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Cervical Cytology: An Audit in a Singapore Teaching Hospital

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ABSTRACT

Objectives: To describe the cervical cytology diagnoses and cyto-histological correlation in the Department of Pathology, National University of Singapore in 1997 and to compare the data with international figures.

Methods: A database search of all cervical cytology cases diagnosed in the department in 1997 as well as follow-up biopsies was carried out. The data was then critically analysed.

Results: 10,207 cases were reviewed. 96% of the cases had a diagnosis of "negative". Under 1% of cases were labelled as "inadequate". "Atypia" was diagnosed in 1% and dysplasia and/or malignancy was diagnosed in 1%. These figures correlate well with international data. Of the dysplasia cases, 78% were followed by biopsy. Of the high-grade dysplasia cases that were biopsied, 97% of the biopsy diagnoses were within the acceptable concordance range with the cytology diagnoses and in only 3% was there a significant discrepancy. Of the cases diagnosed as atypia, 39% were subsequently biopsied at the same institution as the next procedure and only one showed high grade dysplasia. A total of six cases showed a significant discrepancy between the cervical cytology result and the subsequent biopsy diagnosis and these were reviewed to elucidate the reasons for the discrepancies.

Conclusion: The cervical cytology service is of a high diagnostic standard. A subset of patients is probably being prematurely biopsied and may benefit from having a repeat smear instead. Specific clinical protocols regarding subsequent therapy following cytology results and closer cyto-histological correlation are two main areas where the cytology service can be improved.

Keywords: cervix, cytology, review, screening, ASCUS

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INTRODUCTION

The introduction of cervical screening programmes has arguably been one of the most successful cancer detection and prevention strategies in the history of medicine. Cervical screening programmes in many countries have been shown to reduce the death rate from cervical carcinoma significantly[1-4]. Carcinoma of the uterine cervix is the 4th commonest cancer among women in Singapore, making up 7.2% of all female cancers diagnosed between 1993 and 1997[5]. While a coordinated national programme for cervical cancer screening is about to be established, cervical smears have been carried out in increasing numbers, in both the public and private sectors (no figures available). The age-standardised rate of cervical cancer incidence in Singapore has been declining over the years from 18 per 100,000 per year in 1968 to 14 per 100,000 per year in 1997[5]. This figure is very close to countries with an established screening programme (like the 13.7 per 100,000 per year reported in the Birmingham, UK, study) and contrasts with other Asian countries with no such programmme (38.9 per 100,000 per year in Madras, India)[6].

The cervical cytology service plays a key role in the cervical screening/investigation process. The quality of a cervical cytology service is in part monitored by the overall percentages of the various diagnostic categories diagnosed, the review of routine cases as well as the histological and clinical follow-up[1,7,8]. These in turn allow for evaluation of the false-positive and false-negative rates.

Our objective is to describe the cervical cytology diagnoses in the Department of Pathology, National University of Singapore (NUS)/National University Hospital (NUH) in 1997, to compare the data with international figures and to correlate the cytological diagnoses with histopathological and clinical follow-up. In doing so, we will pay special attention to those cases with histo-cytological discrepancy, reviewing every aspect of the diagnostic procedure (cytology, histology, and other technical/clerical aspects).

Table I. Overall figures.

Diagnosis	Numbers	% of total
Negative	9824	96.25
Inadequate	70	0.69
Reactive atypia	94	0.92
Koilocytosis	25	0.24
ASCUS/Atypia	94	0.92
Dysplasia, NOS	1	~0
Mild dyskaryosis (LSIL)	54	0.53
Moderate and severe dyskaryosis (HSIL)	39	0.38
Squamous cell carcinoma	4	0.04
Adenocarcinoma	2	0.02

MATERIALS AND METHODS

A database search of all cervical cytology cases diagnosed in the Department of Pathology, National University of Singapore in 1997 was carried out. This yielded a total of 10,207 cervical cytology cases. The histology slides of each of those cases in which a subsequent biopsy in NUS/NUH was taken, were also obtained for review. The data was then critically analysed. A total of six cases showed a significant discrepancy between the cervical cytology diagnosis and the subsequent biopsy diagnosis. All the diagnostic material and information from these cases was then reviewed by two pathologists (M.S.T. and A.R.) and the cytotechnologist supervisor (B. N.) to elucidate the reasons for the discrepancies.

RESULTS

Overall figures

A total of 10,207 cervical cytology cases were reported on by the department in 1997. Of these, 96% had negative diagnoses (See Table I). Seventy cases (0.69%) were inadequate. Ninety-four cases (0.92%) had diagnoses equivalent to "reactive atypia". This group included diagnoses such as "radiation effect", "reparative changes" and "squamous metaplasia". Twenty-five cases (0.24%) were diagnosed as koilocytosis. Ninety-four cases (0.92%) were diagnosed as "atypical". (This diagnosis in our setting corresponds to the British term "borderline nuclear changes" (BNC), as described in the literature[9], and "Atypical Squamous Cells of Unknown Significance" (ASCUS) as used in the Bethesda system of reporting[10], and the term ASCUS will be used henceforth in this paper for these diagnoses). One case was diagnosed as "dysplasia NOS". There were 54 cases (0.53%) of mild dysplasia/low-grade squamous intraepithelial lesion (LSIL) and 39 cases (0.38%) of moderate or severe dysplasia/high-grade squamous intraepithelial lesion (HSIL). Four cases of squamous cell carcinoma were diagnosed (0.04%) as well as two cases of adenocarcinoma (0.02%). Finally, two cases were wrongly coded: The first was coded as mild dysplasia on cytology and CIN1 on biopsy but, on review of the reports and slides, both cytology and biopsy were negative. The second case was coded as ASCUS on cytology, but was actually reported as CIN III on cytology and biopsy, and this was confirmed by review of the slides.

The ratio of ASCUS to squamous intraepithelial lesions (SIL) was 1.00.

Follow-up data

Histological follow-up data for the cases diagnosed as ASCUS and dysplasia were obtained. Also, cases that were negative for dysplasia or malignancy that subsequently had positive biopsies in the same or following year were analysed.

ASCUS

Of the 94 cases diagnosed as ASCUS, 37 (39%) were subsequently biopsied at NUH as the next procedure. Of these 37 biopsied cases, the histological diagnoses were negative in 27 cases (73%). Six cases (16%) were diagnosed as CIN I. One case was diagnosed as CIN III (3%). Three cases (8%) had other diagnoses: One had an inadequate (unsatisfactory) biopsy and no further follow-up in our records; another had atypical glandular cells and the subsequent biopsy showed endocervical adenocarcinoma; and the third case was originally diagnosed as squamous cell carcinoma on biopsy but, on review, the diagnostic opinion was that the diagnostic tissue fragment was a contaminant (i.e. a "floater") and that the biopsy was negative for dysplasia or malignancy.

MILD DYSPLASIA (LSIL)

Of the 54 cases with mild dysplasia, 37 (68.5%) had a subsequent biopsy at NUH. Of these, 14 (38%) were histologically negative, 19 (51%) were diagnosed as CIN I, 2 (5%) as CIN II and 1 (3%) as CIN III. Therefore, the positive predictive value of smear cytology showing LSIL for a histological lesion of CIN I or worse is 59%.

MODERATE AND SEVERE DYSPLASIA (HSIL)

Thirty-five (89.7%) of the 39 HSIL cases were subsequently biopsied at NUH. Of these, one was negative, one (3%) had CIN I, nine (26%) had CIN II, 22 (62%) had CIN III and two (6%) had squamous cell carcinoma. The positive predictive value of smear cytology showing HSIL for a histological lesion of CIN II or worse is 94%.

Table II. Review of discrepant results.

Case No.	Original Cytology Dx	Original Biopsy Dx	Consensus Cytology Dx	Consensus Biopsy Dx
1	Neg.	CIN II	CIN I-II	CIN I-II
2	Neg./ASCUS	SCC	Neg.	Neg. (SCC floater)
3	Neg.	CIN II	ASCUS	HPV
4	Neg.	CIN II	No consensus	No consensus
5	CIN I	CIN III	ASCUS/HPV	HPV
6	CIN III	Neg.	CIN III	No consensus

Abbreviations: Dx = Diagnosis; Neg. = negative; SCC = squamous cell carcinoma.

Table III. Comparison of our results with other figures.

Diagnosis	NUS	CAP	NHSCSP	GMH
Inadeq./Unsatis.	0.69%	0.5%	7.0%	Not stated
ASCUS/Atypia	0.92%	2.8%	5.5%	18.37%
LSIL	0.53%	1.6%	5.5%	3.5%
HSIL	0.38%	0.4%	1.6%	1.56%
ASCUS/SIL ratio	1.00	1.3	–	3.63

Abbreviations: NUS = National University of Singapore (this study); CAP = College of American Pathologists (Ref. 7); NHSCSP = National Health Service Cervical Screening Programme (Ref. 8); GMH = Grady Memorial Hospital, Atlanta, Georgia, USA (Ref. 11); Inadeq. = Inadequate; Unsatis. = Unsatisfactory.

CARCINOMA

The two cases diagnosed as adenocarcinoma and the four cases diagnosed as squamous cell carcinoma had subsequent biopsies and/or excisions that confirmed the diagnoses in all the cases.

NEGATIVE FOR DYSPLASIA OR MALIGNANCY

Fourteen cases that were negative for dysplasia or malignancy subsequently had positive cervical biopsies in the same or following year. The median interval between the negative smear and the positive biopsy was 11.5 months. The biopsy diagnoses were CIN I and/or koilocytic atypia (seven cases), CIN II (four cases), CIN III (two cases) and adenocarcinoma (one case). The smears were reviewed and all were confirmed to be negative for dysplasia or malignancy. The negative predictive value of smear cytology that is negative for dysplasia or malignancy is 99.9%.

REVIEW OF SIGNIFICANTLY DISCREPANT CASES

A total of six cases showed a significant discrepancy between the cytological diagnosis and the subsequent biopsy diagnosis. We defined discrepancy as more than 1 grade of difference between the cytology and the biopsy result. These were reviewed by two pathologists (M. S. T. and A. R.) and the cytotechnologist supervisor (B. N.). On re-examination of the cytology and biopsy slides, an attempt was made at consensus diagnoses. The results of this review are shown in Table II.

In one case (Case 1) the cytological diagnosis was, on review, inaccurate. In two cases (Cases 3 and 5) the biopsy diagnosis was inaccurate. One case (Case 2) had a discrepancy for technical reasons (contaminant only detected on review). Two cases were intrinsically difficult, and despite intense scrutiny and discussion, no consensus was reached among the reviewers.

DISCUSSION

From the results of this study we can draw several conclusions regarding our cervical screening service and the population involved in the screening.

Overall results (Table III)

The diagnostic rates for the various diagnostic categories compare well with the benchmark data collected by the College of American Pathologists (CAP) Cytopathology Resource Committee[7]. Their median laboratory reporting rates are 2.8% for ASCUS, 1.6% for LSIL, 0.4% for HSIL and 0.5% for unsatisfactory, with an ASCUS/SIL ratio of 1.3 (See Table III). By comparison, our data show rates for ASCUS, LSIL, HSIL and unsatisfactory of 0.92%, 0.53%, 0.38% and 0.69% respectively. Our ASCUS/SIL ratio is 1.00.

However, our figures differ from the United Kingdom's National Health Service Cervical Screening Programme (NHS CSP) guidelines[8], with ours having lower rates in all diagnostic categories (Table III). Our results were also significantly different from another equally large study of 10,000 consecutive cervicovaginal cytology smears done at the Grady Memorial Hospital in Atlanta, Georgia, USA[10]. We chose to compare our data with this study because it was a single institution study that was well-conducted, and involved smears from a certain calendar year (like our study). The findings of that study of the indigent population

Table IV. Rate of SIL in biopsies following ASCUS. A comparison with other studies.

Authors	Dvorak et al	Malik et al	Williams et al	Yang et al	NUS
Year published	1999	1999	1997	1997	2000
Reference No.	(12)	(13)	(14)	(15)	
No. of ASCUS cases	249	105	284	–	37
% SIL on biopsy	72	71	58	66.67	18.9

showed significantly higher rates of diagnosis of ASCUS, LSIL and HSIL, with only 76.39% of smears being labelled as "negative" (Table III). These results, in part, may reflect the low risk nature of the population screened at the National University Hospital in Singapore. However, they may also be due to a form of self-selection: in Singapore, at the time of the study, cervical screening was done on an *ad hoc* basis and women were not actively called for screening in a systematic manner on a nation-wide scale. This allowed many women to be screened on an annual basis (more often than the British Screening Programme recommends), with a consequently higher rate of negative smears in this cohort.

ASCUS

The review of subsequent histological diagnoses of the cases with ASCUS showed that there was a relatively low rate of SIL being diagnosed on biopsy (19%). This rate is far lower than several other studies of follow-up biopsies done for ASCUS[12-15] (Table IV).

This relatively low rate of SIL diagnosis on biopsy for a borderline cytological diagnosis could be related to the fact that 39% of the ASCUS cases had a biopsy as the next procedure. This is a relatively high percentage. The NHS CSP document[8] recommends at least one repeat smear for BNC diagnoses before biopsy, and the CAP recommendation is similar[7]. Where those guidelines are followed, the women proceeding to a biopsy are those with persistent abnormality and, as such, the rates of LSIL found on subsequent biopsy in our study population are expected to be lower than in those populations where some degree of selection before biopsy has taken place.

LSIL and HSIL

The biopsy diagnoses of the mild dysplasia (LSIL) and moderate/severe dysplasia (HSIL) cases showed good correlation with the original cytological diagnoses. Ninety-five percent of the LSIL cases and 97% of the HSIL cases had histological diagnoses within one degree of difference in severity from their cytological diagnoses. The positive predictive values of an LSIL smear for at least an LSIL histological lesion and of an HSIL smear for at least an HSIL lesion are 59% and 94% respectively.

Carcinoma

Follow-up histological specimens of the two cases diagnosed as adenocarcinoma showed a poorly differentiated cervical adenocarcinoma in one case and an endometrial adenocarcinoma in the other. The biopsies/resection specimens of the four cases with smears diagnosed as squamous cell carcinoma were diagnosed as poorly differentiated invasive squamous cell carcinoma in two cases, keratinising squamous cell carcinoma in the third case and microinvasive squamous cell carcinoma in the last case.

Negative for dysplasia or malignancy

The 14 false-negative cases were reviewed. The initial cytology slides were reviewed and were confirmed to be negative (i.e. there was no false-negative cytology, but rather false-negative screening tests). The biopsies that followed were mainly done either because of routine annual screening or because of symptoms of abnormal bleeding. Four cases had biopsies one to two weeks after the initial smear because of abnormal appearances of the cervix. The false negatives could possibly be due to either sampling error or the natural history of the disease. Sampling error is likely in many of the cases, especially those with diagnoses of CIN II and above. These cannot be accounted for by the natural history of the disease as it is known that CIN II develops after a much longer interval and usually following CIN I. In support of this is the fact that several of the cases, while considered diagnostically adequate, were lacking in endocervical cells. This could mean that the transformation zone was not adequately sampled. The cases with CIN I or koilocytic changes on biopsy may be due to sampling error or due to the natural history of the disease (i.e. "new" infections with the human papillomavirus).

Significantly discrepant cases

There is a significantly low discrepancy rate in our series. Furthermore, as shown in our figures, the

causes of histo-cytological discrepancy are varied. Interestingly, only in one case out of six is there an instance where inaccurate cytological diagnosis appears to be the cause of discrepancy. Inaccurate histological interpretation and technical failures are significant causes. This serves to highlight that histological samples are also prone to sampling error and have their own false positive and false negative rates. A positive cytological diagnosis with a subsequent negative histology, depending on the type of histological specimen and interval from the time of smear may be due to sampling error of the biopsy or regression of the lesion. Thus it is as important to review the cytology associated with a histological sample as it is to review the histology of a cytological sample. Finally, it is interesting to note that some cases have an intrinsic diagnostic difficulty; but this affects the histological interpretation as much as the cytological one.

CONCLUSION

From our review of the 10,207 cervical cytology cases we can draw the following conclusions.

Firstly, the overall figures of the cervical cytology service of NUS/NUH are well within international standards. They showed reporting rates of the various diagnostic categories that were similar to those reported by the CAP but were somewhat different from the British experience (NHS CSP). Secondly, the figures show some of the peculiarities of the population screened, which may represent low risk cervical abnormality or a self-selection within the population screened. Thirdly, our figures show that our ASCUS cases were probably over-biopsied, and a different clinical protocol to follow these patients is desirable. Instituting the practice of a repeat smear for all borderline cases three to six months after the initial smear may allow selection of a subgroup of patients with persistent abnormalities who would then go on to a biopsy. Finally, our figures stress that in cases of histo-cytological discrepancy a full review of each case is necessary, including the accuracy of the cytological and histological diagnoses, as well as technical/clerical aspects involved in the case. A few controversial cases in which a consensus diagnosis is not possible will also contribute to apparent discrepancies.

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