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Special article

Meeting report of the 72nd Japanese Gastric Cancer Congress

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The annual Congress of the Japanese Gastric Cancer Association (JGCA) was held at Niigata, February 17–19, 2000. In spite of the weather forecast for heavy snow in this famous ski district, the 1200 participants enjoyed a perfect blue sky during the 3 days of the meeting.

Since the inauguration of the JGCA in 1997, this has been the first congress organized by a non-surgeon president. H. Watanabe, Professor of Pathology, Niigata University, made every effort to establish a program that a surgeon president would not conceive of, and 8 of the 13 major sessions had a theme related to pathological research. Summaries by the chairmen of the symposia, panels, and workshops are given below.

Chairmen's summary of the symposia, panels, and workshops

Symposium 1. *To what extent is the endoscopic mucosal resection of undifferentiated-type adenocarcinoma allowed?* (chaired by M. Mai, Kanazawa University, and T. Hamada, Social Health Insurance Hospital)

Endoscopic mucosal resection (EMR) of early gastric cancer (EGC) is usually indicated for mucosal carcinoma of differentiated type (Diff). The indication of EMR for carcinomas of undifferentiated type (Undiff; poorly differentiated adenocarcinoma and signet ring cell carcinoma) is controversial. This symposium focused on the possibility of extending the current EMR criteria to Undiff tumors.

It is known that one of the histopathological characteristics of Undiff carcinoma is that superficial ulceration frequently occurs in the IIc area, resulting in the breakdown of the muscularis mucosae, followed by nodal metastasis. It has also been demonstrated that Undiff early cancers are frequently associated with horizontal infiltration into the middle layer of the mucosa. These have been the main reasons why Undiff tumors have not been considered to be suitable for EMR.

The first three speakers discussed the possibility of EMR for Undiff tumors based on retrospective analyses of nodal metastasis in surgical series. J. Fujisaki, Jikei University, Tokyo, and A. Chonan, JR Sendai Hospital, proposed that EMR would be possible in some Undiff tumors, but the number of cases was too small to provide statistical evidence. H. Ono, National Cancer Center Hospital, Tokyo, showed the largest number of surgical cases (426 mucosal, Undiff tumors) and analyzed nodal metastasis. The only category of mucosal Undiff tumors that had no nodal involvement was those smaller than 10 mm and without intra-tumoral ulceration. Even in their large series, there were only 12 cases in this category.

T. Oyama, Saku Central Hospital, Nagano, reported their experience of 17 EMRs for Undiff tumors. The rate of local recurrence was high (17.6%), but additional treatments, including surgery and laser therapy were successful. H. Shimao, Kitasato University, Kanagawa, presented the results of laser therapy for Undiff tumors in patients with high operative risks. Again, the rate of residual disease was high, but the treatment showed good palliative effects. T. Nakamura, Kobe National Hospital, reported photodynamic therapy for Undiff carcinomas. Their new method of 2-consecutive-day therapy was effective for the local control of Undiff tumors.

In the discussion, the following criteria were approved for EMR of Undiff mucosal carcinomas: the tumor is smaller than 5 mm, or smaller than 10 mm without ulcer or ulcer scar; the resection is one-piece,

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not piecemeal; and the resection margin is wider than that for the usual EMR.

These are rather rare tumors, and in order to extend the criteria, we need to collect a large number of cases to provide statistical evidence. Collaborative studies by leading hospitals are essential. (Reported by *M. Mai*)

Symposium 2. *The significance of gastric and intestinal mucin phenotype in differentiated gastric cancer* (chaired by T. Shimoda, National Cancer Center Hospital, Tokyo, and Y. Ajioka, Niigata University)

Gastric cancer is histologically classified into two major types: differentiated (D-ca) and undifferentiated (UD-ca) types, by Nakamura; and intestinal and diffuse types, by Lauren. The differentiated type corresponds to the intestinal type and the undifferentiated type corresponds to the diffuse type. However, mucin histochemical and immunohistochemical examinations have recently demonstrated that gastric cancers consist of three mucin phenotypes; gastric, intestinal, and gastrointestinal mucin phenotypes. The gastric foveolar mucin phenotype is detected by immunostaining with gastric mucin (45 M1 or MUC 5AC) antibody, and pyloric gland type mucin is demonstrated by immunostaining with MUC 6 antibody or by mucin histochemical staining with paradoxical concanavalin A type III horseradish peroxidase. Another mucin protein MUC 2 characterizes goblet cell differentiation, and the CD 10 antibody is localized to the brush border of the small intestine and intestinal metaplastic glands. The significance of the gastric and intestinal mucin phenotypes in differentiated gastric cancer was reported and discussed in this symposium.

A. Saito, National Cancer Center Hospital, Tokyo, reported the relationship between the histological types of tumor (D-ca, UD-ca, or mixed type) and the mucin phenotypes in early gastric cancers (EGCs). The vast majority of EGCs smaller than 5 mm are D-ca, while in larger EGCs, the proportions of D-ca and UD-ca are similar, which suggests histological conversion from D to UD according to tumor growth. In EGCs with the gastric or the gastrointestinal mucin phenotype, D-ca accounted for 75% of tumors smaller than 10 mm, but for only 29% of tumors larger than that. In EGCs with the intestinal mucin phenotype, however, the proportion of D-ca did not change according to the tumor size. This suggests that the histological conversion from D-ca to UD-ca occurs mainly in tumors with the gastric mucin phenotype.

T. Takizawa, Tokyo Metropolitan Komagome Hospital, reported that, in D-ca, papillary adenocarcinoma was associated with a higher incidence of expression of the gastric mucin phenotype and a higher incidence of lymph node metastasis than well differentiated adenocarcinoma. They emphasized that papillary adenocarcinoma should be treated as a highly malignant tumor.

R. Kushima, Shiga University of Medical Science, studied intestinal metaplasia, adenomas, and well differentiated adenocarcinomas, employing various molecular methods, including the detection of loss of heterozygosity (LOH) of microsatelite or *APC* genes on 5q21. They suggested different histogenetic pathways in tumors with the gastric and intestinal mucin phenotypes.

Y. Endo, Yamagata University, demonstrated E-cadherin mutation in exon 9 in some D-ca with the gastric mucin phenotype. They suggest that these tumors convert from D-ca to UD-ca in an early stage of progression.

In conclusion, this symposium highlighted that gastric adenocarcinoma could be classified into gastric and intestinal types according to the mucin phenotype, and emphasized that tumors with different phenotypes show different histogenesis and clinical behavior. (Reported by *T. Shimoda*)

Symposium 4. *Clinical application of information from experimental gastric carcinogenesis studies* (chaired by M. Tatematsu, Aichi Cancer Center Research Institute, and K. Miwa, Kanazawa University)

Almost all important studies of experimental gastric carcinogenesis have been performed in Japan. This symposium focused on the clinical application of data accumulated regarding experimental gastric carcinogenesis.

M. Kurihara, Showa University, Tokyo, summarized the development of experimental canine cancer models. Gastric carcinoma induced by N-ethyl-N′-nitro-N-nitrosoguanidine (ENNG) in the dog closely mirrors human gastric cancer, and the value of using canine tumors in studies of chemotherapy was discussed. Epidemiological cohort studies have established that, after distal gastric resection, there is a higher risk of gastric carcinoma. It is likely that a main contributory factor is the excessive duodenogastric reflux caused by the surgery. T. Hattori, Shiga University of Medical Science, reported that primary duodenogastric reflux through the pylorus also induced carcinomas in gastric antrum that had not been subject to surgery. K. Miwa, Kanazawa University, employed a jejunal pouch interposition or Roux-en-Y (RY) after partial gastrectomy to prevent reflux of duodenal juice. These clinical procedures led to a significantly lower incidence of positivity for *Helicobacter pylori*, which is related to gastric cancer.

Gene therapy could potentially revolutionize the treatment of gastrointestinal tract cancer. N. Matsukura, Nippon Medical School, Tokyo, has attempted

to establish a practical method of gene transfer, which would be applicable to human gastric cancer. The *Ad.CAGHSV-TK* gene was introduced into primary tumors and regional lymph nodes of the stomach in dogs by in-situ transfer with endoscopy. *Ad.CAGHSV-TK*/ganciclovir in-situ suicide gene therapy induced apoptosis and fibrosis in rat stomach cancers. Combination treatments of surgery and molecular biological methods (gene therapy) may be applicable to human gastric cancer in the near future. M. Tatematsu, Aichi Cancer Center Research Institute, showed that *H. pylori* enhanced glandular stomach carcinogenesis in Mongolian gerbils treated with chemical carcinogens and that the eradication of *H. pylori* may be useful as a preventive approach against stomach cancer. Tumor-like lesions induced by *H. pylori* alone disappeared after its eradication.

These data for experimental gastric cancer presented in this symposium clearly indicate that prevention of reflux of duodenal juice and eradication of *H. pylori* seem to be quite important for the prevention, of human gastric cancer, with the possibility of gene therapy as a treatment approach. (Reported by *M. Tatematsu*)

Symposium 5. *Differentiated-type versus undifferentiated-type gastric cancers: correlation between clinicopathological characteristics and molecular biological alteration* (chaired by M. Ogawa, Kumamoto University, and A. Ochiai, National Cancer Center Research Institute East, Kashiwa)

Gastric cancer is classified into two types, differentiated and undifferentiated, from its morphological and biological aspects. Clinicopathological evidence has accumulated that differentiated-type gastric cancer cells forming a glandular structure is manifested by frequent hematogenous metastasis, and undifferentiated-type cancer cells showing loose cell-to-cell adhesion is manifested predominantly by peritoneal dissemination. This symposium focused on the characterization of both types of gastric cancers, based on molecules detected by recent molecular biological technology.

Y. Kitadai, Hiroshima University, presented their findings regarding the relationship among *Helicobactor pylori* infection, the histology of gastric cancer, and the extent of atrophic gastritis or intestinal metaplasia. The *H. pylori* infection rate is associated with gastric cancer, and the extent of both atrophic gastritis and intestinal metaplasia is significantly correlated with differentiated-type gastric cancers. Y. Nabeya, Chiba University, reported the induction of *H. pylori*-induced mono ADP ribosilation in gastric cancer cells. They found two ADP-ribosilated proteins in gastric cancer cell lines, but not in colon cancer cell lines.

Tumor angiogenesis may play an important role in both types of gastric cancer. Y. Maehara, Kyushu University, reported a correlation between the expression of vascular endothelial cell growth factor (VEGF) and transforming growth factor beta 1 (TGFβ-1) and histological type in gastric cancers. They found that differentiated-type cancers showed high VEGF expression, while the undifferentiated type showed TGFβ-1 expression and infiltrative growth. Y. Takahashi, Kanazawa University, reported a close association between the expression of VEGF in tumor cells and PD-ECGF in macrophages surrounding tumor cells, and differentiated-type histology.

S. Shimada, Kumamoto University, reported a close correlation between the expression of glycogen phosphorylase (BGP) and differentiated-type cancers with production of intestinal-type mucin. K. Miyachi, Dokkyo University, compared the expression of telomerase-mRNA and telomerase activity in both histological types of gastric cancers and found that the expression of telomerase, and telomerase activity, were significantly higher in differentiated-type gastric cancers, as well as in their surrounding mucosa. These data indicated the presence of different carcinogenic pathways for these two histological types of gastric cancers.

Cell-cell and cell-matrix adhesion systems are also involved in cancer cell biology and morphology. Y. Doki, Osaka University, investigated the function of IQGAP, a low-molecular weight G protein, in an E-cadherin-mediated cell adhesion system and found that aberrant localization of IQGAP and loss of α-catenin expression may cause dysfunction of the E-cadherin-mediated cell adhesion system in undifferentiated-type gastric cancer. Y. Ishii, Keio University, reported an inverse correlation between beta 4 integrin expression and peritoneal dissemination, both in vitro and in a peritoneal dissemination animal model. A significant inverse correlation between these factors was also found in surgical specimens.

In summary, this symposium highlighted the difference between differentiated- and undifferentiated-type gastric cancer detected on the basis of molecules developed by recent molecular technology. The use of only the molecules discussed in this symposium could not elucidate the mechanism of the morphological and biological differences between these two types of gastric cancers, but the findings indicated a new direction for research to help us understand the biology of gastric cancer. (Reported by *A. Ochiai*)

Symposium 6. *Basic research work and its clinical application for patients with gastric cancer* (chaired by M. Mori, Kyushu University, Beppu, and H. Tahara, Tokyo University)

The purpose of this symposium was to introduce new methodologies for the treatment of gastric cancer. In particular, the symposium focused on the clinical applications of new evidence derived from basic research on gastric cancer. Five papers were presented.

T. Sekikawa, Hiroshima University, presented ways of evaluating the sensitivity of anticancer drugs in individual patients. He first studied the correlation between the expression profiles of five genes relating to anticancer drug sensitivity in cell lines and the actual in-vitro efficacy of the anticancer drugs. With the results of this work, he expanded the study to clinical patients. Preliminary results demonstrated the usefulness of the expression profile study in clinical gastric cancers for determining the most appropriate anticancer drugs for each patient.

Peritoneal dissemination is one of the major problems in the treatment of patients with gastric cancer. Two presentations were related to the treatment of peritoneal dissemination; one regarding the use of a new drug and the other regarding gene therapy. Y. Otani, Keio University, Tokyo, reported that marimastat, a matrix metalloproteinase inhibitor, inhibited metastatic lesions in the peritoneum of BALB/c nude mice, producing tumor dormancy in the mice. A. Mori, Kyoto University, reported that the inhibition of the VEGF/Flt-1 system by means of HVJ-liposomes inhibited peritoneal dissemination in mice, probably via an anti-angiogenic function. These two studies should provide useful strategies to overcome peritoneal dissemination, because the methodologies were quite simple. However, there were several problems with both types of treatment, and further studies are needed to translate the findings for practical use.

The two other studies in this symposium were related to tumor-specific immunotherapy. Y. Obata, Aichi Cancer Center, Nagoya, reported the identification of gastric cancer antigens by the SEREX expression cloning method. He identified 136 antigens, and these could become target genes for cancer-specific immunotherapy. He investigated these antigens to determine those that could be detected only in cancer patients. This method should be useful to identify new cancer-specific antigens. N. Sadanaga, Kyushu University, Beppu, reported a clinical trial of tumor-specific immunotherapy for patients with gastric cancer. He prepared dendritic cells from the patients, pulsed them with MAGE-peptides, and injected them into the patients. No side effects were recognized in any patients. Immunological study disclosed that four of seven patients showed the induction of MAGE-peptide specific cytotoxic T lymphocytes. A reduction in serum tumor markers was recognized in most patients, and imaging showed a minute response in three patients. This is the first trial in the world of tumor-specific immunotherapy for patients with gastric cancer.

All five presentations were exciting, and will open up new avenues in the strategy of gastric cancer therapy. However, some methodologies were still experimental. The chairpersons hope that these new treatment modalities will come into the practical use very soon. (Reported by *M. Mori*)

Panel 1. *Treatment of gastric lymphoma: the front line* (chaired by T. Sano, National Cancer Center Hospital, Tokyo, and R. Narisawa, Niigata University)

The diagnosis and treatment of gastric lymphoma has seen a revolutionary change since the introduction of the concept of mucosa-associated lymphoid tissue (MALT) lymphoma. Evidence has accumulated that the eradication of *Helicobacter pylori* induces the remission of some MALT lesions. Although surgery has always played a central role in the treatment of gastric lymphoma, the roles of chemotherapy and radiotherapy have grown. These various situations seem to confuse clinicians who seldom encounter this disease, and this Panel Discussion was organized to clarify the currently available facts.

As an introduction to the Panel, S. Nakamura, Aichi Cancer Center, reviewed the history of the histological classification of gastric lymphoma, with special reference to MALT lymphoma. In Japan, the diagnosis of "reactive lymphoid hyperplasia" had been employed until the introduction of the MALT concept, and he explained, for the benefit of clinicians, the compatibility of these terms. T. Doi, National Shikoku Cancer Center Hospital, Matsuyama, presented their recent research on molecular markers in gastric lymphoma. They studied tissue telomerase activity, hTERT, FISH, and apoptosis-inducing proteins and compared the relationship of these factors with the clinical course of the disease. They suggested a future role in the use of these markers in therapeutic decision-making concerning gastric lymphoma.

The treatment choice for gastric lymphoma has been the subject of great controversy, because the different modalities of surgery, chemotherapy, and radiotherapy are all effective to some extent in various stages of the disease. Two surgeons presented their retrospective case series, in which surgery played the central role. S. Hokita, Kagoshima University, analyzed findings for 82 B-cell and 5 T-cell gastric lymphoma patients, and T. Oshiro, National Kyushu Cancer Center, Fukuoka, reported 62 patients. In both these series, early-stage lymphomas showed an excellent outcome following surgery alone, while chemotherapy had a supportive or primary role for advanced stage disease. Both surgeons emphasized the importance of histological grading and accurate staging before a treatment decision is made.

Non-surgical treatment modalities were then highlighted in three presentations. According to T. Kato, Niigata Cancer Center Hospital, the eradication of *H. pylori* alone induced complete tumor disappearance in the majority of patients with low-grade MALT lymphoma, while chemotherapy brought about a complete response with long-term survival in many patients with high-grade, aggressive lymphoma. He warned surgeons to be more careful in deciding on surgical treatment as the primary modality. M. Fujishiro, National Cancer Center Hospital, Tokyo, showed their experience of *H. pylori* eradication in 49 patients with low-grade MALT lymphoma followed by close endoscopic observation. Complete histological response was achieved in 71% of the patients and complete endoscopic response was achieved in 44%. One patient, however, showed tumor regrowth and subsequently underwent surgery. They demonstrated that the timing to start additional treatments following the failure of eradication treatment was difficult to decide. A. Ohtsu, National Cancer Center East, Chiba, presented a newly commenced phase II multi-institutional prospective study to evaluate non-surgical treatments for gastric lymphoma. The protocol consists of two regimens: for low-grade MALT lymphoma, *H. pylori* eradication, and irradiation if residual tumor is present; and for aggressive lymphoma, CHOP and irradiation. They plan to recruit 55 patients.

In the final discussion with the panel, it was agreed that histological differentiation between low-grade MALT and aggressive lymphoma is essential, and that the roles of surgical and non-surgical treatments should be evaluated further in prospective studies. (Reported by *T. Sano*)

Panel 2. *Clinical significance and prediction of lymph node micrometastasis in gastric cancer* (chaired by T. Aikou, Kagoshima University, and M. Kitajima, Keio University, Tokyo)

This panel focused upon four main points: (1) the clinical significance of lymph node micrometastasis, (2) the detection rates of lymph node micrometastasis by various methods, (3) the prediction of lymph node micrometastasis by biological examination using biopsy specimens, and (4) the presence of lymph node micrometastasis in sentinel node navigation surgery.

The clinical significance of lymph node micrometastasis is, at present, evaluated by patients' outcome. J.R. Izbiki, Hamburg University, Germany, emphasized that nodal micro-dissemination was an independent prognostic factor. M. Sasako, National Cancer Center Hospital, Tokyo, reported that lymph node micrometastasis did not influence 5-year and 8-year survival rates in patients with T2 tumor, compared with rates in those without micrometastasis. S. Natsugoe, Kagoshima University, defined "micrometastasis" as a cluster of tumor cells with stromal reaction, and "tumor cell microinvolvement" as individual tumor cells without a stromal reaction. The latter was clinically more significant than the former in paraaortic lymph nodes.

The detection rate of micrometastases by various methods was problematic. M. Mori, Kyushu University, Beppu, reported that the positive detection rate increased from 20% by histological examination to 60% by reverse transcription-polymerase chain reaction (RT-PCR) examination. H. Ajisaka, Kanazawa University, and S. Natsugoe also stressed that the RT-PCR method was superior to immunohistochemical examination for the detection of lymph node micrometastasis. However, some problems with RT-PCR examinations, such as the type of primer that is suitable and the way we can deal with false positive results should be solved by further studies.

Concerning the prediction of lymph node micrometastases, Y. Takahashi, Kanazawa University, clarified that mRNA expression of collagenase and E-cadherin in biopsy specimens, determined by in-situ hybridization, was related to metastases harbored in lymph nodes. S. Natsugoe also reported that the reduced expression of E-cadherin and α-catenin in biopsy specimens correlated with the presence of lymph node micrometastasis. It is important to evaluate tumor properties prior to surgery in the planning of the treatment approach. Further examination should be carried out in many patients, especially in patients with early gastric cancer.

Recently, sentinel node navigation surgery has been introduced for carcinomas of the gastrointestinal tract. Y. Kitagawa, Keio University, Tokyo, reported that they were able to identify sentinel nodes in all patents by a radioisotope method. Lymph node metastasis was found only in sentinel nodes in four of five patients with involved nodes. H. Ajisaka reported that the number of involved nodes shown in sentinel nodes by RT-PCR examination was three times that shown by routine histological examination. M. Mori presented details of a rapid RT-PCR technique that can be used during surgery. The presence or absence of lymph node micrometastases must be clarified when sentinel node navigation surgery is performed.

This panel presentation can be summarized as follows. First, we should establish a definition of the term "micrometastasis", considering its clinical importance. With this definition, lymph node micrometastasis in a large number of patients could be evaluated. Second, the biological properties of individual tumors seem to be an important factor for the prediction of lymph node micrometastasis. In sentinel node navigation surgery, some new techniques, such as rapid

immunohistochemistry and RT-PCR examination, could facilitate the detection of micrometastasis during surgery. Finally, the most important point to be clarified is the impact of micrometastasis on clinical practice. To date, nobody has the precise answer, and all participants in the panel agreed that continued studies were necessary on this important issue. (Reported by *T. Aikou*)

Panel 3. *Strategies for treating gastric cancer in stage IIIb and IV: from the viewpoint of evidence-based medicine* (chaired by S. Yoshida, National Cancer Center East, Kashiwa, and T. Yamaguchi, Kyoto Prefectural University of Medicine)

Because the 5-year survival rate of patients with advanced gastric cancer without serosal invasion has been extremely good (near 80%) in recent years in Japan, the remaining problem should be how to treat those with serosal invasion. In this sense, our session presented a very good opportunity to reach a consensus regarding the strategy for treating patients with such advanced disease. As a keynote address from the surgical point of view, T. Ochiai, Chiba University, presented a retrospective comparison between patients treated with D2 lymphadenectomy (693 cases) and those treated with D3/D4 lymphadenectomy (127 cases). In their series, no clinical benefit of D3/D4 was observed in those at stage IV, although there was a clinical benefit in those at stage III. Because these were results from retrospective observations, which could include a selection bias, he concluded that the indications for D3/D4 should be very limited. From the viewpoint of medical oncology, N. Boku, National Cancer Center East, Kashiwa, presented the results of the recent phase III study, of Japan Clinical Oncology Group (JCOG)9205, in which no significant differences were observed in survival time between patients receiving regimens of 5-fluorouracil (5-FU) alone and 5-FU + cisplatin (CDDP). Accordingly, he concluded that 5-FU alone could still be regarded as a standard regimen, theoretically, although it was not realistic in terms of daily clinical work. Also, he proposed minimum requirements of efficacy for systemic chemotherapy, considering the latest results in phase II studies of CPT-11 + CDDP, TS-1, and so on, to be a median survival time (MST) of more than 240 days and a 2-year survival rate of more than 10%. Because their results were the same as the results with noncurative surgery, he insisted that those in stage IV, for whom operation would be expected to end noncuratively, should be treated with chemotherapy as the first choice.

Concerning the efficacy of adjuvant chemotherapy for those in stages IIIb and IV, J. Sakamoto, Aichi Prefectural Hospital, commented that it was not yet confirmed in Japan, because positive data had been obtained only from nonrandomized studies or subset analysis in randomized trials. T. Nakajima, Cancer Institute Hospital, Tokyo, commented on the surgical indications for good responders to systemic chemotherapy among patients with far-advanced disease. He reported that a 5-year survival rate of 56% was achieved only in those who had undergone R0 operation (n = 10), and the remaining 21 patients all died within 1 year after surgery. He therefore concluded that the surgical indications may be for patients who have neither liver nor peritoneal metastasis and whose metastatic nodes could be completely removed by surgery. Y. Arai, Aichi Cancer Center, Nagoya, who developed a technique of arterial redistribution as an application of interventional radiology, reported the efficacy of arterial infusion therapy, using this technique for patients with liver metastasis. In his series of phase II trials, the response rate and MST were much better in his single institutional study than in multicenter trials (72% vs 56% response rate, and 15.0 months vs 10.3 months MST), indicating the importance of learning skill.

It is common knowledge that patients with peritoneal dissemination are not candidates for surgery. Nevertheless, Y. Yonemura, Kanazawa University, demonstrated that a 5-year survival rate of 38% (n = 11) was achieved in patients with limited peritoneal metastasis when they were treated with subtotal peritonectomy without macroscopic tumor residue, combined with continuous hyperthermic peritoneal perfusion and intra- and postoperative high-dose intraperitoneal chemotherapy.

From the above, the topics considered to advance evidence-based medicine (EBM) for patients in stage IIIb or IV were summarized as follows: (1) to clarify the surgical indications, (2) to clarify the effectiveness of adjuvant chemotherapy, (3) to clarify active chemotherapeutic regimens, and (4) in order to make a breakthrough in EBM, to clarify the efficacy of newly developed therapies with specialized techniques, such as arterial infusion or multidisciplinary approaches to peritoneal dissemination. (Reported by *S. Yoshida*)

Panel 4. *Risk of second malignancies after gastrectomy for stomach cancer: results of a long-term follow-up of comparative studies* (chaired by K. Yoshino, Tokyo Dental College, and H. Furukawa, Sakai City Hospital)

This panel focused on the incidence and the risk of second malignancies after treatment of stomach cancer, with special reference to the results of a long-term follow-up of comparative studies.

Y. Seto, University of Tokyo, investigated the differences in the incidence of second malignancy in relation to surgical procedures and reconstruction methods. He concluded that the size of gastric resection

and the type of reconstruction did not affect the incidence of second malignancy. T. Yoshikawa, Nagaoka Chuou General Hospital, presented findings on the incidence of multiple primary cancer after gastrectomy on long follow-up. In the past 10 years, 1263 patients who had undergone gastrectomy were followed-up, and 60 second malignancies were detected. Thirty-one of the 60 patients died, and 24 of the deaths were caused by the second malignancy. He reported that periodic routine examinations after the initial gastrectomy had enabled early detection of second malignancies in many patients.

Y. Yamashita, Hiroshima University, investigated esophageal carcinogenesis after gastrectomy through manometric analysis and pH monitoring. He suggested that duodenal fluid reflux with high pH into the lower esophagus, particularly with Billroth II reconstruction, could induce esophagitis and cancer. J. Fujimoto, Osaka University, reported that the incidence of second malignancy could be increased by adjuvant chemotherapy after gastrectomy. After the long-term follow-up of two studies of adjuvant chemotherapy (1975–1981; with mitomycin C, and mitomycin C + 5-FU), they found a second malignancy in 5 of 84 patients (6%) treated with surgery alone, and in 12 of 75 patients (16%) treated with surgery and chemotherapy.

I. Honda, Chiba Cancer Center, performed multivariate analysis on the risk of metachronous multiple cancer in a total of 512 patients who had undergone gastrectomy for early gastric cancer between 1977 and 1988. Among several parameters analyzed, including sex, histological type, and adjuvant chemotherapy, only a hereditary background of malignancy was significantly related to second cancers. H. Furukawa, Sakai City Hospital, reported the risk of second malignancy after adjuvant chemotherapy in a retrospective study and in a randomized controlled study. In the retrospective study, the observed number of second malignancies was compared with the expected number, calculated by the person-year method, and the relative risk was not high in patients treated with adjuvant chemotherapy. In the randomized study, the hazard ratio of a second malignancy in patients with adjuvant chemotherapy was 1.5, but this risk was not significant.

After these presentations, H. Tsukuma, medical statistician at Osaka Medical Center for Cancer and Cardiovascular Diseases, gave a lecture concerning the methods of statistical analysis of the risk for second malignancy. He emphasized the importance of correct follow-up data, and explained the differences in appropriate methods to be used for retrospective studies and prospective randomized studies.

The panel concluded that there is no clear evidence that adjuvant chemotherapy increases the risk of second malignancy, although some of the speakers, as well as audience members, believe that chemotherapy does increase this risk. The risk of a second malignancy should be studied as a secondary endpoint in randomized controlled trials of adjuvant chemotherapy. (Reported by *H. Furukawa*)

Workshop 1. *The present status and the future perspectives of immunochemotherapy for gastric cancer, from the viewpoint of the functioning mechanism* (chaired by M. Kaminishi, University of Tokyo, and Y. Maehara, Kyushu University, Fukuoka)

This session focused on the functioning mechanism of immunochemotherapy for gastric cancer. Six of the most up-to-date papers were presented; the first presentation concerned the activity of enzymes which metabolize an anticancer drug; there were two studies on apoptosis, one on genetic polymorphism, and one on cytokines, and the last study was a meta-analysis of immunochemotherapy.

K. Yoshida, Hiroshima University, reported on the expression and activity of thymidylate synthase (TS) and dihydropyrimidine dehydrogenase (DPD) in 98 gastric carcinomas, using immunohistochemical staining. In the TS-positive group, the patients treated with 5-fluorouracil (5-FU) chemotherapy had a better prognosis than those without chemotherapy. In patients with far-advanced or recurrent disease, DPD activity and chemosensitivity for 5-FU was inversely correlated. These results suggested the usefulness of determining TS and DPD activity in regard to examining the efficacy of chemotherapy.

S. Tsujitani, Tottori University, reported that apoptosis-regulating proteins were related to the effects of imunochemotherapy for gastric cancer. In curatively operated patients with gastric carcinoma invading the serosa, postoperative chemotherapy, including 5-FU, prolonged the survival of patients with p53-negative, p21-negative, and Bax-positive cancer cells. Y. Sugiyama, Gifu University, reported that combined therapy of lentinan with low-dose CDDP/5-FU increased the number of apoptotic cells in gastric cancer cell lines. In a clinical trial, this combined therapy was useful, with few side effects.

M. Yano, Osaka University, presented findings on the relationship between genetic polymorphism of NAD(P)H:quinone oxidoreductase (NQO1), which activates mitomycin C (MMC), and the chemosensitivity of gastric cancer cells to MMC. The IC50 of MMC in the wild-type was lower than that in heterozygote or homozygote. T. Fujimoto, Kanazawa University, studied cytokine dynamics in ascites after the intraperitoneal injection of MMC and OK-432. OK-432 induced interleukin-12 and interferon-γ, cytokines which may contribute to the anticancer effects.

J. Sakamoto, Aichi Prefectural Hospital, evaluated the effect of PSK, in a meta-analysis of nine randomized trials, including 5288 patients with gastric cancer. Adjuvant immunochemotherapy with PSK prolonged patient survival, especially in those with positive PPD and low IAP.

All these presentations profiled the functioning mechanism of immunochemotherapy for gastric cancer. They pointed out the advantages of each therapy and the problems that need to be solved in the future. Through these studies, type-oriented immunochemotherapy would be further developed. (Reported by *M. Kaminishi*)

Workshop 3. *Carcinoma of the gastric cardia* (chaired by M. Koike, Tokyo Metropolitan Komagome Hospital, and T. Nishimaki, Niigata University)

This workshop focused on carcinoma of the gastric cardia, including both adenocarcinoma and squamous cell carcinoma of the esophagus arising within 2 cm from the esophagogastric junction. The pathological analyses presented here in this session were mainly directed to adenocarcinoma of the gastric cardia, while squamous cell carcinoma was analyzed only from the viewpoint of surgery. Carcinoma of the gastric cardia was found most frequently among aged men in each of the institutes in this workshop.

Y. Tajima, National Cancer Center, Tokyo, analyzed the phenotype of mucin production in carcinoma of the gastric cardia in comparison with the phenotypes in carcinoma arising from other parts of the stomach and adenocarcinoma arising in Barrett's esophagus. Mucin production of the "gastric" phenotype was most frequently observed in adenocarcinoma of the gastric cardia (AGC), followed in descending order of frequency, by other gastric carcinomas (ANGC) and carcinoma in Barrett's esophagus (AB). Mixed "gastric" and "intestinal" phenotype was most frequent in AB, followed by ANGC and AGC. Intestinal metaplasia (IM) of the surrounding mucosa adjacent to the cancer was less frequent in carcinoma of the gastric cardia than in the other gastric carcinomas. Such a tendency was also reported by Y. Ohkura, Saitama Cancer Center, except that carcinoma with pure "gastric" phenotype was rare in his study.

N. Tuji, Osaka Medical Center for Cancer and Cardiovascular Diseases, analyzed the background mucosa in relation to IM, and suggested that carcinomas of the gastric cardia may include those arising in the original cardiac gland mucosa and in highly intestinalized mucosa. The incidence of papillary adenocarcinoma was high in AGC. However, A. Kawaguchi, Shiga University of Medical Science, mentioned that staining with high iron diamine-alcian blue showed the same incidence of positivity in AGC and AB, suggesting that the both AGC and AB had their origins in intestinal metaplasia. Furthermore, adenocarcinoma of the lower esophagus showed higher positivity for cyclin-D1 than did AGC and AB.

The clinicopathological aspects, especially concerning lymph node metastasis in carcinoma of the gastric cardia, were analyzed by surgeons; F. Miyazono, Kagoshima University, and K. Ohta, Cancer Institute Hospital.

In the future, it will be important to investigate the normal histology and the physiological aspects of the esophagogastric junction, especially in regard to differences between the cardiac gland mucosa and the esophageal cardiac gland. Furthermore, diagnostic criteria should be standardized among pathologists (through an overview of identical specimens); this will lead to an understanding of the histogenesis of adenocarcinoma in the gastric cardia. (Reported by *M. Koike*)