Prospects for Conquering Stomach Cancer in the 21st Century

February 16, 2002
International Conference Hall
Aichi Cancer Center
Nagoya, Japan
Aichi Cancer Center
International Symposium VIII

Prospects for Conquering Stomach Cancer in the 21st Century

Committee of the Aichi Cancer Center International Symposium
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February 16, 2002
Aichi Cancer Center, Nagoya, Japan
PROGRAM OF SYMPOSIUM

9:30-9:35 Opening Remarks: Suketami Tominaga

Molecular and Epigenetic Bases of Stomach Cancer

Chairperson: Youlin Qiao (Cancer Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College)
Masae Tatematsu (Aichi Cancer Center)

9:35-10:05 Toshikazu Ushijima (National Cancer Center)
Epigenetic Alterations in Human Stomach Cancers

10:05-10:45 Parry J. Guilford (University of Otago, New Zealand)
E-cadherin Germline Mutations in Familial Gastric Cancer

10:45-11:15 Hiroyuki Aburatani (Tokyo University)
Molecular Classification of Stomach Cancer by Gene Expression Profiling

The Battle against Helicobacter pylori for Stomach Cancer Prevention

Chairperson: Parry J. Guilford (University of Otago, New Zealand),
Hiroyuki Aburatani (Tokyo University)

11:15-11:55 Youlin Qiao (Cancer Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College)
Helicobacter pylori Seropositivity and Cardia Stomach Cancer: Positive Association in a Prospective, Nested Case-cohort Study from Linxian, China

11:55-12:15 Nobuyuki Hamajima (Aichi Cancer Center)
Polymorphisms of Fucosyltransferase Genes and Helicobacter pylori Infection Risk

12:15-13:15 Lunch
13:15-13:35 Masae Tatematsu (Aichi Cancer Center)
Helicobacter pylori Is a Promoter of Stomach Cancer rather than an Initiator

13:35-14:05 Naomi Uemura (Kure Kyosai Hospital)
Effect of Helicobacter pylori Infection and Eradication on the Development of Gastric Cancer

**Strategies for Cure of Stomach Cancer**

Chairperson ⓠ Roderich E. Schwarz (University of Medicine and Dentistry, New Jersey)
Tsuneya Nakamura (Aichi Cancer Center)

14:05-14:35 Hiroyuki Ono (National Cancer Center)
Endoscopic Mucosal Resection for Early Gastric Cancer
- Indication and New Techniques, IT Knife Method -

14:35-15:05 Michitaka Fujiwara (Nagoya University)
Current Status and Future Perspective of Laparoscopic Operation for Early Gastric Cancer

15:05-15:25 Coffee Break

Chairperson ⓠ C. J. H. van de Velde (Leiden University Medical Center),
Mitsuru Sasako (National Cancer Center)

15:25-15:45 Yasuhiro Kodera (Nagoya University)
Update of J COG 9501 Study; a Randomized Controlled Trial to Evaluate Para-aortic Lymphadenectomy for Gastric Carcinoma

15:45-16:25 Roderich E. Schwarz (University of Medicine and Dentistry, New Jersey)
Surgery and Adjuvant Therapy for Gastric Carcinoma in the USA

16:25-17:05 C. J. H. van de Velde (Leiden University Medical Center)
Ten Year Results of Prospective Randomized D1/D2 Gastric Cancer Trial Limited but Definitive Benefits

17:05-17:10 Concluding Remarks: Ryuzo Ohno
Welcome Remarks

Suketami Tominaga
President, Aichi Cancer Center

On behalf of the organizing committee, I would like to welcome all of you to the Eighth Aichi Cancer Center International Symposium. The first international symposium entitled “From Prevention to Treatment” was held in 1994 when Aichi Cancer Center celebrated its Thirtieth Anniversary and the International Conference Center was newly built. Since then the symposium has been held annually and the organizing committee has selected timely topics on basic research, prevention, diagnosis, treatment and translational research on cancer.

This year, the organizing committee has selected the main theme to be “Prospects for Conquering Stomach Cancer in the 21st Century”. This main theme is important because stomach cancer is still a most common cancer in Japan as well as in other Asian countries.

This symposium consists of three sessions; the first session is “Molecular and Epigenetic Basis of Stomach Cancer”, the second session is “The Battle against Helicobacter pylori for Stomach Cancer Prevention” and the third session is “Strategies for Cure of Stomach Cancer”.

It is our great pleasure to have this symposium and we really hope that all participants will enjoy this symposium and that this symposium will contribute to control of stomach cancer in Japan and all over the World.
Epigenetic Alteration in Human Stomach Cancers

Toshikazu Ushijima, Atsushi Kaneda and Takashi Sugimura
Carcinogenesis Division, National Cancer Center Research Institute
Tokyo, Japan

CpG methylation plays important roles in carcinogenesis. To search for tumor-suppressor genes and genes with altered expressions using aberrant CpG methylation as a marker, we previously developed a comprehensive genome-scanning method for differential methylations, methylation-sensitive-representational difference analysis (MS-RDA) [Ushijima et al., PNAS, 94; 2284, 1997].

A pair of a gastric cancer and its surrounding normal tissue was analyzed by MS-RDA. Six DNA fragments were isolated as being flanked by a CpG island (CGI) and possibly hypermethylated. Three of the six flanking CGIs were confirmed to be hypermethylated in the cancer, and two of them had known genes in their vicinities.

DNA fragment 3A1 was derived from a CGI in the 5’ region of the Insulin-induced protein 1 (INSIG1/CL-6) gene. Hypermethylation of the CGI was present in 50% of the primary gastric cancers (11 of 22), and the hypermethylation was associated with reduced expression of INSIG1. When a cell line with hypermethylation and reduced expression of INSIG1 was treated with 5-aza-2’-deoxycytidine (aza-dC), a demethylating agent, demethylation of the CGI and re-expression of INSIG1 were observed. INSIG1 is known to be expressed when a fibroblast differentiates into an adipocyte, and it was suggested that the silencing of INSIG1 was related to malignant phenotypes in gastric cancers.

DNA fragment 3B4 was derived from intron 7, near exon 8, of the p41-Arc gene. A CGI spanning exon 8 was found to be hypermethylated in 10 of the 22 gastric cancers. p41-Arc expression was markedly reduced in seven cancers, five of which contained signet-ring cancer cells. A CGI in the p41-Arc 5’ upstream region was hypermethylated in one of these five cancers. p41-Arc is known to be essential in actin polymerization and cell-shape control. It was suggested that its decreased expression was involved in gastric cancer cell morphology, especially in signet-ring cell cancers.

The role of these new players in gastric carcinogenesis is being studied by their introduction into gastric cancer cell lines.
Toshikazu Ushijima, M.D., Ph. D.

Chief
Carcinogenesis Division
National Cancer Center Research Institute
Tokyo, Japan

1986 University of Tokyo, M.D.
1986 Hematologist, Tokyo University Medical School
1989 Research Resident, National Cancer Center Research Institute (NCCRI)
1991 Staff Scientist, Carcinogenesis Division, NCCRI
1994 Section Head, Section for Preneoplastic Lesions, Carcinogenesis Division, NCCRI
1996 University of Tokyo, Ph. D.
1999- Chief, Carcinogenesis Div., NCCRI
E-cadherin Germline Mutations in Familial Gastric Cancer

Parry J. Guilford
Cancer Genetics Laboratory, Department of Biochemistry, University of Otago Dunedin, New Zealand

Hereditary diffuse gastric cancer (HDGC) is a cancer syndrome caused by inactivating germline mutations in the gene for the homophilic cell-to-cell adhesion protein E-cadherin (CDH-1). This syndrome is typified by early-onset, histologically diffuse gastric cancer. HDGC families also have a six-fold increased risk of developing breast cancer, but do not present with the intestinal form of gastric cancer. The penetrance of HDGC is higher in females than males (83% and 67% respectively) and the age of cancer onset ranges from 14 years upwards. There is no evidence for any phenotype variation associated with mutations at different locations in the CDH-1 gene.

To date, about 25 families from a broad range of ethnic groups have been identified with inactivating CDH-1 germline mutations. However, in Asian populations, the only germline CDH-1 mutations found in gastric cancer families have been substitution mutations. It is probable that the high rate of sporadic gastric cancer in Asia is masking the “true” inherited gastric cancer families. For reasons which are not yet clear, HDGC is over-represented in the New Zealand Maori population. We speculate that the CDH-1 mutations may have led to a heterozygote advantage, perhaps related to E-cadherin’s role as a receptor for the bacterial pathogen Listeria monocytogenes.

Unlike other familial cancers, LOH is not a common mechanism for inactivation of the second allele. Instead, the dominant mechanism for the 2nd hit on CDH-1 appears to be promoter hypermethylation. The demonstration that the 2nd hit on CDH-1 need not be an irreversible event suggests that environmental or physiological factors which lead to sustained downregulation of E-cadherin can influence the genetics of tumor progression. Therefore, the maintenance of E-cadherin expression must be regarded as a critical target for chemopreventative strategies.

Recent detailed histological analyses of HDGC gastrectomies have shown that stomachs from HDGC patients develop multifocal clusters of signet ring cells at a relatively early age. One patient we analysed recently had >45 independent lesions. The existence of these multiple foci, which have lost all E-cadherin expression, suggests that the second CDH-1 hit has occurred in multiple cells at a similar moment in time.
This broad 2nd hit argues strongly for the involvement of an environmental trigger such as a carcinogen, or a general physiological event such as inflammation, in the progression of HDGC. The multifocal disease also suggests that few irreversible genetic hits are required for the development of signet ring cells. These lesions are, however, likely to be slow growing and may constitute precursor lesions that are not yet fully invasive.
Parry J Guilford, Ph.D.

Research Director,
Pacific Edge Biotechnology Ltd,
Centre for Innovation, University of Otago,
Dunedin, New Zealand

Principal Investigator,
Cancer Genetics Laboratory,
Dept. Biochemistry
University of Otago,
Dunedin, New Zealand

1989      Ph.D., University of Cambridge
1990      Research Scientist, DSIR, Auckland, New Zealand
1991-1994 Postdoctoral Fellow, Unité de Génétique Moléculaire Humaine,
           Institut Pasteur, Paris
1995      Senior Research Fellow, Cancer Genetics Laboratory, University of
           Otago
1996-      Cancer Genetics Laboratory, University of Otago
**Molecular Classification of Stomach Cancer by Gene Expression Profiling**

**Hiroyuki Aburatani**  
Genome Science Division, Research Center for Advanced Science and Technology, University of Tokyo, Tokyo, Japan

Recent molecular analyses have clarified many genetic alterations in gastric carcinogenesis, such as p53, β-catenin, E-cadherin, TFF1 and c-met, but it is still hardly enough to understand common pathway of carcinogenesis and progression of gastric cancer. Furthermore, gastric cancer shows diverse clinical properties such as histological type, metastatic status, invasiveness and responsiveness to chemotherapy. Only a little is known about genes associated with these characteristics.

To gain molecular understanding of carcinogenesis, progression and diversity of gastric cancer, 22 primary human advanced gastric cancer and 8 non-cancerous gastric tissues were analyzed by high-density oligonucleotide microarray in this study. Based on expression analysis of approximately 6800 genes on HuFL array, a two-way clustering algorithm distinguished cancer tissues from non-cancerous tissues. Subsequently, differentially expressed genes between cancer and non-cancerous tissues were identified with Mann-Whitney’s U-test; 162 and 129 genes highly expressed (P<0.05) more than 2.5 fold in cancer and non-cancerous tissues, respectively. In cancer tissues, genes related to cell cycle, growth factor, cell motility, cell adhesion and matrix remodeling were highly expressed, while genes related to gastrointestinal specific function and immune response were highly expressed in non-cancerous tissues. Furthermore, we identified several genes associated with lymph node metastasis including Oct 2 or histological types including L1 cadherin. These results provide not only a new molecular basis for understanding biological properties of gastric cancer, but also useful resources for future development of therapeutic targets and diagnostic markers for gastric cancer.
Hiroyuki Aburatani, M.D., Ph.D.

Professor,
Genome Science Division
Research Center for Advanced Science and Technology,
University of Tokyo
Tokyo, Japan

Education
University of Tokyo, Tokyo, Japan, M.D. 1980 Medicine
University of Tokyo, Tokyo, Japan, Ph.D. 1988 Medicine

Employment
1980-1981 Internship in Internal Medicine, University of Tokyo
1981-1982 Clinical Fellow, Toshiba Central Hospital, Tokyo
1982-1983 Clinical Fellow, Tokyo Metropolitan Komagome Hospital, Tokyo
1983-1988 Clinical Research Fellow, Third Department of Internal Medicine, University of Tokyo
1988-1991 Assistant Professor, Third Department of Internal Medicine, University of Tokyo
1988-1994 Visiting Scientist, Center for Cancer Research, MIT, Cambridge, MA, USA
1995-1999 Assistant Professor, Third Department of Internal Medicine, University of Tokyo
1999-2001 Associate Professor, Genome Science Division, Research Center for Advanced Science and Technology, University of Tokyo
2001 Professor, Genome Science Division, Research Center for Advanced Science and Technology, University of Tokyo
Helicobacter Pylori Seropositivity and Cardia Stomach Cancer: Positive Association in a Prospective, Nested Case-cohort Study from Linxian, China

Youlin Qiao
Department of Cancer Epidemiology, Cancer Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College Beijing, PR China

Background: H. pylori carriage is the well-known risk factor for non-cardia stomach adenocarcinoma. However, the association between H. pylori and cardia stomach cancer risk remains controversial.

Objective: To explore the sub-site specific stomach cancer risks associated with H. pylori persistent infection by measuring seropositivity.

Methods: A prospective, nested case-control study was designed. Subjects were identified from among the participants of a large (n=29,584) nutrition intervention trial previously conducted in Linxian, China. Serum samples collected 9-12 months prior to the onset of intervention were used to determine H. pylori infectious status. Baseline characteristics were derived from a pre-trial evaluation. Incident stomach cancers were diagnosed over 5.25 years (duration of the intervention period). In total, 99 cardia stomach cancer cases, 82 non-cardia stomach cancer cases, and 192 cancer-free controls were included. H. pylori whole cell antibodies and H. pylori cagA antibodies were measured using regionally-validated enzyme-linked immunosorbent serum assays. Seropositivity was defined as one or both serum assays being positive. Odds ratios for stomach cancer were estimated using multivariate logistic regression analyses. All statistical comparisons were performed two-sided with alpha equal to 0.05.

Results: Both types of H. pylori serum antibodies were more common among cases than controls. Defined as one or both assay results positive, H. pylori seropositivity rates for subjects with gastric cardia cancer, non-cardia gastric cancer, and gastric cardia and non-cardia cancers combined were 70% (p=0.02), 72% (p=0.01), and 71% (p=0.003), versus 56% for controls. Odds ratio estimates based on H. pylori seropositivity were 1.87 (95% confidence interval [CI] = 1.10 to 3.17) for cardia stomach cancer, 2.29 (95% CI = 1.26 to 4.14) for non-cardia stomach cancer, and 2.04 (95% CI =
1.31 to 3.18) for both stomach cancer sub-sites combined.

**Conclusions:** H. pylori seropositivity was associated with similarly increased risks for both cardia and non-cardia stomach cancer in this well-characterized cohort.

**Implications:** Contrary to most earlier reports, these data suggest that the procarcinogenic potential of H. pylori carriage is whole stomach, rather than limited to the cardia stomach. Future studies should address whether or not H. pylori eradication represents a logical stomach cancer prevention strategy in this high-risk population.
Youlin Qiao, M.D., Ph.D.

Professor and Chief,
Department of Cancer Epidemiology
Cancer Institute and Hospital Chinese Academy of Medical Sciences and Peking Union Medical College (CAMS/PUMC)
Beijing, The People's Republic of China

1980 Medical Diploma, Sichuan Medical College, Chengdu, China
1983 M. P. H. (Epidemiology), Dalian Medical College, Dalian, China
1996 Ph. D. (Environmental Health Sciences), Johns Hopkins University, The School of Hygiene and Public Health, Baltimore, Maryland, USA
1980 Assistant Researcher, Department of Basic Medicine, Institute of Medical Biology, CAMS/PUMC, Kunming, China
1983-1985 Assistant Researcher, Department of Epidemiology, Cancer Institute and Hospital, CAMS/PUMC, Beijing, China
1989 Assistant Professor, Department of Cancer and Nutrition, Cancer Institute and Hospital, CAMS/PUMC, Beijing, China
1991-1997 Visiting Associate, Cancer Prevention Studies Branch, Division of Cancer Prevention and Control, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
1997-5/1998 Associate Professor and Chief, Dept. of Cancer Epidemiology, Cancer Institute and Hospital, CAMS/PUMC, Beijing, China
6/1998- Professor and Chief, Dept. of Cancer Epidemiology, Cancer Institute and Hospital, CAMS/PUMC, Beijing, China
2000 National Coordinator for Cervical Cancer Screening in China
2001 Member of Steering Committee, World Alliance of Cancer Research Organizations, Philadelphia, USA
Polymorphisms of Fucosyltransferase Genes and Helicobacter pylori Infection Risk

Nobuyuki Hamajima
Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute
Nagoya, Japan

Helicobacter pylori (HP) infection increases the risk of diseases including peptic ulcer and stomach cancer. Although the infection largely depends on the environmental factors, especially sanitary conditions in childhood, the genetic factors play a role in the infection, as a twin study shows. To date, as well as HLA types, polymorphisms of TNF-A, Lewis (Le, fucosyltransferase 3), secretor (Se, fucosyltransferase 2), IL-1B, and myeloperoxidase have been reported to be possible genetic factors associated with the infection. The latter four genes were found out of fifty polymorphisms screened in Aichi Cancer Center. In this presentation, I focus on the association of polymorphisms of Le and Se with the persistent HP infection.

HP with babA2 gene encoding blood-group antigen-binding adhesin (BabA) has binding activity to Le\(^\text{b}\) and H type I antigens. Se and Le enzymes metabolize Type I precursor into H type I and Le\(^\text{a}\) antigens, respectively. H type I is further metabolized into Le\(^\text{b}\) by Le enzyme. Commonly observed in Japanese are Se1, Se2, Le, and le3 for functional alleles (Se and Le) and sej, se5, le1, and le2 for reduced/no-functional allele (se and le), respectively.

We examined the associations between anti-HP IgG antibody and the above genotypes for 241 non-cancer outpatients, and found that individuals with se\(^\text{e}\)/se & Le/Le genotypes had the lowest seropositivity (33.3%, 9/27) and those with Se\(^\text{e}\)/Se & le/le, Se/Se & Le/le, or Se\(^\text{e}\)/se & le/le genotypes the highest (83.8%, 31/37), and the rest intermediate (62.3%, 109/175 excluding two not genotyped). Sex-age-adjusted OR of being infected relative to the lowest group was 3.34 for the intermediate and 10.21 for the highest.

The expression of Le\(^\text{a}\) and Le\(^\text{e}\) antigens depending on the genotypes was confirmed in gastric foveolar epithelium. These findings suggest that Se and Le genotypes influence the risk of the continued HP infection through the expression of ligands for BabA.
Nobuyuki Hamajima, M.D., Dr. Med. Sci., M.P.H.

Section Head,
Division of Epidemiology and Prevention
Aichi Cancer Center Research Institute
Nagoya, Japan

1980 M. D., Nagoya University School of Medicine
1984 Dr. Med. Sci., Nagoya University Graduate School of Medicine
1984-1986 Research Associate, Department of Preventive Medicine,
Nagoya University School of Medicine
1986-1987 M. P. H., University of Washington,
School of Public Health and Community Medicine, Seattle, USA
1987-1991 Assistant Professor, Department of Preventive Medicine,
Nagoya University School of Medicine
1991-1993 Associate Professor, Department of Public Health,
Gifu University School of Medicine
1992 Visiting Scientist, Department of Public Health,
University of Sydney, Australia
1993-2000 Section Head, Division of Epidemiology,
Aichi Cancer Center Research Institute
2000- Section Head, Division of Epidemiology and Prevention
Helicobacter pylori Is a Promoter of Stomach Cancer rather than an Initiator

Masae Tatematsu
Division of Oncological Pathology, Aichi Cancer Center Research Institute
Nagoya, Japan

In 1994, the World Health Organization/International Agency for Research on Cancer concluded that “Helicobacter pylori (Hp) is a definite carcinogen” based on the epidemiological evidence. For detailed analysis of the role of Hp in stomach carcinogenesis, it is essential to establish a small animal model. We have established experimental models of stomach carcinogenesis in Mongolian gerbils (MGs) using the chemical carcinogens, N-methyl-N’-nitro-N-nitrosoguanidine (MNNG) and N-Methyl-N-nitrosourea (MNU). The lesions were generally well differentiated, although poorly differentiated adenocarcinomas were also found. Hp infection enhances glandular stomach carcinogenesis in MGs treated with MNNG or MNU. Animals with high titers of anti-Hp antibodies are at greatest risk of developing neoplasms. Hp infection and high-salt diet administration are both considered being important factors for gastric carcinogenesis in man. Hp infection exerts stronger promoting effects than a high-salt diet on gastric carcinogenesis, and that the two factors act as synergistically to enhance development of stomach cancer.

Eradication diminishes enhancing effects of Hp infection on glandular stomach carcinogenesis in MGs. Hp eradication may be useful as a prevention approach.

On the other hand, submucosal proliferative tumor-like lesions are also induced in the glandular stomach with Hp infection alone, and often they are similar to carcinomas. To explore if the role of Hp infection is promotion or initiation, we established an experimental model of long term Hp infection and eradication in MGs, without chemical carcinogens. Submucosal tumor-like lesions thereby develop with a phenotypic shift towards intestinalization. Eradication of the bacteria diminished the submucosal tumor-like lesions, so they were considered to be reversible, rather than malignant in character. The role of Hp infection thus appears to be strong promotional influence, rather than initiation of gastric carcinogenesis.
Masae Tatematsu, M.D., Ph.D.

Vice Director and Chief
Division of Oncological Pathology
Aichi Cancer Center Research Institute
Nagoya, Japan

1971 Nagoya City University Medical School
1975 Doctor Degree of Medical Science, Nagoya City University
1975 Staff Doctor, Department of Pathology, Nagoya City Higashi General Hospital
1977 Assistant Professor, First Department of Pathology, Nagoya City University Medical School
1979 Lecturer Professor, First Department of Pathology, Nagoya City University Medical School
1980 Research Fellow, Department of Pathology, University of Toronto
1982 Chief, Department of Pathology, Nagoya City Higashi General Hospital
1986 5th Incitement Award of the Japanese Cancer Association
1990 Chief, Laboratory of Ultrastructure Research, Aichi Cancer Center Research Institute
1993 Chief, Laboratory of Pathology, Aichi Cancer Center Research Institute
2001- Vice Director and Chief, Division of Oncological Pathology, Aichi Cancer Center Research Institute
Effect of Helicobacter pylori Infection and Eradication on the Development of Gastric Cancer

Naomi Uemura
Department of Gastroenterology, Kure Kyosai Hospital
Kure, Japan

Since the discovery of H. pylori, concept of diagnosis and treatment of upper gastrointestinal diseases has been changing greatly from conventional belief. Histological gastritis in human was found to have been attributable to infection with H. pylori, and subsequently various reports indicated that eradication of H. pylori markedly improved inflammatory cell infiltration, characteristic of H. pylori-related gastritis and inhibited recurrence of peptic ulcer. Recently, it has been reported that H. pylori infection is causally related to the incidence and growth of low grade of gastric MALT (mucosa-associated lymphoid tissue) lymphoma and that eradication leads to the regression of MALT lymphoma.

With regard to association with gastric cancer, WHO/IARC stated in 1994 that there is sufficient evidence in humans for the carcinogenecity of infection with H. pylori based on epidemiological evidence and histopathological study. Also, as for impact of eradication on development of gastric cancer, based on a follow-up study on patients who underwent eradication therapy after endoscopic mucosal resection of early gastric cancer (EMR), a possibility of eradication to inhibit the development of metachronous cancer, which occurs in a site different from treated lesion, was reported. Based on this report, remaining gastric mucosa after EMR is positioned as one of the indications of eradication therapy.

In Japan, where the incidence of gastric cancer is the highest in the world, due to its different health care insurance system from Europe and the US, early-stage gastric cancer is more often discovered by endoscopy. In the symposium I will describe about dynamics of H. pylori infection in gastric cancer patients and effect of eradication in Japan.
Naomi Uemura, M.D.

Chief,
Department of Gastroenterology, Kure Kyosai Hospital
Kure, Japan

Education:
1979: Graduated from Faculty of Medicine, University of Hiroshima
1979: Earned Medical Doctor degree, University of Hiroshima
1989: Earned PH.D. degree, University of Hiroshima

Career History:
1 Postgraduate student, University of Hiroshima (Hiroshima, Japan) 1979-1981
2 Postgraduate student, Setoda Hospital (Hiroshima, Japan) 1981-1983
3 Research Fellow, 1st Dept. of Internal Medicine,
   University of Hiroshima (Hiroshima, Japan) 1983-1987
4 Research Fellow, University of Alabama at Birmingham
   (Birmingham, USA) 1987-1989
5 Chief Doctor, Dept of Gastroenterology, Kure Kyosai Hospital
   (Kure, Japan) 1989-1999

Current Professional and Memberships:
1. A member of Japanese Gastroenterology Association
2. A member of Japanese Gastroenterological Endoscopy Association
3. A member of Japanese Internal Medicine Association
4. A member of Japanese Helicobacter Association
Endoscopic Mucosal Resection for Early Gastric Cancer
- Indication and New Techniques, IT Knife Method -

H. Ono
Endoscopy and GI Oncology Division, National Cancer Center Hospital
Tokyo, Japan

Endoscopic mucosal resection (EMR) has been extended for a treatment of early gastric cancer (EGC) in the world, especially in Japan from the beginning of the 1980s. It has an advantage over surgical gastrectomy in patient’s quality of life.

Because EMR is just a local treatment, we should choose appropriate candidates with low possibility of lymph node metastasis. We analyzed about 1,700 patients with solitary, intramucosa, and surgical treated early gastric cancer. An early gastric cancer confined to the mucosa has to meet the following criteria in order to be resected endoscopically: 1. Histologically differentiated adenocarcinoma, 2. Size of less than 30 mm if the tumor has ulcerative changes. (no limitation of the size without ulcer), 3. Absence of lymphatic vascular involvement.

Recently, dramatic developments have occurred in the operational mechanism and design of the accessory apparatus. To obtain the “complete resection” histologically for large and difficult lesions, we developed a special endoscopic knife in 1996 named Insulation-tipped electrosurgical knife (IT knife). This knife can cut submucosa safely and remove a lesion completely. We also developed an improved technique named “PTA-EMR: Percutaneous Traction-assisted EMR”. We raise up a clip attached on the edge of a lesion by a thin retractor through the abdominal wall (like percutaneous endoscopic gastrotomy), and then resect the lesion by IT knife. It can give counter traction to the lesion as well as surgical mucosection and can be carried out without systemic anesthesia.

On the other hand, there is some possibility of complications, such as perforation of the gastric wall and active bleeding. Especially, up to now, a surgical operation has been required to treat them and it causes the deterioration of the patient’s QOL. I introduce how to manage and rescue the patients endoscopically from perforation after EMR without surgical treatment.

At all events, a picture is worth a thousand words. I will show video demonstration of EMR using IT knife and how to treat perforation endoscopically.
Hiroyuki Ono, M.D.

Staff doctor,
Gastroenterology and Endoscopy Division
National Cancer Center Hospital,
Tokyo, Japan

1987  Hokkaido Prefectural Sapporo Medical College (Internal Medicine)
1992  Resident, National Cancer Center Hospital (GI Oncology Division)
1995  Chief Resident, National Cancer Center Hospital (Endoscopy Division)
1997-  Staff Doctor, National Cancer Center Hospital (Endoscopy Division)
Current Status and Future Perspective of Laparoscopic Operation for Early Gastric Cancer

Michitaka Fujiwara
Department of Surgery II, School of Medicine, Nagoya University
Nagoya, Japan

**Background:** Endoscopic mucosal resection (EMR) and laparoscopic wedge resection offer improved quality of life after treatment for early gastric cancer (EGC), but the degree of curability that can be obtained through these procedures in terms of systemic lymph node dissection is severely limited. In 1993, laparoscopy-assisted distal gastrectomy (LADG) with lymphadenectomy emerged as a novel option for treating the EGCs of the middle to lower stomach with potential lymph node involvement. Due to recent refinements in the technique and instruments for laparoscopic surgery, some investigators suggest that LADG can be applied to more advanced disease.

**Where we are today:** Between 1995 and 2001, we have performed 120 laparoscopic operations, including 7 laparoscopic proximal gastrectomies, and one laparoscopic total gastrectomy, for gastric carcinoma that has been diagnosed as confined to the mucosa or the submucosa through endoscopic ultrasonography. The number of patients treated with laparoscopic wedge resection was relatively small at 20, because EMR is primarily indicated for a subset of EGC that is estimated not to have lymph node metastasis. LADG, the most frequently performed procedure under the laparoscopy, was performed in 92 patients. LADG was converted to open surgery in 4 of 92 cases because of uncontrollable bleeding, positive proximal margin, and macroscopic finding of lymph node metastasis (confirmed by frozen section during surgery), but there was no mortality associated with this procedure. When the outcome of these patients was compared with that of the historical control consisting of 80 patients treated with conventional open surgery (1992~1997), no significant differences in the blood loss, morbidity, duration of postoperative fever elevation, and maximum value of CRP were observed. On the other hand, a smaller amount of analgesics was required for the LADG patients who also had better postoperative recovery in terms of the duration before passing of the flatus and ambulation. LADG requires use of costly equipments, but has nevertheless proved less expensive in terms of the total cost required per a patient, due primarily to the shorter hospital stay. These patients have been followed for a mean of 24.8 months (range: 2~58 months). One case from each
group has so far died of the recurrent disease. There was no significant difference in the number of resected lymph nodes. We believe that D2 lymphadenectomy as defined by the Japanese Classification for Gastric Carcinoma can be performed adequately under the laparoscopy, although a longer follow-up time is needed for confirmation of the long-term consequences obtained through this approach.

**Future perspective:** Advanced laparoscopic surgery requires intensive training as well as the use of costly surgical equipments, and can currently be performed only in specialized institutions. Besides constructing an adequate training program, further improvements in surgical devices and navigation systems may facilitate such operation. From this viewpoint, we have started the use of three-dimensional CT angiography for preoperative simulation as well as for navigation during surgery. Further progress in the field of optical technology is warranted.
Michitaka Fujiwara, M.D.

Clinical and Research Associate,
Department of Surgery II
Nagoya University School of Medicine
Nagoya, Japan

1987 M. D., Nagoya University School of Medicine
1987-1988 Resident, Ichinomiya Municipal Hospital, Aichi
1988-1993 Staff Surgeon, Department of Surgery,
Ichinomiya Municipal Hospital, Aichi
1993- Clinical and Research Associate, Department of Surgery II,
Nagoya University School of Medicine
Update of J COG 9501 Study; a Randomized Controlled Trial to Evaluate Para-aortic Lymphadenectomy for Gastric Carcinoma

Yasuhiro Kodera
Department of Surgery II, School of Medicine, Nagoya University
Nagoya, Japan

**Background:** Radical gastrectomy with D2 lymphadenectomy has been a standard procedure for treatment of gastric carcinoma in Japan and is considered responsible for the excellent stage-by-stage survival of these patients. Some patients nevertheless have recurrences in the para-aortic lymph nodes. Long-term survivors have been reported among the population treated with systemic resection of these nodes in several pilot studies.

**Study design:** A multi-institutional randomized controlled trial was performed to compare treatment results of para-aortic lymphadenectomy with those of standard Japanese-style D2 resection. Patients with histologically proven gastric adenocarcinoma who at laparotomy was found to have cancer invasion as far as or beyond the subserosa (≥T2), negative cytology (CY0), and no distant or extensive node metastases (N0~2, M0) were randomized to receive either the standard D2 resection (Group A) or D2 plus extensive para-aortic lymph node dissection (Group B). Primary endpoint of this trial is the overall survival that is to be evaluated after 5 years of follow-up. Secondary endpoints include recurrence-free survival, morbidity, operative mortality, postoperative hospital stay, and QOL.

**Results:** The patient accrual started in June 1995 and was completed in April 2001. A total of 523 patients were randomized into Groups A (n=263) and B (n=260). Cumulative 4-year survival rate was 69.7%. Difference in survival between the 2 groups has not been evaluated at this time. Two deaths due to postoperative complications and another two due to rapid disease progression were observed, hence the overall hospital mortality of 0.8%. Operative time was longer (300 mins versus 237 mins) and bleeding amount greater (660 mL versus 430 mL) for Group B, as has been expected. There was no difference between the groups in the incidence of major surgical complications such as leakage, pancreatic fistula, and intra-abdominal abscess, although complication as a whole was more frequent among Group B. Complications
specific to Group B were paralytic ileus and prolonged lymphorrhea. The mean number of lymph nodes retrieved was 54 (range: 14–161) for Group A and 74 (range: 30–235) for Group B. The mean number of para-aortic lymph nodes resected by the super-extended lymphadenectomy was 25 (range: 4–75).

**Conclusion:** Extended lymphadenectomy with and without para-aortic lymph node dissection is safe and feasible when performed at specialized centers in Japan. Super-extended lymphadenectomy was associated with longer operating time, greater blood loss, and higher incidence of surgical complications. Final survival analyses to assess whether these shortcomings can be compensated for by a significant survival benefit is eagerly awaited.
Yasuhiro Kodera, M.D., Ph.D.

Assistant Professor,
Department of Surgery II,
Nagoya University School of Medicine
Nagoya, Japan

1985 M. D., Nagoya University School of Medicine
1985-1986 Resident, Komaki Municipal Hospital, Aichi
1986-1991 Staff Surgeon, Komaki Municipal Hospital, Aichi
1991-1994 Clinical and Research Associate, Department of Surgery II,
Nagoya University School of Medicine
1994 Ph. D., Department of Surgery II,
Nagoya University School of Medicine
1994-2001 Attending Surgeon, Department of Gastroenterological Surgery
Aichi Cancer Center Hospital
2002- Assistant Professor, Department of Surgery II,
Nagoya University School of Medicine
Surgery and Adjuvant Therapy for Gastric Carcinoma in the U.S.A.

Roderich E. Schwarz
Cancer Institute of New Jersey and Department of Surgery
University of Medicine and Dentistry of New Jersey
Robert Wood Johnson Medical School
New Brunswick, U.S.A.

Gastric cancer, still the predominant cause of cancer death in the U.S. 60 years ago, has significantly decreased in incidence and mortality. Physicians diagnosing or treating gastric cancer in the U.S. are facing specific characteristics and challenges: significant social and ethnic patient heterogeneity, geographic variations in incidence, advanced stages at diagnosis, significant comorbidity, a growing number of elderly patients, and a continuing trend in the prevalence of cardia or proximal disease location. Treatment is increasingly influenced by managed care organizations, and access to specialized cancer centers can be limited. Thus, the majority of patients continue to be treated in a low-volume setting.

Gastrectomy remains the mainstay of therapy for potentially curable gastric cancer. Although radical regional resections, including extended lymph node dissection (ELND), had been utilized here since the middle of the 20th century, ELND is still not widely practiced throughout the country. In a nationwide survey, survival after gastrectomy in the U.S. remains inferior to that obtained in Japan or Western Europe. Specialized centers, however, in which ELND has been routinely applied, are generating stage-adjusted survival after gastrectomy which approaches that achieved in Japanese centers or series. Morbidity and length of hospital stay have continued to decrease during the past decade. Patterns of first recurrence after gastrectomy and ELND suggest that transserosal and hematogenous dissemination are operational in the vast majority of clinical relapses, but isolated regional (nodal) recurrences remain sparse.

A recent U.S. Intergroup trial of postoperative adjuvant chemoradiation followed by chemotherapy (INT 116) has resulted in a significant overall survival and relapse-free survival benefit. While the chemoradiation therapy (CRT) components were well quality-controlled, the operative treatment was not; only 10% of patients underwent formal ELND. CRT appeared to primarily reduce “local” and “regional” recurrences,
and was associated with an increase in the relative frequency of distant relapses. It is unclear whether the radiation component could functionally substitute in part for the limited regional resection extent.

In light of the specific characteristics of gastric cancer treatment in the U.S., one can conclude that: there is room for standardization of quality assurance of operative treatment; postoperative adjuvant chemoradiation therapy has shown a measurable benefit; CRT has not been validated for patients having undergone ELND; and routine use of CRT in different settings (outside the U.S., different recurrence patterns) appears not warranted at this time. Adjuvant therapy strategies should be tested for disease-specific challenges as indicated by dominant relapse patterns.
Roderich E. Schwarz, M.D., Ph.D., F.A.C.S.

Attending Surgeon, Division of Surgical Oncology
Director, Pancreatic Cancer Program
The Cancer Institute of New Jersey
Assistant Professor of Surgery
University of Medicine and Dentistry of New Jersey
Robert Wood Johnson Medical School
New Brunswick, U.S.A.

1978 Abitur, Grosse Schule Wolfenbüttel, Germany
1984 M. D., Medical School Hannover, Germany
1985 Ph. D., Medical School Hannover, Germany
1985-1986 Resident, Abdominal and Transplant Surgery
Medical School Hannover, Germany
1987-1989 Postdoctoral Research Fellow, Pittsburgh Cancer Institute
Pittsburgh, PA
1989-1994 Resident, General Surgery, University of Pittsburgh
Pittsburgh, PA
1994-1996 Fellow, Surgical Oncology, Memorial Sloan-Kettering Cancer Center
New York, NY
1996-2001 Attending Surgeon and Section Head, Upper Gastrointestinal and
Pancreatobiliary Surgery, City of Hope National Medical Center
Duarte, CA
2001-present Assistant Professor of Surgery,
University of Medicine and Dentistry of New Jersey,
Robert Wood Johnson Medical School
New Brunswick, NJ
Ten Year Results of Prospective Randomized D1/D2 Gastric Cancer Trial Limited but Definitive Benefits

C. J. H. van de Velde
Department of Surgery, Leiden University Medical Center
Leiden, the Netherlands

In the Netherlands 80 hospitals participated in a randomized trial to compare morbidity, hospital mortality survival and cumulative relapse risk after D1 versus D2 lymphnode dissection for gastric cancer. Between 1989 and 1993, 996 patients were randomized by the Leiden University Medical Center in a study with extensive quality control in patients with a mean age of 65 years and no age limit. A total of 711 patients underwent the allocated treatment with curative intend. Strict quality control measures were undertaken to avoid interaction of both techniques. All operations were supervised and pathology revised. D2 operations were only performed under supervision of one out of 12 qualified D2-surgeons. D2-patients had higher postoperative mortality and significant more complications, surgery was performed according to the original rules of the JRSGC. Although 5-years survival rates were not different for D1 versus D2 patients(45 versus 47%), D2-patients with N1 disease generally with TNM-stages  invade or  invading A significantly benefited from a D2-dissection. Aspects of selection, sentinel node dissection will be discussed in view of the ten-year follow-up the Dutch Gastric Cancer Trial.
Cornelis J. H. van de Velde, M.D., Ph.D.

Professor,
Department of Surgery,
Leiden University Medical Center
Leiden, Netherlands

1975 M. D., Leiden State University, Netherlands
1977 Ph. D., Leiden State University, Netherlands
Fellow, M. D. Anderson Hospital, Houston
1982 General Surgeon, Leiden University Medical Center
1987 Professor, Department of Surgery
Leiden State University

Awards/Prizes
1978 Faculty Prize for Research
1995 Silver Medal Society of Gastroenterology
1998 European Digestive Oncology Prize
1998 F. R. C. S. London
1999 ESSO Award Vienna
1999 American Commission on Cancer Award Lecturer, American College of Surgeons
2000 Honorary Member Colombian Surgical Society
2000 F. R. C. P. S Glasgow
2000 Member Royal Academy of Sciences of the Netherlands
2001 Honorary Member of the Society of Surgical Oncology
2001 Gold Medal of the Associations of Surgeons of the Netherlands
List of Speakers and Chairpersons

Hiroyuki Aburatani, M.D., Ph.D.  Professor
Genome Science Division
Research Center for Advanced Science and Technology, University of Tokyo
4-6-1 Komaba, Meguro-ku, Tokyo 153-8904
Japan
Phone: 03-5452-5352
Fax: 03-5452-5355
E-mail: haburata-tky@umin.ac.jp

Michitaka Fujiwara, M.D.  Clinical and Research Associate,
Department of Surgery II
Nagoya University School of Medicine
65 Tsurumai-cho, Shouwa-ku, Nagoya 466-8550
Japan
Phone: 052-741-2111
Fax: 052-744-2785
E-mail: mfuji@med.nagoya-u.ac.jp

Parry J. Guilford, Ph.D.  Principal Investigator
Cancer Genetics Laboratory, Department of Biochemistry, University of Otago
Dunedin, New Zealand
Phone: 64-3-4795116
Fax: 64-3-4797738
E-mail: parry.guilford@otago.ac.nz

Nobuyuki Hamajima, M.D., Dr.Med.Sci., M.P.H.  
Section Head
Division of Epidemiology and Prevention
Aichi Cancer Center Research Institute
1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681
Japan
Phone: 052-762-6111
Fax: 052-763-5233
E-mail: nhamajim@aichi-cc.jp
Yasuhiro Kodera, M.D., Ph.D.  
Assistant Professor  
Department of Surgery II  
Nagoya University School of Medicine  
65 Tsurumai-cho, Shouwa-ku, Nagoya 466-8550  
Japan  
Phone: 052-741-2111  
Fax: 052-744-2785  
E-mail: ykodera@med.nagoya-u.ac.jp

Hiroyuki Ono, M.D.  
Staff doctor  
Gastroenterology and Endoscopy Division  
National Cancer Center Hospital  
5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045  
Japan  
Phone: 03-3547-5420  
Fax: 03-5565-1753  
E-mail: hyono@gan2.ncc.go.jp

Ryuzo Ohno, M.D., Ph.D.  
Director  
Aichi Cancer Center Hospital  
1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681  
Japan  
Phone: 052-762-6111  
Fax: 052-764-2963  
E-mail: director@aichi-cc.jp

Youlin Qiao, M.D., Ph.D.  
Professor and Chief  
Department of Cancer Epidemiology  
Cancer Institute and Hospital Chinese Academy of Medical Sciences and Peking Union Medical College (CAMS/PUMC)  
Beijing 100021  
The People's Republic of China  
Phone: +86-10-6771-3648  
Fax: +86-10-6771-3648  
E-mail: qiaoy@public.bta.net.cn
Roderich E. Schwarz, M.D., Ph.D., F.A.C.S  
Attending Surgeon, Division of Surgical Oncology  
Director, Pancreatic Cancer Program  
The Cancer Institute of New Jersey  
Assistant Professor of Surgery  
University of Medicine and Dentistry of New Jersey  
Robert Wood Johnson Medical School  
U.S.A.  
Phone: 732-235-6950  
FAX: 732-235-8098  
E-mail: schwarz@umdnj.edu

Mitsuru Sasako, M.D., Ph.D.  
Chief  
Associate director of the Hospital  
National Cancer Center Hospital  
5-1-1 Tsukiji, Chuo-ku Tokyo 104-0045 Japan  
Phone: 03-3547-5420  
Fax: 03-5565-1753  
E-mail: msasako@ganz.ncc.go.jp

Suketami Tominaga, M.D., Ph.D.  
President  
Aichi Cancer Center  
1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681 Japan  
Phone: 052-762-6111  
Fax: 052-764-2963  
E-mail: tominaga@aichi-cc.jp

Masae Tatematsu, M.D., Ph.D.  
Vice Director and Chief  
Division of Oncological Pathology  
Aichi Cancer Center Research Institute  
1-1 Kanokoden, Chikusa-ku, Nagoya 467-8681 Japan  
Phone: 052-762-6111  
Fax: 052-764-2963  
E-mail: mtatemat@aichi-cc.jp
Naomi Uemura, M.D.  
Chief  
Department of Gastroenterology  
Kure Kyosai Hospital  
Nishi-chuo 2-3-28, Kure 737-0811  
Japan  
Phone: 0823-22-2111  
Fax: 0823-25-1597  
E-mail: n-uemura@mua.biglobe.ne.jp

Toshikazu Ushijima, M.D., Ph.D.  
Chief  
Carcinogenesis Division  
National Cancer Center Research Institute  
5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045  
Japan  
Phone: 03-3547-5420  
Fax: 03-5565-1753  
E-mail: tushijim@ncc.go.jp

Cornelis J. H. van de Velde, M.D., Ph.D.  
Professor  
Department of Surgery  
Leiden University Medical Center  
Leiden 2300, RC  
Netherlands  
Phone: 071-5262309  
Fax: 071-5266750  
E-mail: c.j.h.van_de_velde@lumc.nl