



## Special article

# Meeting report of the 73rd Japanese Gastric Cancer Congress

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The 73rd Congress of the Japanese Gastric Cancer Association (JGCA) was held at Kanazawa City, March 1–3, 2001, and attended by 1350 participants. A total of 517 papers were presented. In addition to free papers and poster presentations, a variety of gastric cancer topics ranging from molecular biology to frontline surgical techniques were discussed at two special symposia, four regular symposia, two video symposia, four panel discussions, four workshops, and four debate sessions. An open educational session entitled “Basic principles of diagnosis and treatment for gastric cancer” was organized for the first time at the 73rd JGCA congress, and the meeting hall was unexpectedly packed to overflowing with young attendees.

The JGCA completed the first edition of the *Guideline for Gastric Cancer Treatment* just before the congress, and a special forum was held for the editorial members to present the principal points. This guideline is expected to serve as the standard not only in clinical practice but also for clinical trials in the future.

Discussions of some of the main topics of the congress are summarized below by a chairperson of the session.

### **Chairman’s summary of the symposia, panels, and workshops**

**Symposium 2.** *Evaluation of various reconstruction methods after gastrectomy* (chaired by K. Hioki, Kansai Medical University, and Y. Uchida, Oita Medical University)

Among the various gastric functions that are lost after partial or total gastrectomy, some may be restored by

surgical techniques. In this session, reconstruction methods after gastrectomy were discussed.

K. Nakamura, Tokai University, evaluated the survival rates in patients who had undergone various reconstructive procedures after distal and total gastrectomy. They reported that higher 5-year survival rates were observed in patients who had undergone gastroduodenostomy and jejunal interposition, allowing food to pass through the duodenum, than in those who had undergone gastro- or esophagojejunostomy. They suggested that reconstruction enabling food to pass through the duodenum should be performed irrespective of the disease stage.

Y. Nakane, Kansai Medical University, reported that reconstruction with a jejunal pouch after total gastrectomy was effective in the prevention of the small stomach syndrome, but that long-term emptying disorders were observed in some patients after Roux-en-Y anastomosis with a jejunal pouch. H. Kashimura, Jikei University, reported that the ileocolon interposition was superior to the Roux-en-Y method after total gastrectomy because less reflux esophagitis and more food intake occurred at each meal.

K. Yamaguchi, Sapporo Medical University, evaluated jejunal pouch interposition after proximal gastrectomy both clinically and experimentally. They performed jejunal pouch interposition or esophagogastrostomy in beagles and showed that the former was superior to the latter in terms of changes in gastrointestinal hormones, maintenance of body weight, and emptying of the residual stomach. They concluded that jejunal pouch interposition should be considered after proximal gastrectomy.

S. Kinami, Kanazawa University, evaluated jejunal pouch interposition after distal gastrectomy. As compared with the Billroth I method, the incidences of dumping syndrome, bile reflux and inflammation of the remnant stomach, and *Helicobacter pylori* infection were all low.

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T. Noguchi, Oita Medical University, reported that the jejunal pouch double-tract method after distal gastrectomy was more effective than other reconstruction methods in terms of recovery of body weight, food intake, and emptying of the residual stomach and pouch. They also found that the incidence of postoperative complications was lower with the double-tract method compared with other procedures.

The group of Y. Yamada, Nara Medical University, performed pylorus-preserving gastrectomy (PPG) for the treatment of early gastric cancer in the gastric body and pylorus-preserving near-total gastrectomy with jejunal interposition (PPNTG) for relatively early cancer in the proximal stomach. They reported that the incidences of dumping syndrome and reflux esophagitis were lower in the PPG and PPNTG groups than in the gastroduodenostomy and Roux-en-Y groups.

In summary, the jejunal pouch was generally considered a useful gastric substitute, reflux can be prevented by peristaltic movement of a jejunal segment with sufficient length or by constructing an antireflux valve structure, and the duodenal route appears to result in better recovery of body weight than other methods. These points should be considered in selecting the reconstruction method after gastrectomy in individual patients. (Reported by Y. Uchida)

**Symposium 3. Molecular-biological approach to invasion and metastasis of gastric cancer** (chaired by M. Kitajima, Keio University, Tokyo, and W. Yasui, Hiroshima University)

The major cause of death from cancer is metastases that are usually resistant to conventional treatment. Cancer metastasis consists of a series of sequential steps that include proliferation at the primary site, neovascularization, invasion into stroma, entrance to the vessels, survival in the circulation, adhesion to endothelial cells and extravasation, and regrowth at the secondary site. In these steps, multiple genetic and epigenetic alterations are involved that are crucial targets for the diagnosis and therapy of cancer metastasis. To understand the precise molecular mechanisms of cancer invasion and metastasis, seven speakers reported their recent progress in research on tumor suppressor genes, apoptosis-related genes, cell adhesion molecules, etc.

C. Sakakura, Kyoto Prefectural University of Medicine, opened the symposium by discussing a novel tumor suppressor gene, *AML2* (*RUNX3*), in gastric cancer. Hemizygous deletion and reduced expression was found in 20% and 65% of gastric cancers, respectively. Introduction of *AML2* into gastric cancer cell lines inhibited cell growth and reduced tumorigenicity in nude mice.

K. Miyachi, Dokkyo University, reported on the mRNA expression of the antiapoptotic gene *survivin* in

gastric cancer. Levels of *survivin* were higher in cancer tissues in comparison with levels in nonneoplastic mucosa. Moreover, the expression of *survivin* was increased in cancers with lymph node metastases.

T. Ashizawa, Tokyo Medical University, presented the results of flow cytometric analysis of the expression of sialyl Lewis antigens ( $Le^a$ ) in gastric cancer. The expression of sialyl  $Le^a$  as monitored by the reactivity to CA19-9 antibodies was significantly correlated with liver metastasis and poor prognosis.

K. Ito, Tokyo Medical University, reported the abnormal expression and promoter hypermethylation of E-cadherin in gastric cancer. Reduced expression examined by immunohistochemistry and CpG island methylation assessed by methylation-specific polymerase chain reaction were closely associated with infiltrative growth and peritoneal dissemination. M. Tanaka, Saga Medical School, described the relationship between the mucin phenotype and E-cadherin expression in early gastric cancer. Abnormal E-cadherin expression was more strongly associated with mucin phenotype than with histological classification. Reduced expression of E-cadherin frequently occurred in *MUC1*-positive cancers.

H. Nishimori, Sapporo Medical University, investigated factors that cause differences among hematogenous, peritoneal, and lymphatic metastases using cancer cell sublines obtained using a mouse metastasis system. Combined alterations in cell adhesion, motility, and the expression of integrals and vascular endothelial growth factor were heavily involved in which type of metastasis occurred.

M. Yashiro, Osaka City University, reported on the mechanism responsible for peritoneal metastasis and on the development of a new therapy against metastasis. Increased matrix metalloproteinase-1 production and reduced E-cadherin expression were noted in gastric cancer cell lines with highly metastatic potential. CD44H and integrin ( $\alpha 2\beta 1$  and  $\alpha 3\beta 1$ ) participated in attachment to the peritoneal surface, which was abolished by administration of inhibitory peptides RGD/YIGSR.

There was a general discussion on the implications of the present findings in clinical practice. Recent technology and knowledge should be applied actively and effectively for cancer control and prevention of cancer deaths in the 21st century. (Reported by W. Yasui)

**Panel 1. Sentinel lymph node navigation surgery** (chaired by T. Ochiai, Chiba University, and N. Tanigawa, Osaka Medical College)

A new technique, intraoperative lymphatic mapping and sentinel node (SN) identification, has emerged as a simple method to determine whether metastatic disease

is present. The clinical significance of this concept was described in 1992 by Morton et al. and thereafter confirmed in melanoma by various investigators. It was also confirmed in breast cancer, as reported by Morton's colleague Giuliano, in 1994, followed by numerous other reports. Professor K. Miwa, president of the JGCA, initiated the investigation of the applicability of this concept in gastric cancer in 1994. However, the SN technique has not yet been clearly defined in gastric cancer. Against this background, intriguing presentations and discussions touching on the various issues inherent in the implications of the SN concept in gastric cancer were given by seven experts.

M. Hiratsuka, Osaka Medical Center for Cancer and Cardiovascular Disease, reported the experience of his group in evaluating 119 patients using intraoperative subserosal injection of indocyanine green (ICG) and postulated that subserosal dye injection was preferable to intramucosal injection. N. Fukushima, Yamagata Prefectural Central Hospital, presented pessimistic data on the SN concept after using intramucosal ICG injection during gastrotomy in 43 patients. H. Higashi, Kagoshima University, focused on the significant difference between micrometastasis identified by cytokeratin immunohistochemistry and metastasis detected by HE staining, and postulated that SNs identified by ICG and RI (technetium [Tc]-Sn colloid) in 15 patients did not always predict micrometastasis in the regional lymphatic basins. T. Sawada, Osaka City University, reported experience with intraoperative endoscopic mucosal injection of isosulfan blue-vital blue dye (Lymphazurin) in 101 patients with early-stage cancer and demonstrated that lymphatic drainage from the peritumoral area was generally based on the definition of lymph node groups, that is, from group 1 nodes to group 2 nodes, except in four patients (3.7%) in whom SN was identified in the group 2 station, but not in group 1.

One of the important subjects in SN navigation surgery is the development of an accurate method to detect SNs. ICG and radioisotopes are now available. N. Narihara, Jikei University, introduced infrared radiation to detect macroscopically invisible SNs after injection of ICG. Y. Takagi, Tokyo Medical University, investigated the optimal dose of  $^{99m}\text{Tc}$ -Sn colloid when used with a gamma probe. Finally, Y. Kitagawa, Keio University, presented the experience of his group in a total of 121 gastric cancer cases with SN navigation. They injected Tc-Sn colloid and detected SNs using a gamma probe.

SN navigation is important for cancer surgery in the new century, although basic research such as that presented in this panel discussion is mandatory for further improvement of its clinical applications. (Reported by T. Ochiai)

**Panel 2.** *New methods for preoperative diagnosis of gastric cancer* (chaired by M. Maruyama, Foundation for Detection of Early Gastric Carcinoma, Tokyo, and K. Yoshino, Keio University, Tokyo)

This panel discussion focused on new methods for preoperative diagnosis which are essential for the treatment of gastric cancer. Seven speakers discussed whether the diagnostic efficacy of their methods exceeds that of conventional methods.

E. Mochiki, Gunma University, reported his experience in using  $^{18}\text{F}$ -fluorinated deoxyglucose (FDG) positron-emission tomography (FDG-PET) in the diagnosis of gastric cancer, and evaluated its diagnostic efficacy in terms of the detection of the primary focus and metastatic lymph nodes. The primary focus was detected with FDG-PET, while computed tomography (CT) detected only 21% (3/14) of the primary foci. On the other hand, no metastatic nodes were discovered using FDG-PET, whereas CT detected nodal involvement in 57% (4/7). It was concluded that at present FDG-PET does not surpass CT in the detection of lymph node metastasis.

J. Fujisaki, Jikei University, reported the utility of three-dimensional endoscopic ultrasonography (3D-EUS) in the diagnosis of the invasive depth of early gastric cancer. She described the correct diagnosis of invasive depth in 86% of cases (48/56) with radial scanning alone, which improved slightly to 91% of cases (51/56) with 3D-EUS. She also emphasized that 3D-EUS enables helical scanning in multiple directions, which permits the assessment of the deepest point of cancerous invasion not only in the linear but also in the radial direction. In addition, 3D-EUS is expected to reduce the false-negative rate in the diagnosis of invasive depth which results from a lack of skill in conventional EUS.

R. Ishihara, Osaka Medical Center for Cancer and Cardiovascular Diseases, introduced the results of diagnosis of invasive depth using infrared endoscopy. In this method, both invasive depth and horizontal spread of cancer can be diagnosed based on abnormal patterns of vessel formation in the deep layer of the mucosal membrane as shown by differences in the absorption rate of ICG after exposure to infrared radiation. He reported that the diagnosis of invasive depth was correct in 94% of cases of early gastric cancer and emphasized that this method is effective regardless of the presence of ulceration in the primary lesion.

E. Bhunchet, Tsuchiura General Hospital, reported the usefulness of fluorescein electronic endoscopy in determining the horizontal spread of early gastric cancer. In this method, the effect of fluorescein is observed with an electronic endoscope equipped with special filter 5–10s after injection. The principle of this method is based on the fact that the difference in fluo-

rescence reflects the difference in stromal volume between normal mucosa and cancerous tissue. Although he emphasized that this method allows easy determination of the horizontal spread of early gastric cancer, which was not possible even with indigocarmine chromoendoscopy, the horizontal spread could also have been determined without difficulty by simple observation or by chromoendoscopy in most of his tissue samples.

M. Niki, Osaka Medical College, described his experience in the use of multidetector-row CT (MDCT) in the preoperative staging of gastric cancer. He emphasized that MDCT enables better visualization of enlarged lymph nodes along the vessels in the perigastric region compared with conventional CT. Moreover, he stressed that dynamic delineation of the vessel pattern in the perigastric region with MDCT can assist surgeons in making preliminary plans for surgery.

The final two speakers discussed the usefulness of preoperative laparoscopic diagnosis of peritoneal dissemination of gastric cancer. Y. Iwasaki, Tokyo Metropolitan Komagome Hospital, who performed laparoscopy under local anesthesia, reported that the laparoscopic diagnosis of peritoneal dissemination agreed with the results after surgery in 94% of cases, and with the results of lavage cytology in 97%. He emphasized that preoperative laparoscopy and lavage cytology are indispensable to confirm peritoneal dissemination in advanced cancers in which the invasive depth is estimated to be T3 or deeper.

Y. Yano, Osaka University, who carried out preoperative laparoscopy under general anesthesia in most cases, stated that peritoneal dissemination was detected in 13 (40.6%) cases of advanced cancer. Dissemination was not detected by other diagnostic imaging modalities, and he stressed that second laparoscopy played a decisive role in determining the indications for salvage surgery after neoadjuvant chemotherapy in patients in whom the first laparoscopy was positive for peritoneal dissemination. (Reported by *M. Maruyama*)

**Workshop 1.** *Is low-dose chemotherapy combining 5-fluorouracil with cisplatin really effective for advanced gastric cancer?* (chaired by S. Yoshida, National Cancer Center East, Kashiwa, and Y. Yamamura, Aichi Cancer Center, Nagoya)

This workshop attempted to clarify the therapeutic efficacy of low-dose chemotherapy combining 5-fluorouracil (5-FU) with cisplatin (low-dose FP), which is widely used as the standard regimen for advanced gastric cancer in Japan. In this session, seven speakers presented their treatment results. According to them, low-dose FP is broadly indicated not only for inoperable or recurrent cases (by Y. Michiwa, Keiju Medical Center, Y. Yamashita, Osaka City University, K. Ohmura,

Kanazawa University, and R. Suto, Nagasaki University) but also for advanced operable cases (by H. Suzuki, Chiba University and K. Kondo, National Nagoya Hospital) or for those assessed as Curability B after surgery (by R. Suto and Y. Asada, Fukuiken Saiseikai Hospital). All the speakers emphasized the favorable treatment results with low-dose FP, including higher response rates or longer survival times with more limited toxicities than those in the historical controls, except that K. Kondo found no survival benefit between patients with stage IV disease treated preoperatively with low- and mid-dose FP.

Nevertheless, all the results reported were based on retrospective analyses of a limited number of cases (generally 30–60) compared with a small number of historical controls, and no prospective study or randomized controlled trial was included in the assessment. In addition, all the regimens presented used different drug doses (250–750 mg/m<sup>2</sup> or/body for 5-FU, 5–15 mg/m<sup>2</sup> or/body for cisplatin) and schedules of administration (2 days or 2 weeks or 4-week continuous). From a scientific point of view, therefore, nothing could be concluded from these reports.

In the discussion following the presentations, the chairpersons asked the speakers whether low-dose FP would be replaced by the new oral anticancer drug S-1, which has shown high response rates and low toxicities in late phase II studies. All the speakers except for H. Suzuki replied that they would hereafter use it as the first choice for gastric cancer chemotherapy in place of low-dose FP. In addition, Y. Michiwa commented that he and his group were conducting a trial of a new chemotherapy regimen of S-1 combined with low-dose cisplatin.

It appears that low-dose FP became widespread in Japan over the past several years without any definitive evidence and that it will also fall into disfavor without any definitive evidence. The experience with low-dose FP teaches the valuable lesson that nothing can be clarified from individual clinical experience comparing present and past results. It also indicates the unreliability of and lack of experience with gastric cancer chemotherapy in Japan, due to the lack of development of practical clinical trials. We therefore have reservations that the new regimen of S-1 combined with low-dose cisplatin may meet the same fate as low-dose FP. (Reported by *S. Yoshida*)

**Workshop 2.** *Extended operation to be continued in the future* (chaired by M. Kitamura, Bokuto Metropolitan Hospital, and H. Furukawa, Sakai City Hospital)

Seven papers were presented in this session. They were classified into two categories: paraaortic node dissection (PAD) for advanced cancer, and left upper abdominal exenteration (LUAE) for scirrhous carcinoma. The

presentations and discussions focused on the following three points: 1) aims and outcomes of extended operation, 2) reasons for continuation in the future, and 3) future plans for multicenter, controlled trials.

T. Kinoshita, National Cancer Center East, reported no surgical deaths and good quality of life (QOL) after PAD. He emphasized that surgeons need experience with 20 to 30 cases to be able to perform PAD. A randomized, controlled study is ongoing in the Japan Clinical Oncology Group (JCOG). M. Terashima, Iwate Medical School, reported that nerve-preserving PAD is better than common PAD in terms of QOL, and feels that a Japanese surgeon with more than ten years of training can perform this operation. Since the surgical procedure is too complicated, a multicenter, randomized controlled study cannot be carried out. C. Kunisaki, Yokohama City Medical School, reported that a surgeon with seven to eight years of training can perform PAD. Postoperative complications increase but the survival rate improves. T. Kosaka, Kanazawa Medical School, reported that surgeons who trained for 10 years can perform PAD. However, post-PAD complications frequently occur, leading to high costs to the Japanese health care system. PAD is not a standard procedure worldwide. All speakers thought that PAD improves survival, but because of surgical risks or postoperative complications, it will not become standard surgery worldwide. The JCOG will report the results of a phase III study of PAD in five years.

H. Furukawa, Sakai City Hospital, reported that surgical death, pancreatic fistula, and 5-year survival rates were 3.7% (in the early period), 30%, and 40% (stage III disease), respectively, after LUAE for scirrhous gastric cancer. Well-trained surgeons can perform LUAE with low risk and few complications. Only LUAE has improved the survival rate in scirrhous carcinoma patients, while other treatments including various postoperative chemotherapies are not curative in this disease. A multicenter, randomized controlled study should be done to evaluate LUAE.

E. Nomura, Osaka Medical School, reported that surgical death, pancreatic fistula, and 5-year survival rates after LUAE were 4.2%, 29.2%, and 46.8%, respectively. He also emphasized that a randomized controlled trial is necessary. S. Ohyama, Cancer Institute Hospital, reported that surgical death, pancreatic fistula, and 5-year survival rates after LUAE were 1.2%, 11.9%, and 13.4%–66.7% (N3–N0 disease), respectively. He recommended that every surgeon attempt LUAE. He is developing a protocol to evaluate LUAE in scirrhous carcinoma or large type 3 cancer. The original LUAE procedure (Kajitani) indicated multiple organ resection (total gastrectomy with left liver, pancreas, spleen, gallbladder, left adrenal, and transverse colon resection). In this workshop, a more

rational surgical procedure (total gastrectomy with transverse colon and spleen resection) was proposed. A multicenter, randomized controlled study was recommended to evaluate “rational LUAE.” (Reported by H. Furukawa)

**Workshop 3.** *Problems in intraoperative peritoneal lavage cytology of gastric cancer* (chaired by N. Kaibara, Tottori University, and Y. Kato, Cancer Institute, Tokyo)

Since intraoperative peritoneal lavage cytology of gastric cancer was adopted in the 13th edition of *The General Rules for Gastric Cancer Study*, interest in lavage cytology has revived. In practice, however, some problems remain, including: (a) the site for collecting lavage specimens; (b) management of the collected specimens; (c) differentiation of reactive mesothelial cells from cancer cells; (d) detection of cancer cells through the molecular-biological approach and its reliability; and (e) methods of treating stage P0/CY1 gastric cancer.

*The General Rules of Intraoperative Peritoneal Cytology for Patients with Gastric Cancer* published by the Japanese Society of Clinical Cytology suggests peritoneal washing with instillation of 100 to 200 ml of physiological saline after initial laparotomy, with subsequent collection of the fluid from the pouch of Douglas, which serves as the specimen. T. Kanda, Niigata University, intraoperatively collected lavage specimens from three sites per patient: the right subhepatic space, left subphrenic space, and pouch of Douglas. Some patients survived long term without recurrence when the cytology was positive in only one of the three specimens. However, the outcome was extremely poor when the cytology was positive in two or more of the specimens. He concluded that it is more reliable to collect lavage specimens from multiple sites.

The method of recognizing carcinogenic embryonic antigen mRNA in lavage specimens obtained through the left subphrenic space and pouch of Douglas is superior in its high sensitivity to cancer cells; one problem in this method is that it can induce false-positive reactions (H. Tokuda, Kagoshima University). On the other hand, as the exposure to serosal invasion increases, the cytological positive rate becomes higher (Y. Kato, Osaka City University). This finding is well known and accepted, but the overall cytological positive rate of gastric cancer differs significantly among medical institutions, which strongly indicates the importance of quality control of cytological specimens. Our success rate in treating patients with stage P1CY1 gastric cancer has been extremely low, but when the stage is P0CY1, some patients survive for more than 5 postoperative years (I. Miyashiro, Osaka Medical Center for Cancer and Cardiovascular Diseases). This favorable outcome of stage

POCY1 gastric cancer is mainly due to the effectiveness of chemotherapy. Finally, K. Kurozumi, Osaka Police Hospital, published a noteworthy report concerning intraoperative peritoneal hyperthermochemotherapy, which has significantly improved the outcome of stage POCY1 gastric cancer. (Reported by *N. Kaibara*)

**Workshop 4.** *Chemotherapy for gastric cancer from the viewpoint of quality of life and cost-benefit analysis* (chaired by T. Konishi, Kanto Medical Center NTT EC, Tokyo, and A. Ohtsu, National Cancer Center Hospital East, Kashiwa)

Although gastric cancer cannot be cured by chemotherapy alone, recent developments in biochemical modulation appear to contribute to improved results of chemotherapy. In this workshop, six presenters and Professor J.P. Kim, Korea, discussed recent progress in chemotherapy for gastric cancer from the viewpoint of QOL and economic impact.

Y. Sano, Jikei University, reported that construction of the button-type jejunostomy enables safe, simple enteral nutrition, thus opening the way for delivering home chemotherapy smoothly. H. Makino, Yokohama City University, reported that intraaortic infusion of antineoplastic agents at low doses results in a high efficacy ratio with fewer adverse reactions and thus effectively improves QOL in terms of performance status, increased oral food intake, etc.

The other four speakers discussed the new oral anti-neoplastic agent S-1 and outlined its advantages. I. Takano, Kyushu University, stated that serious adverse events are rare with S-1, and that, because high antitumor efficacy can be achieved with oral administration, it can be administered on an outpatient basis. M. Murakami, Showa-inan General Hospital, reported that

a combination of 5-FU, mitomycin C, and cisplatin (FMP) followed by S-1 as maintenance chemotherapy appeared to be effective in 23 patients with advanced gastric cancer. Survival of the 23 patients appeared superior to that of 15 patients treated with best supportive care alone. However, the validity of this strategy remains to be confirmed, particularly the use of FMP as first-line therapy and the timing of the change to S-1.

B. Nakata, Osaka City University, also demonstrated the efficacy of S-1 in 22 patients with advanced gastric cancer. In addition, he compared medical costs between patients treated with S-1 and with low-dose FP. The costs of each agent were comparable, although low-dose FP required additional costs for hospital stay. He concluded that S-1 had cost-benefit advantages and resulted in a better QOL as compared with low-dose FP. R. Kim, Hiroshima University Hospital, reported that treatment with S-1 in 25 patients yielded a response rate of 46% and was associated with mild toxicity. S-1 also provided clinical benefit in 60% or more patients with peritoneal dissemination. Compared with their experience with low-dose FP, S-1 yielded an identical response rate without the requirement of hospital admission. These reports suggest that S-1 is active against advanced gastric cancer, with superiority to other regimens in terms of QOL and cost, although the results should be confirmed in future clinical trials with large sample size.

At the end of the session, Professor J.P. Kim, Inje University, Korea, added comments from the viewpoint of Korean surgical data. He reported on the efficacy of peritonectomy and chemoimmunotherapy in stage IV disease and indicated the need for the development of new agents to improve the results in advanced disease. (Reported by *T. Konishi*)