Detection of Cervical Neoplasia: Reducing the Risk of Error

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Of the many responsibilities assumed by the physician, none is more important than the detection of cancer at the earliest possible opportunity. Excluding the breast, carcinoma of the uterine cervix is the most frequent neoplasm encountered in women; about 10,000 women died from this disease in the past year.

Various diagnostic methods are currently employed in the critical work-up for cervical cancer. If the limitations and advantages of each method can be fully understood and properly utilized, it should be possible to approach the goal that "none should die" from carcinoma of the cervix.

Cytology

With the introduction of cytology, cervical cancer is now found at a much earlier stage. In addition, cytology is capable of diagnosing the precursors of cervical cancer: carcinoma in situ and dysplasia. Initially it was felt that cervical cancer in its invasive form could be eliminated by the widespread use of cytologic screening. However, this aim has not been achieved even in populations which have been thoroughly screened in their entirety once a year. This is largely because of the high false-negative smear rates, which according to numerous studies range from 1.8 percent to 20 percent. The true false-negative rate is difficult to determine since a cervix that is clinically normal and has a negative cytologic smear is usually not examined further. From a total of 495, 114 patients screened in 19 cytologic screening projects supported by the United States Public Health Service, only 6,064 women with negative Papnicolaou smears also had a histopathologic examination.

False-negative results are usually attributed to different levels of cytologic expertise. However, it is necessary to distinguish between the diagnostic accuracy of the cytopathologist and the diagnostic accuracy of cytology as a method. The diagnostic accuracy of a well-trained cytopathologist might be very high but the final diagnosis depends on the material presented to him. Failure of cytology as a method depends on many factors, such as smears which are poorly taken, poorly fixed, poorly stained, too thin, too thick, too bloody. Or the lesion may be too small, may exfoliate only a few cells or may be quiescent.

A detailed study of published reports shows with surprising clarity that the difference in results lies not in the failure of the cytopathologist or technical problems, but in the methods by which women with negative cytology are examined further.

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Most studies evaluating the false-negative rate of cytology rely on a clinical examination alone to assess the status of the cervix in the patient with a negative smear. Yet, Younge, et al. demonstrated that only six percent of in situ carcinomas of the cervix have an abnormal gross appearance. Therefore, the evaluation of patients with negative cytology, using clinical examination alone without routine biopsies, is completely inadequate. Gusberg, who employed a coning endocervical biopsy in the evaluation of patients with negative cytology, found a 12.5 percent false-negative rate. In studies where routine multiple cervical biopsies were obtained from Schiller-negative areas in all patients with negative cytology, false-negative rates of 18.2 percent and 20.4 percent were reported. Mattingly, et al. screened a group of patients with both exfoliative cytology and the irrigation smear and demonstrated a false-negative exfoliative cytology rate of 15.4 percent. Studies in which both colposcopy and cytology were used demonstrated a false-negative rate of cytology between 10.7 and 13.0 percent.

The only accurate way to evaluate the false-negative rate of cytology is to perform a conization in all patients, even those with negative cytology, and to examine the cone in serial sections. Any other diagnostic technique is a compromise and is associated with varying degrees of inaccuracy.

Schiller’s Test

Examination of the human cervix with the naked eye reveals no difference between the cervix with a premalignant lesion and one with a benign change. A carcinoma in situ on the surface of the portio is not elevated above the level of the surrounding epithelium nor is it conspicuous by a difference in color. The only alteration which may indicate the presence of an early carcinoma is contact bleeding at the time the cytologic smear is obtained, yet a great many benign conditions, including inflammation, ectopy, and atrophic change, may also produce contact bleeding.

During the reproductive years, the squamocolumnar junction appears on the portio vaginalis of the cervix. This causes the region around the cervical os to appear red and somewhat granular on direct visualization. To differentiate this red columnar epithelium of the endocervical canal from metaplasia, dysplasia or neoplasmia is extremely difficult. While it is possible to visualize “white patches” against this red background, such leukoplakic areas usually represent only hyperkeratosis or parakeratosis and seldom is significant early pathology found.

In 1929, Schiller noted that while large amounts of glycogen were present in normal squamous epithelium, glycogen was conspicuously absent in early squamous carcinoma of the cervix. He found that a weak aqueous iodine solu-
tion would stain the glycogen contained in the normal cervical epithelium a dark-mahogany color, leaving areas of carcinoma unstained. But it soon became apparent that not all areas of the cervix which failed to stain with iodine represented foci of carcinoma. Columnar epithelium, inflammatory areas, recent biopsy sites and metaplastic areas also failed to take the iodine stain.

Despite these drawbacks, the Schiller iodine test is still helpful in delineating suspicious areas for biopsy. The composition of the iodine solution is critical: iodine—3.0 gm; potassium iodide—6.0 gm; distilled water—100.0 cc.

| Table 1. Accuracy of Cervical Biopsy |
|-------------------------------------|
| Biopsy method | Error rate (False-negative) | Average |
|----------------|-----------------------------|---------|
| Four-quadrant “blind” | 24% 12% 33% 26% 14% | 22% |
| Multiple sites, multiple sections | 6% 8% 6% | 6.6% |
| Schiller-directed, multiple sections with endocervical curettage | 3.1% | 3.1% |

Schiller’s test is best summarized by Kern who stated that “if the portio is iodine positive (Schiller dark) the patients may be advised by 99 percent accuracy that they do not have cancer or a preinvasive lesion.” However, 75 percent of all patients examined will exhibit some Schiller light areas, the significance of which must be determined by another method. Therefore, while the iodine reaction can tell where the carcinoma is not, it is unable to tell where the carcinoma is.

**Biopsy**

High error rates associated with the “blind” four-quadrant punch technique—between 26-33 percent—led to evaluation of multiple biopsies with multiple histologic sections from each tissue fragment. Dilts and his colleagues found that of 196 cases diagnosed as carcinoma in situ by this technique, only 12 were later shown to have minimal to marked invasion on conization or hysterectomy, an error rate of approximately six percent. In other series, reported by Sabatelle, et al. multiple biopsies failed to show the most serious pathology eight percent of the time.

Younge advocated using the Schiller’s test as a means of directing the biopsy to the most suspicious areas. In addition, he made use of multiple biopsies taken on more than one occasion from the same patient, and studied multiple sections of each biopsy. Endocervical curettage was used as a means of evaluating those lesions not involving the portio. Of 300 patients treated for carcinoma in situ of the cervix, only one patient was found to have invasive carcinoma which was missed by the combined use of Schiller staining, cervical biopsy, and endocervical curettage.

Direct visual examination. Schiller’s test alone, and blind four-quadrant biopsies of the cervix have an unacceptably high error rate in the hands of even the most experienced observer and cases of carcinoma in situ and invasive cancer can be missed. When the Schiller’s test is used to direct multiple biopsies and an endocervical curettage is performed to evaluate the tissue higher in the canal, and when all these tissue samples are histologically examined at multiple levels in the block, a higher rate of accuracy—comparable to that of conization—is obtainable. (Table 1.)
Conization

In institutions equipped to evaluate every suspicious cervix with directed biopsies, endocervical curettage and examination of multiple sections in a meticulous fashion, conization has been reserved for investigation of the "unusual" case in which repeated cytologic evidence of anaplasia could not be confirmed by biopsy or in which an occult invasive carcinoma could not be excluded.

A large majority of clinicians, however, forced to depend on the accuracy of the undirected punch biopsy, have come to rely on the cold-knife conization of the cervix as the prime method for evaluating the suspicious cervix. When done properly, this method insures the pathologic examination of an adequate amount of epithelium properly oriented to the subjacent stroma without distortion or the artifacts of crushing and abrasion. Again, the number of sections examined is crucial. For example, false results will increase by a factor of 22 percent if only 15 sections are examined from each cone instead of 80 sections. However, most investigators have reported a fairly consistent overall rate of diagnostic error for conization of 3.5 percent with a range between 0.6 percent and 9.0 percent.\(^{13,11,16,18,21}\)

Cold-knife conization of the cervix consists of the annular removal of a cone-shaped wedge of tissue from the cervix uteri. The operative specimen must include uninvolved endocervical epithelium above the lesion and uninvolved ectocervix beyond any lesion on the portio. During the reproductive years, most lesions are found on the portio, so the cone will usually have a broad base and a wide angle. On older women, where the squamocolumnar junction has shifted to a location higher in the endocervical canal, the cone specimen will be long and narrow with a sharp angle. (Fig. 1.) The width of the base, is best determined by including within the cone

Fig 1 Conization specimens in (top) ectocervical lesion, (bottom) endocervical lesion.
margins all Schiller light areas of the portio.

Preoperative vaginal examination should be strictly limited and most operators will forego the routine preoperative preparation of the cervix proper, as both these procedures may denude epithelium crucial for the diagnosis.

The three most frequent complications of the conization procedure are early or delayed hemorrhage,\textsuperscript{13,21} cervical stenosis,\textsuperscript{12} and uterine perforation.\textsuperscript{13,22} To this must be added the risk of pelvic infection if hysterectomy follows conization. The infection rates vary with the time interval between cone and hysterectomy, ranging from eight percent if performed within an interval of 72 hours to 60 percent if the interval is lengthened to 21 days. Only after four to six weeks does pelvic infection cease to be a significant risk.\textsuperscript{23} Dysmenorrhea, contact bleeding, and dyspareunia have been mentioned as frequent late complications of the procedure.\textsuperscript{12}

Of all the complications of sharp conization of the cervix for diagnostic purposes, none is more significant than the morbidity encountered in the pregnant patient. Most authors agree that there is an increased incidence of hemorrhage when the procedure is performed during the pregnant state. The average fetal loss reported approximates 1.5 percent.\textsuperscript{21-24}

Therefore, sharp conization of the cervix for diagnostic reasons can yield a high degree of accuracy, but at the cost of a certain incidence of morbidity and a considerable financial burden. For these reasons, a better method of evaluating the suspicious cervix must be sought.

**Colposcopy**

Unfortunately, for many years colposcopy and cytology were considered competitive methods in early cancer detection, but both methods actually complement one another. It should be emphasized that cytology is a laboratory method of detection while colposcopy is a clinical method. Each method deals with a different aspect of neoplasia. Cytology evaluates the morphological changes in the exfoliated cells, while colposcopy evaluates the changes in the terminal vascular network of the cervix which reflects the biochemical and metabolic changes in the tissue. (Figs. 2-6.)

Many studies have been done which compare the diagnostic accuracy of colposcopy and cytology. Most studies show that the false-negative rate of colposcopy is greater than that of cytology. It is obvious that colposcopy will fail to

![Fig 2. Negative colposcopy. Tongues of squamous metaplasia are visible. Squamocolumnar junction fully visible.](image)

![Fig 3. Abnormal colposcopic lesion on the anterior lip (white epithelium). Directed biopsy showed mild dysplasia.](image)
detect lesions which are inside the cervical canal; and in these cases the squamo-columnar junction will not be visible. Such cases, however, should be properly classified as "unsatisfactory" rather than "negative." Excluding the cases with unsatisfactory colposcopic findings, the true false-negative rate of colposcopy is extremely low.

From all available reports, one fact is clear: the combination of both methods increases the diagnostic accuracy of each method used separately. Yet it is difficult to use both methods on a large scale in view of the limited number of experienced colposcopists. The ideal situation would be to train physicians in colposcopy and to use it as a routine examination method in place of speculum examination of the cervix by direct vision. Unfortunately, this ideal situation is neither practical nor economical at this time, and cytology is unquestionably the most practical method for cervical cancer screening. At the present time, the main role of colposcopy lies in the clinical evaluation of patients with abnormal cytological smears.

The colposcope is a stereoscopic microscope which provides a three-dimensional magnified image in bright illumination. Various magnifications are available for examination of the cervix, vagina, or vulva.

The technique of colposcopic examination is quite simple. After insertion of an unlubricated self-retaining speculum, cytologic smears are taken from the ectocervix and from the cervical canal. Mucus is carefully removed from the cervix, using dry gauze swabs, and the coloscope is then focused on the cervix. Since a dry epithelial surface is insufficiently transparent and allows only a poor view of the vascular pattern, inspection of the cervix is first performed after it has been moistened with normal saline. Next, a four percent solu-

![Fig. 4 Abnormal colposcopic lesion on the anterior lip (mosaic pattern). Directed biopsy: carcinoma in situ.](image1)

![Fig. 5 Highly atypical vascular pattern. Biopsy: invasive carcinoma.](image2)
Vascular Pattern: Changes in the vascular pattern correspond closely to the degree of histological changes. During the first stage of carcinogenesis, the morphology of the tissue proper is not yet altered. The blood vessels, however, do react to these changes in tissue metabolism and cell biochemistry. Such vascular alterations constitute the first morphological abnormality in the development of cervical neoplasia. These changes are not detectable in five-micron histological sections, but they are clearly visible through the colposcope.

Color Tone: Different colposcopic lesions show different colors, varying from white to deep-red. The difference between the color before and after the acetic acid test is very important: if there is a marked change from deep-red to white, a more serious histological lesion may be expected.

Clarity of Demarcation: The borderline between normal squamous epithelium and inflammatory lesions, or mild dysplasias, is quite diffuse. On the other hand, severe dysplasias and carcinoma in situ usually produce sharp-bordered lesions, distinctly demarcated from the adjacent epithelium.

Clinical diagnosis and follow-up of patients with abnormal cytology is outlined in Figure 7. All patients with abnormal cytology should have colposcopic examinations. According to the colposcopic findings, patients are divided into three major groups: (1) Patients with normal colposcopic findings. This group includes patients in whom the squamocolumnar junction is fully visible but no focal suspect colposcopic lesion is found. In these patients, cervical neoplasia is not expected and the patients are followed up by cytology only. A diagnostic conization is indicated only if the follow-up cytology becomes either positive or repeatedly suspicious. (2) Patients with unsatisfactory colposcopy. In patients in whom the squamocolumnar junction is not fully visible, the colposcopy is classified as unsatisfactory because of the inability to exclude a lesion higher in the endocervical canal. In these patients, colposcopy is unable to fully evaluate the patient and therefore if the referring cytology is positive or repeatedly suspicious, a diagnostic conization is indicated. (3) Patients with abnormal colposcopic findings. In these patients, a directed biopsy under colposcopic vision is always indicated. An impression of the anticipated cervical pathology can be gained from the degree of

Intercapillary Distance: During coloscopy, an estimation of the intercapillary distance in abnormal areas can best be performed by comparing it with that of the capillaries found in the adjacent normal epithelium. In preinvasive and invasive carcinoma of the cervix, the intercapillary distance increases as the stage of the disease advances.

Surface Contour: The stereoscopic magnification also greatly facilitates the study of the surface contour, which may be smooth, uneven, granulated, papillomatous, or nodular. Normal squamous epithelium has a smooth surface, while carcinoma in situ and particularly early invasive cancer may both have an uneven, slightly elevated surface.
of colposcopic changes, but the final diagnosis will depend on the histology of the directed biopsy. In patients with a suspect colposcopic lesion, diagnostic conization is indicated only if there is a major discrepancy between the diagnosis in the directed biopsy and the cytology or if the colposcopic lesion extends into the endocervical canal.

We believe that colposcopy is a practical, accurate and inexpensive method of low morbidity that can be used to evaluate the cervix with an abnormal cytologic smear and that will detect the unusual case of early neoplasia missed by cytologic screening. It is also one of the most valuable means of accurately diagnosing and managing pregnant patients with abnormal cytology. The physiologic eversion of the pregnant cervix affords excellent colposcopic visualization of the entire squamocolumnar junction.

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Fig 7. Follow-up of patients with abnormal cytology
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The Last Surviving Cancer Cell

It is just as hard to reduce 100 leukemic cells to one with drugs, as it is to reduce 10,000 cells to 100 or 1,000,000 cells to 10,000. The reduction in each example is 99 percent of the number present before treatment. A particular drug treatment eliminates about the same percentage of cells present at the start, not the same absolute number of cells. This situation, which is certainly real, is likely to seem strange at first to anyone who is not familiar with it. It is, however, quite widespread in nature. —William S. Wilcox. The Last Surviving Cancer Cell: The Chances of Killing It. Cancer Chemotherapy Reports 50:541, 1966.