Doi:10.1136/jcp.35.1.1
- 13 Bonita R, Beaglehole R, Kjellström T. *Epidemiologia Básica*. 2a ed. São Paulo, SP: Santos; 2010
- 14 Kietpeerakool C, Srisomboon J, Prompittayarat W, Kanjanavaha P, Peuwsai R, Dheerakul C. Can adenocarcinoma in situ of the uterine cervix be predicted before cervical conization? *Asian Pac J Cancer Prev* 2006;7(04):522–524
- 15 Miller RA, Mody DR, Tams KC, Thrall MJ. Glandular lesions of the cervix in clinical practice: a cytology, histology, and human papillomavirus correlation study from 2 institutions. *Arch Pathol Lab Med* 2015;139(11):1431–1436. Doi:10.5858/arpa.2014-0633-OA
- 16 Patil PR, Jibhkate SN. Cytohistopathological correlation of Papanicolaou smears: a hospital based study. *Int J Reprod Contracept Obstet Gynecol* 2016;5:1695–1699. Doi:10.18203/2320-1770.ijrcog20161424
- 17 Naik R, Minj AM, Panda R, Satpathi S, Behera PK, Panda KM. Cytohistological correlation and accuracy of the Pap smear test in diagnosis of cervical lesions: a hospital based cross-sectional study from Odisha, India. *Med Sci* 2015;3:242–249. Doi:10.29387/ms.2015.3.3.242-249
- 18 Alves RRF, Teixeira TS, Netto JCA. Performance da citologia e colposcopia frente à histopatologia no rastreamento e diagnóstico das lesões precursoras do câncer do colo uterino. *DST J Bras Doenças Sex Transm*. 2002;14:33–38
- 19 Sankaranarayanan R, Thara S, Sharma A, et al; Multicentre Study Group on Cervical Cancer Early Detection in India. Accuracy of conventional cytology: results from a multicentre screening study in India. *J Med Screen* 2004;11(02):77–84. Doi:10.1258/096914104774061056
- 20 Wu Q, Zhao X, Fu Y, et al. A cross-sectional study on HPV testing with type 16/18 genotyping for cervical cancer screening in 11,064 Chinese women. *Cancer Med* 2017;6(05):1091–1101. Doi:10.1002/cam4.1060
- 21 Bigras G, de Marval F. The probability for a Pap test to be abnormal is directly proportional to HPV viral load: results from a Swiss study comparing HPV testing and liquid-based cytology to detect cervical cancer precursors in 13,842 women. *Br J Cancer* 2005;93(05):575–581. Doi:10.1038/sj.bjc.6602728
- 22 Cárdenas-Turanzas M, Nogueras-Gonzalez GM, Scheurer ME, et al. The performance of human papillomavirus high-risk DNA testing in the screening and diagnostic settings. *Cancer Epidemiol Biomarkers Prev* 2008;17(10):2865–2871. Doi:10.1158/1055-9965.EPI-08-0137
- 23 Yeoh GP, Chan KW. The accuracy of Papanicolaou smear predictions: cytohistological correlation of 283 cases. *Hong Kong Med J* 1997;3(04):373–376
- 24 Coste J, Cochand-Priollet B, de Cremoux P, et al; French Society of Clinical Cytology Study Group. Cross sectional study of conventional cervical smear, monolayer cytology, and human papillomavirus DNA testing for cervical cancer screening. *BMJ* 2003;326(7392):733. Doi:10.1136/bmj.326.7392.733
- 25 Mayrand MH, Duarte-Franco E, Rodrigues I, et al; Canadian Cervical Cancer Screening Trial Study Group. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. *N Engl J Med* 2007;357(16):1579–1588. Doi:10.1056/NEJMoa071430
- 26 Petry KU, Menton S, Menton M, et al. Inclusion of HPV testing in routine cervical cancer screening for women above 29 years in Germany: results for 8466 patients. *Br J Cancer* 2003;88(10):1570–1577. Doi:10.1038/sj.bjc.6600918
- 27 Ronco G, Cuzick J, Pierotti P, et al. Accuracy of liquid based versus conventional cytology: overall results of new technologies for cervical cancer screening: randomised controlled trial. *BMJ* 2007;335(7609):28. Doi:10.1136/bmj.39196.740995.BE
- 28 Moy LM, Zhao FH, Li LY, et al. Human papillomavirus testing and cervical cytology in primary screening for cervical cancer among women in rural China: comparison of sensitivity, specificity, and frequency of referral. *Int J Cancer* 2010;127(03):646–656. Doi:10.1002/ijc.25071
- 29 Arbyn M, Sankaranarayanan R, Muwonge R, et al. Pooled analysis of the accuracy of five cervical cancer screening tests assessed in eleven studies in Africa and India. *Int J Cancer* 2008;123(01):153–160. Doi:10.1002/ijc.23489
- 30 Kim SH, Lee JM, Yun HG, et al. Overall accuracy of cervical cytology and clinicopathological significance of LSIL cells in ASC-H cytology. *Cytopathology* 2017;28(01):16–23. Doi:10.1111/cyt.12351
- 31 Underwood M, Arbyn M, Parry-Smith W, et al. Accuracy of colposcopy-directed punch biopsies: a systematic review and meta-analysis. *BJOG* 2012;119(11):1293–1301. Doi:10.1111/j.1471-0528.2012.03444.x
- 32 Aue-Aungkul A, Punyawatanasin S, Natprathan A, Srisomboon J, Kietpeerakool C. “See and treat” approach is appropriate in women with high-grade lesions on either cervical cytology or colposcopy. *Asian Pac J Cancer Prev* 2011;12(07):1723–1726
- 33 Bryson P, Stulberg R, Shepherd L, McLelland K, Jeffrey J. Is electrosurgical loop excision with negative margins sufficient treatment for cervical ACIS? *Gynecol Oncol* 2004;93(02):465–468. Doi:10.1016/j.ygyno.2004.01.028
- 34 Jiang Y, Chen C, Li L. Comparison of cold-knife conization versus loop electrosurgical excision for cervical adenocarcinoma in situ (ACIS): a systematic review and meta-analysis. *PLoS One* 2017;12(01):e0170587. Doi:10.1371/journal.pone.0170587