

THE SIGNIFICANCE OF DOUBTFUL SMEARS AND THEIR MANAGEMENT USING COLPOSCOPY

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SYNOPSIS

The significance of doubtful smears is not certain and their management not clearly defined. Colposcopy was performed in 170 patients to assess the value of this procedure in the diagnosis and management of patients with doubtful smears. There was a clinically accurate correlation between colposcopic impression and directed biopsy histology in 75%. A histological diagnosis was available in 119, it was negative (normal/cervicitis) in 63 (53%), mild dysplasia in 15 (12%), moderate dysplasia in 14 (12%), severe dysplasia/carcinoma-in-situ in 23 (19%), microinvasion in 1 (1%) and invasive carcinoma in 3 (3%). We feel, that doubtful smears should not be merely followed up but are an indication for further investigation. Colposcopy and directed biopsy help to select out those with significant disease. With such evaluation the diagnostic cone biopsy rate was only 3% and treatment was not unnecessarily delayed in those harbouring significant disease.

INTRODUCTION

Screening for preclinical carcinoma of the cervix by exfoliative cervical cytology followed the classic publication of Papanicolaou and Traut in 1954 (1). Today the value of screening for detection of cervical intraepithelial neoplasia (CIN) and preclinical squamous cell carcinoma is accepted. In places such as British Columbia, Kentucky and Finland where screening is intensive there has been a fall in the incidence of and mortality from squamous cell cancer of the cervix (2) and the detection of intraepithelial carcinoma has increased markedly.

There is continuing disagreement between cytologists in the terminology and classification of cervical smears. Various classifications are used to convey to the clinician the relative probability of malignancy being present in the patient from whom the smear is obtained. In the Papanicolaou classification (3), cervical smears are divided into 5 classes. Class I and Class II smears are

considered as negative, Class III as suspicious and Class IV and V as positive for malignant cells. Others (4), use a contracted and simpler classification into negative, doubtful/suspicious and positive smears.

In our hospital a modified Papanicolaou classification is used as follows: Class I and II — negative, Class IIR — doubtful, please repeat, Class III — suspicious and Class IV and V — positive. Of smears which are not in the unsatisfactory or negative categories, 57% are reported in the Class IIR category and these are considered "doubtful". The suffix R indicates that a repeat smear is requested. The cytological changes which are reported in Class IIR smears range from a marked atypia of cells to those of moderate dyskaryosis. We were uncertain as to the significance of these "doubtful" (Class IIR) smears and so decided to study all patients with such cervical smears using colposcopy. This paper reports our findings.

PATIENT AND METHODS

From early 1979 till early 1982 all patients in our unit who had either a Class IIR, Class III, Class IV, or Class V cervical smear were recalled for colposcopy. A total of 326 patients had colposcopy performed. Of this group, 170 patients has a Class IIR (doubtful) smear.

Colposcopy was performed using a Zeiss colposcope on an outpatient basis and we used the clinical methods and criteria recommended by Coppleson et al (5) and Kolstad and StafI (6). An initial inspection was performed after cleansing the cervix with normal saline, followed by application of acetic acid. If the entire transformation zone (TZ) could not be seen, the examination was defined as unsatisfactory colposcopy. A colposcopic impression was formed of any abnormal area and this used to predict the histology of the directed biopsy(ies). The categories of colposcopic impression used were similar to those of the histological classification of the biopsies, which were into negative (normal/cervicitis), mild dysplasia (CIN I), moderate dysplasia (CIN II), and severe dysplasia/carcinoma-in-situ (CIN III). The other grades used were microinvasion and invasive carcinoma. Biopsies were performed with a Teischler or a Kervorkian-Younger biopsy forceps and endocervical curettage was not included as a routine. When mild dysplasia or moderate dysplasia on colposcopic impression was confirmed by directed biopsy histology, the patients were either followed up or treated with cryosurgery. When the colposcopic impression of severe dysplasia/carcinoma-in-situ was confirmed in the directed biopsy histology, a conization of the cervix was done for treatment. Cone biopsy was also done when the entire TZ could not be visualized and when there was considerable discrepancy between cytology, colposcopic impression and directed biopsy histology. All patients had follow-up for at least a year after the initial examination.

RESULTS

The age distribution of the 170 patients with a doubtful smear is shown in Table 1. Eighty-eight percent of the patients fell between the ages of 20 to 44 years and the mean age of the patients was 33 years. The parity of the patients ranged from 0 to 5 with a mean of 2.5. The number of induced abortions per patient ranged from 0 to 5 with a mean of 0.7.

The colposcopic impression in these 170 patients was negative in 74, mild dysplasia in 56, moderate dysplasia in 31 and severe dysplasia/carcinoma-in-situ

in 4. In 3 patients the colposcopic impression was of invasive carcinoma and it was indeterminate in 2.

Of the 170 patients, 52 did not have a directed biopsy done at time of initial colposcopy. Of the 52 without initial directed biopsy, 1 patient had a hysterectomy 2 years later because the smear was persistently doubtful, the colposcopic impression progressed from mild dysplasia to moderate dysplasia and directed biopsy showed carcinoma-in-situ, which was confirmed in the hysterectomy specimen. In the remaining 118 patients, the directed biopsy was negative (normal/cervicitis) in 63, mild dysplasia in 15, moderate dysplasia in 18, and severe dysplasia/carcinoma-in-situ in 18. One patient had microinvasion in the directed biopsy while 3 others had invasive cancer.

TABLE 1
AGE DISTRIBUTION OF 170 PATIENTS WITH
DOUBTFUL SMEARS

AGE (YEARS)	n
20	1
20 — 24	21
25 — 29	40
30 — 34	46
35 — 39	24
40 — 44	20
45	18
Total	170

The correlation of colposcopic impression and directed biopsy histology is shown in Table 2. There were 118 patients who had both a colposcopic impression formed of anticipated cervical pathology and directed biopsy histology available for correlation. The central lined zone shows the 89 cases in which there was correlation between the colposcopic impression to within 1 grade of severity of the histological diagnosis in the directed biopsy. There was a correlation between the colposcopic impression and the histology to within one grade of neoplasia in 75% (89/118) of cases. The details of cases that fell outside the central lined zone are given in footnotes to Table 2.

Of the 170 patients, cone biopsy was done in 22 (13%); in 17 (10%) it was for therapy of cervical intraepithelial neoplasia and in 5 (3%) it was diagnostic. Simple hysterectomy was done in 4 patients. One patient had a simple hysterectomy with vaginal cuff and another had radical hysterectomy with pelvic lymphadenectomy. The reasons for the operations are given in Table 3.

The final histological diagnosis made in 119 of the 170 patients is shown in Table 4. There was no histology available in 51 patients. The most advanced histological diagnosis obtained either in the directed biopsy, cone biopsy or hysterectomy specimen was used to assign the final histological diagnosis in these 119 patients.

TABLE 2
CORRELATION OF COLPOSCOPIC IMPRESSION AND DIRECTED BIOPSY HISTOLOGY

COLPOSCOPIC IMPRESSION	DIRECTED PUNCH BIOPSY HISTOLOGY						
	No Biopsy	Normal/Cervicitis	Mild Dysplasia	Moderate Dysplasia	Severe Dysplasia/Carcinoma-in-situ	Micro/Possible Invasion	Invasive Carcinoma
Negative	46	26	1	1 ^a	0	0	0
Mild Dysplasia	5	28	10	5	8 ^b	0	0
Moderate Dysplasia	0	7 ^c	3	12	9	0	0
Severe Dysplasia/Carcinoma-in-situ	0	1 ^d	1 ^e	0	1	1	0
Microinvasion	0	0	0	0	0	0	0
Invasive Carcinoma	0	0	0	0	0	0	3
Indeterminate	1	1 ^f	0	0	0	0	0

a : No further biopsies, electrocautery done.

b : 6 had carcinoma-in-situ in cone biopsy while 1 had moderate dysplasia. In 1 a small focus of severe dysplasia resolved without treatment, directed biopsy mild dysplasia at 1 year and cervical smear normal.

c : 2 had repeat colposcopy which was normal. In 1 a mild dysplasia on repeat colposcopy and in another, cervical smear doubtful on follow-up. 3 patients defaulted.

d : Repeat directed biopsy at follow-up showed moderate dysplasia. On follow-up.

e : At colposcopy, acetowhite epithelium with punctation and mosaics but, mild dysplasia on directed biopsy; patient defaulted.

f : Had leukoplakia, directed biopsy cervicitis only, smear normal at 1 year.

TABLE 3

REASONS FOR CONE BIOPSY AND HYSTERECTOMY		
OPERATION	n	REASONS
Cone biopsy	22*	14 Carcinoma-in-situ 4 Severe dysplasia 3 Moderate dysplasia 1 Microinvasive adenocarcinoma in situ
Simple Hysterectomy	4	2 Carcinoma-in-situ 1 Severe dysplasia 1 Microinvasive adenocarcinoma in situ
Simple Hysterectomy with vaginal cuff	1	Post radiotherapy invasive cancer in cervix
Radical Hysterectomy with pelvic lymphadenectomy	1	Endocervical Stage IB cervical cancer

*5 patients had unsatisfactory colposcopy

DISCUSSION

The cervical smear report should indicate to the clinician those patients who need further investigation to exclude the presence of cervical intraepithelial neoplasia (CIN) or preclinical invasive carcinoma of the cervix. The incidence of doubtful smears has been reported to vary from 12 to 60 per thousand of all smears examined (4). In our unit, patients with doubtful smears make up 57% of all those whose smears

TABLE 4

FINAL HISTOLOGICAL DIAGNOSIS MADE EITHER BY DIRECTED BIOPSY IN CONE BIOPSY OR HYSTERECTOMY SPECIMEN IN 119 PATIENTS		
HISTOLOGY	n	%
Normal Cervicitis	63	53
Mild Dysplasia	15	13
Moderate Dysplasia	14	12
Severe Dysplasia	8	6
Carcinoma-in-situ	15	13
Microinvasion	1	1
Invasive Carcinoma	3	2
Total	119	100

are abnormal (doubtful, suspicious or positive) and whom we feel need further investigations. When the cervical smear is doubtful, the nature of the underlying cervical lesion is uncertain and management not clearly defined; most clinicians merely observe the patient or repeat the smears and perform diagnostic cone biopsy only when the smear becomes suspicious or positive.

The class III smear in the Papanicolaou classification (3) is placed in the suspicious category, but others (4) have even considered the Class III smear as doubtful. In 14 studies of doubtful smears reviewed by Coppleson (4), the incidence of carcinoma-in-situ and Stage I cervical cancer ranged from 12 to 60%. Hall and Rosen (7) reported a 30% incidence of CIN of all grades and 1% of unsuspected invasive cancer in 530 patients with a Class III smear. In our study of doubtful

smears histology was CIN of all grades in 44% and in 3% there was more advanced disease of microinvasion and invasive cancer. In the study of Class III smears by Dockery and Ferguson (8), they found a 12% incidence of carcinoma-in-situ against ours of 13%; the incidence of invasive cancer in their study was 4% against ours of 2%. The patients with doubtful smears in our study therefore, have a similar incidence of underlying cervical neoplastic disease as those with Class III smears reported in the two aforementioned studies (7, 8). Since the interpretation of cervical smears is subject to observer variation, some may place a smear into the Class III category only when the cytological changes are more severe and would have a higher proportion of patients with significant disease in this category of smear. Hence, Crapanzano et al (9) had a 30% incidence of carcinoma-in-situ among 30 patients with Class III smears whereas, Schiffer et al (10) reported a 50% incidence of carcinoma-in-situ in 78 patients. The latter of the studies (10) however reports only a 1% incidence of invasive cancer but their findings may have been influenced by the small number studied. In both studies, (9, 10) however, the Class III smear is considered as positive and patients managed like those with Class IV and V smears.

The continuum concept of CIN proposes that CIN lesions may progress to more severe grade and that invasive squamous cancer is nearly always preceded by these precursor forms (11). Since in about half of our patients with doubtful smears there is CIN of all grades and more importantly, since 3% of patients may have microinvasive or invasive cancer, the identification of these patients from the group with doubtful smears becomes an important daily clinical problem. These doubtful smears are in fact, the first indication of an underlying cervical intraepithelial carcinoma or preclinical cancer and therefore should not be dismissed by the clinician. However, without the availability of colposcopy, cone biopsy seems an unnecessarily invasive diagnostic procedure in asymptomatic patients with doubtful smears; in about half of the patients that we studied histologically there were only benign or non-significant histological lesions. There are some clinicians however, who would perform diagnostic cone biopsies even in those with doubtful smears. Cone biopsy is not a simple procedure and is associated with considerable morbidity (12). It has significant effects on future fertility and pregnancies (13) and should be performed for diagnosis only in those with Class III, IV, or V smears when colposcopy is not available.

The rate of cone biopsy in this study of doubtful smears was 13%. However, in 10% of patients colposcopy was satisfactory with severe dysplasia/carcinoma-in-situ (CIN III) in the directed biopsy and cone biopsy was for therapy. The cervical cone biopsy was diagnostic in only 3% of patients. Donohue and Meriwether (14) found that even with colposcopy, a diagnostic conization rate of 15% could still be expected in patients with abnormal cervical smears. With colposcopy and directed biopsy our diagnostic conization rate of 3% is well within acceptable limits and, especially so, since there is nearly always significant pathology in the cone biopsy specimen.

Colposcopy in those with doubtful smears, helps to select patients with significant disease by a simple outpatient method of evaluation without any morbidity or mortality. It minimizes the need for diagnostic cone biopsy, an invasive procedure and allows the early and

reliable detection of patients with cervical neoplasia, especially those with invasive cancer so that definitive treatment is not delayed. Another advantage of colposcopy used in combination with cytology, is the much higher proportion of patients with CIN and preclinical cancer identified, than with either method used alone.

We feel that doubtful smears should not elicit a sense of complacency; instead the finding should be indication for further investigations. The patient should be carefully reviewed and ideally should have colposcopic assessment so that those with intraepithelial neoplasia and invasive cancer are identified without delay. Such an approach quickly and safely identifies those with significant disease, facilitating early application of definitive treatment and minimises the need for diagnostic conization.

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