to the mucosa or submucosa) and T2-MP tumors (invasion confined to the muscularis propria); hence, these patients were not eligible for randomization. Only patients diagnosed with T2-SS (subserosal invasion) or deeper tumors at the time of laparotomy were included in the study. T2-SS is clinically recognized as a white discoloration on the serosal surface, without overt tumor serosal exposure.

During the operation, the para-aortic nodes were inspected to exclude patients with gross metastasis (enlarged and/or hard nodes) in this region. Frozen section diagnosis of the para-aortic nodes was forbidden to avoid technical contamination between the two groups of patients. Peritoneal lavage cytology was performed immediately after initial laparotomy, and absence of free cancer cells was confirmed before enrollment.

Random Assignment

While waiting for the result of lavage cytology, the surgeon examined the above eligibility criteria and started the D2 procedure. When the negative cytology result was obtained 30 to 60 minutes later, he informed the JCOG Data Centre for enrollment. Patients were then randomly assigned either to receive standard lymphadenectomy (group A) or extended lymphadenectomy (group B). The sizes of the groups were balanced according to T stage (T2 *v* T3/T4), tumor growth pattern (expansive *v* infiltrative growth), and institution. The randomization arm was notified to the surgeon immediately, who then completed the operation according to the allocated protocol.

Surgical Methods

Group A: Standard D2 gastrectomy. Patients were treated with gastrectomy and D2 lymphadenectomy. Depending on the location of the primary tumor, the surgeon performed either a total, proximal subtotal, or distal subtotal gastrectomy. D2 lymphadenectomy was a standard procedure for dissection of tumors located in the upper two thirds of the stomach as defined in the 12th edition of the Japanese Classification (1993)[15] when the study was initially designed. An extended D2 lymphadenectomy was performed for tumors located in the lower third of the stomach, which involves further dissecting the hepatoduodenal nodes (No.12a), retropancreatic nodes (No.13) and nodes along the superior mesenteric vein (No.14v). This technique was frequently performed as a standard procedure in the specialized centers, and thus adopted in this study (all except No.13 have been integrated as "D2" in the 13th edition of Japanese classification[16]).

In total or proximal subtotal gastrectomy for proximal tumors, the spleen was removed in principle for splenic hilar lymphadenectomy, while it was preserved in distal subtotal gastrectomy for distal tumors.

Group B: D2 gastrectomy combined with para-aortic lymphadenectomy. Patients in this group had similar procedure to group A, but with additional para-aortic lymph node dissection. The area to be dissected was defined in the Japanese classification (Fig 1). Proximal tumors were treated with the standard D2 lymphadenectomy, and also all "No.16-a2" (para-aortic nodes between the level of the celiac axis and the left renal vein) and "No.16-b1" (para-aortic nodes between the left renal vein and the inferior mesenteric artery) were removed. Standard distal subtotal gastrectomy was performed for the distal tumors including the "No.16-a2" and "No.16-b1" nodes; however, dissection of the left upper lateral nodes ("No.16-a2-lat") was optional.

Both group A and group B patients were followed up according to a fixed schedule, without receiving adjuvant chemotherapy.

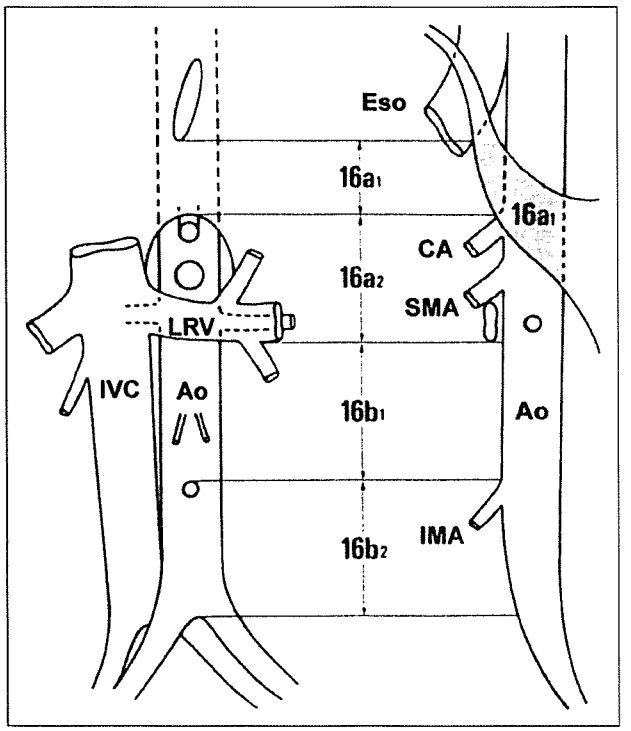

Fig 1. Anatomic definitions of para-aortic lymph nodes.[15] The nodes No.16a2 and No.16b1 are defined as "regional nodes" and were dissected in the extended surgery group. Ao, aorta; CA, celiac artery; Eso, esophagus; IMA, inferior mesenteric artery; IVC, inferior vena cava; LRV, left renal vein; SMA, superior mesenteric artery.

Evaluation of Operative Morbidity and Mortality

Operative methods and pathology results were recorded according to the 12th edition of the Japanese Classification of Gastric Carcinoma.[15] The following information was included on the case report form for prospective data collection concerning the four major groups of operative morbidity: presence or absence of anastomotic leak, pancreatic fistula, abdominal abscess, and pneumonia. Anastomotic leak was diagnosed radiologically either on routine postoperative contrast swallow or based on clinical suspicion, and was recorded regardless of its clinical significance. Pancreatic fistula was usually diagnosed when fluid with a high amylase concentration drained from the peripancreatic area for more than 7 days.

Other complications were recorded on a free format. The duration of surgery, blood loss, blood transfusion requirement and reoperation details were also recorded. Hospital mortality was defined as postoperative death of any cause within 30 days, or death within the same hospitalization.

Sample Size

The projected 5-year survival rates for groups A and B patients were 50% and 62%, respectively, and we initially planned to recruit 412 patients (206 each group) to detect this difference with one-sided α error of .05 and statistical power of 80%. At first, the recruitment was slow, but it improved as the study progressed. When the planned recruitment was almost achieved, the JCOG Clinical Trial Review Committee approved the amendment to increase the number of patients to 520 (260 each group) to

Table 2. Patients' Demographics and Tumor Characteristics

	Group A (n = 263)	Group B (n = 260)	Total (N = 523)
Male-female ratio	176/87 = 2.02	182/78 = 2.33	358/165 = 2.17
Age, years			
Median	60	61	61
Range	25-75	27-75	25-75
Tumor diameter, cm			
Median	5.5	5.5	5.5
Range	2-17	2-15.2	2-17
T-stage (macroscopic)			
T2-SS	99	93	192
T3	150	159	309
T4	14	8	22
Tumor location			
Upper 1/3	53	47	100
Middle 1/3	103	103	206
Lower 1/3	107	110	217

NOTE. All data are numbers of patients except where otherwise indicated.
Abbreviation: SS, subserosal invasion.

enforce the statistical power to detect 8% difference in the 5-year survival rates, with a 5.5-year accrual period and an additional 5-year follow-up.

Institutions and Quality Control of Surgery

The approval of the institutional review board from all participating institutions was obtained. Initially, the 12 institutions of the Gastric Cancer Surgical Study Group of the JCOG participated in the trial. Twelve institutions were added to increase patient recruitment before February 1999.

All participating surgeons agreed to the technical details for surgery during the planning stages of this trial. Significant experience in gastric cancer surgery, especially experience in extended lymphadenectomy, was a prerequisite for a surgeon's participation in the trial. Surgeons with experience of more than 100 D2 gastrectomies, or institutions with a specialized unit with annual gastrectomy volume of 80 cases or more were selected.

During the recruitment period, participating surgeons and Data Centre representatives met three times per year to monitor the study. In each meeting, videos of para-aortic dissection were presented for critique from four or five institutions, and the technical details were discussed. To assess compliance with lymphadenectomy, dissection, node recovery status in all nodal "stations," and the number of dissected nodes in the para-aortic area were recorded in the case report form, and the results were monitored.

Statistical Methods

The operative morbidity and mortality rates were based on the proportion of the number of cases divided by all registered patients based on the intention-to-treat principle. The differences in proportion between groups were evaluated using Fisher's exact test. Differences in length of hospital stay and blood loss were compared by Wilcoxon test. All P values are two-sided, and statistical analysis was done using SAS (SAS Institute, Cary, NC) version 8.12.

RESULTS

Recruitment

Recruitment commenced in July 1995, and closed in April 2001. A total of 523 patients were enrolled: 263 in group A and 260 in group B. A large variance was observed for the number of patients recruited between the institutions. Fifty-three percent of all patients were recruited by the five major hospitals.

The JCOG site-visit audit reported that written consent was available for all except nine patients from one institution. In another institution, an additional six patients had informed consent submitted by a family member.

Patients and Surgery

Patient demographics and tumor characteristics are presented in Table 2. The two groups were well balanced, as there were no significant differences in their baseline data.

The operative details are shown in Table 3. Total gastrectomy was performed in 38% of all patients, and the vast majority of total gastrectomies (186 of 199 cases) were accompanied by splenectomy. Pancreatectomy was confined to those patients whose pancreas was involved by tumor, accounting for 11% of all total gastrectomies. In four cases, proximal subtotal gastrectomy with splenectomy was performed instead of total gastrectomy. Para-aortic lymphadenectomy required longer operation time (median, 63 minutes) and resulted in greater blood loss (median, 230 mL) than the standard D2. Blood transfusion was required approximately twice as often.

Protocol Violation and Ineligible Cases

There were 10 cases of protocol violation (1.9%). In one case, the para-aortic nodes were examined by frozen

Table 3. Operative Details

	Group A (n = 263)	Group B (n = 260)	Total (N = 523)	P
Gastrectomy, No. of patients				.62
Total	102	97	199	
Distal subtotal	160	160	320	
Proximal subtotal	1	3	4	
Splenectomy, No. of patients	98	93	191	.79
Pancreatectomy, No. of patients	9	13	22	.39
Operation time, minutes				< .001
Median	237	300	270	
Range	127-625	153-600	127-625	
Blood loss, mL				< .001
Median	430	660	530	
Range	32-1,810	60-2,885	32-2,885	
Blood transfusion				< .001
No. of cases	37	78	115	
%	14.1	30.0	22.0	
No. of retrieved nodes				< .001
Median	54	74	61	
Range	14-161	30-235	14-235	

section before registration. In another case, the surgeon performed para-aortic dissection despite the allocation to group A because after randomization, he found a positive node behind the common hepatic artery, believed to be strongly suggestive of metastasis in the para-aortic area. The postoperative course of this patient, who was allocated to group A but treated as group B, was uneventful, and analyzing this patient as either group A or group B had no effect on the results in this study. We left this case in group A based on intention-to-treat analysis. In the other eight patients, nodal stations No.13 and/or No.14v were not dissected in distal third tumors.

In another case, the initial histological diagnosis following endoscopic biopsy was poorly differentiated adenocarcinoma but the final histology of the resected stomach revealed gastric lymphoma. We included this patient in the morbidity/mortality analysis, but will exclude their data from the final survival analyses.

Operative Morbidity

The overall operative morbidity rate was 24.5%. The morbidity for group B patients was higher than group A (28.1% and 20.9%, respectively), but the difference did not reach statistical significance ($P = .067$). The incidence of the four major surgical complications was not different between the two groups (Table 4).

There were various other complications reported, and the incidence was significantly higher in group B than group A patients. Paralytic ileus causing significant delay of recommencement of oral feeding, abdominal and/or left pleural lymphorrhea requiring prolonged drainage for more than 1 week, and severe diarrhea, were specific to the extended para-aortic dissection group (Table 4). Reoperation was needed in 12 patients (2.3%), and there was no difference in the reoperation rate between the two groups. Median hospital stay after surgery was 21 days in group A, and 24 days in group B ($P < .01$).

Hospital Mortality

There were four hospital deaths (0.8%)—two in each group. Each group had one patient who died of postoperative complications, and one died of rapidly progressive cancer. All other patients recovered from surgery and were discharged from hospital.

DISCUSSION

In this randomized controlled trial, the role of para-aortic dissection will be evaluated in terms of survival benefit,

Table 4. Operative Morbidity and Hospital Mortality

	Group A (n = 263)		Group B (n = 260)		
	No. of Patients	%	No. of Patients	%	P
Any complication	55	20.9	73	28.1	.067
Anastomotic leak	6	2.3	5	1.9	.99
Pancreatic fistula	14	5.3	16	6.2	.71
Abdominal abscess	14	5.3	15	5.8	.85
Pneumonia	12	4.6	4	1.5	.072
Others	24	9.1	52	20.0	< .001
Obstruction or ileus	5		11		
Lymphorrhea	0		10		
Left pleural effusion	1		6		
Severe diarrhea	0		3		
Reoperation	5	1.9	7	2.7	.57
Hospital death	2	0.8	2	0.8	.99

operative morbidity/mortality, and quality of life. The results will provide important information and should guide decision making regarding the choice of operative methods. The quality of life and survival among these patients are still in the follow-up phase, and the analyses will take place in 2004 and 2006, respectively. This report compares the morbidity and mortality rates of D2 plus para-aortic node dissection with standard D2 dissection.

There is a wide variation in operative morbidity and mortality following gastric cancer surgery among countries and institutions. The presence of comorbid disease that affects patient fitness for surgery, surgical experience of the operator, and the workload volume seem to be important factors.[17,18] The mortality for gastrectomy in Western countries often exceeds 5% and approaches 16% in some series.[19-21] Conversely, Japanese studies have consistently reported a mortality rate of lower than 2% in retrospective observations. To date, the present study is the first large-scale prospective randomized controlled trial in Japan to compare surgical techniques under strict quality control and data management. The extremely low hospital death rate after extended para-aortic lymphadenectomy (0.8%) in this multi-institutional setting confirms the findings from previous retrospective reports.

This trial is a striking contrast to the the Dutch[4] and British[5] D1/D2 trials, in which D2 lymphadenectomy was associated with operative mortality rates of 10% and 13%, respectively. One important criticism of the European randomized trials was the issue of learning curve, as many British and Dutch surgeons participating in the trials were new to the D2 procedure. Surgical experience, specific anatomic knowledge, and careful postoperative managements by experienced teams are crucial to the success of this type of surgery. An Italian group appropriately carried out a phase 2 study of D2 lymphadenectomy in selected institutions[22] until an acceptable operative mortality rate was achieved, before conducting a randomized controlled trial comparing D1 and D2 gastrectomies.

The D2 gastrectomy procedure is known as "extended lymphadenectomy" in Western countries, while Japanese surgeons employ D2 as a standard technique, and reserve the term "extended" for para-aortic dissection. Lymphatic drainage from the stomach flows to the perigastric nodes and then to the nodes around the celiac axis and its main branches. From here it enters the para-aortic nodes before joining the systemic circulation via the thoracic duct. Hence, the para-aortic nodes may be regarded as the final station of nodes that can be dissected to remove the threat of systemic metastases originating from the lymphatic system. Many Japanese surgeons in specialized centers who performed para-aortic dissection found microscopic metastases in this region, and believe that this type of surgery may be potentially worthwhile. However, the risk associated with para-aortic dissection dictates advanced operative skills and intensive postoperative care. Therefore, scientific evidence supporting a survival benefit must be obtained before employing this technique in routine gastric cancer surgery.

The very low operative morbidity and mortality achieved in this JCOG trial can be attributed to several factors: (1) we selected a group of fit patients who could tolerate para-aortic dissection in the study. (2) Only specialist surgeons with an established track record of extended lymphadenectomy participated in the trial. (3) High-throughput centers were selected for their operative skills and standardized postoperative management. (4) Pancreatectomy was avoided whenever possible, while splenectomy accompanied total gastrectomy in most cases. We report that there was no significant difference in the overall complications between the two groups; however, the para-aortic dissection group had significantly higher "other" complications (on free format) compared with standard D2. Lymphorrhea and paralytic ileus were more specific to this operation. This observation may be biased because of the surgeon's awareness of the patient's randomization arm of para-aortic dissection.

In the British and Dutch trials, splenectomy with or without distal pancreatectomy was highlighted as a major risk factor for operative morbidity and mortality.[5,23] Total gastrectomy for proximal tumor requires more advanced surgical skill and is associated with a higher morbidity compared to distal gastrectomy. Proximal gastric tumors are rapidly increasing in number in the western countries,[24,25] while the incidence remains stable in Japan,[26] and this may partly explain the superior results obtained in Japanese studies. However, no difference was observed in the distribution of the primary tumor location between the Dutch[4] and the Japanese cohort. The proportion of total to distal gastrectomy was also very similar. Therefore, variation in tumor location and type of gastrectomy could not account for the difference in morbidity/mortality, at least between these trials. JCOG recently launched a randomized controlled trial to evaluate the role of splenectomy combined with total gastrectomy in proximal tumors.[27]

Gastric cancer, though decreasing in incidence worldwide, remains a major health problem in many countries. R0 (no residual disease) resection is the only curative measure; but the more extended the surgery, it is believed the greater is the risk of operative morbidity and mortality. The type of gastrectomy and the extent of lymphadenectomy must be carefully planned for each individual patient with gastric cancer. The Japanese guidelines clearly define D2 gastrectomy as standard surgery[28] based on the excellent results in Japanese studies, while the British cancer guidance[6] discourages D2 based on the poor results of their randomized trial. This contrast should be addressed by surgeons' efforts, such as establishment of specialized standard training systems or production of evidence by high-quality randomized trials in specialized centers.

In conclusion, this study has shown that specialized surgeons could safely perform gastrectomy with D2 lymphadenectomy in patients with low operative risks. Extending the surgery to para-aortic lymphadenectomy did not increase the major operative complications and hospital deaths. However, compared with the D2 procedure, para-aortic dissection requires a longer operation time, leads to a larger volume of blood loss, and longer hospital stay. Until survival benefits are clarified when the data mature sufficiently, para-aortic lymphadenectomy for gastric cancer should be regarded as experimental surgery[28] and only performed in specialized institutions within the context of a well-designed clinical trial.

Appendix

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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Review article

TNM and Japanese staging systems for gastric cancer: how do they coexist?

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Abstract

Two staging systems for gastric cancer, International Union Against Cancer (UICC)/TNM and the Japanese classification, have been used widely for clinical practice and research. The two systems started independently in the 1960s, and underwent several revisions and amendments in order to approach each other, but have become more divergent in the latest editions because of characteristics based on different philosophies. The TNM system adopted a number-based system for N-staging that provides easy and accurate prognostic stratification. Comparative studies have shown that the TNM system has greater prognostic power than the Japanese classification. It contains, however, no treatment guidance and should primarily be used as a guide to prognosis. In contrast, the Japanese classification has been designed as a comprehensive guide to treatment, originally for surgeons and pathologists, and today for oncologists and endoscopists as well. Its anatomical-based N-staging was established based on analysis of lymphadenectomy effectiveness, and naturally provides direct surgical guidance. Clinicians should understand the roles of each system and must not mix the systems or terminology when they report their study results.

Key words Stomach neoplasms · Classification · TNM · Japanese classification · Stage

Introduction

Gastric cancer is the world's second commonest cancer, superseded only by lung cancer in this undesirable world ranking. While the incidence of gastric cancer continues to decline steadily in the West, it is still the commonest malignancy in Japan. However, the chance of cure from the disease remains highest in Japan, where there has been a steady improvement in survival rate over the past three decades. Much of this is due to increased diagnosis of early gastric cancer, which accounts for half of all cases, as well as more radical intervention for advanced disease. By contrast, the majority of the cases in the West present late with advanced disease, and there has not been a significant improvement in the overall survival, despite improvements in surgical technique.

Narrowing the gap between Western and Japanese outcomes will probably require changes at many levels. However, attempts to compare gastric cancer outcomes have been hampered by differences in both the philosophy and practicality of staging the disease in Japan and the West [1].

The two main staging systems for gastric cancer are the TNM staging system of the International Union Against Cancer (UICC), and the Japanese Classification of Gastric Carcinoma by the Japanese Gastric Cancer Association (JGCA). Similarities between these two staging systems exist; namely, that staging is dependent on the extent of the primary tumor, the extent of lymph node involvement, and the presence or absence of distant metastasis. However, there still remain fundamental differences between the two staging systems. The most recognizable difference lies with the classification of regional lymph node spread. The UICC/TNM staging system divides N stage on the basis of the number of metastatic lymph nodes, while the Japanese classification stresses the location of involved nodes.

Staging has a variety of functions, which should be reflected in the staging systems used. In addition to providing an indication of prognosis, staging should ideally be able to provide a framework for treatment decisions, and should allow for evaluation of treatment with meaningful comparisons between different treatments or the same treatment modalities by different groups.

The purpose of this review is to outline the philosophy, background, and major features of the current staging systems and to assess their suitability to serve the above functions.

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Two main classifications

The current main classification systems for gastric cancer are the sixth edition of the UICC/TNM classification (2002) [2] and the thirteenth edition of the *Japanese classification of gastric carcinoma* (second English edition [3] (1998), downloadable from http://www.jgca.jp/PDFfiles/JCGC-2E.PDF), herein referred to as the JGCA classification. Other systems have been proposed, which will be discussed briefly later in the text.

UICC/TNM classification

In 1954, the UICC appointed a Committee on Tumor Nomenclature and Statistics, which subsequently agreed on a technique for classification of cancer according to the anatomical extent of the disease. Gastric cancer was first included in the TNM staging system in 1966. There have been relatively few revisions to the UICC classification, which is now still only in its sixth edition.

The UICC/TNM system was originally a purely clinical classification, so that a disease stage could be decided before any treatment. In gastric cancer, however, surgical findings were indispensable for classification, because the principal prognostic factors were diagnosed only after surgical exploration. The American Joint Committee on Cancer Staging and End Results Reporting (AJCC) was organized in 1959 to develop a staging system acceptable to the American medical profession, basically using the UICC/TNM format. In 1970, the AJCC published a TNM-based staging system, using clinical, surgical, and histological information [4]. The background database was from 1241 patients with gastric cancer, which had been analyzed by a task force from seven American institutions. The system used penetration of stomach wall (T), proximity to the primary cancer of metastatic perigastric lymph nodes (N), and presence or absence of distant metastases (M), including nodes not in the perigastric area, as these criteria had the greatest impact on outcome in the above cohort.

The third edition of the UICC/TNM in 1978 contained a unified classification with the AJCC. The T stage was defined by stomach-wall invasion, but the "clinical T" and "pathological T" had different definitions. The N stage was defined by anatomic location of nodes from N0 to N3. N1 nodes were defined as metastatic perigastric nodes within 3 cm of the primary, and N2 nodes were nodes beyond 3 cm from the primary, or along the celiac, splenic, left gastric, or hepatic arteries. N3 nodes were paraaortic and hepatoduodenal nodes. In the fourth of the TNM classification edition (1987), T stage was unified to the style of the current edition, and the N3 category was dropped and reclassified as M1 (Table 1).

Table 1. TNM classification, 4th edition; 1987

		M0			M1
		N0	N1	N2	
M0	T1	IA	IB	II	
	T2	IB	II	IIIA	
	T3	II	IIIA	IIIB	
	T4	IIIA	IIIB		
M1					IV

N1, perigastric nodes within 3 cm of the primary tumor; N2, nodes beyond 3 cm from the primary, or along the celiac, splenic, left gastric or hepatic arteries

Table 2. TNM classification, 5th edition; 1997

		M0				M1
		N0	N1	N2	N3	
M0	T1	IA	IB	II		
	T2	IB	II	IIIA		
	T3	II	IIIA	IIIB		
	T4	IIIA				IV
M1						

N1, 1–6 involved nodes; N2, 7–15 involved nodes; N3, >15 nodes

The fifth edition (1997) of the TNM classification contains several amendments from the previous edition. The greatest change was that, whereas previously N status was determined by the anatomical site of involved lymph nodes, in the new classification, N stage is determined by the number of metastatic lymph nodes from a minimum yield of 15 lymph nodes in total (N1, 1–6 involved nodes; N2, 7–15 involved nodes; and N3, >15 nodes; Table 2). This had been explored as an option for some time and a proposal to add the number of involved lymph nodes to the anatomical-based N stage was published by the UICC in 1993 [5]. The idea of adopting a number-based N-staging for gastric cancer had also been proposed by some Japanese surgeons [6,7]. Data from a German multicenter gastric cancer study showed the effectiveness of the new proposal in providing better prognostic stratification than previous systems [8].

The new classification was developed, with four N categories (N0 to N3) instead of three as was initially proposed, and was presented in Seoul, Korea, at the 12th International Seminar of the WHO Collaborating Centre for Gastric Cancer in 1996 [9].

In addition to the change in N status, hepatoduodenal nodes are now once again regarded as regional nodal metastases rather than distant metastases, and the stage grouping has been altered, with all N3 patients now classified as stage IV (Table 2). T4N1 disease has also been changed to stage IV, having previously been classified as stage IIIb in 1987.

The latest edition of the TNM classification (sixth edition; 2002) amends pT2 into the subgroups pT2a and pT2b, which represent invasion confined to the muscularis propria and subserosa, respectively. This equates to T2 MP and T2 SS in the JGCA classification.

Japanese classification

The first edition of the General Rules for Gastric Cancer Study was published by the Japanese Research Society for Gastric Cancer in 1962. Stage groups were defined by the extent of serosal involvement (S stage), the location of involved lymph nodes depending on the site of the primary tumor (N stage), and the extent and sites of distant metastases (M, H, and P stages for distant metastasis, and hepatic and peritoneal disease, respectively). In its twelfth edition, the General Rules changed from the S-stage to a T-stage system, which was equivalent to the T-staging of the UICC system.

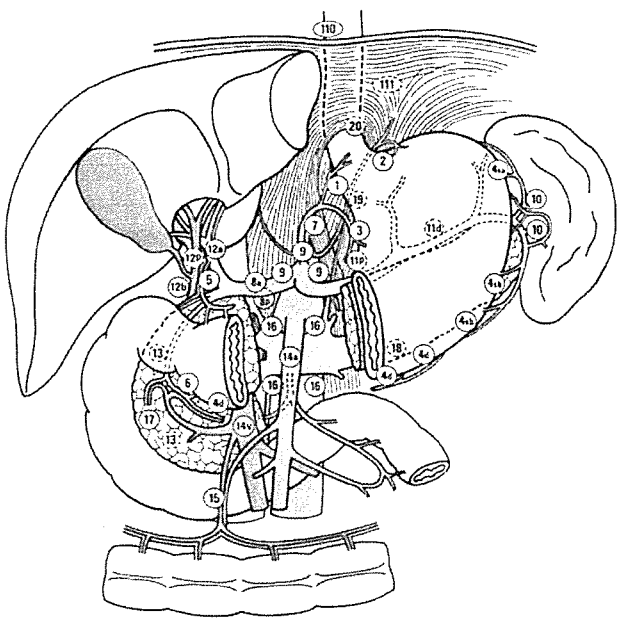

Fig. 1. Lymph node station numbers (*circled*) in the Japanese classification of gastric carcinoma [3]. These stations are further classified into N1/N2/N3 according the location of the primary tumor

The JGCA classification gives a number to all of the regional lymph node stations (Fig. 1), which are classified into three tiers according to the location of the primary tumor. Radical lymphadenectomy in gastric cancer surgery has long been commonplace in Japan and large databases of the incidence and sites of lymph node involvement exist, depending on the site of the tumor and its T stage. The purpose of the meticulous lymph node classification in the General Rules was therefore to guide surgeons to decide the extent and location of lymphadenectomy, so that any potentially involved nodes could be removed according to the site and depth of penetration of the primary gastric cancer.

Lymph node staging was characterized on the basis that gastric cancer metastasizes to groups of lymph nodes arranged radially around the stomach in tiers. The nomination of different lymph node groups to their respective tier was based upon the results of anatomical and physiological studies on lymph flow with different tumor sites.

Various amendments to the original classification followed, and the most recent classification is aimed at surgeons, pathologists, oncologists, and endoscopists who carry out endoscopic mucosal resection (EMR).

English versions were published in the *Japanese Journal of Surgery* in 1973 [10] and 1981 [11] and were referred to in Western studies. However, they were only a digest and could not fully convey the concept or details of the General Rules. The first comprehensive English edition was published in 1995 [12], based on the twelfth Japanese edition, and was named *Japanese classification of gastric carcinoma* (Table 3). The second English edition was based on the thirteenth Japanese edition, and was published in *Gastric Cancer* in 1998 [3].

There were a variety of changes in the most recent edition of the JGCA classification [13], such as rules for EMR and for staging carcinoma of the remnant stomach, and peritoneal cytology has been included in staging.

The most important changes in the current edition from a surgical point of view are the revision of lymph node staging and the consequent limitation of dissection level. Lymph node groups were reallocated from four tiers (N1 to N4) to three tiers (N1 to N3) on the basis of a detailed study of the effectiveness of dissection of different lymph node stations for tumors in the various locations within the stomach. Some lymph node groups, even some perigastric nodes for specific tumor locations, are no longer regarded as regional nodes if involved, but are regarded as sites of distant metastasis (M). This follows because their involvement is rare, and if it occurs, it invariably reflects a very bad prognosis [14]. One example would be the involvement of no. 2

Table 3. Japanese classification, 12th edition; 1993 (1st English edition; 1995 [12])

		P0, H0, M0				P0, H1, N0-2
		N0	N1	N2	N3	
P0 H0 M0	T1	Ia	Ib	II	IIIa	IVa
	T2	Ib	II	IIIa	IIIb	
	T3	II	IIIa	IIIb	IVa	
	T4	IIIa	IIIb	IVa	IVb (N4, P2,3, H2,3, M1, etc)	
P1, H0, T1-3		IVa				

Table 4. Japanese classification, 13th edition; 1999 (2nd English edition; 1998 [3])

		M0				M1
		N0	N1	N2	N3	
M0	T1	IA	IB	II	IV	
	T2	IB	II	IIIA		
	T3	II	IIIA	IIIB		
	T4	IIIA	IIIB	IV		
H1, P1, CY1, M1						

(left paracardial) nodes in the case of antral tumors. Other node groups, such as 14v (nodes along the superior mesenteric vein) and 12a (along the proper hepatic artery) are common sites of nodal metastasis for lower gastric tumors, and their dissection, even when positive, is often associated with survival. These groups have thus been brought into the N2 tier from the previous N3 tier. As a consequence, the D2 dissection, including all N2 node stations, is more radical than was previously the case, and is better targeted to actual rather than theoretical patterns of spread. D2 dissection can now be applied as standard surgical treatment for advanced gastric cancer. D3 dissection should be regarded as investigational treatment and is not standard. Following the revision of the N staging, there is no longer a category of "D4" dissection. The effect of the changes on stage grouping is that all N3 disease is regarded as stage IV, which is now no longer substratified.

There was a striking resemblance in the staging tables between the second English edition of the JGCA classification (Table 4) and the fifth edition of the TNM classification (Table 2), with the only difference being for the assignment of T4N1 disease, although the definition of N is totally different, as mentioned.

Evaluation and comparison

Similarities and contrasts between staging systems

Unification of staging systems or the concepts of staging is desirable and dialogue between Japanese and Western groups has resulted in alterations in both staging systems to take account of their different approaches.

In 1978, the UICC refined the anatomical-based N grouping into two tiers to reflect radial nodal spread, in keeping with the Japanese principles. N1 involvement was confined to perigastric nodes close to the primary, and N2 nodes referred to those along the hepatic, left gastric, splenic, or celiac arteries, as well as more distant perigastric nodes. This allowed some comparison between Japanese and UICC classifications, as N1 and N2 nodes corresponded to some extent across the two systems, although the anatomical details differed considerably.

The recent change of TNM staging to a number-based node status was a major turnaround that might separate irreversibly the two classifications, which had been converging. However, as far as prognosis is concerned, it has made direct comparison between Western and Japanese patients much easier, as the same data are available for both sets of patients. Now the clinical data recorded by the JGCA system can be exactly translated to the TNM system. The opposite is totally impossible, because the number-based system is a post-hoc pathological staging and bears no relationship to patterns of lymph node spread.

By contrast with the JGCA classification, which provides comprehensive and meticulous guidance to clinicians, the TNM classification is a simple staging system. There is little guidance on management, except that a minimum of 15 lymph nodes is recommended for accurate staging. The stage stratification from the TNM system is simple to apply and gives good prognostic information, but the use of lymph node number alone means that, without supplementary information, stage-dependent management cannot be practiced before final histology is available, as it is impossible to assess the exact number of positive lymph nodes radiologically or even surgically.

Differences in surgical philosophy between Japan and the West

It was Moynihan [15] who said that "Surgery of malignant disease is not the surgery of organs; it is the

anatomy of the lymphatic system". This is undoubtedly a basic principle of Japanese surgical practice. The commonest site of metastasis for gastric cancer is to lymph nodes. Japanese surgeons believe lymph node metastasis is orderly and progresses through the tiers of nodes in a stepwise manner. By defining the lymph node groups in each tier, the surgeon can remove all nodes to the level above that in which positive nodes are apparent or likely, on the basis of preoperative and intraoperative staging.

The JGCA classification is much more than a simple staging system, as it outlines a whole approach to gastric cancer. Rules are defined for diagnosis, surgical procedures, histology, and staging, as well as details of how to prepare the surgical specimen and lymph nodes. The JGCA classification details which node groups to remove depending on the site of the tumor and the level of dissection required. Stage grouping for prognosis naturally uses the same nodal tier basis for N-stage stratification, as it reflects both the spread of the disease and its treatment strategy.

On the other hand, the focus in Western surgical philosophy has been that prognosis is determined to a great extent by the biology of the primary tumor, and that lymph node metastasis is a marker of tumor dissemination [16]. Extended clearance of lymph nodes, unless obviously involved, is perceived to incur excessive morbidity with doubtful survival advantage. Thus, the TNM system places emphasis on prognostic staging and provides little treatment guidance.

Nevertheless, some European surgical groups consider the extended lymphadenectomy as an effective local tumor control and continue to employ D2 dissection and Japanese style N-staging [17].

Prognostic value

Japanese versus TNM classification. Since the introduction of number-based nodal staging in the UICC/TNM system, several Japanese authors have been able to compare prognosis by Japanese and TNM staging in the same patients.

In a study by Fujii et al. [18], 1489 patients were classified retrospectively according to the two classifications. They found that the survival curves in relation to the nodal staging of the two classifications were more or less similar, in that a decrease in survival was associated with an increase in the nodal classification. However, there was more homogeneity in the TNM stage groups than with the JGCA: when the patients with "n1" metastasis by the JGCA system were subdivided according to the TNM number-based system, there were significant differences in survival between "n1/pN1" and "n1/pN2". The same was true for JGCA "n2" patients classified as pN1 or pN2 by TNM stage. However, there was no difference in survival when each of TNM pN1 and pN2 groupings was subdivided into JGCA "n1" and "n2", i.e., patients with "pN1/n1" or "pN1/n2" shared similar survival curves, as did those with "pN2/n1" and "pN2/n2". This suggests that the prognostic impact of TNM pN stage is superior to that of JGCA "n" staging.

Ichikura et al. [19], Hayashi et al. [20] and Ichikawa et al. [21] also published their results from patients who underwent clinically curative gastric resection, using the JGCA and the fifth TNM classifications. All three groups of authors concluded that the TNM classification for lymph node involvement was superior to the JGCA classification in terms of homogeneity and prognostic value.

Similar conclusions were drawn by Kodera et al. [22], and they found that, even when lymphadenectomy was limited to perigastric lymph nodes, as in a standard Western style D1 resection, there was a difference in survival between pN1 and pN2, which supports the use of the new TNM classification.

In summary, therefore, the number-based N staging has greater prognostic power than the anatomical-based system.

Old TNM (1987) versus new TNM (1997) classification. Direct comparisons of the old and new TNM systems have been published by a variety of authors. Katai et al. [23] analyzed the results of 4362 patients who underwent resection for gastric cancer and found that the new system provided better prognostic stratification than the old system. However, patients classified as "pT4N1" in the new system fared better than other patients in stage IV and would have been better classified as stage IIIB.

Karpeh et al. [24] looked at the old and new AJCC/TNM classifications in 1038 patients, the majority of whom had undergone extended lymph node dissection; they also concluded that node numbers provided more homogeneous survival curves and better prediction of outcome than sites of metastases as defined by the 1987 AJCC/TNM criteria. These authors also strongly countenanced the minimum requirement of 15 nodes to limit stage migration.

Kranenbarg et al. [25] evaluated the old and new TNM classifications for their practicality and prognostic value, using the data of 1078 patients from the Dutch Gastric Cancer Trial. They found that the new (1997) TNM classification gave better prognostic stratification than the old (1987) classification.

The above studies differed from the conclusion reached by Mendes-de-Almeida et al. [26], who found the new TNM classification not very effective in improving the prognostic stratification of lymph node involvement when compared with the old TNM classification. A similar conclusion was drawn by de Manzoni et al.

[27], who concluded that both the site and the number of positive lymph nodes were independent prognostic factors in gastric cancer. Lee et al. [28] did not find superiority of the new classification, and questioned the validity of the current cutoff point for N-staging.

Practicalities of the classifications

Pre- and intraoperative staging. The TNM staging system was originally designed to help plan management before any treatment, and it is often applied in a preintervention setting, but offers little descriptive information on gastric cancer. Treatment planning often relies on supplementary information, in addition to the TNM or stage descriptor.

The recent change in TNM nodal staging further limits the ability to accurately stage patients before treatment. It is true that, in any case, the preoperative assessment of regional lymph nodes in gastric cancer using radiological imaging methods has a low accuracy rate, but counting involved lymph nodes radiologically is impossible, whereas identification of the sites of abnormal nodes is included within standard radiological reporting. Because neoadjuvant chemotherapy is attracting increasing interest today, the importance of pretreatment staging inevitably increases. The N-staging of the current TNM system does not function in this regard, and some modification might be required in the future.

The intraoperative findings during surgery may include macroscopic laparotomy findings, frozen section examination, cytology results, and the macroscopic findings of the resected specimen. Within the JGCA classification, there is clear guidance on the relevance of metastatic disease in the peritoneal cavity or any of the relevant lymph node groups, enabling surgical strategy to be decided on the basis of knowledge of the likely oncological outcome of the patient. While all the same information is available to the Western surgeon, TNM staging has little to offer in regard to strategy, unless frank, previously unrecognized metastases are found.

One example is positive peritoneal cytology, which represents stage IV disease by the current JGCA classification and is equivalent to distant metastasis in terms of prognosis. A positive finding will render a procedure palliative [29,30], and should restrict the need to pursue a radical resection.

Peritoneal cytology is not represented in the current TNM classification, and requires additional annotation if it is to be included in trials or treatment protocols.

Lymph node retrieval. The processing of lymph nodes is detailed and time-consuming with the Japanese system [31], and has been criticized for being complicated and unnecessarily labor-intensive, as it is performed by the surgical team. By contrast, in the West, the pathologist is in charge of the resected specimen, is often unaware of the precise location of the relevant lymph nodes, and is unlikely to be able to allocate each lymph node to its corresponding site and tier following an en-bloc resection. Now the number-based system can be easily applied in the West.

The TNM classification stated, in the fifth edition that, for pN0, "histological examination of a regional lymphadenectomy specimen will ordinarily include 15 or more lymph nodes". While many authors have supported the validity of the minimal number of 15 for staging [32,33], some surgeons have suggested that it could be reduced without influencing the prognostic analysis, thereby considerably reducing "unclassified (pNX)" cases. Kranenbarg et al. [25] suggested that a minimum of 5 consecutive negative nodes would suffice to stage gastric cancer as pN0, based on the data from the Dutch D1/D2 trial. Ichikura et al. [34] found that the survival rate for patients with 10 to 14 negative nodes was as good as the rate for those with 15 or more negative nodes, and suggested that the minimum number to be examined for pN0 could be reduced to 10.

In the latest edition of the TNM classification, the following sentence has been added to the pN0 definition: "If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0". This appears to mean that the figure of 15 is a recommendation, but no longer a requirement, for pN0 staging.

In node-positive patients, the current TNM classification may cause serious problems of underestimation. For example, if 6 lymph nodes only were retrieved, and all were positive for cancer cells, the staging would be assigned as pN1 in this system. It is highly likely that such a patient would have had further positive nodes that had been dissected, but not retrieved, and thus could have been staged as pN2 or pN3 if 16 or more nodes had been retrieved. This is not an unlikely situation in Western general hospitals; Mullaney et al. [35] assessed the number of lymph nodes documented for surgically managed patient in the West Midlands, United Kingdom, and found that only 31% of surgically resected patients could be staged with at least 15 nodes.

Furthermore, some authors have even suggested that 15 nodes may not be sufficient for accurate staging of metastatic nodes. Lee et al. [36] reported a retrospective analysis of 4789 patients with gastric cancer and suggested that, for advanced disease and in particular for stage IIIB, more than 15 nodes may be required for optimal staging. They indicated that, with a smaller number of nodes examined, there is a high possibility of underestimation and stage migration.

Ichikura et al. [34] emphasized that, though the mini-

mum number for pN0 could be reduced from 15 to 10, accurate staging of pN1 and pN2 requires the examination of 20 or more nodes, because the number of metastatic nodes was significantly correlated with the number of examined nodes.

Stage migration. The issue of stage migration, or the "Will Rogers phenomenon" [37], is frequently cited as a potential cause of differences in outcome between Japanese and Western patients [1]. Japanese patients undergo D2 dissection as the standard treatment, and, because more nodes are harvested, they are more likely to have positive nodes picked up compared to D0/D1 gastrectomy. The same patients in an extended lymphadenectomy series will thus be allocated a worse prognostic stage than their counterparts who had a D0/D1 gastrectomy. This will improve the survival data for all stages, purely by reallocation of patients with lymph node metastases into higher stages [38].

The introduction of the number-based N-staging may reduce stage migration among the groups with different extents of lymphadenectomy [39], if the resected nodes are fully retrieved. However, enthusiasm for nodal retrieval rather than extent of lymphadenectomy may directly influence the N-staging in this system.

Japanese surgeons usually retrieve as many lymph nodes as possible, because the nodes are literally their "harvest" of cancer surgery, while Western pathologists would be reluctant to retrieve more than the minimum requisite. The only means to prevent or minimize stage migration in the number-based system is to keep nodal retrieval at a high level (e.g., at least 15). Now that the minimum requisite of 15 is practically abolished in the sixth TNM edition, underestimation and consequent stage migration may further enlarge the apparent differences in treatment results between Japan and the West.

Other Classifications

Numerous classifications have been proposed by individual groups after sub-analysis of their own data. Most are adaptations of either anatomical or numerical systems of N-staging, as in the two major classifications.

Adachi et al. [40] and Whiting et al. [41] both employ anatomical nodal staging, with junctional nodes between conventional N1 and N2 tiers. Whiting et al. [41] suggested that junctional nodes could be assessed during surgery to decide whether or not to proceed to D2 dissection, if these nodes were involved. The rationale is based on the apparently high morbidity of D2 dissection in Western series, and they suggested that D2 dissection should be avoided if possible.

Kato et al. [42] address the issue of limited nodal dissection and describe the predictive value of the number of metastatic nodes in the Japanese (old and new classifications) "n1" perigastric stations. They found their system to have higher sensitivity, specificity, and accuracy than the TNM system or the Japanese system.

Finally, Yu et al. [43] have proposed a frequency system, based on the ratio of metastatic to dissected regional lymph nodes (more or less than 25% involved). Such a system weights against limited nodal dissection, and is a relevant approach, assuming extended lymphadenectomy has an independent survival impact.

Conclusion

Despite repeated comparisons between Japanese and Western staging systems, the systems do not, and were not designed to, fulfill the same role. The JGCA classification is a comprehensive guide to the anatomical-based treatment of gastric cancer and its regional metastases. The staging system within the JGCA classification is highly detailed and anatomically based, and it is inseparable from the guidance on surgical treatment, which is its primary focus.

The TNM system is primarily used as a guide to prognosis. It contains no treatment guidance and has recently changed to a number-based N stage, which most accurately reflects metastatic burden and, hence, prognosis. It provides a simple and reliable means of comparison of outcome between series. In Western practice, importance is placed on both surgeon and pathologist to ensure a nodal yield of at least 15 nodes. The value of the number-based nodal system for comparison will be lost if node yields are low, as a consequence of stage migration, and comparison between patients classified by the TNM and Japanese systems will remain inadequate, as the Japanese approach of D2 dissection and specimen preparation invariably results in greater node yields.

As the two systems are different in principle, it is important that clinicians involved in the treatment of gastric cancer understand the roles of each system. Surgeons using the Japanese system are able to report results by both the Japanese and the TNM staging, which will help comparisons of outcome. However, the two systems are not interchangeable, and the systems and their terminology should not be mixed if clarity is to be maintained.

Alternative staging systems continue to be proposed. Most adapt either anatomical or number-based systems, confirming the independent value of each approach.

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Meeting Report

Report of the Seventeenth International Symposium of the Foundation for Promotion of Cancer Research: Recent Advances in Gastric Cancer

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INTRODUCTION

The Seventeenth International Symposium of the Foundation for the Promotion of Cancer Research, "Recent Advances in Gastric Cancer", was held in Tokyo on March 15 to 17, 2004. The symposium was organized by Drs M. Sasako, J. Ajani, S. Hirohashi, A. Ohtsu, D. Saito, T. Sano and T. Ushijima with Dr T. Kakizoe as advisor.

WELCOME AND OPENING ADDRESS

Professor T. Sugimura [President Emeritus, National Cancer Center (NCC)] opened the Seventeenth International Symposium. Since 1987 over 500 speakers from around the world have been invited to discuss various cancers and this was the second symposium at which gastric cancer was discussed, the first being in 1998. Professor Sugimura stated his personal interest in this year's topic and recounted the history of his own gastric cancer, detected at screening and successfully treated at the NCC by total gastrectomy. Professor A. Ajani gave the opening address. Although there have been many successes in the diagnosis and treatment of gastric cancer there remain many unanswered questions. In epidemiology, environmental and genetic factors need to be identified and perhaps modified to reduce cancer rates. The differing incidences between the sexes and the geographical variation of sites of cancer occurence require explanation. Would it be possible to improve responses to chemotherapy and to target cancers with individualized therapy? These are major issues and this symposium offered a unique opportunity to discuss these dilemmas and challenges in detail.

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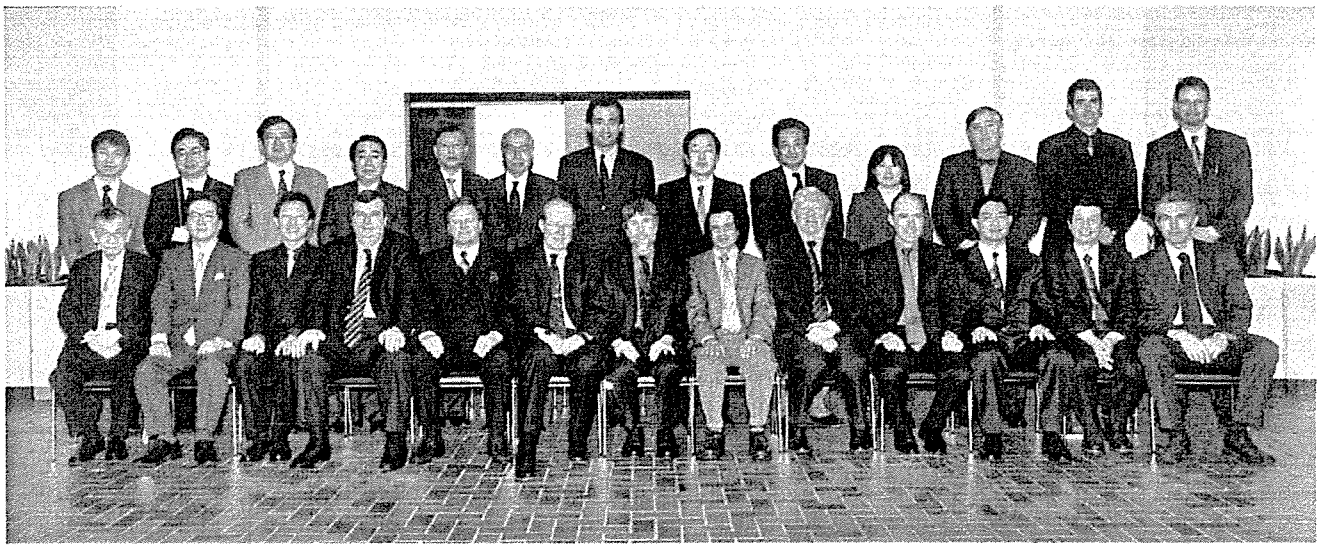
SESSION 1: EPIDEMIOLOGY, GENETICS AND PREVENTION OF GASTRIC CANCER

EPIDEMIOLOGY: CHAIRMAN PROFESSOR ADRIAN LEE

Professor P. Boyle [International Agency for Research on Cancer (IARC), Lyon, France] delivered the first presentation. Gastric cancer remains the second most common cause of cancer death in men and the fifth in women. There are large variations in incidence worldwide, rates being particularly high in the Far East and Eastern Europe. Etiological factors include smoking, salt intake, and incidence of *Helicobacter pylori*. Early studies of *H.pylori* underestimated its prevalence and more recent evidence suggests an odds ratio of at least 6.0 for the development of gastric cancer, an association exceeded only by that of cigarettes and lung cancer. Since the 1950s most countries have seen the incidence of gastric cancer halved. In the West this reduction has made the largest single contribution to the overall reduction in cancer mortality. Even now the exact reasons for this decline are not clear.

Trends in the incidence of gastric cancer in Japan were presented by Dr M. Inoue (NCC, Tokyo). Although lung cancer has recently become the leading cause of cancer related death, gastric cancer continues to be more common. The age-standardized incidence in Japan has fallen dramatically while the rapid ageing of the Japanese population has resulted in an increase in the absolute number of cases, increasing until 1995 before leveling off. The proportion of early disease increased from 25% in the 1970s to over 50% now. It is predicted that both age-standardized incidence and death rates will decline but that total cases will remain static and that the proportion of patients over the age of 80 will increase from 16% to nearly 40%. This will present many challenges for the future.

The incidence of tumors of the gastro-esophageal junction (GEJ) is thought to be increasing. Dr P. Hainaut (IARC, Lyon, France) addressed this issue. Carcinomas of the lower



esophagus (Siewert Type I) and those of the GEJ (Siewert Type II) are thought by many physicians to be synonymous. That they are different is witnessed by specific patterns of cytokeratin staining, differing expression of p53 mutation and the lack of Barrett's esophagitis in the type II tumors. Non-acid-secreting cardiac type mucosa is frequently seen at the GEJ and to many it represents a metaplastic change. In embryos however this cardiac mucosa is universal, marking it as a constitutive entity. After re-examining data on type I and II tumors and correcting misclassifications, the incidence of GEJ tumors has remained constant although there is little doubt that the incidence of adenocarcinomas of the lower esophagus is increasing rapidly.

Genetics: Chairman Professor Christian Wittekind

The Lauren intestinal and diffuse types of gastric cancer differ and Dr T. Ushijima (NCC Research Institute, Tokyo) summarized many of the genetic differences. Oncogene activation (β-catenin, K-ras and c-erbB2) and p53 mutations are frequent in intestinal type tumors (40%) compared with diffuse types (15%), but the greatest difference is in e-cadherin mutations, present in up to 50% of diffuse tumors but rare in the intestinal type. As well as direct genetic mutations, epigenetic inactivation of genes occurs and methylation of DNA, especially of promoter areas, is frequently a mechanism that prevents gene transcription. Methylated DNA is preserved after DNA replication preventing gene expression in daughter cells. Nine genes were identified as frequently methylated in gastric cancer cell lines and four were confirmed as methylated in tumors. One of these genes Lysyl Oxidase (LOX) has since been identified as a new tumor suppressor gene, suppressing the growth of tumors in LOX transfected nude mice.

Hereditary diffuse gastric cancer (HDGC) caused by germline e-cadherin mutations was first described in 1998 by Dr P. Guilford (University of Otago, Dunedin, New Zealand) who updated the symposium on its current status. Forty-four differing mutations have been identified worldwide with a penetrence of 80% in males and 70% in females. Within resected stomachs there are multiple signet ring micro-cancers (range 8–>300) with a predisposition for the transition zone between the body and antrum. There are no reports of prophylactic gastrectomy where tumor has not been found, indicating that these micro-cancers are potentially very slow growing and require a "second hit" to initiate invasion. Micro array gene mapping has identified c-src gene activation as one potential second hit. From a practical viewpoint endoscopy has previously missed many cancers but the use of Congo red dye spray has increased sensitivity such that endoscopy can be considered reliable.

Genetic alterations such as p53, β-catenin and e-cadherin are frequent in gastric carcinogenesis and the ability of gene micro array experiments to analyze thousands of genes has allowed classification of tumors at the molecular level as well as having identified novel molecular targets for therapeutics and diagnostics. Professor H. Aburatani (University of Tokyo) compared cancerous gastric and non-cancerous gastric tissue by micro array and identified genes associated with lymph node metastasis (Oct 2) or with type of tumor (LI cadherin). To assist with the interpretation of the vast amount of data produced (up to 51 000 genes) a new visualization tool, an "expression imbalance map" has been developed to allow differing gene expression to be visualized easily.

Prevention: Chairman Dr Jae-Moon Bae

High salt intake is a risk factor for gastric cancer. Dr S. Tsugane (NCC, Tokyo) presented two studies examining this relationship. The Eco cancer study selected 633 people aged 40 to 49 years from five geographical areas with large differences in gastric cancer mortality. There was a good correlation between salt intake and gastric cancer. A cohort study examined 100 000

people aged 40 to 69 years and again there was a good correlation between amount of salt consumed and subsequent development of cancer. A similar cohort study demonstrated a trend for reduced gastric cancer rates in people with higher consumption of fruit and vegetables. An RCT of vitamin C supplementation involving 439 randomized subjects demonstrated increased vitamin C plasma levels and a smaller change in pepsinogen I/II ratio (a surrogate maker for progression to atrophic gastritis) in the high dose group. Based on these results, reduction in salt intake and encouragement of consumption of fresh fruits and vegetables have the potential to reduce the risk of gastric cancer in Japan.

SESSION 2: *HELICOBACTER PYLORI* AND PATHOLOGY OF GASTRIC CANCER

HELICOBACTER PYLORI: CHAIRMAN DR PIERRE HAINAUT

Professor A. Lee (University of New South Wales, Sydney, Australia) presented evidence for *H.pylori* as a carcinogen. The Correa hypothesis of gastric carcinogenesis through gastritis, atrophy, intestinal metaplasia and dysplasia is widely accepted. *H.pylori* has been shown to be a potent initiator of inflammation and is classed as a carcinogen by the World Health Organization (WHO) although with an odds ration of only 1.92 many remain skeptical. Atrophy and intestinal metaplasia represent a hostile environment for *H.pylori* and early studies underestimated the extent of past infection. More recent studies suggest much higher ORs of up to 23. The location of gastritis is thought to determine the outcome of the disease with antral disease predisposing to duodenal ulcer and pangastritis predisposing to gastric ulcers or cancer. *H.pylori* cannot survive in the most acid producing areas of the stomach thriving only within a restricted pH range, most frequently found at the transition zone between body and antrum. In animal models as well as in humans reduction in pH with PPI, vagotomy or atrophy allows *H.pylori* to migrate proximally. There is mounting evidence that *H.pylori* strains that produce cagA, vacA or IL1B, as well as promoting carcinogenesis by inflammation, also have direct mitogenic effects on host cells.

In Mongolian gerbils (MGs) *H.pylori* infection results in chronic gastritis, peptic ulcers and intestinal metaplasia. Dr M. Tatematsu (Aichi Cancer Center Research Institute) updated the symposium on the status of these animal models. *H.pylori* infection and treatment of the stomach with N-nitroso compounds results in gastric cancers with an intestinal appearance. High salt diets acted synergistically. The duration of infection with *H.pylori* correlated with the risk of cancer, infection early in life enhancing it while eradication reduces the risk. There is some disagreement with the literature regarding *H.pylori* as a promoter or initiator of carcinogenesis, Dr Tatematsu's group finding *H.pylori* infection alone, insufficient for carcinogenesis. Experiments using chimeric mice demonstrate that each gastric gland has a single progenitor cell and that cancers are likewise clonal. The submucosal tumor-like lesions reported by others as induced by *H.pylori* are not clonal suggesting these are regenerative phenomena and that *H.pylori* acts only as a promoter of carcinogenesis.

The role of *H.pylori* eradication in reducing cancer risk remains controversial. Dr N. Uemura (International Medical Center of Japan, Tokyo) presented a follow-up study of 1526 endoscopy patients. No gastric cancers developed in the *H.pylori*-negative group ($n = 280$) but 2.9% of the *H.pylori*-positive group (36/1246) developed cancers. To investigate the role of *H.pylori* eradication, 132 patients with early gastric cancers (EGC) treated by endoscopic mucosal resection (EMR) had either *H.pylori* eradication ($n = 65$) or no eradication ($n = 67$). 16% ($n = 11$) or the non-eradicated group developed further cancers compared with 3% ($n = 2$) in the eradicated group ($P = 0.04$). Intragastric pH in the eradicated group reduced from a mean of 6 to 3. A cohort study from China supports these findings. 1630 *H.pylori*-positive patients, half with dysplasia ($n = 824$), were randomized to *H.pylori* eradication ($n = 820$) or not ($n = 810$). In the patients without initial dyplasia 1.5% (6/391) patients in the control group developed cancer versus 0% (0/413) in the eradicated group. For patients with initial dysplasia the figures were 1.5% (6/391) and 1.7%(7/407), respectively.

Having seen some evidence for the benefits of *H.pylori* eradication, Dr D.Saito (NCC, Tokyo) discussed some outstanding questions. Worldwide it is estimated that at least 60 million people are infected with *H.pylori* yet the incidence rate for gastric cancer among them is only 0.4%. Many countries with high infection rates have low cancer rates. Host and environmental factors are important but which is most important is unclear. There are also potential adverse effects of *H.pylori* eradication related to the recovery of gastric acid secretion with acute gastro esophageal erosions and gastro esophageal reflux disease (GERD) more prominent. GERD can predispose to Barrett's metaplasia a potentially premalignant lesion. There are published studies of *H.pylori* eradication and of these a Chinese and a South American study report benefit whilst an American Study did not. An intervention study in Japan has randomized 342 patients to eradication and 340 as a control group. End points are development and progression to mucosal atrophy and the trial is due to report in March 2004. Until the reports of this and other larger scale trials are known eradication cannot be recommended to all *H.pylori*-positive patients.

PATHOLOGY: CHAIRMAN PROFESSOR CORNELIS JH VAN DE VELDE

There are differences in the histological classifications used in the West and in Japan and Dr T. Shimoda (NCC, Tokyo) discussed the difficulties that arise in the diagnosis and differentiation of intramucosal carcinoma and dysplasia. In Japan the diagnosis of intramucosal carcinoma is based on structural features and cellular and nuclear atypia and invasion is not required. This has led to Western pathologists diagnosing cases

as low grade dysplasia that under Japanese classification were definite carcinomas. The Vienna classification allows five categories from 1 (negative for carcinoma) to 5 (invasive carcinoma). Category 4 (non-invasive high-grade dysplasia) includes as subgroups: high-grade adenoma, non-invasive carcinoma (carcinoma *in situ*) and suspicion of invasive carcinoma. Using this classification disagreements between Western and Japanese pathologists were limited to categories 4 and 5, both of which require treatment.

The most commonly used classifications for gastric cancer are the WHO, UICC and JGCA systems. Professor C. Wittekind (University Klinikum Leipzig, Germany) presented the differences and also the latest UICC classification. The WHO classification is based on the predominant histological subtype. Although reproducible, it suffers as most tumors are heterogeneous and it has limited prognostic value. The UICC and JGCA both stage tumors according to a TNM system and have very similar T and M stages. In the N classification, the UICC adopts a numerical system based on the number of involved nodes and the JGCA use an anatomical classification based on the site of involved lymph nodes relative to the tumor. The UICC state that: to allow accurate classification the minimum number of lymph nodes retrieved should be 16 but in cases where fewer nodes are found, so long as they are all negative, the tumor should be staged as N0 not Nx. Most parties agree that the UICC system is more accurate in determining prognosis but there are concerns that it offers no guidance to surgeons as to the extent of the required lymphadenectomy.

Dr H. Katai (NCC, Tokyo) presented the results of examining 4524 patients treated at the NCC between 1969 and 1990 for potential prognostic factors. Overall survival was 70.1% ranging from 13.7% for stage IV to 92.3% for 1A. Factors that were found to be significant include (Hazard ratio and 95% CI interval): D1 dissection (1.95; 1.69–2.25); Depth (1.31; 1.26–1.36); male sex (1.21; 1.08–1.35); older age (1.03; 1.02 −1.037); type IV macroscopic type (2.13; 1.76–2.58). Hazard ratios for N stage by JGCA were: for N1 1.39 (1.18–1.62); N2 2.58 (2.22–3.00) and N3 5.18 (4.28–6.27). The Hazard ratios for N stage by UICC were similar although the UICC had better discriminating power between pN1 and pN2 and poorer discrimination between pN2 and pN3. The importance of complete examination of lymph nodes was also demonstrated as there was downward stage migration in 14.9% of cases if nodes of 5 mm or less were ignored and 1.5% if nodes of 2 mm or less were ignored.

SESSION 3: SCREENING AND DIAGNOSIS OF GASTRIC CANCER

SCREENING: CHAIRMAN DR PARRY GUILFORD

Professor I. Tsuji (Tohoku University Graduate School of Medicine, Sendai) started the session with a report on screening in Japan. In 2001, 5.3 million people underwent mass screening representing 20% of the target population of all people aged 40 years or over. Each of the seven standard barium views of the stomach were reviewed by two radiologists. Sensitivity and specificity has been estimated at 70–90% and 80–90%, respectively, with a positive predictive value of 0.8–2.3%. Of those screened 10.3% were referred for endoscopy and 5275 cases of gastric cancer were diagnosed. Although the efficacy of mass screening has never been confirmed in randomized controlled trials, several observational studies demonstrate benefit. Three case–control studies show a pooled odds ratio of 0.39 (95%CI 0.29–0.52) for mortality in men from gastric cancer in the screened group and a ratio of 0.50 (0.34–0.72) for women. The reduction in mortality is attributable to the higher proportion of early gastric cancers in the screened group. Recent developments in screening revolve around changes in pepsinogen I/II ratios, measurable in a simple blood test, which are predictive of atrophic gastritis, a precursor of gastric cancer. Accuracy of this test is similar to that of contrast screening, but further proving trials are required before it can be considered for implementation.

Dr Jae-Moon Bae (NCC, Seoul, Korea) presented the rapid development of the national screening program in Korea. The program is targeted at lower income groups; those patients on Medicaid and beneficiaries of the National Health Insurance Corporation (NHIC). Screening is offered biannually to persons over the age of 40 years. As an incentive, the screening program qualified people for a 20% reduction in HNIC premiums, despite this the group's screening rate was 57.4% compared with 107.4% in the Medicaid group. In 2002, 806 699 people were screened using either double contrast barium meal or endoscopy, dependent on patient preference. The detection rate for gastric cancer was 0.11% in the Medicaid group and 0.13% in the NHIC group. The screening program was limited by a budget that, at $30.5 million, equated to $21 900 to detect each case of gastric cancer and a remarkable $38 to screen each person. The population in Korea aged over 40 years is 17 million and a randomized controlled trial of the effectiveness of the screening program was suggested before extending the screening program further.

DIAGNOSIS: CHAIRMAN PROFESSOR PETER BOYLE

Dr M. Kida (Kitasato University East Hospital, Sagamihara) presented recent developments in endoscopic ultrasound (EUS). EUS is 91.3% accurate for the diagnosis of intramural cancer but suffers in the diagnosis of submucosal (sm) cancer (67.7%) and invasion of the deeper muscle layers (65.7%). This is of crucial importance as new Japanese guidelines allow tumors with no likelihood of metastasis to be treated by endoscopic mucosal resection. These cancers are well-differentiated, intramural cancers and well-differentiated tumors less than 3 cm diameter with sm invasion <500 μm. A new development, three-dimensional EUS (3D-EUS) promises to improve accuracy significantly. In 3D-EUS a small scanning

head rotates as the head is automatically withdrawn within a sheath. The operator can set the speed of rotation and withdrawal and the resulting spiral image is akin to a spiral CT scan. Data can be manipulated to allow reconstruction in various planes including linear images and radial series. Accuracy is estimated at 5–10% higher than conventional EUS and importantly, for lesions larger than 0.5 cm diameter, depth of sm invasion can be determined with 75–100% accuracy.

Another new technology was presented by Dr G. Iinuma (NCC, Japan). Modern multi-detector row CT (MDCT) scanners perform highly detailed scans within a single breath hold. Computer manipulation of MDCT data allows the display of virtual endoluminal images (VEIs), views familiar to any endoscopist, as well as 3D reconstructions of the stomach. In 2003, 86 gastric cancers in 84 patients were assessed using VEIs and 3D views and compared with conventional diagnostic and staging data. Of the early lesions VEIs revealed 21/44 (47.7%) and 3D reconstructions 18/44 (59.5%). For advanced lesions 25/42 (59.5%) were identified on VEIs and 32/42 (76.2%) by 3D reconstruction. Whilst accuracy is presently insufficient for clinical use, the development of CT scanners with 16 scanning arrays compared with the current four, will lead to great improvements in resolution and the potential to revolutionize diagnosis and staging of gastric cancer.

Positive cytology of peritoneal washes is a poor prognostic indicator equating to M1 (cy1). However peritoneal recurrences occur in patients with negative cytology. To explain these recurrences Dr Y. Kodera (Nagoya University Graduate School of Medicine) reported the results of reverse transcriptase polymerase chain reaction (RT-PCR) with CEA as the target using a real time, Light Cycler instrument to detect and quantify CEA mRNA. Positive results were strongly predictive of peritoneal recurrence (83%) but this technique was unreliable in primary tumors not expressing CEA. To improve this accuracy RT-PCR against cytokeratin 20 (CK20) was performed in 195 patients but results were disappointing with accuracy of just 54% in predicting peritoneal recurrence. CEA RT-PCR remains the most sensitive method for predicting free cancer cells in the peritoneal cavity.

The effect of isolated tumor cells (ITC) detectable only by immunohistochemistry (IHC) or RT-PCR in lymph nodes has caused considerable controversy. They are frequently detected even in pT1A tumors (12–18%) and several papers report poorer prognosis when present. Dr M. Sasako (NCC, Tokyo) presented definitive data dismissing their importance. 402 patients from four centers with pT2pN0 (n = 221) and pT2pN1 (n = 181) tumors underwent D2 or greater surgery. ITC was detected by IHC in 187 cases, 81 (37%) of the pT2pN0 group and 106 (58%) of the pT2pN1 group. For ITC(−) the 5-year survival rate was 84.4% and 10-year survival 70.4%, for ITC(+) the rates were 83.9% and 72.9% (NS). For the pT2pN0 subgroup rates were 90.7% and 76.6% for ITC(−) and 91.4% and 78.2% for ITC(+) (NS). There were no significant differences between any of the survival curves and in multivariate analysis ITC was not an independent prognostic factor.

SESSION 4: SURGERY AND ADJUVANT THERAPY FOR GASTRIC CANCER

SURGERY 1 AND 2: CHAIRMEN PROFESSOR JAFFER A. AJANI AND DR ALAN ANTHONEY

The extent of lymph node dissection during gastrectomy continues to cause controversy with high mortality and lack of efficacy reported by the Dutch and British MRC randomized controlled trials (RCTs). Interim analysis of two D1/D2 and the final report on the Dutch RCT trials were reported.

Dr M. Degiuli (Division of Surgery, Turin, Italy) presented convincing evidence that D2 gastrectomy can be performed safely in the West. The Italian Gastric Cancer Study Group (IGCSG) RCT of D1 versus D2 resection involves five centers and has recruited 203 patients (97 D1 and 106 D2). To avoid excess mortality the protocol forbids distal pancreatectecomy and splenectomy unless there is direct organ invasion. Recruitment is ongoing. Morbidity is low at 4.1% in the D1 group and 6.6% in the D2 group. Only 3/203 (1.45%) patients have died, one from the D1 group and two after D2. There is a high proportion of T1 tumors (33%) and as these are less likely to have lymph node metastasis, there was some suggestion that this may cause the trial to be underpowered.

In Taiwan an RCT of D1 versus D2 has completed recruiting. Uniquely this trial with 110 D1 and 111 D2 cases was performed in one center by three surgeons allowing excellent surgical quality control with no post-operative mortality. Morbidity was higher in the D2 group (17.1% versus 7.3%), the difference largely attributable to intra-abdominal abscess formation (8.1% versus 0%) and minor anastamotic leak (4.5% versus 0%). Professor C.W. Wu (National Yang-Ming University, Taipei, Taiwan) presented the interim survival analysis. At a median follow-up of over 5 years there appeared to be a small survival advantage for the D2 group. After correcting for confounding factors that biased the results against the D2 group, 5-year survival was stated to be 15% better in the D2 group. The trial is due to complete when all patients have completed 5-year follow-up.

Professor C.J.H. van de Velde (Leiden University Medical Center, Netherlands) discussed the long term results of the Dutch RCT of D1 versus D2 trial. Follow-up is now available to 11 years and survival remains the same in both groups (31% versus 35% NS). The excess surgical mortality and morbidity in the D2 group was largely attributable to the distal pancreatectomy (DP) and splenectomy (S) but what is frequently not realized is the contribution that these procedures make to ongoing mortality, biasing results against the D2 group. In subgroup analysis excluding patients with DP and S, the higher mortality still seen in the D2 group is not significant (3.8% versus 6.3%) and survival differences at 5 (47% versus 56%) and 10 years (33% versus 47%) were significantly better in the

D2 group. Even though numbers are small the benefit of D2 gastrectomy was largely in patients staged as N2 by the new UICC staging system.

Three large RCTs have been organized by the Japanese Clinical Oncology Group (JCOG) examining the extent of surgery required in the treatment of gastric cancer and Dr T. Sano (NCC, Tokyo) appraised these trials. JCOG 9501 recruited 523 patients to a trial of D2+ para-aortic lymphadenectomy versus D2 for T2b/T3/T4 tumors. Morbidity was higher in the group undergoing more extensive surgery (29% versus 21%) but mortality was identical with only two deaths in each group. The final analysis is due in 2006. The current trial (JCOG 0110) commenced in 2002 and will recruit 500 patients with T2 or greater proximal cancers. Randomization will be between splenectomy and spleen preservation. Although splenectomy is performed without increased mortality in Japan JCOG 0110 will compare reduction in morbidity associated with spleen preservation against the risk of local recurrence. JCOG 9502 was a trial comparing abdominal (A) approach versus thoracoabdominal (TA) approach with dissection of some mediastinal nodes for gastric cancer with esophageal invasion. The TA approach was expected to prove superior. After 8 years the first interim analysis was performed on 165 patients. There was only one death in the TA group but morbidity was significantly higher (47% versus 34%). Survival was better at all times in the A group (NS). The estimate for the possibility of a significant survival advantage occurring in the TA group if the trial was completed was 3.65% and the trial was halted.

Following trials the discussion turned to surgical techniques. In 2001 in Japan 959 cases of laparoscopy assisted distal gastrectomy (LADG) were performed, up from just 59 in 1996. Professor S. Kitano (Oita University) presented his department's results with LADG. The technique involves a laparoscopic dissection including D1 + α and mobilization of the stomach. Division of the stomach and reconstruction are then performed via a mini laparotomy. Of 136 patients treated mean operating time was 238 minutes with 7% morbidity. Two non-gastric cancer deaths occurred and there has been no recurrent disease. Professor Kitano suggested that for an individual experienced in both open gastric surgery and laparoscopic surgery the learning curve would be relatively short, about 10 cases.

Continuing the theme of less extensive surgery, Dr Y. Kitagawa (Keio University School of Medicine) talked on sentinel node biopsy and its applications in gastric cancer. In a proving study with 270 patients with T1/2 N0 disease, 99 m-Technetium Tin colloid was injected endoscopically in to the tumor basin prior to conventional D2 gastrectomy. Sentinel nodes were detected using a hand held gamma probe and confirmation was by histology using routine H&E stain to detect the colloid. Frequently more than one sentinel node was found (average 4.1) and the detection rate for sentinel nodes was 97% with 99% accuracy. In 37% of cases sentinel nodes were found in JGCA N2 nodes. Laparoscopic wedge resection with confirmation of N0 status requires absolute accuracy from sentinel node mapping and the application of real time intraoperative RT-PCR is being investigated.

ADJUVANT THERAPY

CHAIRMAN: DR AL BENSON

The results of the South Western Oncology Group trial of adjuvant chemoradiotherapy (SWOG9008) have caused a re-examination of the role of adjuvant and neoadjuvant therapies in gastric cancer. Dr D. Ciot (Memorial Sloan-Kettering Cancer Center, New York, USA) and Professor C.J.H. van de Velde (Leiden University Medical Center, Netherlands) discussed the history of such treatments, the implications of SWOG9008 and future directions for trials.

Most prospective RCTs of adjuvant therapy have failed to demonstrate a benefit and have been criticized as being underpowered, using out dated treatments and having heterogeneous patient populations. Recent meta-analyses of these trials have suggested a small benefit in the order of 3–5%. SWOG9008 randomized 566 patients to either observation or postoperative 5-FU/leucovorin and 4500 cGy of fractionated radiotherapy. Improvements in median survival (27 versus 36 months) and 3-year survival (41% to 50%) were seen. Toxicity was a problem and despite the trial being limited to fit patients a third of the chemoradiotherapy arm were unable to complete treatment. The benefit of treatment appears to be largely related to improved locoregional control but both in this and in survival, the observation arm did particularly badly compared with patients in the Dutch D1/D2 trial, and the treatment arm had only comparable results with the Dutch group. This may be explained by the majority of cases having had inadequate clearance of even the N1 nodes (D0). Application of the Muruyama Index (MI) that rates the probability of lymph node metastasis based on the primary tumor's characteristics suggested considerable residual disease. Paradoxically in the subgroup where the probability of residual disease was low the beneficial effects of chemoradiotherapy appeared greater. Both surgeons concluded that although chemoradiation demonstrated benefit after poor surgery, the result could not be extrapolated to show benefit after surgery with a more radical lymph node clearance. Professor van de Velde outlined the proposal for a new Pan European Gastric Adjuvant Study with Uniform Surgery (PEGASUS), comparing adequate (D1 or greater with preservation of spleen and pancreas) surgery alone with adequate surgery with chemoradiotherapy.

The Japanese perspective on adjuvant therapy was given by Dr T. Kinoshita (NCC East, Tokyo). Two large RCTs of adjuvant treatment versus observation JCOG 8801 (MMC + 5-FU + oral UFT) with 579 patients and JCOG 9206 (MMC + 5-FU + CA + oral 5-FU) with 252 patients failed to demonstrate benefit. The results of JCOG 9206-2 with 282 patients comparing surgery + cisplatin + 5-FU + oral UFT with surgery alone are expected soon. S-1 is a new orally available agent with low toxicity and high single agent response rate. The