Special article

Meeting report of the 76th Congress of the Japanese Gastric Cancer Association

NOBUAKI KAIBARA, YOSHIHIDE OTANI, HARUHIRO INOUE, YOSHIHIKO MAEHARA, MICHIO KAMINISHI, WATARU YASUI, YUTAKA TAKAHASHI, HIROKI YAMAUE, YOSHITAKA YAMAMURA, MASAHIRO HIRATSUKA, SHIGEAKI YOSHIDA, TAKANORI HATTORI, WASABURO KOIZUMI, KENTARO SUGANO, TSUKASA TSUNODA, KOSEI HIRAKAWA, SUMIO MATSUMOTO, and TOSHIRO KONISHI

Introduction

The 76th Congress of the Japanese Gastric Cancer Association (JGCA) was held at the Yonago Convention Center “Big Ship,” Tottori, March 4–6, 2004. Although the JGCA annual meeting usually takes place in February, we postponed the meeting to early March to avoid traffic congestion due to heavy snow in the region. Ironically, after exceptionally fine weather in February, snow fell in March, and flights from all over Japan were disrupted. Nevertheless, 1800 physicians and researchers attended the congress, and 664 papers (the largest number in the history of the congress) were presented.

We set the main theme as “Cooperation in Asia”, and organized two international symposia to promote better understanding of gastric cancer disease in Asian countries. We also invited two distinguished doctors for special lectures: Professor Hideaki Tahara, Institute of Medical Science, University of Tokyo, Japan for “Dendritic cells; biology and their potential in cancer immunotherapy”, and Professor Stephen B. Howell, University of California, San Diego, California, United States, for “Copper transporters mediate uptake and efflux of the platinum drugs.”

Discussions about some of the main topics of the congress are summarized below by the chairpersons of each session.

Special symposium 1. *Frontline of sentinel lymph node biopsy for gastric cancer* (chaired by S. Kitano, Oita University, and Y. Otani, Keio University, Tokyo)

The sentinel node (SN) is the lymph node (LN) that receives the first lymph flow from a malignant tumor, and SN biopsy specimens are taken to determine whether standard lymphadenectomy can be avoided in patients with clinically node-negative cancer.

Six speakers made presentations. Y. Kitagawa, Keio University, explained the historical background and the current status of SN biopsy for gastric cancer. SN biopsy

for gastrointestinal tract cancer was introduced in 1999 in Japan. Already 127 out of 458 member institutes of the JGCA which answered a JGCA questionnaire have started using SN biopsy or planned to introduce it in clinical practice. Y. Kitagawa emphasized, at the end of his presentation, that large-scale clinical trials were indispensable to confirm the feasibility of SN biopsy. T. Fujimura, of Kanazawa University, presented their original method of “lymphatic basin dissection”, using intraoperative endoscopic lymphatic mapping (IELM). Y. Uenosono, Kagoshima University, referred to the appropriate size of radioactive colloids as tracers for SN detection. H. Hayashi, of Chiba University, noted the advantages of a combined dye and radioactive colloid method for laparoscopic SN biopsy. I. Miyashiro, Osaka Medical Center for Cancer and Cardiovascular Diseases, presented the procedure and results of a dye method using indocyanine green (ICG). The final speaker, H. Nimura, of Jikei University, presented a method of SN detection by infrared ray, which made ICG-stained green nodes in fat tissue more visible.

After these presentations, five updated subjects of interest for SN biopsy were discussed by six speakers: (1) the appropriate stage of gastric cancer for an SN biopsy indication, (2) selection of tracers — radioactive colloid or dye, (3) timing of and method for the injection of tracers under the lesion, (4) methods for collecting radioactive or dye-stained LNs — simple isolation of the node from fat tissue, or lymphatic basin dissection, (5) diagnosis of positive nodes — microscopic observation of H&E-stained or cytokeratin-immunostained sections, or reverse transcription-polymerase chain reaction (RT-PCR).

In the last part of the discussion, the necessity for multicenter trials in order to advance the clinical application of SN biopsy in gastric cancer surgery in Japan was reconfirmed by all speakers and by the audience at the symposium. Two protocols were presented for

randomized controlled trials for the feasibility test of SN biopsy for gastric cancer. One was the JCOG 0302 (Japan Clinical Oncology Group, <http://www.jcog.jp/>) protocol and the other was the Japanese Society of Sentinel Node Navigation Surgery (<http://web.sc.itc.keio.ac.jp/surgery/snns/>) protocol. It is believed that the common use of SN biopsy procedures will make the SN biopsy a valuable tool for gastric cancer surgery, especially for function-preserving surgery for early gastric cancer. (Reported by Y. Otani.)

Special symposium 2. *Latest advances in endoscopic mucosal resection* (chaired by S. Yoshida, National Cancer Center Hospital East, and H. Inoue, Showa University Northern Yokohama Hospital)

In this symposium, the latest advances in endoscopic mucosal resection (EMR) were presented, and the procedural refinements were precisely discussed. Conventional EMR is, in principle, based upon snare strangulation of the target mucosa. With this method, the size of specimens was limited to 2 to 3 cm, with an unclear resection margin, and, therefore, histopathological evaluation of the resected specimen often remained unsatisfactory. Regardless of the tumor size, single-fragment resection is considered to be essential for accurate histopathological analysis, particularly to expand the criteria.

In 1995, Ono and Hosokawa developed the “insulation-tip (IT) knife technique”, later termed “endoscopic submucosal dissection (ESD)”. Their procedure consists of two parts; marginal cutting of the lesion, followed by submucosal dissection of the isolated mucosa. With ESD, theoretically, lesions of any size can be resected as a single fragment and can be precisely evaluated by pathologists regarding the microscopic characteristics of the superficial cancer. Although ESD has a great advantage for a large-block resection, some problems remain for ordinary endoscopists. The procedure may take a very long time, with a relatively high risk of complications, such as massive bleeding and perforation. H. Ono, Shizuoka Cancer Center, in his presentation, emphasized the significance of one-block resection and recent technical improvements. The concept of one-block resection by ESD has now become accepted, and is generally recommended to all endoscopists, but the original IT knife procedure still demands high technical skills. Any easy techniques and devices that will make ESD technically feasible for all endoscopists are awaited.

In this session, some important technical refinements of ESD were discussed. T. Oyama, Saku General Hospital, advocated the practical usefulness of the “hook knife technique”. So far, they have performed ESD in 312 patients, and single-fragment resection was possible in 301 (96%). Perforation occurred in only 3

patients (0.96%). The hook knife is a technically sophisticated device, but it generally demands a longer time than the IT knife method. T. Gotoda, National Cancer Center Hospital, Tokyo, reported their 3-year experience of 708 patients. In 13% of the patients, it took more than 2 h to complete the procedure. They now recommend a combination use of the IT knife with some other modalities (needle knife, distal attachment, and so on). A. Hosokawa, National Cancer Center Hospital East, also advocated a combination method, with the IT knife and other, new, modalities, namely, “hole-to-hole and jerking and scratch method”. M. Kaise, Tokyo Jikeikai Medical University, presented a combined technique with marginal cutting and mucosal resection, using a monofilament hard snare. H. Ono also reported a minor improvement of IT knife devices which makes the original IT knife procedure much easier for ordinary endoscopists. Y. Oda, Hattori Gastrointestinal (GI) Hospital, recommended, from an educational point of view, that ESD should first be tried for small and distally located lesions in the stomach, while ESD for large and proximally located lesions should be done by expert hands.

In this session, we confirmed that the use of some advocated modifications of the IT knife method makes ESD a more feasible and effective procedure. (Reported by H. Inoue.)

International symposium 1. *Chemotherapy for gastric cancer in Asia* (chaired by Y. Maehara, Kyushu University, and M. Terashima, Fukushima Medical University)

Gastric cancer remains the most common cause of cancer death in Asia. The treatment outcome has been much improved during the past few decades, mainly due to earlier diagnosis. However, the prognosis of patients with advanced or recurrent gastric cancer still remains poor. 5-Fluorouracil (5-FU) has been a key chemotherapeutic agent in the treatment of advanced or recurrent gastric cancer. Despite several phase III studies, a standard chemotherapeutic regimen has not been established worldwide. In the 1980s, the FAM regimen was employed as standard chemotherapy. In recent years, new anticancer agents have been introduced and are being tested as single agents, or in combinations. These include the taxanes, irinotecan (CPT-11), oxaliplatin, capecitabine, and S1. Therapeutics with molecular-targeted agents such as tyrosine kinase inhibitors will be tested in the near future.

Y.H. Kim, Korea University, and Y.J. Bang, Seoul National University, reported a review of gastric cancer chemotherapy in Korea. In a randomized phase III study, 5-FU + cisplatin (CDDP) (FP) was compared with 5-FU alone or FAM treatment, and FP had a higher response rate and longer time to progression. To

improve the response rate with combination treatment, 5'DFUR + CDDP; and capecitabine + CDDP were investigated. Capecitabine + CDDP was highly active, with a response rate of 54.8%, with manageable toxicities. Epirubicin, CDDP, and UFT plus leucovorin were tested, and a significant response rate of 54%, with tolerable toxicity, was obtained. Currently, a phase III trial comparing SKI-2053R + 5-FU versus CDDP + 5-FU is ongoing.

K.M. Chu, University of Hong Kong, presented a review and outline of the prospects of gastric cancer chemotherapy in Hong Kong, and Li.-T. Chen, National Health Research Institute, Taipei, reviewed chemotherapy in Taiwan; a two-stage sequential approach (HDFL/cisplatin followed by docetaxel and irinotecan) and salvage biweekly OXFL₄₆ seemed promising, with prolonged overall survival.

H. Baba, Kyushu University; A. Ohtsu, National Cancer Center Hospital East; and H. Takiuchi, Osaka Medical University, reported the final results of a phase III study comparing 5-FU vs 5-FU + CDDP (FP) vs UFT + mitomycin C (MMC), conducted by the Japan Clinical Oncology Group (JCOG). The overall survival of patients treated with FP was not different from that of patients receiving 5-FU alone. Newer regimens are being evaluated in terms of survival advantage, in three randomized controlled trials: 5-FU vs CPT-11 + CDDP vs S-1 as a JCOG study; S-1 vs S-1 + CDDP; and 5-FU/leucovorin vs S-1 as company-sponsored postmarketing studies. These ongoing randomized trials in Japan will clarify the true impact of the newer-generation regimens for advanced gastric cancer.

After these presentations, the question of what was the current standard chemotherapy for gastric cancer in Asia was discussed. The current status of chemotherapy using new anticancer agents, such as irinotecan, the taxanes, oxaliplatin, and S-1 were also discussed. Finally, we discussed the problems that needed to be overcome in order to perform international clinical trials of chemotherapy for advanced gastric cancer in Asian countries in future. (Reported by Y. Maehara.)

International symposium 2. Gastric cancer surgery in Asia (chaired by K. Maruyama, International Medical and Welfare University, and M. Kaminishi, University of Tokyo)

The prevalence of gastric cancer is still high in Asian countries. It is reported that gastric cancer is the second leading cause of cancer-related death in Japan, Korea, China, and Turkey, and it is the fourth leading cause of cancer-related death in Hong Kong and Taiwan. The present status of and future aspects of treatment for gastric cancer in various countries and regions were presented.

Surgery plays the central role in potentially curative treatment. Reported survival rates after surgery depend on the proportion of patients with early gastric cancer in the study, and the scope of lymphadenectomy. D2 lymphadenectomy has been the gold standard for treatment of advanced gastric cancer, and the results of D2 lymphadenectomy from Korea and Shanghai showed a 60%–65% 5-year survival rate. Furthermore, comparative studies of D1 and D3 gastrectomy for advanced gastric cancer (T2–4) from Turkey and Taipei revealed a better prognosis after D3 gastrectomy. In contrast to western countries, D2 or more extended radical surgery has been performed as a standard treatment for advanced gastric cancer at specialized institutions in Asian countries.

Chemotherapy, whether neoadjuvant or adjuvant, has become an important tool for the treatment of highly advanced gastric cancer following the recent development of new anticancer agents. However, there were many debates on the selection of drugs and the effectiveness of chemotherapy. No definite regimens have been established. The necessity for global cooperation in randomized controlled trials of surgery and chemotherapy was postulated.

Of note, the proportion patients with early gastric cancer has been increasing in many countries, resulting in increasing interest in limited and less invasive treatment. Laparoscopic gastrectomy has been adopted in Japan and Korea, and favorable results have been reported. However, there are still some disadvantages, such as technical difficulties, few long-term results, time-consuming operation, high cost (because of the use of many instruments and expensive equipment), and lack of establishment of training systems. Further improvement to overcome these difficulties is mandatory for standardization of this procedure. The application of the SN concept in gastric surgery is being reviewed. A combination of laparoscopic surgery and SN navigation may provide much less invasive treatment than that previously used for early gastric cancer. (Reported by M. Kaminishi.)

Symposium 1. Molecular biology of gastric cancer and its clinical implications (chaired by W. Yasui, Hiroshima University, and M. Mori, Kyushu University)

Recent advances in molecular biology have uncovered the precise mechanism of the development and progression of gastric cancer. Various genetic and epigenetic alterations are accumulated in the course of multistep stomach carcinogenesis. These alterations include mutation and loss of heterozygosity (LOH) of tumor suppressor genes, microsatellite instability (MSI), and gene silencing by promoter hypermethylation. In this symposium, we discussed the significance of molecular analysis from the clinical viewpoint, especially in terms

of diagnostics and new approaches to search for novel genetic markers.

The silencing of tumor suppressor genes by promoter hypermethylation participates in carcinogenesis. K. Hibi, Nagoya University, reported the detection of promoter methylation in the serum of cancer patients and its use for diagnosis. Promoter methylation of the *p16*, *HLTF*, and *CDH13* genes was examined in gastric cancer tissues by methylation-specific PCR, and in 68% of patients, the tissues showed hypermethylation of at least one gene. Hypermethylation of the *p16* promoter was detected in the serum of 15% of patients with *p16* methylation in the tumor. The examination of combinations of suitable gene promoters will be valuable to screen for gastric cancer in the serum. It is of clinical importance to clarify the relation between molecular characteristics and sensitivity to anticancer drugs. M. Yashiro, Osaka City University, examined LOH in the *APC*, *p53*, *DPC4*, *PTEN*, and *CDH1* genes, as well as MSI, in advanced gastric cancer, and studied the relationship of these parameters to sensitivity to treatment with CDDP and 5-FU (FP therapy). A high frequency of MSI and/or LOH of the *p53* gene were associated with sensitivity to FP therapy, indicating that these parameters may be good markers for chemosensitivity. As to abnormalities of the *p53* and *PTEN* genes, E. Oki, Kyushu University, demonstrated that LOH of the *PTEN* gene was associated with *p53* mutation and a poor prognosis.

Detection of cancer cells in the peritoneal cavity has crucial clinical implications; however, routine cytology is not sensitive. H. Taniguchi, Osaka University, reported the usefulness of the detection of carcinoembryonic antigen (CEA) and cytokeratin 20 mRNAs, by real-time RT-PCR, using a LightCycler, in preoperative peritoneal lavage fluid. For patients whom genetic markers were positive by PCR but negative by cytology preoperatively, MMC and CDDP were administered intraperitoneally, and 60% of patients had become negative by PCR at surgery. This strategy is applicable for selecting suitable adjuvant therapy.

Using genomic science, including the global analysis of gene expression and bioinformatics, the individual characteristics of each cancer can be determined precisely, and this is directly connected to personalized medicine. A better knowledge of the molecular bases of gastric cancer may lead to new approaches to diagnosis and treatment. Multiple-color spectral karyotyping (SKY) is a useful tool to identify novel chromosomal aberrations. Y. Yamashita, Kyoto Prefectural University, examined the chromosomal state of gastric cancer by SKY. Complex karyotyping in all chromosomes could be analyzed, and many breakpoints (including 8q24, 1q13, and 20q11.2) and various rearrangements (including 8q24.1/13q14 and 8q24.1/11q13) were identi-

fied. This information is valuable for isolating novel genes that participate in stomach carcinogenesis and new genetic markers for cancer diagnosis. Serial analysis of gene expression (SAGE) is a powerful technique that allows global analysis of gene expression in a quantitative manner, without prior knowledge of the sequence of the genes. N. Oue, Hiroshima University, reported that *REGIV* (regenerating gene type IV) was identified by comparing the gene expression profile of scirrhus-type gastric cancer with that of normal gastric epithelia. *RegIV* was found to be secreted by cancer cells, and *RegIV* inhibited apoptosis, suggesting that *RegIV* may serve as a novel biomarker and therapeutic target for gastric cancer. (Reported by W. Yasui.)

Symposium 2. New agents for gastric cancer chemotherapy (chaired by M. Fujii, Nihon University, Tokyo, and Y. Takahashi, Kanazawa University)

The emergence of new chemotherapeutic agents, such as S-1, CPT-11, and the taxanes, increases the response rate in patients with far advanced and unresectable gastric cancer. Therefore our next questions are how to use these drugs and how to select among them.

B. Nakata, Osaka City University, reported a phase I study of low-dose CDDP (days 1, 2, 3, 4, and 5, every week) combined with S-1 (80 mg/m², 4 weeks on and 2 weeks off) with measurements of serum 5-FU concentration, and the recommended dose (RD) of CDDP at 4 mg/m². Y. Takahashi, Kanazawa University, reported a randomized controlled phase II trial of tailored CPT-11 (which employed individualized doses by limiting the toxicity to grade 2) combined with S-1 (80 mg/m², 2 weeks on and 2 weeks off) vs S-1 (80 mg/m², 4 weeks on and 2 weeks off); the results showed varied individualized doses of CPT-11, ranging from 25 mg/m² to 125 mg/m² (RD determined by phase I study). These two trials are like "chronic chemotherapy"; in other words, using lower doses or tailored doses and obtaining longer survival by repeating drug regimens over longer periods of time, with less toxicity.

H. Nomura, Osaka Medical College, reported the significance of chemosensitivity tests and their evaluation, and recommended the use of 5-FU, CDDP, and CPT-11 as first-line combination treatment. W. Ichikawa, Saitama Medical School, reported on prediction of the efficacies of S-1 and CPT-11, based on thymidylate synthetase (TS) and dihydropyrimidine dehydrogenase (DPD) levels. This study suggested that we should select S-1 for patients with lower TS levels and S-1 combined with CPT-11 for those with higher TS levels. These reports indicate the importance of tailored chemotherapy based on various chemosensitivity tests, including drug-related enzymes and genes.

H. Narahara, Osaka Medical Center, reported good feasibility and antitumor effects with their clinical trials

of CPT-11 (50 mg/m², days 1, 8, and 15) combined with docetaxel (50 mg/m²; day 1) and CPT-11 (80 mg/m²; days 1 and 15) combined with S-1 (80 mg/m²; 3 weeks on and 1 week off), and recommended the latter regimen as first-line therapy. Y. Emi, Hiroshima, Red Cross Hospital and K. Yoshida, Hiroshima University, reported favorable results with weekly paclitaxel (80 mg/m²) as second-line therapy, which showed less toxicity than conventional regimens, with better effects, including prolonged stable disease. T. Doi, National Cancer Center Hospital East, Chiba, reported a summary of 2778 patients treated with a single drug (S-1; 80 mg/m²; 4 weeks on and 2 weeks off). Toxicities, including grade 3 and higher, were observed in only 5% of patients, excluding hemoglobin reduction (12%). The response rate was 38%. Median survival time and time to progression (TTP; time to progressive disease [PD]) were 369 days and 137 days, respectively. The 1-year and 2-year survival rates were 52% and 23%, respectively.

The results of these six reports suggest that new drugs such as S-1, CPT11, and the taxanes showed higher response rates, with less toxicity, than conventional drugs in treating gastric cancer. Unfortunately, there is still no standard chemotherapy for gastric cancer. However, it is expected that, in the near future, some good candidate regimens will be decided on for first- and second-line therapies, from among the ongoing clinical trials that include these new drugs. (Reported by Y. Takahashi.)

Symposium 4. *New strategy of immunotherapy for gastric cancer* (chaired by S. Saji, Gifu University, and H. Yamaue, Wakayama Medical University)

Cancer immunotherapy has entered a new era, allowing us to understand well the immune mechanism, including the precise sequences of cancer-related antigen peptides, and the mechanism of antigen presentation by dendritic cells (DCs). Eight speakers reported on new strategies of immunotherapy for patients with gastric cancer; two speakers focused on antibody studies, and five speakers clarified the anticancer effects of peptide-pulsed DCs. Also, J. Cai, Hebei Medical University, China, reported that gene transduction of DCs has been successfully performed with a retroviral vector, and suggested that immunogene therapy may be an effective tool for the treatment of gastric cancer.

First, K. Kono, Yamanashi University, reported on a new aspect of Herceptin, which recognizes the HER-2 antigen expressed in various tumor cells, including gastric cancer cells. Herceptin exerts anticancer effects by antibody-dependent cellular cytotoxicity (ADCC); however, in this report, HER-2 specific cytotoxic T-lymphocytes (CTL) augmented their MHC-restricted activity, and HER-2 restricted cytolytic

activity when CTLs were treated with Herceptin *in vitro*. J. Sakamoto, Kyoto University, reported another antibody in a phase I clinical study. His group has developed a new monoclonal antibody, huA33, which recognizes the cancer-related antigen A33, which is widely distributed in gastrointestinal cancer tissues. Thirteen patients with gastric cancer received huA33 in a phase I clinical trial, and no toxicity was observed, except for one patient with mild fever (grade 1). However, one should consider that there are differences in the expression of the A33 antigen in primary tumor sites and metastatic sites.

Next, the symposium focused on cancer vaccination, using peptide-pulsed DCs. K. Mimura, Yamanashi University, reported that CTLs which recognized HER-2 peptides could be generated from peripheral blood mononuclear cells obtained from gastric cancer patients; N. Tokunaga, Okayama University, reported the clinical efficacy of treatment with p53 protein-pulsed DCs injected into gastric cancer tissues as neoadjuvant immunotherapy. Two speakers demonstrated novel approaches in DC therapy. Y. Ueda, Kyoto Prefectural University, used OK432 as an agent for the *in vitro* maturation of DCs. DCs expressed CD83 on their cell surfaces on stimulation with interleukin (IL)-4 and OK432, and OK432-stimulated DCs secreted various cytokines, including tumor necrosis factor (TNF)- α , and granulocyte-macrophage-colony-stimulating factor (GM-CSF). S. Kashimura, Fukushima Medical University, reported the clinical benefits of a combination of immunotherapy, using DCs, with chemotherapy, using a taxane. The final topic was reported by K. Okita, Sapporo Medical University. His group clarified a relationship between gastric cancer cells and monocytes in the process of metastasis, as well as a relationship between metastasis and chemokines, including RANTES (Regulated on Activation, Normal T Expressed and Secreted) a chemokine that is a physiological ligand for the HIV-1 coreceptors CCR3 and CCR5. RANTES may be a useful molecular target for the inhibition of cancer metastasis.

In summary, we discussed new strategies of immunotherapy for gastric cancer; this could be a promising approach for the treatment of patients with advanced gastric cancer. (Reported by H. Yamaue.)

Panel discussion 1. *Diagnosis and management of gastrointestinal stromal tumors (GIST)* (chaired by A. Yanagisawa, Kyoto Prefectural University of Medicine, and Y. Yamamura, Aichi Cancer Center)

Most gastrointestinal mesenchymal tumors (GIMTs), which characteristically reveal a smooth protrusion of gastrointestinal wall lined by intact mucosa, had been considered to derive from smooth muscle and were generally classified as leiomyomas and leiomyosarcomas.

Through various immunohistochemical studies, a majority of these tumors has come to be classified nowadays as gastrointestinal stromal tumors (GISTs). The etiology of GISTs has been elucidated through mutation analysis of the *KIT* protooncogene. Recent progress in the understanding of GISTs has led to confusion among Japanese clinicians and investigators regarding the diagnostic criteria of this disease entity. It was more than appropriate, therefore, that GIST was selected as one of main subjects to be discussed at this congress.

Of six presentations, one referred to GISTs as spindle-cell tumors and another referred to GISTs as GIMTs, reflecting the confusion as regards the definition of GIST. The participants were asked to adhere, in future, to the definition of GIST established at the previous congress: a proliferative neoplasm of spindle cells that fulfills either of the following criteria; (1) immunohistologically positive for either or both KIT protein and CD34, (2) immunohistologically negative for the markers of myoid or neural origin if neither KIT protein nor CD34 is expressed.

Immunohistological examination of the tissue specimens is mandatory for the diagnosis of GIST. GIST tumor tissues are rarely accessible by endoscopic biopsy; however, because they are lined with intact mucosa. In general, therefore, GIST is diagnosed as a submucosal tumor, and follow-up is performed by 3- to 6-monthly endoscopic examinations until the tumor reaches the size of 2 cm (A. Sawaki, Aichi Cancer Center) to 4 cm (Y. Tatsutomi, Tokyo University). A. Sawaki reported that endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB) was a useful tool for the preoperative diagnosis of the tumor.

When a diagnosis of GIST is obtained, surgery is the treatment of choice. Although sporadic cases associated with LN metastases have been reported (T. Sato, Cancer Institute Hospital, Tokyo), wedge resection without systematic LN dissection is the recommended treatment option (H. Katai, National Cancer Center, Tokyo), and this can now be performed safely by a laparoscopy-assisted approach.

Imatinib mesylate is indicated for the treatment of unresectable/recurrent GIST. Although a complete response was rarely achieved, survival benefit was observed among patients who had stable disease, indicating that the treatment should be continued until disease progression (T. Kanda, Niigata University, and H. Endo, National Cancer Center East, Kashiwa). Evidence is, so far, lacking as regards the value of this drug in the neoadjuvant setting.

Various studies of the diagnosis and management of GIST are currently ongoing, and the audience was convinced that there will be more to come in the very near future. (Reported by Y. Yamamura.)

Panel discussion 2. *Current status and future prospects of peritoneal cytology for gastric cancer patients* (chaired by M. Hiratsuka, Itami City Hospital, and H. Nishidoi, Tottori Red Cross Hospital)

In this panel discussion, several important topics related to peritoneal cytology for gastric cancer; in particular, novel molecular-based methods for detecting cancer cells with high sensitivity, were presented and discussed by five distinguished surgeons in this research field.

I. Miyashiro, Osaka Medical Center for Cancer and Cardiovascular Diseases, presented findings showing the prognostic significance of conventional peritoneal lavage cytology (PLC), with special reference to the relationship between the number of cancer cells detected in PLC and patient prognosis. This group clearly showed that the number of cancer cells in PLC served as an important prognostic indicator.

The following three speakers talked about molecular-based methods for the detection of cancer cells in peritoneal washings. Y. Kodera, of Nagoya University, reported their attempts to increase sensitivity for the detection of peritoneal cancer cells, using a real-time PCR assay for CEA mRNA. They found that a real-time PCR assay for CEA mRNA in peritoneal washings was more sensitive than conventional PLC. The sensitivity and specificity of the real-time RT-PCR assay (84% and 94%, respectively) were higher than those for conventional cytology (56% and 91%, respectively). M. Takahashi, Yokohama City Hospital, reported on the prognostic significance of telomerase reverse transcriptase mRNA (hTERT-M) expression in the peritoneal washings of P0/cT3–4 gastric cancer patients. Their group showed, by multivariate analysis, that hTERT-M was the most significant prognostic factor among various conventional prognostic factors analyzed. The reports of these two groups suggest that a real-time PCR assay for the expression of CEA mRNA or hTERT mRNA has potential as a new molecular-based method for the detection of peritoneal cancer cells, with higher accuracy than conventional PLC. K. Mori, University of Tokyo, reported a novel approach for the selection of marker genes, using microarray technology. First, they tried to select the most useful marker genes, taking advantage of microarray analysis of the expression of 10000 genes in the gastric cancer cells and peritoneal washings of early-stage patients. They found that five genes, i.e., *CK20*, *FABP1*, *MUC2*, *TFF1*, and *TFF2*, were the best marker genes. Secondly, they showed that a nested RT-PCR assay, performed on these five marker genes, for the detection of cancer cells in the peritoneal washings, was highly sensitive and specific.

T. Inada, of Tohigi Cancer Center, reported their results of chemotherapy with 5-FU for CY1 (positive cytology) gastric cancer patients. They found that the overall 5-year survival rate of the CY1 patients was

11.7%, and, interestingly, the median survival time of patients with DPD-negative cancers (2.38 years) was longer than that of those with DPD-positive cancers (1.43 years).

It is well established that information derived from conventional PLC plays a very important role in treatment decision-making for gastric cancer patients, and therefore, the development of new more accurate methods for the detection of peritoneal cancer cells has been awaited for a long time. In this panel discussion, very promising results on the detection of peritoneal cancer cells with a novel molecular-based method were presented. The molecular-based method seems to be superior to conventional PLC. However, the results presented in the panel discussion are still preliminary, and confirmatory studies definitely need to be done before this new method can be accepted as a standard of care. (Reported by M. Hiratsuka.)

Consensus meeting 2. *Need for the implementation of a nationwide fact-finding inquiry on endoscopic mucosal resection (EMR) for early gastric cancers* (chaired by S. Yoshida, National Cancer Center Hospital East, and Y. Ohtani, Keio University)

Since 1987, when Tada and colleagues initially devised the “strip biopsy”, endoscopic mucosal resection (EMR) has been used widely in Japan as a standard treatment for early gastric cancer. With recent technical innovations, large tumors or those with ulcer scars can be targets of EMR, and the expansion of the EMR criteria in the JGCA guidelines is being discussed. Nevertheless, the actual end results of EMR have been reported only at the institutional level, with possible publication bias in the literature. The JGCA, therefore, organized an ad-hoc committee to survey the actual situation of EMR in Japan (EMR Committee). D. Saito, from the National Cancer Center Hospital, chairman of this committee, emphasized the importance of a nationwide fact-finding inquiry in order to clarify the following issues; (1) validity of the JGCA guidelines, (2) adequacy of general rules concerning EMR procedures, (3) efficiency of surveillance after the treatment, (4) actual therapeutic efficacy, or gastric cancer death rates in patients with long follow-up, and (5) the incidence of expected and unexpected complications.

M. Tada, Saitama Cancer Center, reported the treatment results of “strip biopsy”, based on his 2100 cases during the past 15 years. He concluded that the therapeutic efficacy of the procedure was proven, without any severe complications or gastric cancer death, for patients meeting the criteria of the guidelines, though local recurrence that was treated with re-strip biopsy had been detected in 7% of the patients. Also, he referred to the difficulty of complete follow up of the patients for a long time after the treatment. T. Gotoda,

National Cancer Center Hospital, and M. Fujishiro, Tokyo University Hospital, showed that their results for the treatment of more than 600 lesions exceeding the criteria of the guidelines were satisfactory, as long as they completed single-fragment resection for the histologically differentiated type of mucosal cancer, using an endoscopic submucosal dissection (ESD) technique, with which the complete resection rate was more than 90%. T. Gotoda also emphasized the importance of careful follow up after multiple-fragment EMR, particularly in lesions that did not meet the criteria of the guidelines, because the risk of treatment failure (including cancer death) is not low after histological underdiagnosis of the resected specimens. He pointed out that the mooted nationwide inquiry could be useful for urging the government to set up adequate funding for the cost of ESD. M. Fujishiro emphasized the importance of prospective registration, because several essential data parameters, such as bleeding volume and operation time, cannot be checked by retrospective investigation.

T. Doi, National Cancer Center Hospital East, proposed an Internet registration system and outlined a registration form to be used for the implementation of a nationwide inquiry on EMR. He commented that the development of such a prospective investigation would be indispensable, because, in 2005, we will face an amendment of the Pharmaceutical Business Law by which we are required to carry out investigational clinical trials for newly developed endoscopic instruments to be approved by the government.

In the general discussion, consensus on the following points was obtained: (1) a nationwide fact-finding inquiry on EMR for early gastric cancer should be carried out; (2) to confirm the feasibility of Internet registration, by the end of this year, 13 member institutions of the EMR Committee register data on all patients treated by EMR during the calendar year of 2001, and assess the feasibility of the system in 2005. (3) If the system works well, nationwide prospective registration should start in 2006. (Reported by S. Yoshida.)

Workshop 2. *Micrometastasis of gastric cancer* (chaired by T. Hattori, Shiga University of Medical Science, and Y. Kato, Osaka City University)

Micrometastasis seems to be a prognostic factor for gastric cancer, but its clinical significance has not been fully elucidated. M. Ikeguchi, Tottori University, reported that it was uncertain whether cancer cells appearing in peripheral blood as a result of surgical procedures led to real metastasis. M. Miyagi, Kurume University, and K. Oyama, Fukushima Medical University, emphasized the importance of detecting micrometastasis in sentinel LNs. For the detection of micrometastasis, M. Ikeguchi

and K. Oyama, employed an RT-PCR method, and T. Ishii, Osaka University, reported a new transcription-reverse transcription concerted reaction (TRC) system. H. Akiyama, Yokohama City University, pointed out the necessity for diagnosing micrometastasis in paraaortic LNs for their successful resection. Y. Mochizuki, Aichi Cancer Center, reported an animal experiment carried out to assess the effectiveness of omentectomy and paclitaxel chemotherapy to control micrometastasis in the abdominal cavity.

The diagnosis of micrometastasis is now possible, as shown by the speakers at this workshop, but the management of micrometastasis appears to be the next problem to be overcome. (Reported by T. Hattori.)

Workshop 3. Palliative care for advanced gastric cancer (chaired by H. Shiozaki, Kinki University, Osaka, and W. Koizumi, Kitasato University, Kanagawa)

In this session, six presenters spoke about their institutional experience and problems with the treatment or palliative care of patients with advanced/recurrent gastric cancer.

For pain control, it was reported that gastric cancer patients needed more opioids than patients with other digestive cancers. Half of the gastric cancer patients needed additional sedative treatment for pain control.

One of the greatest problems with gastric cancer at this stage is the frequent obstruction of the gastrointestinal tract, which interferes with oral intake. Feeding techniques, such as percutaneous endoscopic gastrostomy (PEG), or percutaneous transesophageal gastrostomy (PTEG) were useful for maintaining nutrition. Endoscopic stenting for stricture and laparoscopic gastrojejunostomy were also helpful in some patients. However, the decision to undertake palliative surgery in patients with obstructive peritonitis carcinomatosa is difficult, because, though it certainly improves quality of life in some patients, it may lead only to surgical complications and pain in other patients.

The clinical significance of providing care for mental problems was also reported in this session. Anxiety and depression are major mental problems in patients with recurrence, and a psycho-oncological approach should be considered in these patients. (Reported by W. Koizumi.)

Workshop 4. *Helicobacter pylori* and gastric cancer (chaired by K. Sugano, Jichi Medical School, and Y. Kinoshita, Shimane University)

A strong link between *Helicobacter pylori* infection and gastric carcinogenesis has now been well established by a number of epidemiological, experimental, and clinical studies. Based on this premise, different aspects of the relationship between *H. pylori* and gastric cancer were

discussed in this workshop. Unique data, showing that ADP-ribosylation was associated with *H. pylori* infection, were reported by N. Yoshihiro, Chiba University. As *H. pylori* has mono-ADP-ribosyltransferase activity, N. Yoshihiro's group assume that this property of *H. pylori* may play a part in gastric carcinogenesis. Although they found that ADP-ribosylated proteins were increased in gastric cancer tissues, the ADP-ribosylated proteins were mostly poly-ADP-ribosylated, indicating that this increase was not due to the bacterial enzyme but was due to an intrinsic host reaction. Thus, the role of the mono-ADP-ribosyltransferase activity of *H. pylori* in gastric carcinogenesis is still unresolved.

N. Uemura, International Medical Center of Japan, Tokyo, presented two sets of data showing the effect of *H. pylori* infection on the development of gastric cancer. The major part of the internationally acclaimed data he presented at this workshop has been published previously in two papers, but, in this talk, he presented updated follow-up data, showing that a few patients in their *H. pylori*-eradicated group had developed gastric cancer. Therefore, it is now realized that *H. pylori* eradication may retard the development of gastric cancer, but eradication is not sufficient to prevent the risk of cancer progression in high-risk patients who have already developed early gastric cancer.

Animal studies, presented by M. Tatematsu, Aichi Cancer Center, also demonstrated that *H. pylori* has a profound effect on the promotion of gastric carcinogenesis. He emphasized that high salt intake increased the risk of gastric carcinogenesis. In this animal model, earlier, compared with later, eradication of *H. pylori* was more effective in preventing gastric cancer development. Together with Uemura's data, this finding suggests that we should consider starting *H. pylori* eradication programs in younger age groups.

Two studies, by N. Onoda, Osaka City University, and T. Miyashita, Kanazawa University, dealt with the problems of *H. pylori* infection after gastrectomy. N. Onoda showed a discrepancy between endoscopic gastritis and histologic gastritis in the remnant stomach, and indicated that *H. pylori* infection was responsible for the histological gastritis, while duodenal regurgitation was more relevant in the endoscopic gastritis. T. Miyashita presented findings that *H. pylori* tended to show spontaneous disappearance after gastrectomy. He indicated that, although eradication of *H. pylori* after gastrectomy may be effective for preventing remnant cancer development, this eradication required deliberate consideration, because in his group had experience of patients who developed stomal ulcer after successful *H. pylori* eradication. The topics presented in this workshop represent only part of the large issue of the role of *H. pylori* in gastric cancer. Therefore, we should keep

focusing our attention on the progress of this issue by continuing to hold workshops or symposiums in the coming JGCA meetings. (Reported by K. Sugano.)

Workshop 5. Carcinoma of the cardia (chaired by Y. Kato, Cancer Institute, Tokyo, and T. Tsunoda, Kawasaki Medical School, Kurashiki)

The optimal surgical approach for carcinoma of the cardia has been controversial, even with the introduction of new anastomotic instruments. Some authors have advocated the use of a left thoracotomy and laparotomy, while others have recommended laparotomy alone. Since 1996, when Siewert and Stein published their article entitled “Carcinoma of the cardia: carcinoma of the gastroesophageal junction — classification, pathology and extent of resection”, many surgeons have chosen to use this classification, because its clinical use is very simple and easy. When the tumor center or more than two-thirds of the tumor mass is located more than 1 cm above the anatomical gastroesophageal junction, the tumor is classified as an adenocarcinoma of the distal esophagus (type I). When the tumor center or tumor mass is located within 1 cm orally or 2 cm aborally of the anatomical gastroesophageal junction, the tumor is classified as a true carcinoma of the cardia (type II). Adenocarcinomas of the gastroesophageal junction that have their tumor center or more than two-thirds of the tumor mass located more than 2 cm below the anatomical gastroesophageal junction are classified as subcardial tumors (type III). For a type I tumor, a radical transhiatal esophagectomy plus two-field LN dissection should be adopted. For type II and III tumors, an extended total gastrectomy with D2 LN dissection should be adopted.

Siewert’s classification of carcinoma of the cardia was approved at a consensus conference during the Second International Gastric Cancer Congress held in 1997, and is commonly used. However, there are some unresolved practical problems.

The concept of Siewert’s classification is based on the pattern of lymphatic spread, and the classification is not relevant with regard to a safe resection margin of the esophagus. Most surgeons today accept that extended lymphadenectomy may improve the prognosis in patients with carcinoma of the cardia who have a limited number of positive LNs. However, in our workshop, five speakers reported that no patients with positive LNs in the lower posterior mediastinum had survived for 2 years after operation. The speakers at this workshop reported that recurrence at the resection margin reduced the survival rate. Thus, it seems that the most important point at issue is the resection margin, which is directly related to the surgical approach; with or without thoracotomy, or a subtotal esophagectomy using a transhiatal blunt esophagectomy approach or a gastrec-

tomy plus resection of the lower part of the esophagus (extended total gastrectomy).

Siewert’s classification is made according to the location of the tumor center, but a huge or invasive tumor can be far from the gastroesophageal junction. Basically, it is unreasonable to select an operative procedure or approach from the viewpoint of the tumor center. Moreover, as we discussed in this workshop, the invasive pattern differs among histological types. For example, poorly differentiated or signet-ring cell type shows more “skip lesions” far from the tumor margin than other histological types. To select the optimal surgical procedure for individuals, more precise data should be obtained.

In the first place, as discussed at our workshop, what is the gastroesophageal junction? Is it the mucosal junction, vascular junction, luminal junction, or muscular junction? Furthermore, it is difficult to make such an analysis when the gastroesophageal junction has been destroyed by cancer invasion. Therefore, the method for classifying the gastroesophageal junction should be stated when carcinoma of the cardia is discussed.

Because there are still many unresolved problems with carcinoma of the cardia, as mentioned, we should discuss it again in the near future. (Reported by T. Tsunoda.)

Workshop 6. Intraperitoneal chemotherapy for gastric cancer (chaired by K. Hirakawa, Osaka City University, and Y. Yonemura, Shizuoka Cancer Center)

Peritoneal metastasis is fatal in patients with gastric cancer and is rarely cured. The treatment options for peritoneal dissemination from gastric cancer are extremely limited. Some surgeons have removed the peritoneal dissemination by surgery. However, this operative procedure, peritonectomy, should be carried out along with chemo-hyperthermic peritoneal perfusion (CHPP) to totally eliminate peritoneal metastasis, as micrometastases may spread all over the peritoneal surface. Intraperitoneal chemotherapy, with or without hyperthermia, has been investigated in some trials, although the results remain controversial and unsatisfactory.

In this workshop, five speakers presented their findings on clinical outcome (one of them reported the results of CHPP), and one speaker presented experimental findings. N. Ohashi, Nagoya University, demonstrated that the peritoneal micrometastases of gastric cancer cell lines in nude mice disappeared after the intraperitoneal administration of paclitaxel. He concluded that intraperitoneal chemotherapy with paclitaxel might be useful as a prophylactic treatment for peritoneal micrometastasis. Next, two speakers reported the results of neoadjuvant intraperitoneal chemotherapy. S. Fushida, Kanazawa University, noted

that laparoscopic intraperitoneal examination should be done preoperatively for patients with a high risk of peritoneal metastasis. He demonstrated that pre- or postoperative intraperitoneal chemotherapy with a taxane prolonged the survival of patients who underwent gastrectomy. Y. Fujiwara, Osaka University, argued that, in CY0 patients with a positive molecular diagnosis of peritoneal metastasis (made using peritoneal lavage fluid obtained by laparoscopy) the disease was susceptible to neoadjuvant intraperitoneal chemotherapy with cisplatin and mitomycin. S. Katayanagi, Tokyo Metropolitan Komagome Hospital, pointed out the usefulness of repeat intraperitoneal chemotherapy with CDDP, using an intraperitoneal port after operation. K. Ohta, University of Tsukuba, stated that intraperitoneal chemotherapy was useful for patients with P0CY1 or macroscopically resected P1 disease, but that it should not be administered to patients with unresectable P1. On the other hand, C. Kunisaki, Yokohama City University, reported disappointing results of CHPP in both the prophylactic and treatment settings.

To summarize the workshop discussions, the clinical usefulness of intraperitoneal chemotherapy was suggested in gastric cancer with intraperitoneal micro- or minimally disseminated disease. (Reported by K. Hirakawa.)

Video symposium. *Progress of endoscopic surgery from laparoscopy-assisted distal gastrectomy (LADG)* (chaired by S. Matsumoto, Fujita Health University, Nagoya, and M. Ninomiya, Hiroshima City Hospital) The procedure of gastrectomy consists of three elements; removal of the primary lesion, lymphadenectomy, and reconstruction. It is true that laparoscopic surgery needs more hemostatic procedures than those required in open surgery. Around 1990, the hemostatic methods in laparoscopic surgery were confined to the use of compression, endoclips, and electrocautery. The advent of ultrasonic cavitation shears has enabled safe and easy LN dissection, which has facilitated the development of LADG.

In this symposium, six panelists presented videos to demonstrate that the same quality of radical operation could be achieved in LADG as in open surgery.

M. Ninomiya, Hiroshima City Hospital, in his open-surgery video, showed the detailed technique of autonomic nervous system preservation for early gastric cancer, while K. Kojima, Tokyo Medical and Dental University, reported his laparoscopic procedure for the preservation of the pancreatic, hepatic, and celiac autonomic nerve branches.

One of the important points in laparoscopic surgery is to secure a good visual field. Y. Ohmura, Okayama Rosai Hospital, reported that the operative field for

lymphadenectomy could be effectively extended by elevating the stomach toward the anterior abdominal wall with Nylon strings placed around the corpus and the pylorus of the stomach. I. Uyama, Fujita Health University, Nagoya, demonstrated D2 LN dissection with hand-assisted laparoscopic surgery (HALS). He said that, by retracting the spleen and the pancreas in total gastrectomy, HALS could secure a good visual field for the removal of LNs along the splenic artery.

S. Kanaya, Himeji National Hospital, reported a gastroduodenostomy method named "Delta anastomosis" using a linear stapler. Y. Kakeji, Kyushu University, Fukuoka, demonstrated that intracorporeal ligation and anastomosis are easily performed under the view with a three-dimensional view, using the "da Vinci" manipulator.

We concluded that laparoscopic surgery has constantly been improved in quality with the development of new devices and surgeons' experience. (Reported by S. Matsumoto.)

Educational seminar. *Critical pathways in the diagnosis procedure combinations (DPC) era* (chaired by T. Konishi, Kanto Medical Center NTT-EC, and H. Furukawa, Sakai Municipal Hospital)

The Educational Seminar was held on the day before the start of the scientific sessions. Despite the very unfavorable weather, with sleet, more than 300 people participated in this seminar, reflecting the increasing interest in the topics of "diagnosis procedure combinations" (DPC) and "critical pathways" (CP). At present, the DPC system is used at only 82 hospitals in Japan, but it is anticipated that the system will be introduced at all acute care facilities in the not-so-distant future, and that its effects on the management of medical institutions will be huge. Additionally, CP are garnering attention as an efficient tool with which to tackle this issue.

During the lecture part of the seminar, first of all, T. Konishi, one of the chairpersons, gave an overview of the current status of the introduction of CP for gastric cancer therapy in Japan. Then M. Kobayashi, Keio University, Tokyo, explained the essence of the current DPC, giving examples of the way in which the health insurance system calculates, reimbursement and outlining the design of CP under the DPC system. M. Terashima, Fukushima Medical University, presented the objectives and utility of the introduction of CP for cancer chemotherapy; then he outlined the cost effects of the 2004 DPC revision, based on an example from the clinical practice of chemotherapy for gastric cancer. He also referred to a comparative analysis of the DPC system and a system based on reimbursement of the actual costs of treatment. H. Baba, Kyushu University, Fukuoka, touched on the national policies for the improvement of safety in health care and showed the

importance of CP for risk management and improved safety. Finally, S. Takahashi, Shizuoka Cancer Center, reported on CP for gastric cancer surgery with different postoperative admission periods depending on the surgeons; he also outlined the CP that their center used in their electronic medical record system.

In the plenary discussion, S. Ohyama (Cancer Institute Hospital, Tokyo), T. Noie (Kanto Medical Center NTT-EC), H. Yamanaka (Kishiwada City Hospital, Osaka), and W. Takiyama (Hiroshima Asa Municipal Hospital) joined the speakers as panelists. They discussed, among other topics, the role of CP in the era of DPC, the need or lack of need for modifications of CP, and methods for establishing the use of CP. Many doctors from hospitals where DPC have already been intro-

duced, as well as those from hospitals where this system has not yet been used, also participated in the discussion. Consensus was achieved in that the introduction of DPC and the use of CP must not affect the safety of medical care. Examples of the increased efficiency of medical care, owing to DPC and CP leading to changes in the number of beds and the distribution of personnel, were also given. As a result, it was agreed that CP in response to DPC should not be introduced from the management point of view, but “should be promulgated for progress towards quality care, giving primary importance to safe health care for the patient, based on clinical guidelines and evidence, and being revised according to the results of variance analysis.” (Reported by T. Konishi.)