MINIREVIEW SERIES FOR THE 50TH VOLUME

Dr. Soju Kurihara: increased awareness of cytologic diagnosis

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(Received for publication on August 21, 2000)

Abstract. Cytopathology is now regarded as an important tool for detecting cancer, especially uterine cervical cancer. There was, however, a hard way to acquire the current status. This technique, the diagnosis of cancer by light microscopic examination of exfoliated cells, was first established by Dr. Papanicolaou in the 1940's. For spreading this technique and acknowledgement of this clinical field by conservative pathologists, many doctors including Dr. Kurihara, Professor emeritus of Department of Obstetrics and Gynecology, School of Medicine, Keio University, have made efforts for about fifty years. Dr. Kurihara and his colleagues made a clinical study and revealed the natural history of uterine cervical cancer from dysplastic lesions. Based on these results, he supported the establishment of the new screening system for uterine cervical cancer, "Tohbo-Hoshiki", which is now widely employed in Japan. This system has played an important role to decrease the mortality from uterine cervical cancer. Dr. Kurihara is one of the founders of the Japanese Society of Clinical Cytology, which has played a central role in the development of cytologic diagnosis in Japan, and he also contributed to bring up many gynecologic oncologists specializing in cytopathology and the treatment of cancer. Although remarkable progress has been made in computer-related technology and the automation of cytologic diagnosis is no longer a dream, the results of the untiring efforts of Dr. Kurihara and his colleagues will continue to play an instrumental role in the future advancement of cytologic diagnosis. (Keio J Med 50 (4): 213–216, December 2001)

Key words: gynecologic oncology, uterine cervical cancer, screening, cytopathology

Importance of Cytologic Diagnosis

Cancer to the gynecologist most commonly conjures up thoughts of cancer of the uterus. Uterine cancer is a major cause of mortality among women, with an annual incidence of about 5,000 deaths. The control of uterine cancer thus remains an important problem. However, mortality from uterine cancer in Japan has decreased recently. Until 30 years ago, uterine cancer was the second most common cause of mortality among all malignant tumor-related deaths in Japanese women, ranking just behind gastric cancer. In 1998, uterine cancer ranked as the 7th leading cause of mortality from malignant tumors in women, behind cancer of the stomach, colon, lung, liver, breast, and pancreas. The cardinal rule of cancer management is early detection and early treatment. The decline in mortality from uterine cancer is largely due to improved detection of early cancers as well as to progress in therapy, such as new surgical procedures and anticancer agents. In fact, patients with early uterine cervical cancer who undergo partial excision of the cervix by laser conization, a relatively noninvasive procedure, have a nearly 100% chance of a cure. This simple technique is done without an overnight hospital stay at some centers in North America and Europe. Of course, the biggest advantage of laser conization for women who want to have children is preservation of the uterus. Laser conization also offers other benefits in terms of quality of life.

Laser conization is indicated only for the treatment of early cervical cancers, such as carcinoma *in situ* or early invasive carcinomas. Most cases of early uterine cancer are found in patients without symptoms such as irregular bleeding. Nearly all cases are discovered on

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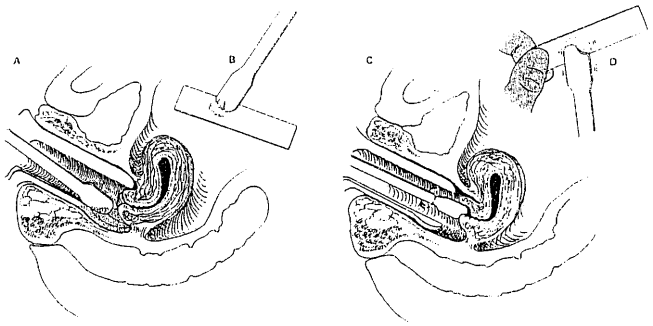

Fig. 1 Preparation of a Papanicolaou cytosmear. (Reproduced from Long AE: Gynecologic history, examination, & diagnostic procedures. In: Benson R, eds, Current Obstetrics & Gynecologic Diagnosis & Treatment, 4th Ed, CA, Lange Medical Publications, 1982; 102–124, requesting permission)

examination of women presenting with symptoms such as lower abdominal pain. Many women are now aware of, and participate in, local screening programs for uterine cancer. Women concerned about the risk of uterine cancer frequently consult gynecologists. Early detection of uterine cancer is now often taken for granted; however, it is to be recognized that current diagnostic systems were enabled by the untiring efforts and devotion to research of our senior colleagues.

Cancer can occur in either the cervix or body of the uterus, and each type of cancer has its own set of diagnostic procedures. Screening for uterine cancer generally refer to procedures for the diagnosis of cervical cancer. Because the cervix protrudes into the vaginal cavity, it can be directly examined and biopsied (Fig. 1). Colposcopy with cytologic examination can be done to detect and evaluate cancer or its precursor lesions. The establishment and widespread use of colposcopy and cytologic diagnosis, now considered routine among gynecologists, can largely be attributed to Dr. Soju Kurihara, Professor Emeritus of Keio University.

Progress of Cytopathology in the 20th Century

Attempts to diagnose cancer by light microscopic examination of exfoliated cells date back to the middle of the 19th century. The earliest attempts to find cancer cells in body fluids were recorded by Sanders (urine),[1] Hampeln (sputum),[2] and Lucke and Klebs (thoracic and abdominal fluid).[3] The detection of cancer cells in body fluids was of course enabled by the development of Papanicolaou's stain. Papanicolaou was initially studying the relation between the menstrual cycle and cellular changes in vaginal smears when he accidentally noticed some strange cells, which were in fact exfoliated cancer cells, in a smear obtained from a patient with uterine cervical cancer. After extensive studies and establishment of an academic framework for clinical cytology, Papanicolaou published ''Diagnosis of Uterine Cancer by the Vaginal Smear'' in 1943.[4] This book was instrumental in establishing cytodiagnosis throughout the world.

Unfortunately, with the outbreak of the Second World War, Japan was academically isolated from Europe and North America. Shortly after the war, Dr. Kakuichi Ando, Dr. Kurihara's mentor, a leading gynecologist who was acutely aware of new international developments in the field, and some other pioneers introduced cytodiagnosis to Japan. Dr. Kurihara graduated from the School of Medicine, Keio University in 1949, the year when academic relations with Europe and North America resumed. After serving as an intern for 1 year, Dr. Kurihara entered the Department of Obstetrics and Gynecology, School of Medicine, Keio University in April, 1950. He served as a resident at the department and affiliated hospitals and returned to the department in 1952. Dr. Kurihara worked in the laboratory of gynecological pathology of the Department of Obstetrics and Gynecology. Dr. Andoh assigned him the research topic of ''carcinoma *in situ*'' of the cervix.

In the early 1950's, cytologic diagnosis was shown to be useful and practical in gynecology[5], but new diagnostic techniques for cancer often met resistance. Some pathologists insisted that cancer should be diagnosed at the histological level and regarded cytologic diagnosis as of second importance for the definite diagnosis of cancer. Such thinking considerably delayed the academic evaluation of cytopathology. Increased awareness and acceptance of clinical cytology required documentation of its diagnostic usefulness. Using cytopathology and colposcopic examination to study gynecological outpatients, Dr. Kurihara focused on the diagnosis and treatment of cancer. In 1959 Dr. Kurihara founded the ''Cancer Clinic,'' the first outpatient clinic in Japan to specialize in cancer. He then initiated large follow-up studies of carcinoma *in situ* and severe dysplasia, considered characteristic of benign/malignant borderline lesions of the cervix. Currently, nearly 100,000 patients are registered at the Cancer Clinic of the Department of Obstetrics and Gynecology, School of Medicine, Keio University. In 1961 histopathological studies were compiled on the basis of research done at the Cancer Clinic, contributing substantially to the development and increased awareness and acceptance of cytologic diagnosis.

Also in 1961, the 1st International Congress of Cytology was held in Vienna. Cytologic diagnosis, a technique essential for the detection of ''early clinical stage cancer'' in gynecology, was internationally confirmed to be clinically useful.[6] At this congress, histological criteria for carcinoma *in situ* and for the classification of severe and mild dysplasia, defined as cancer-like epithelial deviations, were decided internationally. In the

same year, The Japanese Society of Clinical Cytology was founded in Japan. Dr. Kurihara served as a key member of the Society since its conception and acted as chairman of the 26th Annual Scientific Meeting.

Progress of Cytopathology in Japan

The Japanese Society of Clinical Cytology played a central role in the development of cytologic diagnosis in Japan and currently has about 9,000 active members. Cytologic diagnosis of exfoliated cells, performed in the early days of cytology, has shifted to more aggressive techniques for sampling cells, such as surface biopsy or aspiration biopsy. Eventually, these techniques were adopted by other specialties such as surgery, internal medicine, urology, dentistry, and oral surgery. The Society strongly recommended that qualified cytotechnologists should be responsible for cytodiagnostic screening and other technical aspects of cytologic diagnosis. It also established a system for cytopathologists, assigned to be responsible for the education and training of cytotechnologists, the final diagnosis of cytologic samples, and testing for their qualification. This led to a two-tier examination system in Japan: a cytotechnologist initially screens cell samples and makes a preliminary diagnosis; then a cytopathologist makes the final diagnosis. There are currently about 1,800 registered cytopathologists in Japan. Hospitals affiliated with Keio University have approximately 90 cytopathologists, accounting for about 5% of all cytopathologists in Japan. This is largely due to the efforts of Dr. Kurihara, registered cytopathologist No. 25, and other senior colleagues of the Laboratory of Gynecological Pathology, Department of Obstetrics and Gynecology, School of Medicine, Keio University.

Dr. Kurihara was appointed as assistant professor, Department of Obstetrics and Gynecology, School of Medicine, Keio University in 1966. Leading the Laboratory of Gynecological Pathology, Dr. Kurihara continued to study new possibilities for cytologic diagnosis. In the same year, he published ''Dyplasia and carcinoma *in situ* of the uterine cervix with special reference to follow-up observations''[7] in Acta Obstetrica et Gynaecologica Japonica (Nippon Sanka Fujinka Gakkai Zasshi). In 1972 Dr. Kurihara was appointed as professor and presented ''Studies of precancerous lesions of the uterine cervix – Focus on benign/malignant borderline lesions'' as a guest lecture at the 24th General Meeting of The Japan Society of Obstetrics and Gynecology. This presentation described the natural history of cancer of the uterine cervix from severe dysplasia to carcinoma *in situ*. In addition to cytologic diagnosis, Dr. Kurihara promoted the use of colposcopy and continued to study non-cervical cancers. He previously served as board member of The Japan Society of Clinical Oncology and councilor of The Japanese Cancer Association. In 1984 Dr. Kurihara was appointed Chairman of the 5th International Federation for Cervical Pathology and Colposcopy and reported the latest Japanese developments in gynecological cancer therapy to the rest of the world.

Progress of the Screening System of Uterine Cervical Cancer in Japan

In medicine, as well as in other fields, research solely for the purpose of research results only in self-gratification. The outcome of research must be applied clinically. Studies done before 1960 demonstrated that cancer could not be effectively controlled by waiting for a tumor to develop. It became clear that the early detection and diagnosis of cancer, while still asymptomatic, by newly established cytodiagnostic techniques was the most effective policy. Before 1960, the mean age at detection of cancer of the uterine cervix was 50 to 55 years.[8] Since most cancers were already too advanced at this stage, the recommended age for enrolling in screening programs designed to detect early uterine cervical cancer was lowered considerably. From the mid 1960's, the Ministry of Health and Welfare and Public Health Centers started to screen asymptomatic women in their thirties for uterine cervical cancer, and many mobile screening programs began. In 1963 The Japan Association of Obstetricians and Gynecologists established a Cancer Control Committee and started to examine the most effective means of screening women for uterine cervical cancer. In 1965 the ''Tohbo-Hoshiki,'' guidelines for primary cytodiagnostic screening were initiated by the members of The Japan Association of Obstetricians and Gynecologists. As one of the members, Dr. Kurihara participated in the planning, conception and coordination of educational meetings, and founded a cytodiagnostic center at The Tokyo Health Association, Inc. Dr. Kurihara also played an instrumental role in the conception and development of MP fixation solution to ensure good staining properties of shipped samples. As chairman of the Cancer Control Committee of The Japan Association of Obstetricians and Gynecologists from 1976 through 1980, Dr. Kurihara actively promoted screening programs. As a cytopathologist, Dr. Kurihara was involved in training since the foundation of the cytodiagnostic center and developed it into a model center for Japan. In 1968, the first year of screening, 3,315 women were examined for cancer. The number of women undergoing screening has since increased year by year. The cumulative number of women screened in 2000 is likely to exceed 5 million, higher than in any other country. The ''Tohbo-Hoshiki,'' originally one model for cancer screening programs in Japan, seems to have been successfully adopted throughout the country.

Since the start of screening by the ''Tohbo-Hoshiki'', 10,431 cases of cancer have been diagnosed. Of this total, 45.7% have been early cancers. Although some initially questioned the usefulness of screening, a report made by the Study Group to Evaluate the Effectiveness of Screening Programs for Cancer, submitted to the Ministry of Health and Welfare in February, 1998, concluded that screening programs for cancer of the uterine cervix effectively contribute to decreased mortality and a decreased incidence of invasive cancers. This outcome can also be attributed to the propagation of ''Tohbo-Hoshiki.'' In acknowledgment of the establishment and dissemination of screening programs for cancer of the uterine cervix, Dr. Kurihara was awarded The Japan Cancer Society Prizes in 1996.

Dr. Kurihara is strict with respect to science, but has a very gentle personality. Many of his former students worked at the Laboratory of Gynecological Pathology. The list is long and includes many leading Japanese gynecologic oncologists specializing in the cytopathology and treatment of cancer, such as Dr. Shiro Nozawa, currently Professor, Department of Obstetrics and Gynecology, School of Medicine, Keio University; Dr. Hiroaki Ohta, Professor, Department of Obstetrics and Gynecology, Tokyo Women's Medical University; Dr. Yasuhiro Udagawa, Professor, Department of Obstetrics and Gynecology, Fujita Health University School of Medicine; Dr. Takao Shinozuka, Associate Professor, Department of Obstetrics and Gynecology, School of Medicine, Tokai University; and Dr. Katsumi Tsukazaki, Associate Professor, Department of Obstetrics and Gynecology, School of Medicine, Keio University. Dr. Kurihara's sincere attitude toward science and his inquisitive spirit have been passed on to his successor. Professor Shiro Nozawa served as Chairman of the 41st Annual Meeting of The Japanese Society of Clinical Cytology and is currently Chairman of The Committee of Cytopathologists. In addition, the close affiliation between Dr. Kurihara and Professor Wied, the University of Chicago, the founder of The International Association of Clinical Cytology, has permitted many research fellows to study abroad, contributing to closer relations between Japan and the United States in Cytopathology.

Future Advance of Cytopathology and the Role of "Keio Medicine"

Already half a century has passed since the development of cytologic diagnosis as an independent technique. During this period, cytologic diagnosis has become a widely accepted means of screening for cancer and is now a well established discipline. Owing to technological progress and interaction with other fields, cytological diagnosis has evolved into a diagnostic science with a natural-science background. Next year, cytologic diagnosis will enter a new century. We believe that further progress in cytologic diagnosis in Japan will be enabled by the active participation of specialists from many different disciplines. Recently, remarkable progress has been made in computer-related technology and information systems in the so-called information technology revolution. In clinical cytology as well, the automation of cytologic diagnosis, *i.e.*, the possibility that automated systems will replace cytologic examinations now done by trained humans using a microscope, is no longer a dream.[9] However, regardless of how much progress is made in computerized image-resolution ability, automated diagnosis is impossible without the input of our accumulated cytodiagnostic know-how. As stated above, ''Keio Medicine'' has contributed substantially to developing the foundation for cytologic diagnosis, the result of the untiring efforts of our colleagues over the course of more than 40 years. I sincerely hope that Dr. Kurihara, who remains very active, and other colleagues from Keio University will continue to play an instrumental role in the further advancement of cytologic diagnosis and that cancer will become a manageable disease within the next century.

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