Colposcopy, Cervicography, Speculoscopy and Endoscopy

IAC Task Force Summary

Willem A. van Niekerk, M.D., F.I.A.C., Capetown, South Africa
Chairman

Charles J. Dunton, M.D., Philadelphia, Pennsylvania, U.S.A.
Ralph M. Richart, M.D., F.I.A.C., New York, New York, U.S.A.
Cochairs

Manuel Hilgarth, M.D., F.I.A.C., Harubumi Kato, M.D., Ph.D., F.I.A.C.,
Raymond H. Kaufman, M.D., Laurie J. Mango, M.D., Shiro Nozawa, M.D., Ph.D.,
M.I.A.C., and Max Robinowitz, M.D.
Contributors

Issues

The colposcope was developed in 1925 and is well established in clinical gynecologic practice for defining and delineating cytologically detected lesions mainly of the cervix but also the vagina and vulva. Additionally, various endoscopic procedures in gastroenterology, pulmonary and urologic lesions enhance the cytologic detection and histologic verification of precancerous and cancerous lesions. The cost-effectiveness of all these devices and their applicability, particularly in countries with a limited health budget, is a major issue. This task force considered aspects of the present state of the art and the challenges in the 21st century.

Consensus Position

Automated cytology can interface with colposcopic examination in a number of significant ways. Automated cytologic analysis of conventional cervical smears can potentially direct colposcopic examination by predicting the nature of a lesion, assist in determining which patients should receive colposcopy and, in some settings, thereby reduce the number of colposcopies. Potentially, various combinations of automated cytology and colposcopy may be used to generate screening protocols that might result in more effective and inexpensive screening.

The role of cervicography, or high-resolution cervical photography, as a screening device remains to be defined. Sensitivity for high grade lesions is generally no greater than that in cytology, and specificity appears lower. The interpretation of cervical photographs in triage of mildly abnormal cytology may prove to be useful in countries with established cytology programs. In areas of the world where cytology screening programs are not in place, the interpretation of cervical photographs may have its most dramatic effect. Cost-effectiveness analyses are needed. There are, at present, insufficient data for the evalua-
tion of speculoscopy, a procedure using chemiluminescent illumination of the cervix for visualization of acetowhite areas.

Basic training in colposcopy should be integrated into the residency programs of obstetrics and gynecology. Criteria for the adequate training of colposcopists should be developed. Continuing education programs in colposcopy should be developed when they are not already in existence. The cost-effectiveness of integrating colposcopy as a primary screening technique should be evaluated.

Following a high-grade squamous intraepithelial lesion (HSIL) cytology result, colposcopically directed punch biopsy should be taken with or without endocervical curettage. This generally should precede the loop electrosurgical excision procedure (LEEP); however, in certain circumstances direct LEEP may be indicated.

LEEP under colposcopic vision is an efficient way to treat an HSIL lesion of the cervix because the histologic extent and margins can be determined, unlike with laser surgery or cryosurgery. It is also more cost-effective than cold knife conization because general anesthesia and an operating room are unnecessary. Following LEEP, the endocervical canal should be examined colposcopically for any evidence of involvement. Lesions in the endocervix can then be removed with a different-shaped loop.

Further research into Raman spectroscopy as a diagnostic aid in cervical pathology is needed, as is the use of microcolpolhysteroscopy for in vivo cytologic analyses, especially of the endocervical canal and transformation zone.

Hysteroscopy is the most direct method for the diagnosis and treatment of intrauterine diseases. Hysteroscopic endometrial biopsy is more accurate than conventional biopsy methods. Cervical invasion of endometrial cancer can be detected by hysteroscopy. The depth of invasion, however, is more accurately determined by magnetic resonance imaging or computed tomography.

Ongoing Issues

Many topics for ongoing research and/or implementation are mentioned under “Consensus Position,” above. In considering the future of colposcopy, cervicography, speculoscopy and endoscopy, we should be aware that cost constraints in medical care as well as the demand for better quality control will intensify. The use of new technologies in these fields for better and more cost-effective patient care, is the challenge we will have to meet in the 21st century.

On a global scale, the most important ongoing issue is finding the most cost-effective way of detecting and treating HSIL and invasive cancer of the cervix in countries with a very small health budget and a population with minimal financial resources. Women from these countries are the largest group in the world. Their plight should be focused on. (Acta Cytol 1998;42:33–49)

Keywords: colposcopy, endoscopy, cervicography, speculoscopy.

Introduction

Willem A. van Niekerk, M.D., F.I.A.C.

Technologic advances, such as new optical lenses, fiberoptic light cables and more sophisticated video cameras with digital computer enhancement, all played a part in advances in colposcopy and endoscopy for viewing and evaluating the epithelial surfaces of body cavities. More accurate assessment of the epithelium of various body cavities results in better cytologic and histologic specimens, which contribute to better detection and treatment of neoplastic diseases. In this field, colposcopy, bronchoscopy, gastroscopy, colonoscopy, hysteroscopy and cystoscopy are at present the most frequently used procedures.

Important advances have been made in endoscopic evaluation of the gastrointestinal tract. Endosonography and cytology play an important role in the diagnosis and staging of pancreatic carcinoma. Endobiliary brush cytology and biopsy are being used for the diagnosis of malignant bile duct stricture. Endoscopic brushing is also used for the diagnosis of gallbladder carcinoma. Anoscopy and colonoscopy are well established in the early diagnosis of colon, rectal and anal pathology.

In the urinary tract, cystoscopy is essential to the histologic diagnosis of urothelial lesions detected by urinary cytology, dipstick testing for hematuria, quantitative image analysis, flow cytometry and other emerging technologies. Ureterscopic biopsies of the upper urinary tract, as well as percutaneous endoscopy of the renal pelvis, are further developments in this field.

Colposcopy

The historic events related to colposcopy are given in Table I.

Differences in colposcopic observations between low and high grade lesions are given in Figure 1. Using colposcopy, a punch biopsy can be taken from the areas that show the most severe changes. The extent of the lesion and whether it extends into the endocervix can be determined. This information is essential if the loop electrosurgical excision pro-
procedure (LEEP) or large loop excision of the transformation zone (LLETZ) is planned.

Microcolpohysteroscopy, a technique using a magnifying lens, ×150, can observe a 1-mm-diameter field and hence even nuclear detail. Refinements in the 21st century will develop the field of in vivo cytology for determining the extent of the lesion in the endocervical canal.

In considering the future of colposcopy, cervicography, speculoscopy and endoscopy, we should be aware of the following:
1) There are going to be increasing cost constraints in medical care, and the demand for better quality control will intensify.
2) Technical advances will revolutionize this area, and digital imaging, the storage of up to 4,500 images on an optical disk and rapid teletransmission of images will become practical.

The use of these new technologies for better and more cost-effective patient care is the challenge we will have to meet in the 21st century.

The following task force presentations consider aspects of the present state of the art and future challenges. Results of a consensus conference of German-speaking countries on colposcopy are addressed by Prof. Hilgarth. The pitfalls in the practice of colposcopy are discussed by Raymond H. Kaufman, M.D. The interaction between automated cytology and colposcopy is discussed by Laurie J. Mango, M.D. Charles J. Dunton, M.D., outlines the role of cervicography. Shiro Nozawa, M.D., Ph.D., M.I.A.C., discusses the place of hysteroscopy in the 21st century. Max Robinowitz, M.D., summarizes the U.S. Food and Drug Administration approach to new diagnostic devices. Harubumi Kato, M.D., Ph.D., F.I.A.C., writes about the endoscopic appearance of early-stage central type lung cancer and its cytologic correlation.

Table I  Historical Events

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1922</td>
<td>First colposcopic inspection (Mencaglia, Perino &amp; Pilardi, Italy)</td>
</tr>
<tr>
<td>1925</td>
<td>“Invention” of colposcope (Hinselmann, Germany)</td>
</tr>
<tr>
<td>1928</td>
<td>Schiller test with Lugol’s iodine (Schiller)</td>
</tr>
<tr>
<td>1933</td>
<td>“Mosaic” pattern (Hinselmann)</td>
</tr>
<tr>
<td>1938</td>
<td>Acetic acid test (Hinselmann)</td>
</tr>
<tr>
<td>1939</td>
<td>Green filter (Kraatz, Germany)</td>
</tr>
<tr>
<td>1940</td>
<td>Mercury lamp (Hinselmann)</td>
</tr>
<tr>
<td>1942</td>
<td>First photographs of cervix (Treite, Germany)</td>
</tr>
<tr>
<td>1951</td>
<td>First flashlight cervical photographs (Kara-Eneff, Germany)</td>
</tr>
<tr>
<td>1956</td>
<td>Video-colposcopy experiments (Hinselmann)</td>
</tr>
<tr>
<td>1966</td>
<td>Black-and-white photography (Koller, Norway)</td>
</tr>
<tr>
<td>1972</td>
<td>Ultraviolet light (Van Niekerk, Tygerberg)</td>
</tr>
<tr>
<td>1979</td>
<td>Microcolpohysteroscope (Hamou, France)</td>
</tr>
<tr>
<td>1981</td>
<td>Cervicography (Staff, U.S.A.)</td>
</tr>
<tr>
<td>1989</td>
<td>Large Loop Excision of the Transformation Zone = LLETZ (Pendiville &amp; Cullimore, England)</td>
</tr>
<tr>
<td>1991</td>
<td>Loop Electrosurgical Excision Procedure = LEEP (Wright, Gagnon &amp; Richart, U.S.A.)</td>
</tr>
</tbody>
</table>


Low grade

<table>
<thead>
<tr>
<th>Acetowhite epithelium</th>
<th>High grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shiny or snow white, semitransparent</td>
<td>Dull, oyster white color</td>
</tr>
</tbody>
</table>

Surface

| Flat | Irregular contour, microexophytic |

Demarcation

| Diffuse, irregular, flocculated, feathered | Sharp, straight line |

Internal demarcation line absent

| Internal demarcation line present |

Vessels

| Fine, with regular shapes, uniform caliber, normal arborization pattern, spaghetti, changing calibers | Coarse, dilated, increased intercapillary distance, bizarre vessels without arborization, commas, hockey sticks, corkscrews, sharp bends |

Iodine

| Uniform mahogany brown | Mustard yellow, yellow or iodine negative |

Figure 1  Colposcopic grading.

Significance of Colposcopy for the Detection of Incipient Cervical Carcinoma

Results of Consensus Conference of German-Speaking Countries, December 19, 1996, Frankfurt/Main, Germany

Manuel Hilgarth, M.D., F.I.A.C., and Michael Menton, M.D.

Current Status of Cervical Cancer Detection

Currently, improvements in a cancer cure can be achieved only through earlier detection. In the foreseeable future, significant improvements in cancer
cures by new therapeutic regimens are not to be expected, in particular because they are considerably more expensive than earlier cancer detection methods. The cervical cancer screening program is currently the only one with proven efficacy. The reasons are the easy accessibility of the organ and the disease’s relatively high incidence in the past. The currently accepted model of cancer development through various stages of in situ development with a long latency period was first recognized for cervical carcinoma. Elimination of the precancer stages allows one to avoid the final development of an invasive carcinoma.

There are two techniques for earlier detection of cervical carcinoma; both are effective, affordable and acceptable to the patient: colposcopy and cytology.

Advantages of Colposcopy
Colposcopy was developed in the early 1920s by Hinselmann in Germany as an optical method of examining the cervix under magnification. In the late 1920s, Papanicolaou developed cytology as a morphologic method for early cancer detection. Both techniques have advantages and disadvantages and complement each other. In the literature the false negative rate of cervical cytology is relatively high (15–50%).

Advantages and Disadvantages of Colposcopy
Advantages:
1) Colposcopy can be applied at each gynecologic examination with ease and produces an immediate result.
2) The method can be learned by every physician through self-study or continuing education.
3) The method is not very expensive (examination time, four minutes; instrument price, $10,000).
4) A number of cervical diseases, such as infection with the human papillomavirus (HPV), are best detected by colposcopy. Cytologic detection of HPV infection is less reliable; molecular biologic techniques are more expensive. General infections with HPV are currently regarded as one of the prime sources of the development of cervical carcinoma.
5) Based on colposcopic prescreening, cytologic smears may be obtained under colposcopic direction.
6) Cases with a discrepancy between negative cytology and suspicious colposcopy require further action by the treating physician.

Disadvantages of Colposcopy
The only disadvantage of colposcopy is its inability to detect lesions in the endocervical canal. Since intraepithelial precursor lesions occur in the reproductive-age group mainly on the ectocervix, they are easily detected by colposcopy. After menopause, the transformation zone moves into the cervical canal; cytologic techniques are therefore of major significance in this age group.

The advantages of simultaneous application of colposcopy and cytology are as follows:
1) Obtaining the cytologic smear under colposcopic direction improves the smear quality considerably. It is possible to remove mucus and secretions under colposcopic guidance and to obtain the smear directly from the colposcopically suspicious area.
2) In cases of cervical stenosis, the endocervical portion of the smear may be obtained under colposcopic direction with a special instrument.
3) Discrepancies between colposcopy and cytology require further workup. If colposcopy is suspicious and cytology negative, repeat cytologic smears have to be obtained or biopsy performed to avoid false negative cytology. If cytology is suspicious and colposcopy negative, a repeat cytologic smear or biopsy is necessary to avoid overtreatment.
4) The use of colposcopy alone, without cytology, is not permissible.

Only the simultaneous application of both techniques avoids overtreatment as well as undertreatment of cervical carcinoma. In recent decades, cytology was the preferred technique for the early detection of cervical carcinoma. Quality assurance in cytology must include colposcopy in order to improve the technical quality of the smear and its interpretation.

Significance of Colposcopy for Primary Screening
A number of publications support the role of colposcopy in the early detection of cervical carcinoma as a primary screening technique. A number of more recent and large series are compiled in the refer-
ences,2,4,7,11,12,21,34 The results confirm that the simultaneous application of colposcopy and cytology detects a high rate of precancerous lesions. Tawa and colleagues24 examined 3,271 patients in a prospective screening study, with anonymous, independent evaluation of cytology and colposcopy; they found a fivefold-higher rate of dysplasia on colposcopy. Of 11 cases of histologically confirmed high grade dysplasia, 5 were detected cytologically. In 1994 similar results, by Coibion and coworkers,6 were published in the British Journal of Cancer. There, 4,015 patients were examined. Of particular interest is the fact that colposcopy showed higher sensitivity among patients under 35 years of age. These results are of particular significance because MacGregor and coworkers19 found, in a large study composed of 306,608 cytologically screened women, that the mortality rate from cervical carcinoma and its precursors had increased in women under 45.

Integrating Colposcopy into an Early Cervical Cancer Detection Program

As a basis for a cervical examination, the gynecologist scans the cervix in the area of the external os and then obtains a cervical smear under colposcopic direction. Subsequently, the definitive colposcopic examination is performed. By adding additional techniques, such as the application of acetic acid, differential colposcopy is performed, allowing, with a high margin of security, the separation of benign and premalignant and malignant reactions. Correlation with a subsequent cytologic result is possible. If there is a discrepancy between cytology and colposcopy, it is the obligation of the gynecologist to clarify the situation by further examination.

Technical Prerequisites

A binocular colposcope with $12 \times$ magnification and an integrated illumination system with a green filter, acetic acid (3–5%) and Schiller solution are necessary.

Qualifications of the Examiners

Basic knowledge of colposcopy should be integrated into the obstetrics and gynecology residency. Continuing education courses should be developed.

Reductions in the Cost of the Cervical Cancer Detection Program by Integrating Colposcopy as a Primary Screening Technique

1) The decrease in false negative cytology leads to higher efficiency of detection of precancerous lesions and thus to a decrease in the costs of treating overt cervical carcinoma.
2) The decrease in false positive cytologies decreases the frequency of unnecessary treatment.
3) Screening colposcopy may decrease the number of cytologic repeat examinations, often recommended by examiners, without optical guidance for obtaining smears in order to avoid false negative smears.
4) DNA cytometry may be reduced to a few cases with peer indications.
5) The expensive technique of human papillomavirus (HPV) typing may also be restricted to a few cases because treatment of precancerous lesions should depend on the grade of morphologic atypia and not on the presence of HPV. Only in young women in the reproductive-age group might it be of assistance in the choice of treatment. HPV infections are recognized by colposcopy with a higher rate of sensitivity than by cytology.

References


Participants

Hans Kurt Bauer, M.D., Wiesbaden, Germany
Kurt Bilek, M.D., Leipzig, Germany
Fritz Girardi, M.D., Baden, Austria
Jürgen Heinrich, M.D., Stralsund, Germany
Siegfried Heinzl, M.D., Basel, Switzerland
Manuel Hilgarth, M.D., Freiburg, Germany
Martin Link, M.D., Dresden, Germany
Armin Malter, M.D., Munich, Germany
Michael Menton, M.D., Tübingen, Germany
Klaus Neis, M.D., Saarbrücken, Germany
Stefan Seidl, M.D., Hamburg, Germany


Future Research on Colposcopy

Manuel Hilgarth, M.D., F.I.A.C.

Future research in colposcopy should concentrate on four main subjects:

1) Computerized colposcopic documentation and consecutive analysis of colposcopic findings.

2) Clinical significance and biologic behavior of minor lesions visible with colposcopy in the presence of different human papillomavirus (HPV) types.
3) Clinical significance and relation to HPV infection of minor lesions beyond the transformation zone.

4) Vulvar lesions in vulvodynia related to HPV infection.

The results of colposcopic investigations over the last 10–15 years have had a great influence on the treatment of cervical intraepithelial neoplasia. Today, more laser vaporization than conization of the cervix is performed because of better diagnostic methods and the good possibility of sufficient follow-up. In spite of this excellent development in colposcopic research, there is still the problem that colposcopy in general is not integrated in screening programs. One reason might be the lack of a generally accepted classification.

In 1990, the introduction of the new international nomenclature and European classification proposals fundamentally improved this situation. The new colposcopic classification system offers the opportunity for precise and more objective grading and documentation of colposcopic findings. In many studies, colposcopy had high sensitivity as compared to cytology and confirmed by histology. However, colposcopy is still generally not accepted in screening programs. This is probably due to the lack of an inexpensive and reliable documentation system. Colpophotography might be useful for studies or teaching but costs too much for the daily routine. New developments in computer hardware and software might be able to solve these problems. Therefore, this seems to be the right time to develop those powerful and inexpensive documentation systems.

Although there are already computerized analysis systems for cytology, there is still a lack of comparable systems in colposcopy, so colposcopic findings are still classified only by the subjective criteria of the investigator. To improve cancer screening it might be useful to develop computerized image analysis systems.

There are many clinical trials showing that HPV 16 is present mainly in high grade lesions and cervical cancer, but the clinical significance of HPV 16 in minor lesions is unknown. We think that HPV 16 might be a prognostic factor, but clinical investigations have not been convincing. There are many women who are positive for HPV 16, but only a few of them will develop cervical cancer. Long-term studies with exact colposcopic, cytologic and histologic data are necessary to clarify the clinical significance of HPV 16. HPV investigations should be done with polymerase chain reaction in those clinical trials. This seems to be one of the most urgent questions for the near future.

Acetowhite lesions beyond the transformation zone are well known and generally regarded as harmless, without any influence on cancerogenesis. Because there have been a few long-term studies on those lesions, we should concentrate our interest on etiology and the clinical significance of described lesions. Furthermore, we should find out more about the incidence and prevalence of HPV infection in those lesions.

Increasing numbers of women are complaining of vulvar itching, vulvodynia and dyspareunia. If we perform colposcopy on those women, we often see acetowhite lesions, sometimes corresponding to the site of itching. If we take punch biopsies, we often find HPV-related histologic overdiagnosis. However, according to recently published data, there is no relation to HPV infection. If we screen the literature for those questions, we must recognize that there is a significant lack of knowledge in this field. It is of great clinical importance to study this well-known problem.

Additional Reading


Heinzl S: The relevance of various elements contributing to colposcopic diagnosis. Cervix 1989;7:93–99


Pitfalls in the Practice of Colposcopy

Raymond H. Kaufman, M.D.

The most frequent pitfall in the practice of colposcopy today is inadequate training of colposcopists. In many training programs, the obstetric and gynecologic resident and residents in family practice have scant exposure to colposcopy. In addition, supervision of their colposcopic experience is minimal. Thus, they have not been exposed to the variety of colposcopic changes that develop in association with intraepithelial and invasive neoplasia involving the cervix and vagina. I will divide my following remarks into several categories: current colposcopic nomenclature, mistakes colposcopists are prone to make, and knowledge of the histopathologic changes seen in association with colposcopic findings.

I. Classification

There have been a variety of classifications of colposcopic findings proposed over the years. The International Federation of Cervical Pathology and Colposcopy agreed upon the following terminology in 1990:

- Normal colposcopic findings
  - Original squamous epithelium
  - Columnar epithelium
  - Normal transformation zone
- Abnormal colposcopic findings (within the transformation zone)
  - Acetowhite epithelium
    - Flat
    - Micropapillary or microconvoluted
  - Punctuation
  - Mosaic
  - Leukoplakia
  - Iodine negative
  - Atypical vessels
  - Colposcopically suspect invasive carcinoma
  - Unsatisfactory colposcopy
    - Squamocolumnar junction not visible

- Severe inflammation or atrophy
- Cervix not visible
- Miscellaneous findings
  - Nonacetowhite micropapillary surface
  - Exophytic condyloma
  - Inflammation
  - Atrophy
  - Ulcer
  - Other
- Minor changes
  - Acetowhite epithelium, fine mosaicism, fine punctuation, thick leukoplakia
- Major changes
  - Dense, acetowhite epithelium, coarse mosaicism, coarse punctuation, thick leukoplakia, atypical vessels, erosion

There is still some disagreement regarding the above classification as well as regarding understanding of what specifically is meant by “abnormal” and “atypical.” However, the above is a satisfactory working classification that colposcopists should be able to utilize.

As indicated above, one of the major pitfalls in colposcopy is lack of experience in examining a large enough patient population to become familiar with all the changes listed above. Another pitfall is inadequate supervision during the acquisition of this experience. One of the positive recommendations that this committee could propose is criteria for adequate training of colposcopists. This should include a recommendation for first participating in a local, international or national postgraduate colposcopy course for beginners. Following this, the trainee should be exposed to a broad range of colposcopic examinations under the supervision of a knowledgeable tutor. How many examinations would one consider appropriate? This is a question that needs to be answered by a discussion of the committee members. Included in this experience should be a review of the cytology and histopathology on patients upon whom colposcopy is performed. Many individuals performing colposcopy today have not the slightest insight into the cytologic findings associated with various types of cervical pathology and are not thoroughly familiar with the histopathologic changes seen. Thus, it is very difficult to closely correlate colposcopic findings with cytologic and histopathologic findings. Often the colposcopist relies completely upon the recommendation of pathologists. This often leads to disastrous results.

A proposal has been made by some that in the
presence of a high grade cytologic report, directed cervical biopsies and endocervical curettage are not necessary and that one can proceed directly to loop electrode excision of the transformation zone. For a variety of reasons, I object to this approach and would recommend that a colposcopic examination with directed biopsies and endocervical curettage continue to be performed on such women.

II. Colposcopy Mistakes

Mistakes colposcopists are most prone to make occur because of lack of experience, as indicated above. However, two of the major pitfalls are failure to recognize unsatisfactory colposcopy: i.e., nonvisualization of the entire transformation zone and lesions present. There is still some controversy regarding whether endocervical curettage should be performed as part of the evaluation of a patient with abnormal cytology. One position is that if the entire transformation zone and lesions are visualized, there is no need to perform endocervical curettage. The other position, which I favor, is that endocervical curettage, even in the presence of an apparently satisfactory colposcopic examination, is added insurance that lesions within the endocervical canal that are not visualized will be detected.

One mistake made most often by the neophyte colposcopist is the problem of “past pointing.” An attempted biopsy is taken of a visualized colposcopic abnormality yet the portion of tissue obtained does not come from the area of abnormality but from the adjacent normal epithelium. This can easily be prevented by visualizing with the naked eye or through the colposcope sites of biopsy after they are taken.

It is only through knowledge of the histopathologic changes seen in association with colposcopic findings that the colposcopist can become secure in his or her evaluation of the cervix. Such already well defined characteristics as thickness of the lesion and intercapillary distance will have meaning only if the colposcopist becomes familiar with the histopathology of the normal and abnormal cervix. Unfortunately, in today’s training programs, at least in the United States, the lack of adequate training in pathology tends to increase this problem.

III. New Technologies

There are several new techniques that may offer some promise in the future for evaluation of the cervix. These include the use of fluorescence and Raman spectroscopy of the cervix. Mitchell et al completed studies demonstrating that a ratio of fluorescence intensities at 340 and 440 nm and 383 and 460 nm could differentiate between malignant and nonmalignant cervical tissues with a predictive value of 77–95%.

In further studies they were able to successfully differentiate normal tissues from cervical intraepithelial neoplasia with a sensitivity of 91% and specificity of 82%.

Recently, Raman spectroscopy has been used for tissue diagnostics. This technique probes different characteristics of materials and fluorescence. Raman spectroscopy allows characterization of the chemical content of a tissue. Raman signals are obtained from nearly every chemical compound, and so it is a more general phenomenon than fluorescence. FT-IR Raman spectra of cervical tissue have shown that it may be possible to observe sensitive differences between normal and abnormal tissues with Raman spectroscopy. Richards-Kortum and Mitchell have developed algorithms to distinguish squamous intraepithelial lesions from normal tissue with a sensitivity and specificity of 80–85%. The problem with these newer techniques may be their complexity and possible lack of practicality for daily clinical use. However, further study may well result in simplification of the instrumentation needed to proceed in this direction.

References


Interaction Between Automated Cytology and Colposcopy

Laurie J. Mango, M.D.

Automated cytology and colposcopy are both techniques for detecting cervical neoplasia at as early a stage as possible in order to arrest progression of the process. Both are tools that serve in comple-
mentary roles to be “prescribed” in various combinations in screening programs for the prevention of cervical cancer. As the automated cytology technologies continue to mature, they will be increasingly used to direct the frequency and focus of col-

Automated cytology can interface with colposcopic examination in a number of significant ways.

...poscopy. In this way, automated cytologic technologies could potentially interact with colposcopy in three principal manners:

I. Automated cytology may allow more accurate patient triaging to colposcopy and may increase the negative predictive value of the absence of a high grade lesion.

II. Automated cytology may provide more diagnostically precise, quantitatively based cervical smear reports, predicting not only the level of abnormality but also where it may most likely reside (e.g., ectocervix versus endocervix).

III. Automated cytology and colposcopy are technologies that can be prescribed to specifically correlate with a subpopulation’s risk profile; such stratified, prescription screening programs may well be less expensive overall and more effective in preventing cervical cancer.

I. Automated Cytology: Improving Triage to Colposcopy

Automated cytology technologies have tremendous potential for differentiating which patients with atypical or low grade smears should be colposcoped. As adjunctive techniques that can exhaustively search smears for even rare evidence of a more severe abnormality, automated systems can help to identify “high-risk” atypias and low grades—i.e., those smears containing a few suspicious cells. Thus, automated cytology analysis can be used as a tool to help identify any evidence of high grade lesions.

Clinical studies have already been published on this application of automated cytology. For example, Ryan et al reported that 35 of 101 atypical smears were reclassified to squamous intraepithelial lesion (SIL) using PAPNET analysis (Neuromedical Systems, Inc., Suffern, New York, U.S.A.). They concluded that PAPNET testing of atypical smears, “because it facilitates the detection of abnormal cells present in extremely low numbers, may be a means of detecting preneoplastic or neoplastic cells in smears that would otherwise be deemed ‘atypical’ thus facilitating prompt and targeted follow-up.”

Going forward, specialized artificial intelligence pattern recognition techniques, such as neural network computers, might be developed to predict which atypias and low grade lesions are most likely to be associated with benign and which with neoplastic processes. Creation of such computers would involve training sets that include cytologic images and morphologic features from atypical/low grade smears from patients whose lesions subsequently regressed versus images and features from cases known to subsequently develop high grade or malignant lesions. If such a neural network computer had sufficient discriminatory power, this application of automated cytology could reduce the number of colposcopic examinations for atypical and low grade lesions to only those patients deemed at high risk according to the computer.

II. Automation-Based Predictions for Helping Direct Colposcopy

Automated cytology has the potential to characterize and quantify the presence and degree of abnormality in various types of cervical cells. Thus, rather than simply providing a diagnostic categorization, by applying automated cytology, cervical smear reports might include quantitative estimates of the relative numbers and abnormal changes noted in superficial and intermediate squamous cells, metaplastic cells, small/immature metaplastic cells, parabasal cells, endocervical cells, keratinized cells, parakeratotic cells, etc.

Neural network computers might be trained to correlate certain cytologic patterns and distributions with colposcopic findings regarding the location (ectocervical, transformation zone or endocervical) and extent of the lesion, thereby producing predictive indices of the nature of the lesion. For example, the number of abnormal cells present on the smear may be useful in predicting the extent of the lesion when assessed in combination with other features of the abnormal cells and smear background, as well as information regarding which sampling device was used to obtain the specimen. Such detailed reports might assist in directing the colposcopic examination, as well as contributing to
a determination of the need for an endocervical curettage.

III. Relationship of Automated Cytology and Colposcopy to the Screening Interval: Optimized Screening Programs

Techniques that increase screening sensitivity, such as automated cytology and colposcopy examinations, offer the potential to extend the cervical cancer screening interval without concomitant increases in cervical cancer. Future screening programs will most likely involve multiple protocols, each optimized for a particular patient population or risk factor profile. Protocol procedures might require that the outcome of an automated cytology analysis or colposcopic examination dictate whether the other technique should be performed. For example, if the automated analysis of an atypical smear predicted a benign process or did not uncover evidence of a high grade lesion, colposcopy would not be indicated. In contrast, in a patient with persistent atypical smears, if the colposcopic examination did not reveal a lesion, automated cytologic analysis of the atypical smears would be indicated as a type of “second opinion” as to the nature of the abnormality.

Depending on the patient’s risk profile for cervical cancer, she might be triaged into a low-, moderate- or high-risk screening protocol. The protocol specifics would also be driven by the availability and cost of automated cytologic and colposcopic techniques. For example, in regions where colposcopy is frequently performed and inexpensive, a low-risk screening protocol might include the combination of a cervical smear, automated cytology analysis and colposcopy at a five-year screening interval. As an example of a different protocol, which might be more appropriate in regions where colposcopy is not as inexpensive and for patients at moderate risk for cervical cancer, might prescribe a screening interval of every two years. The examination might include a conventional cervical smear and analysis supplemented by preparation of a fluid-based slide from the cytologic residue and an automated analysis of both the smear and fluid-based preparation. Colposcopy would be performed only as indicated by the discovery of a SIL.

In conclusion, automated cytology can interface with colposcopic examination in a number of significant ways. Automated cytologic analysis of conventional cervical smears can potentially direct colposcopic examination by predicting the nature of a lesion, assist in determining which patients should receive colposcopy and, in some settings, thereby reduce the number of colposcopies. In addition, various combinations of automated cytology and colposcopy can be used to generate screening protocols that might result in more effective and inexpensive screening.

Reference

The Role of Cervicography in the 21st Century
Charles J. Dunton, M.D.

Cervicography was introduced by Stafl in 1981. The instrument consists of a 100-mm macrolens connected to a 35-mm camera body. A special illuminating device and focusing ring are mounted on the front of the lens. The camera back records a number on the film for patient identification. The device will take a picture of the entire cervix after application of 5% acetic acid. The user must place the camera along the axis of the vagina so that the entire cervix is in view, focus and press the exposure button. Commercially available cervicography equipment minimizes human error by using a fixed F-stop. Focus is obtained by adjusting the distance from the cervix. Magnification is obtained when the 35-mm slides are projected.

Cervicography awaits completion and publication of two large trials to determine its place in the diagnosis of cervical neoplasia.
should be referred for colposcopy. Evaluation of a cervigram must be performed by experts in colposcopy who then gain experience in reading cervigrams. The basis for the cervigraphic evaluation is identical to that for colposcopy. There is a single company (National Testing Labs) that holds the patent on cervicography. All cervigrams must be read by this company.

Cervicography Reports

The reports generated are considered negative, atypical, positive or technically defective. If a negative report is generated, the evaluator will note if the transformation zone is fully, partially or not visible. If a positive report is generated, colposcopy is recommended. The evaluator will note if they suspect a minor grade lesion, major grade lesion or cancer. Lesion morphology is given in coloscopic terms. If an atypical diagnosis is rendered, recommendations for repeating in 6–12 months will be given and the nature of the lesion characterized as outside the transformation zone, immature squamous metaplasia or of doubtful significance. Reasons for technically defective tests are listed, and the cervigram must be repeated.

Evidence-Based Outcomes for Cervicography

Evidence for the effectiveness of cervicography has been derived from nonrandomized prospective trials comparing it to cytology as a screening device or as a test adjunctive to cytology. Prospective trials of this technique as a triage tool have also been performed. A large, as-yet-unpublished trial was performed in Costa Rica comparing multiple screening modalities (including cervicography, standard cytology, fluid-based cytology and computerized cytologic screening). Currently in the United States, a randomized trial of low grade cytology has begun comparing repeat cytology, colposcopy and human papillomavirus (HPV) testing as triage techniques. Cervicography is included in each arm as a “fail safe” mechanism in the noncolposcopy groups to prevent a missed cancer diagnosis.

Cervicography as Screening

Several studies have addressed cervicography as a test complementary to cytology in screening for cervical cancer and dysplasia.

Reid et al1 compared cytology, cervicography and HPV hybridization techniques for screening 1,012 women. Twenty-three had high grade lesions by biopsy. No single test was able to identify all 23. No single test was superior to the others for screening.

Two recent studies on large numbers of patients examined this type of testing. Baldauf et al2 compared cytology and cervicography in 1,539 women. Sensitivity of cervicography was 53% (vs. 56% for cytology), and specificity was similar (97% vs. 98%). Eight percent of cervigrams were technically defective. The authors concluded that “that cervicography should not be considered as an alternative to cytology . . . since its accuracy is not significantly better and its rate of technically defective tests is significantly higher. The combination of both methods increases sensitivity . . . at the expense of a high recall rate, of which cost effectiveness has to be assessed.”

Coibion et al3 studied 4,015 women, finding higher sensitivity but lower specificity for cervicography in detecting lesions classified as cervical intraepithelial neoplasia (CIN) 1 or more. The higher sensitivity does not apply to detecting lesions of CIN 2 or greater. Cervicography detected a greater number of high grade lesions in women under 35 than cytology. The performance of cervicography was poor in older patients with a transformation zone that was not visualized.

Data from the Costa Rican trial have been presented at several meetings but are not published yet. In a study of >10,000 patients, the following screening modalities were tested in a high-risk population: cervicography, standard cytology, fluid-based cytology and computerized cytologic screening. Invasive carcinoma was detected in 10 women in this group. Cervicography identified all 10 patients. No other screening modality identified all the cancers.

Current evidence does not support the role of cervicography in screening in areas with well-developed cytology screening. It may find a role in the triage of abnormal cytology.
Cervicography as Triage

Several studies have looked at cervicography in evaluating the atypical cytologic findings. In smears showing only atypia, repeat cytologic evaluation will fail to detect 42–83% of patients with dysplasia. In Jones’ study of 236 patients with atypical cytology, 58 (25%) had biopsy-proven CIN. Repeat cytology identified only 17% of these. Cervicography identified 81%, but 15% of the cervigrams were not interpretable.

Spitzer evaluated 97 patients with atypia and showed that while the sensitivity of cervicography (78%) was better than that of repeat cytology, the specificity was poor (50%). Based on these data, he concluded that the cost of screening populations with a high prevalence of disease with cervicography was higher than direct referral of these patients for colposcopy.

August recently reported on 681 patients with atypical smears who underwent cervicography as well as colposcopy and biopsy. CIN was found in 14% (7% with CIN 2 and 3). Cervicography identified 85% of CIN lesions and all CIN 3 lesions. The positive predictive value of cervicography, however, was 60%.

Ferris reported on 685 women with atypia. Cervicography detected 76% with histologically proven CIN. All women with high grade CIN could be detected by cervicography if the transformation zone was fully visualized on the cervigram and high-risk patients were eliminated.

In summary, cervicography may prove to be an effective triage technique for low grade abnormal cervical cytologic smears. Cost analysis in specific patient populations needs to be performed. The National Institutes of Health has begun a trial of HPV testing colposcopy and repeat cytology as triage for low grade abnormal smears. Cervicography will be performed on all patients in this trial, and this should determine the efficacy of this technique as triage for abnormal smears.

Future Directions

Cervicography has been available for more than 15 years. The test has been commercially available for a number of years. Utilization of cervicography has been low in the United States.

The role of cervicography as screening in areas with developed cytology programs appears limited based on the above evidence. Sensitivity is generally no greater than that of cytology, and specificity appears lower. The inability of cervicography to detect lesions when the transformation zone is not visualized limits its usefulness in certain populations. Postmenopausal women who are at risk for cervical cancer would represent such a population. The additional cost of cervicography when added to cytology would argue against the use of both modalities for screening.

The value of cervicography in triage of mildly abnormal cytology may prove to be the best application in countries with established cytology programs. Results of the current National Institutes of Health trial should determine the role of cervicography as triage. In areas with limited colposcopic services, cervicography may speed the diagnosis of high grade disease by more rapidly referring patients with serious abnormalities.

In areas where cytology screening programs are not in place, cervicography may have its most dramatic effect. The difficulty in training large numbers of cytologists and instituting a large scale smear screening program is obvious. Cervicography, however, is easily taught to midlevel practitioners, and an expert reader can examine large numbers of cervigrams in a short amount of time. The ability to detect cancers and high grade precursors in large, unscreened populations could decrease the morbidity and mortality from cervical cancer.

As the 21st century approaches, cervicography awaits completion and publication of two large trials to determine its place in the diagnosis of cervical neoplasia.

References
The Place of Hysteroscopy in the 21st Century

Shiro Nozawa, M.D., Ph.D., Kaneyuki Kubushiro, M.D., Ph.D., Katsumi Tsukazaki, M.D., Ph.D., and Bao-Liang Lin, M.D., Ph.D.

Hysteroscopy is the most direct method for diagnosis and treatment of intrauterine diseases, and its usefulness is already widely recognized. Hysteroscopy is important for the diagnosis of uterine fibromas, endometrial polyps, intrauterine adhesions, uterine anomalies and neoplastic diseases, such as endometrial hyperplasia and endometrial cancer, and also for hysteroscopic myomectomy for submucous myoma and endometrial ablation.

Below, we review the current clinical significance of hysteroscopy and hysteroscopic surgery as well as the prospects for hysteroscopy towards the 21st century.

Hysteroscopy should remain a direct diagnostic method for endometrial neoplasia.

Hysteroscopy for Benign Diseases

Hysteroscopy and a flexible operating hysteroscope are essential to the diagnosis and treatment of intrauterine adhesions and submucous myomas. We developed a partly rigid diagnostic fiberoptic hysteroscope with a 3.7-mm outer diameter, followed by the development of a partly rigid flexible operating hysteroscope with a 4.8-mm outer diameter. Subsequently, this flexible operating hysteroscope was modified to increase its function. Recently, most hysteroscopic examinations have been performed with a flexible fiberoptic hysteroscope. Hysteroscopy can be performed in the office or clinic without cervical dilatation or anesthesia.

In order to facilitate biopsy, a large biopsy forceps, grasping forceps and scissors forceps have been developed. The biopsy forceps can be used to remove an adequate specimen for biopsy or even an entire lesion; the grasping forceps are large enough to grasp an intrauterine device to remove it easily, and the scissors forceps can be used to cut intrauterine adhesions. The operating ability of the small-caliber flexible hysteroscope has undoubtedly been enhanced by the application of these larger instruments.

Indications for resectoscopic operations, including endometrial ablations, in our department are submucous myomas, endometrial polyps, intrauterine adhesions, hypermenorrhea and uterine abnormalities. To increase safety, we designed a three-contrast ultrasound method of monitoring myomectomy in 1985 and a modified laparoscopic method of monitoring metroplasty in 1990. In 1988 we first reported on the rollerball method of endometrial ablation. In 1994, the resectoscope method was designed to ensure easy and complete resection of large, sessile, submucous myomas. Furthermore, four new types of myoma forceps were produced to facilitate the procedure. Almost all the patients experienced an improvement in their symptoms.

Thus, fiberoptic hysteroscopy and hysteroscopic resectoscopy can be performed effectively and safely using various new instruments and methods.

Endometrial Cancer

The incidence of endometrial cancer is gradually increasing in Japan. In fact, the rates of endometrial cancer to all uterine cancers was 14.6% in 1975, 22.4% in 1984 and 26.7% in 1990.

In Japan, to detect endometrial cancer, cytology of endometrial cells is used as an initial screening method, and endometrial biopsy is the second. However, both endometrial cytology and biopsy are “blind” examinations, leaving the possibility of localized cancer undetected in a few cases and associated with submucosal myomas in the uterine cavity. Endometrial biopsy during hysteroscopic examination is more accurate than conventional biopsy methods.

Instruments, such as CCD cameras, videos and display devices (such as a cathode ray tube), have been developed, so hysteroscopy without cervical dilatation makes the procedure easy even in postmenopausal women.

The indications for hysteroscopy can be summa-
rized as follows: (1) cases with positive or suspected positive endometrial cytology, (2) ultrasonographic findings suggesting endometrial thickening, (3) cases in which the endometrial cancer lesion cannot be diagnosed using the conventional method of endometrial biopsy, and (4) detection of possible cervical invasion of malignancy.

Preoperative diagnosis of cervical invasion with hysteroscopy is important, as are ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI).

Cervical invasion associated with glandular involvement is detectable using hysteroscopy. However, MRI and CT are more useful for assessing cervical lesions in terms of depth as compared with hysteroscopy. At present, hysteroscopy, MRI or CT is required for correct evaluation of a cervical invasion.

Although the diagnostic capacity of MRI and CT will probably improve in the 21st century, hysteroscopy should remain a direct diagnostic method for endometrial neoplasia.

Reference

The U.S. Food and Drug Administration’s Point of View

Max Robinowtiz, M.D.

The U.S. Food and Drug Administration (FDA) suggests that validation of any diagnostic device should include data to support the diagnostic performance of the device. There should be studies with the intended population to support claims for accuracy, precision, sensitivity and specificity. Any claims for increased sensitivity should be presented with the specificity of the device for that level of sensitivity for the outcome that is to be detected or measured. Receiver operator characteristics curves are one method that can be used to present these relationships.

The intended use of an in vivo diagnostic device should be stated. Is the device to be an adjunct to conventional cervical cytologic tests, or is it intended to replace the test? Is the device to be used to triage and refer the patient for other testing, or is it to aid in selection of biopsies; whatever use should be clearly stated. The data required for premarket approval are based on what the device is intended to do and what limitations (and contraindications) will be placed in the product labeling by the manufacturer.

Endoscopic Appearance of Early-Stage Central Type Lung Cancer and Its Cytologic Correlation

Harubumi Kato, M.D., F.I.A.C.

Bronchoscopic Findings and Cytologic Features of Early-Stage Lung Cancer

The death rate from lung cancer has been increasing recently throughout the world due to the increase in the number of elderly, environmental pollution (including tobacco smoking and exhaust from automobiles) and delay in detection. In order to control lung cancer, it is necessary to increase early detection and localization of lung cancer. Sputum cytology for detection and endoscopy for localization are effective.

Sputum Cytology Surveys for Early-Stage Central Type Lung Cancer

Lung cancer mass surveys, including sputum cytology, have shown that the detection rate is about 100 per 100,000 people surveyed in Tokyo. Surveys of symptomatic patients treated by general practitioners yield higher detection rates than any other surveys (Table I).

Cytologic Features of Early-Stage Central Type Lung Cancer

Cytologic criteria of early-stage lung cancer, especially carcinoma in situ, were described by Nasiell and Saccomanno the 1970s, as shown in Figure 1. According to their criteria, tumor cells are usually small, round and/or oval, with hyperchromatic nuclei. The characteristic findings of the cytoplasm are usually dense, orangeophilic stain; however, dense, nonorangeophilic cytoplasm can also be seen. A clean background is
also one of the characteristic findings of early central type squamous cell carcinoma. The cells in the sputum are already degenerated because of the exfoliation from bronchial epithelium due to aging. Therefore, the characteristic features of sputum cytology can be observed in the variations of several degenerative processes.

The cytologic criteria of early central squamous cell carcinoma were developed by the author in 1978. The cells usually appear in clusters, with good adhesion. They are usually small and do not always show strong hyperchromasia with fine and/or coarse chromatin. The cytoplasm usually has basophilic staining and is thin. These findings are due to the nature of the procedure used to collect materials.

Clinical Findings of Early-Stage Central Type Squamous Cell Carcinoma of the Lung

Diagnostic images of this type of early cancer show no abnormal findings except for endoscopy. However, even on endoscopy, no abnormal findings are frequently observed. The Japanese Lung Cancer Society has its own criteria for endoscopic findings of early-stage central type squamous cell carcinoma.

The criteria are classified into four categories: non-visible, thickening, nodular and polyploid type. However, mixed findings on the above types are actually the most frequently encountered.

Cytologic Differences Between Early-Stage and Advanced Squamous Cell Carcinoma

Differences between cells are based on cellular adherence, shape, cellular margin, cytoplasm (staining condition), nuclei (position, shape, number, membrane, chromatin), nucleolus (shape, number), background, nuclear DNA, area (cytoplasm, nucleus) and nuclear/cytoplasmic ratio (Table II). There is significance in cellular adherence, cellular shape

<table>
<thead>
<tr>
<th>Survey</th>
<th>No. of examinees</th>
<th>Normal</th>
<th>Sq mpl</th>
<th>Mod</th>
<th>Sev</th>
<th>Sq ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80,857</td>
<td>1,764</td>
<td>79,008</td>
<td>106</td>
<td>56</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>51,154</td>
<td>937</td>
<td>49,510</td>
<td>594</td>
<td>86</td>
<td>27</td>
</tr>
<tr>
<td>Postal survey system</td>
<td>11,860</td>
<td>22</td>
<td>11,788</td>
<td>32</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Health check-up system</td>
<td>4,175</td>
<td>27</td>
<td>43,620</td>
<td>66</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>GP patients</td>
<td>46,331</td>
<td>1,862</td>
<td>4,080</td>
<td>238</td>
<td>247</td>
<td>264</td>
</tr>
</tbody>
</table>

Table I Lung Cancer Detection Rate by Sputum Cytology, by a Survey Group (1989–1993)

Sq mpl = squamous metaplasia, Mod = moderate atypia, Sev = severe atypia, Sq ca = squamous cell carcinoma, survey 1 and 2 = different survey groups as the result of health insurance act for the elderly, GP patients = patients treated by general practitioners.

Table II Cellular Findings in Early Stage Squamous Cell Carcinoma

<table>
<thead>
<tr>
<th>Cellular characteristic</th>
<th>Early</th>
<th>Advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence (single cells)</td>
<td>80.9% (61.7%)</td>
<td>90.5% (58.5%)</td>
</tr>
<tr>
<td>Shape</td>
<td>Polygon</td>
<td></td>
</tr>
<tr>
<td></td>
<td>39.0% (41.0%)</td>
<td>61.0% (69.0%)</td>
</tr>
<tr>
<td>Fiber, tadpole</td>
<td>1.0% (2.0%)</td>
<td>9.0% (14.0%)</td>
</tr>
<tr>
<td>Round, oval</td>
<td>61.0% (59.0%)</td>
<td>38.0% (34.0%)</td>
</tr>
<tr>
<td>Area (&lt;200 µm)</td>
<td>53.0% (47.0%)</td>
<td>45.0% (2.0%)</td>
</tr>
<tr>
<td>Nuclear area (&lt;60 µm)</td>
<td>60.0% (37.0%)</td>
<td>40.0% (17.0%)</td>
</tr>
<tr>
<td>Nuclear/cytoplasmic ratio</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Chromatin distribution</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>DNA volume</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Percentages in parentheses are brushing specimens.
(polygonal, fiber, tadpole, round, oval), area (cellular and nuclear) and DNA amount between early and advanced lesions.

**Problems of Sputum Cytology for the Early Detection of Lung Cancer**

Although sputum cytology is effective for the detection of early-stage central type squamous cell carcinoma, there are some problems: the rate of valid sputum specimens from lung cancer patients is not 100%, diagnostic accuracy is not 100% even if a valid sputum specimen can be obtained, and it is difficult to make a cytomorphologic diagnosis of borderline atypical cells, such as severely atypical squamous metaplastic cells.

**Problems for Early Localization**

Although squamous cell carcinoma can be diagnosed by sputum cytology, in certain patients localization of the lesion is difficult or impossible because of an extremely early lesion, as described above. In such cases bronchial washing (lavage) cytology, blind brushing from central to segmental bronchi and photodynamic diagnosis make use of the photodynamic reaction induced by tumor-specific photosensitizers. Laser photoradiation and autofluorescence bronchoscopy are under evaluation at present.

**Future Applications of Early Detection of Lung Cancer**

In order to solve these problems, intracellular telomerase activity in atypical cells in sputum and malignancy-associated changes are being investigated and hold promise for the future.

**References**