Correlation of Abnormal Pap Smears with Histopathologic Results: Philippine General Hospital Experience (2014-2017)

Dahlia Teresa Ramirez Argamosa,[1] Mark Angelo C. Ang,[1]
Agustina D. Abelardo,[1] Michele H. Diwa[1] and Christopher Alec A. Maquiling[2]

[1]*Department of Pathology, College of Medicine, University of the Philippines Manila*
[2]*Department of Laboratories, Philippine General Hospital*

ABSTRACT

Objectives. To evaluate abnormal Papanicolau smear results at the Philippine General Hospital (PGH) for the past four years by comparing abnormal smear cytology with histologic interpretations. Possible causes of discrepant results were also determined.

Methods. All Pap smears released as abnormal from January 2014 to December 2017 and the corresponding available biopsies were retrieved. Discrepancy between cytologic and histology diagnosis was assessed and pairs with major discordance were reviewed.

Results. There were a total of 30,237 conventional pap smears signed out of which 239 (0.79%) were abnormal and only 56 (23%) had a subsequent tissue biopsy. The overall concordance rate is 75% while strict or absolute concordance rate is 32%. The overall discordance rate is 25%. Positive predictive value is highest for pap smears signed out as atypical glandular cells favor neoplastic (AGC-NEO) (100%), followed by malignant (93%), high grade squamous intraepithelial lesion (HSIL) (83%), and then atypical squamous cells cannot exclude an HSIL (ASC-H) and atypical squamous cell of undetermined significance (ASCUS), both at 67%.

Conclusions. Considering that the Philippine General Hospital is a referral and academic center, we have a low percentage of abnormal pap smears compared to other developing countries and even a lower percentage of patients who had subsequent biopsies. Cytohistologic correlation detected interpretative as well as sampling errors, and the aim is to work on these deficiencies by improving quality assurance protocols and modifying current local practices of both pathologists and clinicians.

Key Words: Papanicolaou smear, cervical cancer screening, quality assurance

INTRODUCTION

Cervical cancer is the second among estimated leading new cancer deaths in our country last 2015, based on the Philippine Cancer Facts and Estimates published by the Philippine Cancer Society.[1] Cervical cancer, which is predominantly the human papilloma virus (HPV) driven, is known to be one of the preventable diseases. An effective screening program to decrease the incidence of cervical cancer, which includes papanicolau smear, is currently lacking in the Philippines. The papanicolau test, or "pap smear", has been proven to be one of the successful screening tools for detecting potentially pre-malignant and malignant cervical lesions. As with any other laboratory test, quality control of cytology process is essential to identify, reduce and rectify errors. One of the recommendations for quality assurance is the comparison of all pre-malignant and

Corresponding author: Dahlia Teresa Ramirez Argamosa, MD
Department of Pathology
College of Medicine
University of the Philippines Manila
547 Pedro Gil Street, Ermita, Manila 1000, Philippines
Telephone: +632 5264550
Email: tetargamosa@gmail.com

malignant gynecologic cytology reports with subsequent histopathology, and determining the reasons for discordant results. This will give the pathologists, primary care physicians and ob-gynecologists and cytotechnologists' insights on areas where improvements or alterations in management are necessary. Unfortunately, cytohistologic correlation is not routinely and systematically done is most hospitals, including our institution in particular.

Access to high standard cytology services is a challenge for most developing countries.[2] Aside from limited resources, other pressing priorities, as well as the burden of encouraging women to have a pap smear test, interpretation of cervical smears is one of the most challenging tasks because it requires competence which can only be acquired by years of experience, ongoing training and appropriate quality control measures.[3] In Mexico, the low quality of cytologic services has been a major barrier to reducing cervical cancer rates. Two of the listed factors include inadequate sampling and accurate interpretation.[4]

This study evaluated cervical cancer cytology screening at the Philippine General Hospital (PGH) by correlating abnormal smear cytology with histopathology. Also, the investigators attempted to determine the causes of discrepant results using a previously described algorithm.

METHODS

The investigators used a non-probability descriptive study design. All pap smears signed out as abnormal from January 2014 to December 2017 and the corresponding available biopsies performed within one year of the cervical cytology were retrieved and reviewed. The computerized database of surgical pathology reports only started in 2014, facilitating a thorough search of all histology biopsy results from both the central laboratory and outpatients laboratory. All pap smears done at the PGH are the conventional type. The slides were submitted to the gynecologic cytology unit of the department of laboratories and screened by the junior and senior cytotechnologists. All pap smears with abnormal findings were referred to and signed out by the supervising pathologist. The Bethesda System[5] was used for the final reports. The discrepancy between cytologic and histology diagnosis was assessed by adapting the Discrepancy Assessment Grid from the American Society of Cytopathology.[6] Agreement classification was based on the original final cytology diagnosis and the final histopathology diagnosis. The "Agree" category included pairs with the exact agreement (absolute concordance). The minor undercall or minor overcall (or acceptable correlation) category included those with one step difference or one level of magnitude between the pap smear and biopsy result (e.g. ASCUS cytology and LSIL tissue biopsy) Discordance is defined as having two step difference or more than one level of magnitude between the paps smear and biopsy result, and are divided into the major undercall and major overcall categories (e.g. HSIL cytology and chronic cervicitis on tissue biopsy). The minor variance category included pairs that cannot be necessarily characterized as overcalls or undercalls.[6]

All cytology-histology pairs with major discrepancies (both overcalls and undercalls) were re-assigned new accession numbers. Names were not given during the review sessions to maintain anonymity, privacy and confidentiality of patient information. These cases were reviewed independently by two of the authors without knowledge of the previous diagnoses. If the original diagnosis was different from the reviewers' diagnosis, a second or third reviewer was consulted in a blinded fashion. A final diagnosis will be selected based on majority opinion. Using the results of the review diagnoses, causes of discrepancy were determined using the Cytohistologic Correlation Algorithm developed by Tritz et al.[7]

All remaining pap smear cases that were signed out as negative were not reviewed in this study because a large proportion of the pap slides and documents were already unavailable. Also, negative pap tests that precede histologically proven squamous intraepithelial lesions as well as glandular lesions cannot be analyzed to compute negative predictive values because biopsies are not routinely taken following these negative pap test.

RESULTS AND DISCUSSION

Abnormal cervicovaginal cases

There were a total of 30,237 pap smears evaluated and signed out from 2014 to 2017. Of these, 239 (0.79%) were abnormal. In comparison with College of American Pathologists (CAP) latest benchmark for laboratory percentile reporting rate for conventional pap smears,[8] results of PGH Atypical Squamous Cell of Undetermined Significance (ASCUS) and Low Grade Squamous Intraepithelial Lesion (LSIL) are within the 5th to 10th percentile, Atypical Squamous Cells cannot exclude an HSIL (ASC-H) in the 25th-50th percentile, High Grade Squamous Intraepithelial Lesion (HSIL) in the 10th—25th percentile and Atypical Glandular Cell (AGC) within 50th-75th percentile. These statistics are well within the acceptable limits for conventional smears. Results however, may suggest that ASCUS and LSIL are diagnosed at a lower frequency than usual.

Of the 239 abnormal pap smears, only 56 (23%) had subsequent tissue biopsy with available histopathology material for review. Of these 56 abnormal cytology cases, 14 were signed out as outright malignant (25%), 11 were signed out as LSIL (20%), and 11 were signed out as atypical glandular cells (20%) (Table 1).

Our rate of abnormal pap smears (0.79 %) is generally lower compared to other countries. In Thailand, for example, 2.2%[9] and 1.9%[10] had abnormal pap smears. In other developing countries, the overall abnormal rates are generally higher than what we found in our study. In

Table 1. Summary of Cervicovaginal Cytology Cases 2014-2017

Cytologic diagnosis	No. of cases	%
Total no. of cases	30237	
		% of total
Total Abnormal	239	1%
		% of total
AGC	35	0.12%
AGC-NEO	6	0.02%
ASC-H	26	0.09%
ASCUS	90	0.30%
HSIL	19	0.06%
LSIL	43	0.14%
Malignant	20	0.07%
Abnormal cases with histopath	56	
		% of total
AGC	11	20%
AGC-NEO	5	9%
ASC-H	3	5%
ASCUS	6	11%
HSIL	6	11%
LSIL	11	20%
Malignant	14	25%

AGC – Atypical Glandular Cells; AGC-NEO – Atypical Glandular Cells Favor Neoplastic; ASC-H – Atypical Squamous Cell cannot exclude High Grade Squamous Intraepithelial Lesion; ASCUS – Atypical Squamous Cell of Undetermined Significance; HSIL – High Grade Squamous Intraepithelial Lesion; LSIL – Low Grade Squamous Intraepithelial Lesion.

particular, Mumbai India, Southern India and Nepal have abnormal rates of 4.05%[11], 3.08%[12] and 1.7%,[13] respectively. A study from a University Hospital in Pakistan however, had a slightly lower abnormal pap smear rate at 0.68%.[14]

Compared with studies done in different institutions in other countries, and considering that PGH is a referral institution, we have a relatively low percentage of abnormal and even lower percentage of patients who had subsequent biopsies. A possible reason is that cytoscreeners and pathologists use high thresholds for calling a smear abnormal. We also cannot exclude the possibility of false negative sign outs in those that were released as benign (negative and reactive cellular changes). All of the cases were prepared using the conventional method, which suffers from poor fixation, artifactual distortions, and thick, uneven smearing. These conventional smears also have larger areas of the slide that need to be assessed and certain spots can be easily missed. Interpretative errors of cytoscreeners and pathologists must also be taken into account.

Patients were lost to follow up and usually do not get tissue biopsies due to several reasons including limited education and awareness, embarrassment, fear of the procedure and diagnosis, and financial constraints. It may also be the case that some of these patients actually get tissue biopsies at other hospitals or clinics.

Cytologic-histopathologic agreement of diagnosis and risk of malignancy

The overall concordance rate (agree + minor overcall + minor undercall + minor variance) is 75% while strict or absolute concordance rate (agree only) is 32%. The overall discordance rate (major overcall + major undercall) is 25%. The concordance rates for malignant pap smear reports is high (absolute – 79%, overall – 93%). The absolute concordance rate for HSIL pap smears is low (33%) but the overall concordance rate is high (83%). A similar finding is seen for LSIL where the absolute concordance rate is relatively low at 45% but the overall concordance rate is high at 91%. (Table 2).

The overall concordance rate (75%) we found in this study is similar to that of overall concordance rates in Pakistan (74%) [14], South India (76%) [12], Mumbai India (70.7%)[11] and Brazil (88.1%)[15]

Our data also showed that the risk of malignancy (positive predictive value) is highest for pap smears signed out as AGC-NEO (100%), followed by malignant (93%) and HSIL (83%). It is worth noting that the risk of malignancy for LSIL pap smears is very low at 9%, while the risk of malignancy of ASCUS and AGC are high a 67% and 55% respectively. (Table 3). There were more biopsies performed for higher grade lesions, specifically those with malignant cytology (70%) and AGC-NEO (83%), which is compatible with the current management recommendations for performing colposcopy and biopsy. However, only 32% of HSIL cytology had subsequent histology.

Table 2. Cytologic-Histopathologic Agreement of Diagnosis

Cytologic Diagnosis	n	Agree	Major overcall	Major undercall	Minor overcall	Minor undercall	Minor variance	Row Total
AGC	n (% of AGC)			6 (55%)	5 (45%)			11
AGC-NEO	n (% of AGC-NEO)					5 (100%)		5
ASC-H	n (% of ASC-H)		1 (33%)			2 (67%)		3
ASCUS	n (% of ASCUS)			4 (67%)			2 (33%)	6
HSIL	n (% of HSIL)	2 (33%)	1 (17%)			3 (50%)		6
LSIL	n (% of LSIL)	5 (45%)		1 (9%)	4 (36%)	1 (9%)		11
Malignant	n (% of Malignant)	11 (79%)	1 (7%)		1 (7%)		1 (7%)	14
Column Total	n (% Overall)	18 (32%)	3 (5%)	11 (20%)	10 (18%)	11 (20%)	3 (5%)	56

AGC – Atypical Glandular Cells; AGC-NEO – Atypical Glandular Cells Favor Neoplastic; ASC-H – Atypical Squamous Cell cannot exclude High Grade Squamous Intraepithelial Lesion; ASCUS – Atypical Squamous Cell of Undetermined Significance; HSIL – High Grade Squamous Intraepithelial Lesion; LSIL – Low Grade Squamous Intraepithelial Lesion.

Table 3. Risk of Malignancy of Cytologic Diagnosis by Histopath Diagnosis

Cytologic Diagnosis	n	benign or low risk	HSIL or Malignant	Grand Total
AGC	n (% of AGC)	5 (45%)	6 (55%)	11
AGC-NEO	n (% of AGC-NEO)		5 (100%)	5
ASC-H	n (% of ASC-H)	1 (33%)	2 (67%)	3
ASCUS	n (% of ASCUS)	2 (33%)	4 (67%)	6
HSIL	n (% of HSIL)	1 (17%)	5 (83%)	6
LSIL	n (% of LSIL)	10 (91%)	1 (9%)	11
Malignant	n (% of Malignant)	1 (7%)	13 (93%)	14
Grand Total	n (% Overall)	20 (36%)	36 (64%)	56

AGC – Atypical Glandular Cells; AGC-NEO – Atypical Glandular Cells Favor Neoplastic; ASC-H – Atypical Squamous Cell cannot exclude High Grade Squamous Intraepithelial Lesion; ASCUS – Atypical Squamous Cell of Undetermined Significance; HSIL – High Grade Squamous Intraepithelial Lesion; LSIL – Low Grade Squamous Intraepithelial Lesion.

Atypical squamous cell of undetermined significance

ASCUS counts the majority of pap smear abnormalities in our institution. According to Cox.[16] "ASCUS is not a diagnosis but an interpretation that is very subjective". The Bethesda has given a list of diagnostic criteria but it suffers low reproducibility with substantial interobserver variation.[17,18] ASCUS can be confused with other entities such as inflammatory changes, air-dying artefactual nuclear enlargement, atypical repair, cell degeneration and atrophy.[5] Prior to the review, an ASCUS reading carries higher risk of HSIL or malignancy (67%) compared to benign or low risk. There were three ASCUS major undercalls that were reviewed, of which two cases were amended to HSIL and ASC-H, and the risk for both benign and malignant became equal. Though ASCUS is the indeterminate or "gray area" in gynecologic cytology, it appears to carry a risk of high grade SIL or more, thus patients with this interpretation should be encouraged to follow up diligently. The study of Cheung et al. showed similar findings.[19] The American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines which are followed in our gynecologic clinics prefer reflex HPV testing for patients with ASCUS, or a repeat pap smear after one year.[20]

Atypical glandular cell not otherwise specified and atypical glandular cell favor neoplastic

Both AGC-NOS and AGC-NEO were detected in approximately 0.12% of all cervical cytologies in our study. AGC interobserver variability has been noted and is problematic.[21] AGC frequency in reports from other countries range from 0.1 to 0.9 %.[8,22-25] Five out of six patients (83%) diagnosed as AGC-NEO had subsequent biopsies which all turned out to be adenocarcinoma (2 cervical primary and 1 endometrial primary with cervical extension). Five of 11 patients (45%) diagnosed with AGC-NOS had benign histology (2 chronic cervicitis, 2 polyps and one radiation change) while the remaining 55% of AGC-NOS turned out to be malignant on tissue biopsy (4 cervical primary, 3 endometrial primary and 1 rectal primary). Our findings are similar to that previously reported by Kim where malignant diseases are present in 14.6% to 57.4% of AGC-NOS pap cases, and that malignant diseases in AGC-NOS cases were not confined only to cervical carcinoma but to endometrial, ovarian and non-gynecologic carcinomas as well.[25] It is interesting to observe that there are more AGC-NOS diagnosis (35 smears) compared to HSIL (19 smears), and both had similar rates of concurrent biopsies (32%).

Atypical squamous cell cannot exclude HSIL

ASC-H interpretation in our institution is 22% of all abnormal cytology diagnosis, which is above the expected rate of less than 10%.[5] ASC-H are associated with higher HPV positive rates and more HSIL (CIN II and III) histology compared to ASCUS[26] but has a lesser positive predictive value when setting against HSIL cytology diagnosis.[27] Our results are in concurrence with these findings, with ASC-H and HSIL cytology having a 67% and 83% positive predictive values respectively.

Squamous intraepithelial lesions

LSIL pap smears were histologically confirmed in 6 of 11 cases (55%). Four cases had chronic cervicitis (minor overcall) and one case had HSIL histology (major undercall). HSIL pap smears had 33% confirmed HSIL histology, 50% malignant histology (squamous carcinoma and adenocarcinoma), and one case with cervical atrophic changes in histology (major overcall). This type of abnormal cell very important to detect, and there are several problematic patterns in HSIL including its detection in atrophic smears.[5,28]

Discrepant results and possible sources of error

A summary of the review of discordant results is shown in Table 4. Most of the errors identified were interpretative errors (Table 5). One case signed out as squamous cell carcinoma in cytology but upon review was radiation change, and histology confirmed the latter. Cellular changes post-radiation mimics that of malignant atypia, and over-interpretation does occur.[29] Three cases were signed out as AGC, NOS in cytology but after review it was signed out as malignant (2 adenocarcinomas and 1 squamous cell carcinoma). Two ASCUS diagnosis was amended to HSIL and ASC-H. The majority of the interpretative errors were major undercalls. In some of the reviewed slides the abnormal

Table 4. Review of Discrepant Results

Diagnosis	Before review	After review	No. of discordant cases reviewed	Remarks
AGC	6	4	3	1 upgraded to ASC-H, 1 upgraded to HSIL, 1 retained
AGC-NEO	3	3	1	downgraded to LSIL
ASC-H	11	8	5	2 retained diagnosis, 2 upgraded to adeno, 1 upgraded to HSIL
ASCUS	5	5	0	
HSIL	11	11	1	upgraded to HSIL
LSIL	6	9	1	retained diagnosis
Malignant	14	15	1	downgraded to Benign (Radiation change)
Radiation change (Benign)	0	1	0	
Total	56	56	12	

Note: 2 Discordant cases not reviewed because of missing slides.

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Table 5. Evaluation of possible sources of error

	Cytology Diagnosis		Histologic Diagnosis		Possible Error Type (Tritz)	
	Before review	After review	Before review	After review		
Patient 30	ASCUS	ASC-H	Microinvasive SCCA	HSIL (minor undercall from original)	Interpretative	major undercall
Patient 33	ASCUS	HSIL	SCCA	SCAA (agree)	Interpretative	major undercall
Patient 38	ASCUS	ASCUS	HSIL	HSIL (agree)	Pap sampling	
Patient 26	ASC-H	LSIL	Chronic Cervicitis, Leiomyoma	Chronic Cervicitis (agree)	Interpretative	minor undercall
Patient 34	AGC	HSIL	Adenosquamous Carcinoma	SCAA (minor variance)	Interpretative	major undercall
Patient 30	AGC	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma (agree)	Interpretative	major undercall
Patient 31	AGC	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma (agree)	Interpretative	major undercall
Patient 32	AGC	AGC	Adenosquamous Carcinoma	SCAA (agree)	Pap sampling	
Patient 39	AGC	AGC	Adenocarcinoma	Adenocarcinoma (agree)	Pap sampling	
Patient 35	LSIL	HSIL	HSIL	HSIL (agree)	Interpretative	major undercall
Patient 25	HSIL	HSIL	Chronic Cervicitis with Atrophy	LSIL (major undercall from original)	COLPO	with histology reading error
Patient 27	SCCA	Radiation changes	Radiation changes	Radiation changes (agree)	Interpretative	major undercall

AGC – Atypical Glandular Cells; AGC – Atypical Glandular Cells Not Otherwise Specified. AGC-NEO – Atypical Glandular Cells Favor Neoplastic; ASC-H – Atypical Squamous Cell cannot exclude High Grade Squamous Intraepithelial Lesion; ASCUS – Atypical Squamous Cell of Undetermined Significance; HSIL – High Grade Squamous Intraepithelial Lesion; LSIL – Low Grade Squamous Intraepithelial Lesion; SCCA – Squamous Cell Carcinona.

cells are very few while others show degenerative changes. Other abnormal cells are almost not conspicuous unless thoroughly screened. It has been well reported in literature that the precision of cytologic interpretation does vary among pathologists,[30] specifically that of atypical squamous cells[31] and glandular lesions.[21] Intra and inter observer variabilities occur and are inevitable[32,33] but cytohistologic correlation can pinpoint unacceptable rates of interpretative error which may significantly affect treatment.[7]

Three possible pap sampling errors were also discovered in this study. Two cases were AGC on the review but squamous cell carcinoma and adenocarcinoma on histology. One case was ASCUS on the review but HSIL on histology. Pap sampling errors may be due to (1) poor technique including inexperience and lack of proper guidance leading to inadequate sampling (2) presence of obscuring blood and mucus material and (3) unsatisfactory smear preparation including delayed or inadequate fixation, uneven smears and

paucity of the specimen on the slide. PGH is an academic and training institution and most of these smears were collected by medical clerks, interns and new residents.

One case was a combined colposcopy sampling and histology interpretative error. It was reviewed as HSIL on cytology but was signed out only as chronic cervicitis on histology. Review of the histology however revealed that it was LSIL. Cytohistologic discrepancies like these are typically attributed to incorrect cytologic interpretation.[34] Errors in histologic diagnosis are also missed because some laboratories focus on the cytology aspect and fail to review the surgical pathology report.[35]

The errors we identified were mostly major undercalls and failure to properly sample the pathologic lesion. Cytohistologic discrepancies were always assumed to be due to pap smear interpretation errors, but there are studies that show that this could also be due to biopsy sampling errors or a combination of sampling and interpretation.[6]

By implementing quality assurance measures, concordance rates can be augmented. Although pap smears suffer from interpretation errors and sampling errors, it is still the most affordable screening test for cervical cancer. At present, pap smears are still widely performed in most hospital and clinics in the Philippines, some in conjunction with visual inspection by acetic acid (VIA) and HPV tests in opportunistic screening. Combined VIA and Pap test appear to have high predictive accuracy in certain groups, including patients in our institution.[32,36] Similar results are found in studies done in Pakistan and Vietnam.[37,38]

CONCLUSIONS AND RECOMMENDATIONS

The report gave an overview of abnormal pap smear test results in a single, large institution for the past four years, the frequency of a subsequent biopsy when an abnormal result was released, the correlation of cytology with the histopathology result and the plausible causes of discordant results. The errors detected include cytology and histology interpretative errors, mostly major undercalls, as well as paps and colpo sampling errors. Most of these discrepancies result in a delay of treatment or under treatment of patients. The value of these findings include prevention of errors by (1) continuous training and careful screening of cytotechnologists and pathologists to increase competence in interpreting smears (2) ongoing improvement and awareness of clinicians in taking samples including specimen handling to avoid drying artifacts (3) adapting measures or provisions to encourage follow up of patients with abnormal pap result, and (4) sustained quality assurance monitoring of both cytology and histology which include detection of significant cytohistologic discrepancies. Cytology-histology correlation protocols are not yet established in our institution. The Discrepancy Assessment Grid and Cytohistologic Correlation Algorithm adapted in this study can be used and may be modified accordingly.

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