Meeting Report

Report of the Eleventh International Symposium of the Foundation for Promotion of Cancer Research: Basic and Clinical Research in Gastric Cancer

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INTRODUCTION

The Eleventh International Symposium of the Foundation for the Promotion of Cancer Research was entitled ‘Basic and Clinical Research in Gastric Cancer’ and was held in Tokyo on April 21-23, 1998. The symposium was organized by Drs M. Sasako, S. Hirohashi, C. van de Velde and S. Yoshida, with Dr T. Sugimura as adviser.

Dr Sugimura opened the symposium with a welcoming address and a review of previous symposia (1-10). He noted that it was perhaps unusual that this was the first of the symposia devoted to gastric cancer, a major problem in Japan. Dr van de Velde in his opening address reviewed the history of European contact with the East, going back 400 years when the first Dutch explorers reached the Japanese coast. Over recent years contacts have been strengthened in the area of cancer research and treatment, with increasing interchange of physicians and ideas, culminating in the randomized trials of D1 and D2 gastrectomy that were featured in this symposium program.

In the keynote address, Dr Mitsuru Sasako of the National Cancer Center Hospital Tokyo (NCCH) addressed the question ‘Is gastric cancer a different disease in the West and Japan?’ This is a key issue; as recently as 1989 a British Journal of Surgery article suggested that the disease was different and that this explains the very different results of treatment reported from Japan and the West (11). Although critical, this issue is difficult to address. For early gastric cancer, there are different attitudes between Western and Japanese pathologists with regard to dysplasia and mucosal carcinoma, making comparison of results difficult (12). Advanced cancer is not subject to histological confusion. However, the more extensive surgery routinely used in Japan means that stage migration (transfer of some patients from n1 to n2, n3, n4, resulting in improved results for each group) will contribute to different stage-specific results. Other possible explanations for the differences include the therapeutic effect of surgical treatment, with more extensive surgery in Japan. The Dutch trial of D1 vs D2 lymphadenectomy showed no overall improved survival, but improved survival in certain subsets. This trial was extensively discussed later. There may also be different outcomes from the same treatment; Western patients generally have more complications and a higher postoperative mortality after extensive gastric surgery than the Japanese. Patient factors — older, with more cardiovascular and respiratory disease — as well as surgeon-related factors — less experience with the operation and with management of the complications — may be significant. Regarding the possibility that there are biological differences, comparisons of histological and genetic factors of Japanese and European tumors showed no differences. Although the question remains unanswered, it is clearly not appropriate simply to attribute the outcome differences to fundamentally different pathology.

CARCINOGENESIS AND CANCER PREVENTION

Dr Anthony Axon from Leeds, UK, reviewed the role of Helicobacter pylori (HP) as a gastric carcinogen. HP was designated a class 1 carcinogen by the World Health Organization in 1994, but its true role in the disease remains controversial. HP is the commonest cause of atrophic gastritis and intestinal metaplasia (IM), conditions known to predispose to gastric cancer. The link between HP-induced gastritis and gastric cancer has not, however, been clearly established. Atrophy related to autoimmunity, bile reflux, genetic predisposition and diet might be more important. Dr Axon reviewed the epidemiological evidence, showing that infection with HP over a longer time is associated with a higher relative risk of gastric cancer. In addition, infection with more virulent strains of HP (CagA positive HP) is more strongly associated with gastric cancer. This is persuasive evidence that HP is directly involved in carcinogenesis: the overall association between gastric cancer and HP is potentially due to the confounding effect of lower socio-economic class, but it is highly unlikely that confounding factors would select for a particular strain of HP. Infection with HP increases cell prolifer-
ation, reduces luminal vitamin C concentration, increases the generation of reactive oxygen metabolites and induces hypochlorhydria. All of these could potentially increase the chance of carcinogenesis, but direct association of HP infection with DNA mutation remains elusive. The final proof of the association between HP and the development of cancer of the distal stomach will rely on controlled studies, comparing the outcome of infected patients treated with either active or placebo therapy.

Dr Daizo Saito of NCCH addressed the HP issue from the Japanese viewpoint. Epidemiological data from Japan support the association between HP and gastric cancer, although the possibility of HP strain differences being significant has not been confirmed in Japan. Animal experiments using the Mongolian gerbil have demonstrated that HP infection can produce gastritis and IM and that long-term eradication of HP leads to regression of the gastritis and some of the IM. This suggests that eradication may reduce the incidence of IM (and hopefully also gastric cancer). Proof may come from the Japanese Intervention Trial for HP eradication (and other intervention trials). The trial involves randomizing those with HP to eradication or not and following the groups until 2004. Trial endpoints are the progress of atrophy and the incidence of gastric cancer.

Dr Toshio Fujioka of the Oita Medical College reported on animal models of HP-induced gastritis in the Japanese monkey and the Mongolian gerbil. In both models, the results demonstrated that HP infection can produce atrophic gastritis, while IM is produced only in the Mongolian gerbil. Infection alone did not produce gastric cancer in either of the animal models. When the known gastric carcinogen MNNG was administered via drinking water to the gerbils, 17% of them developed adenocarcinoma after 1 year. Of the animals infected with HP that also received MNNG, 67% developed carcinoma, suggesting the role of HP not as initiator but as promoter of gastric carcinoma. Dr Masae Tatematsu of Aichi Cancer Research Center also described experiments with carcinogens and HP infection, where HP was again shown to enhance carcinogen-induced adenocarcinomas and also showed that other chemicals, such as catechols, could enhance the effect of the carcinogen MNU.

The etiological role of factors other than HP was addressed. Dr Masayoshi Tokunaga of Kagoshima University and Dr Toyoro Osato of Hokkaido University both presented work on Epstein-Barr virus (EBV). In addition to its well known role in the development of Burkitt’s lymphoma and nasopharyngeal carcinoma, EBV is known to be responsible for the majority (>90%) of the rare gastric lymphoepithelial-like cancers. It has also been implicated in 5–10% of ordinary gastric adenocarcinomas. EBV-associated adenocarcinomas have been found at varying frequency throughout the world and often show distinctive ‘lace-pattern’ histology. Interestingly, the rate of lymph node metastasis seems to be lower in EBV-associated tumors. None of
the T1 tumors studied by Dr Tokunaga had nodal metastases, compared with an expected rate of 15–20% for submucosal T1 tumors. The rate of HP infection did not differ between EBV-positive and -negative tumors. Dr Osato concentrated on the genetics and immune response in EBV-associated gastric cancer, showing that there is clonal proliferation of infected cells and that expression of EBV proteins persisted throughout the disease. A possible mechanism for the infected cells to escape immune surveillance is that only the EBNA1 protein is expressed and this protein is not a target for killer T-cells.

Dr Toshikazu Ushijima of the NCC Research Institute presented progress towards the isolation of a gene imparting resistance to MNNG gastric carcinogenesis. By studying the genetics of crosses between susceptible and resistant rat strains, two loci have been identified. It appears that genes at these loci interact as far as MNNG resistance is concerned. The size of the tumors in resistant and sensitive animals did not differ, suggesting that the genetic variation leads to different susceptibility to tumor induction in response to carcinogen, but not to different tumor phenotype. While certain interesting genes are known to be in the regions identified, there are no definitive candidate genes yet.

Dr Stephen Meltzer of the University of Maryland, USA, reported that microsatellite instability (MSI) has been found to affect the coding sequence of specific genes in specific cancers. For instance, in MSI positive endometrial cancers, the PTEN gene is usually affected. With respect to gastric cancer, the TGF type-2 receptor and the IGF2 receptor appear to be frequently affected by MSI. Mutations in either of these could affect the growth regulatory effect of TGF. Other targets for MSI have been identified, suggesting that MSI-induced mutation of specific genes may be a distinct carcinogenic pathway in MSI-positive tumors. Dr Meltzer is now attempting to define the pattern of MSI ‘mutations’ seen in various cancers.

Dr Shoichiro Tsugane of NCCH East has studied factors that might account for the geographic variation in gastric cancer incidence throughout Japan. Diets high in fruit and vegetable (high levels of β-carotene), high in vitamin C and low in salt were found to be associated with a reduced gastric cancer incidence. Two intervention trials have therefore been developed in an attempt to alter the incidence of gastric cancer in high-risk areas. These involved supplementing the diet with β-carotene and vitamin C in one study and a dietary modification study in a high-risk area in the other. Preliminary results of the dietary modification study showed an alteration in the dietary patterns after instruction. Long-term results are not yet available.

PREMALIGNANCY

Dr Manfred Stolte of Bayreuth, Germany, is attempting to identify the subgroup of patients with gastritis at risk for gastric cancer. This is important, because HP gastritis is a very frequent condition and attempted large-scale eradication would not only be very expensive and probably futile, but also possibly unwise, as the true nature of the interaction between HP and humans is incompletely understood. By comparing the characteristics of gastritis in patients with gastric cancer with those with duodenal ulcer disease, his group has found that severe gastritis in the fundus compared with the antrum was associated with a higher risk of carcinoma. Measures of the severity of gastritis, including degree of gastritis and activity of gastritis, as well as the presence of multifocal intestinal metaplasia, appear to be features that could identify high-risk patients. In Germany, a prevention study has been initiated in which males over 55 with HP gastritis and all three potential risk factors are targeted for intense surveillance.

Dr Norio Matsukura of Nippon Medical School and Dr Hiroshi Yokozaki of Hiroshima University addressed the question of whether IM is a premalignant condition from different viewpoints. Dr Matsukura studied patients with HP-associated gastritis, gastric atrophy and IM and reported that eradication of HP led to reduced inflammation and activity of gastritis in all patients and in three of 16 patients there was evidence of reversal of cases of incomplete IM. To address the genetic characteristics of IM, Dr Yokozaki reported that telomerase activity was often associated with gastric cancer, but was also seen in a significant minority of benign gastric epithelium (9/26). IM was present in all the telomerase-positive gastric mucosa and the degree of telomerase RNA expression was related to the degree of HP infection. MSI studies of IM and gastric cancer also showed some parallels, with MSI seen in about 30% of both gastric cancer and IM.

Dr Jeremy Jass from Brisbane, Australia, and Dr Hidenobu Watanabe of Niigata University discussed the differences in Western and Japanese views of dysplasia and mucosal cancer. Dr Jass summarized the main issue by pointing out that the Western approach is directed by the concern to avoid a false diagnosis of cancer and thus avoid unnecessary surgery. Hence cancer is only diagnosed when there is unequivocal evidence of neoplastic cells with invasion. The term dysplasia may be overused in the West, with many benign or reactive lesions being called mild dysplasia and lesions that are actually well differentiated carcinomas being called severe dysplasia. Dr Jass suggested that it was vitally important for Japanese and Western pathologists to reach a consensus on this issue, so that discussions and collaborations can be based on common understanding. Dr Watanabe continued the discussion and generally agreed with Dr Jass. While Western pathologists stress the importance of invasion into the lamina propria for a diagnosis of carcinoma, cytological and/or architectural features are more important for Japanese pathologists. There are various features that are important in differentiating various early lesions of the mucosa, but the difficulty of distinguishing between them is obvious from a recent paper in which various leading Western and Japanese pathologists reviewed several cases: their diagnoses varied widely. The paradox quoted by Dr Jass impressively demonstrates the actual situation in the two hemispheres: the Japanese treat early cancers of well differentiated type with endoscopic resection whereas Western surgeons treat severe dysplasia with more extensive surgery (with higher mortality).

Dr Takanori Hattori of Shiga University and Dr Tadakazu Shimoda of NCCH then talked about the evolution from early to advanced gastric cancer. Dr Hattori reported that studies of very small cancers of both diffuse and intestinal type showed that the
tumors appear to arise in the neck region of the gastric glandular tubules. Even in the early stages, there were different genetic features such as ploidy variations and oncogene mutations and the pattern of genetic alteration between early and advanced lesions differed in diffuse and intestinal tumors. Dr Shimoda reported that most very small early gastric cancers (<5 mm) are of the intestinal type and that there is more diffuse-type histology in the larger early gastric cancers. The pattern of mucin expression varied with the tumor size and he speculated that there might be conversion from intestinal to diffuse type as the tumors grow in size.

Dr Heinz Karl Höfler from Munich, Germany, and Dr Atsushi Ochiai of NCCRI discussed exciting work using molecular biology to predict tumor behavior. Dr Höfler first reviewed evidence that expression of uPA (urokinase-type plasminogen activator), its inhibitor PAI-1 and other associated molecules indicates a poor prognosis in gastric cancer. Expression of these factors correlates with a tumor with high capacity for invasion/metastasis and so these factors may become useful molecular targets for therapy. Cell surface molecules that are involved with cell–cell or cell–matrix interactions have been characterized and changes in the nature or expression of these molecules may also be prognostically significant. Dr Höfler reported also on new work on the E-cadherin cell adhesion molecule. Somatic mutations have been found in more than 50% of diffuse-type gastric cancers, but only in very small numbers of intestinal-type cancers. The mutations were found in very small tumors as well and were clonal within the tumors examined. Most mutations involve exon 8 or 9: in-frame deletion of exon 9 can be considered a mutational hot spot. In _vitro_ work with E-cadherin null cells transfected with the mutated E-cadherin showed decreased cell–cell adhesion and increased motility compared with those transfected with the wild-type molecule. A specific monoclonal antibody to exon 9 deleted E-cadherin showed specific immunos­
taining of tumor cells, suggesting this may offer a target for specific diagnosis and immunotherapy. When α- and β-catenin (other molecules involved with E-cadherin in cell–cell interaction) were studied, some changes in the E-cadherin adhesion mechanism were found in all diffuse type cancers and many intestinal cancers as well, suggesting that this mechanism is very important in gastric cancer.

Dr Ochiai reported his work that shows that β4-integrin expression is inversely correlated with peritoneal dissemination. This is critically important in gastric cancer, as peritoneal recurrence is the commonest site of first recurrence and is a leading cause of death from gastric cancer. Adhesion of cancer cells to the peritoneum via integrin was thought to be the most critical step in development of peritoneal dissemination. Using a SCID mouse model of peritoneal dissemination, Dr Ochiai found that there was a clear inverse correlation between β4-integrin expression and peritoneal dissemination. This dissemination was suppressed in low-expressing cell lines by introducing a β4-integrin expression construct, suggesting that the relationship was causative. Clinical studies of T3N0 serosa-invading gastric cancers (at high risk of peritoneal recurrence) found that the tumors expressing high levels of β4-integrin expression had a low incidence of peritoneal dissemination at surgery, a longer disease-free interval prior to peritoneal recurrence and a better prognosis. These studies indicate that β4-integrin expression may be a useful marker for clinical management of gastric cancer and provide an insight into peritoneal dissemination to guide further studies.

Dr Yoshitaka Tsubono of Tohoku University and Dr Kazumasa Miki of Toho University presented papers on different approaches to screening for gastric cancer. Dr Tsubono studied the effect of screening using barium contrast studies in Miyagi Prefecture. In 1995, approximately 6100 gastric cancers were identified, with a calculated sensitivity and specificity of 80 and 90%, respectively. In cohort studies and case control studies, it appears that screening may reduce the gastric cancer specific mortality by about 50%, but unfortunately there are no data from randomized control trials and so these results are subject to the well recognized biases of screening programs. In addition, the compliance is low at 20% and the cost effectiveness of the program is unclear. Dr Miki reported progress in the use of the serum level of pepsinogen I and the pepsinogen I/II ratio to select a population at high risk for gastric cancer. Pepsinogen I <70 g/l and a I/II ratio of <3 both correlate with the presence of chronic atrophic gastritis. Dr Miki described the introduction of these tests into workplace screening, with endoscopic assessment of those found to be at high risk. He outlined potential cost and convenience advantages to a blood test-based screening program over a radiographic program. He also outlined theoretical advantages in sensitivity and specificity, positive predictive value and the percentage of early gastric cancer based on his initial results in Tokyo. It was suggested that the apparent relative superiority of the pepsinogen method might be due to the reduced effectiveness of a radiographic screening program once the incident cases (found in initial screening) have been identified. It was agreed that randomized trials would be needed to establish the true effectiveness of the screening options.

Dr Shigeaki Yoshida of NCCH East expanded the discussion on early diagnosis of gastric cancer to review the changes in the nature of early gastric cancers (EGC) being diagnosed in Japan. EGC now makes up more than 50% of new cancers, compared with just over 20% in the early 1960s. It is probable that the widespread use of endoscopy with precise observation, dye spraying and routine biopsy is the reason for this increase. ‘Gastritis-like’ EGC shows only faint mucosal irregularity, with poorly demarcated erythema, localized discoloration and/or mucosal unevenness. It is now the most common type of EGC diagnosed at NCC. Studies using routine endoscopy followed by dye spraying demonstrated that this lesion might easily be missed if dye spraying is omitted.

Dr Masakazu Maruyama of the Cancer Institute Hospital reviewed recent developments with preoperative staging of the tumor and the lymph nodes. Endoscopy with EUS is fairly reliable at assessing the depth of T1 tumors, although there is a 30–40% incidence of mucosal tumors being called submucosal and vice versa. Occasionally T2 mp tumors were diagnosed as being T1 sm. EUS is less accurate for advanced cancers, with T2 ss lesions most subject to error. T3 lesions were correctly diagnosed by EUS in 60–80% of cases. The major role for EUS
at present appears to be in assessing the suitability of mucosal lesions for endoscopic mucosal resection (EMR). CT assessment of nodal metastases is even less encouraging, with an overall sensitivity of only 20%. In fact, preoperative assessment of N stage may be best done by correlating with T staging and tumor size. At present, surgery needs to be planned largely without preoperative knowledge of the lymph node status.

Dr Yutaka Yonemura of Kanazawa University discussed his experience of preoperative diagnosis of peritoneal dissemination using percutaneous peritoneal lavage and analysis with both cytology and RT-PCR. He found that preoperative lavage is positive in about half of all patients found to have peritoneal dissemination at operation, but is positive in only 9% of P0 patients. When the molecular analysis for E-cadherin was added, all patients with peritoneal dissemination were identified. When the cytologically positive patients were followed, all had died within 3 years and there was no difference in survival between the P1 and P0 patients who were cytologically positive. By treating cytologically positive patients with hyperthermic intraperitoneal chemotherapy, it appears that the survival is prolonged, although more patients with more follow-up are needed.

CHEMOTHERAPY

Dr Jaffer Ajani from Houston, USA, and Dr Atsushi Ohtsu of NCCH East reviewed the current state of chemotherapy for gastric cancer. Both agreed that there is no ‘standard’ chemotherapy for advanced disease. FAMTX (5-fluorouracil, Adriamycin and methotrexate), ECF (epirubicin, cisplatin and 5FU) have reported response rates of up to 40% and have been shown to improve survival in those with metastatic disease from 3–4 months (with best supportive care) to 9–10 months, but improved agents are definitely needed. Promising new drugs include taxotere, CPT-11 and S-1. Initial studies have suggested that these are active in many cases of gastric cancer and the results of trials of these agents alone or combined with cisplatin and/or 5FU are awaited. Trials of postoperative adjuvant chemotherapy have not shown a survival benefit. A variety of promising preoperative regimens are now being examined. Dr Stefano Cascinu from Pesaro, Italy, spoke about the possible role of gastrointestinal hormones and other active agents as chemotherapy. Octrtoide may be useful in providing symptomatic relief for patients with chemotherapy-resistant metastatic disease. Other hormonal manipulations may be possible.

SURGERY

The topic of the symposium then moved to surgery for gastric cancer. Dr Blake Cady of Harvard and Brown University, USA, presented a lecture on the basic principles of surgical oncology, where he argued that lymph node metastases are indicators, but not governors, of survival in cancer. He reviewed series of various solid tumors from the USA and observed that almost all 10 year survivors after lung, breast, colon and stomach cancer had either no nodal involvement or a very small number of involved nodes. His data for survival after limited resection for gastric cancer suggested a much worse outlook than seen in Japan, where more extended surgery is generally used. Dr Cady cautioned that stage migration may be a major contributor to the apparent difference and also suggested that most of the difference in outcome is due to early diagnosis of lesions at much earlier stages. The lack of randomized trial data showing improved survival with more radical lymph node dissection is consistent with the general principles.

There were then lectures from Dr Cornelis J H van de Velde from Leiden, The Netherlands, Dr Takeshi Sano of NCCH, Tokyo, and Dr Peter McCulloch from Liverpool, UK, that all addressed the issue of clinical trials in surgery for gastric cancer. Dr van de Velde presented the final analysis of the Dutch gastric cancer trial. The trial was designed to detect a 12% survival difference after 5 years for patients having D1 or D2 dissection; 711 eligible patients who underwent curative surgery were included in the study. The analysis at 7 years could not demonstrate a difference in survival in favor of either of the treatments; splenectomy had an adverse effect on survival; age over 65 and male sex were the most important risk factors for postoperative death (13). Cumulative relapse risk after D2 was significantly less than after D1 in subgroup analysis of those treated without splenectomy and those who had more than 25 nodes dissected. When survival was analyzed according to TNM staging, there was a trend towards better survival after D2 dissection in all stages, but it only reached significance for stage IIIA (about half of this difference could be due to stage migration). Unfortunately, TNM staging cannot be used preoperatively. The conclusions from the trial were that in Western settings, patient selection is vital and older obese male patients must be approached with caution. As there is a significant incidence of morbidity, it is important that surgeons and hospitals are equipped to deal with the complications and that the surgical procedure should be selected with care, avoiding pancreatecetomy and splenectomy except in cases of direct invasion. D2 dissection should be reserved for antral tumors or patients likely to be stage II or IIIA.

Dr Sano described the current D2/D4 trial for patients with apparently curable tumors that are at high risk for paraaortic lymph node involvement. The rationale behind this trial is that about 20% of those patients with grossly negative but microscopically positive paraaortic lymph nodes have experienced long-term survival. He also showed that many patients who had more than seven positive nodes dissected survived more than 5 years. The difference in postoperative morbidity between the Japanese and the Dutch patients is striking, with no operative deaths and no serious morbidity reported from the first 140 patients entering this trial.

Dr McCulloch provided commentary on Western D1/D2 trials, discussing the problems that have occurred in both Dutch and British trials and the lessons that can be learnt from them. Major factors can be seen in these trials that may affect the results. The first is compliance and contamination, where patients randomized to a certain operation actually have either less or more surgery than planned and the second is the learning curve effect, where poorer results occurring while a surgeon is learning a new procedure might affect the outcome of a trial. Great care is needed
to ensure that the enormous effort required to mount a randomized trial of a surgical technique does result in a conclusive answer to the fundamental question.

Dr Martin Karpeh of the Memorial Sloan-Kettering Cancer Center, New York, reviewed the Memorial experience to address the role and impact of splenectomy in association with D2/3 gastrectomy for gastric cancer. By comparing groups who had gastrectomy with splenectomy with or without pancreatectomy and performing multivariate analysis, including relevant patient, tumor and surgical factors, he concluded that splenectomy with or without pancreatectomy increases the morbidity and mortality of extended lymphadenectomies for gastric cancer without increasing disease-specific survival. The recommendation was therefore to perform a splenectomy only if necessary for tumor clearance.

**FUTURE DIRECTIONS**

Dr Wataru Yasui of Hiroshima University reviewed the current understanding of the molecular genetics of gastric carcinogenesis. In Hiroshima a program has been established in which gastrointestinal lesions are subject to an array of molecular analysis with the aim of identifying those patients who have differential prognosis or who are at risk of developing multiple cancers. Potentially useful information has been gained in about 15% of lesions examined. For example, early cancers limited to the mucosa showing high-grade malignant potential predicted by this examination are treated not by EMR but by surgery with ordinary lymph node dissection.

Dr Shoji Nakamori of Osaka Medical School has been using RT-PCR analysis for cytokeratin-19 of blood and lymph nodes to identify circulating cells or micrometastatic nodal disease. As others have reported, there are potential problems with false positives with CK19 RT-PCR. Dr Nakamori’s group failed to find CK19 in tumor draining venous blood in any of the gastric cancer patients they studied, but were able to find it in 14 (15%) of the 93 histopathologically negative lymph nodes. Whether such results are clinically relevant will require large-scale experiments with more specific and standardized techniques.

Dr Narikazu Boku of NCCH East addressed the topical field of the prediction of chemotherapy response by biological and molecular markers. Results of a study of 64 patients with irresectable gastric cancer and measurable metastatic disease were treated with either 5FU and cisplatin (FP) or cisplatin and CPT-11 (CP). Biopsies of all tumors were examined before treatment for five biological markers: expression of p53, bcl-2, vascular endothelial growth factor (VEGF), thymidylate synthase (TS) and glutathione S-transferase π (GST-π). The relationship between the expression of the factors and response to chemotherapy was assessed, with p53 (--), bcl-2 (--), VEGF (+), TS (--) and GST-π (--) being associated with chemoresistance. In the 19 cases with four or more favorable characteristics, the response rate was 75% (6/8) for FP and 73% (8/11) for CP. The best response was for the eight cases with more than four favorable characteristics treated with FP (median survival 474 days).

Dr Yoshio Nitsu of Sapporo Medical University addressed the possibility of using immunotherapy or immunochemotherapy in gastric cancer management. Studies using peptides and mini-genes have shown promise in vitro, but there are no clinically significant results so far. Reasons for the poor results include weak antigenicity of the tumors and possible production of immunosuppressive factor(s) by the tumor cells.

Dr Tetsuro Kubota of Keio University later presented results of experiments designed to predict drug response using a three-dimensional histoculture drug response assay (HDRA). Responses of a range of gastric and colorectal cancers to standard chemotherapeutic agents in the HDRA were compared with the clinical outcome. The accuracy was about 92%, with 100% true negative rate, but only 67% true positive rate. HDRA was used in a blinded trial with 215 patients with advanced gastric cancer who were to be treated with chemotherapy. Those whose tumors were found to be sensitive had a significantly prolonged overall and disease-free survival rate. Clinical trials based on such information are planned to assess whether the information is truly useful. This method seems to be very useful but takes longer and is more labor intensive than the MTT assay.

On a more hopeful note, Dr Hitoshi Kondo of the NCCH presented his unit’s experience with endoscopic mucosal resection (EMR) for early cancers. From 1987 until 1996, 440 cancers have been treated this way, with the mean diameter of the resected cancers being 14 mm and the recurrence rate being only 3%. With increasing experience and the recent introduction of the insulated diathermic knife (the Hosokawa knife), the indications have been expanded. At present mucosal cancers that are up to 30 mm in diameter, without ulceration and without both lymphatic and vascular invasion, are suitable for EMR. A very impressive videotape of an EMR using the Hosokawa knife was shown. EMR is uncommonly practiced in the West, but considering that lesions diagnosed as severe dysplasia are being treated by open surgery, introduction of the technique is an urgent issue.

Dr Anthony Axon summarized the symposium, highlighting the many insights into gastric cancer that had been presented. The whole issue of the role of HP in gastric cancer and the appropriate response to HP infection will remain a topic for debate for some time. It is clear that the differences in pathological assessment of early lesions between the East and the West must be clarified to allow more and fruitful discussion and comparison of results. The endoscopic assessment techniques developed in Japan may be applicable in Western patients and this could lead to the introduction of less invasive treatments such as EMR. Randomized studies of lymphadenectomy have not completely clarified the issue of the most appropriate extent of surgery, but have highlighted differences in the outcomes after surgery in Japan and the West. Similar randomized controlled trials are needed to determine the most appropriate approach to screening for gastric cancer.

Dr Sugimura summarized the views of all participants when he stated that the symposium had been a great success, stimulating a lot of thought and discussion. He proposed that the meeting re-convene in 5 years to review progress.
Acknowledgments

The organizing committee greatly appreciates the contribution of all the speakers and participants of this international symposium and their contribution to its ultimate success. This symposium was supported by the Japan Keirin Association and the Foundation for Promotion of Cancer Research to promote the program of the Second Term Comprehensive 10-year Strategy for Cancer Control by the Ministry of Health and Welfare, Japan.

References