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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Morbidity and mortality after D1 and D2 gastrectomy for cancer: Interim analysis of the Italian Gastric Cancer Study Group (IGCSG) randomised surgical trial☆

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KEYWORDS
Gastric cancer; Extended lymph node dissection; Randomised trial; D1 resection; D2 resection

Summary *Background.* The disadvantages of D2 gastrectomy have been mostly related to splenopancreatectomy. Unlike two large European trials, we have recently showed the safety of D2 dissection with pancreas preservation in a one-arm phase I-II trial. This new randomised trial was set up to compare post-operative morbidity and mortality and survival after D1 and D2 gastrectomy among the same experienced centres that participated into the previous trial.

Methods. In a prospective multicenter randomised trial, D1 gastrectomy was compared to D2 gastrectomy. Central randomisation was performed following a staging laparotomy in 162 patients with potentially curable gastric cancer.

Findings. Of 162 patients randomised, 76 were allocated to D1 and 86 to D2 gastrectomy. The two groups were comparable for age, sex, site, TNM stage of tumours, and type of resection performed. The overall post-operative morbidity rate was 13.6%. Complications developed in 10.5% of patients after D1 and in 16.3% of patients after D2 gastrectomy. This difference was not statistically significant ($p < 0.29$). Reoperation rate was 3.4% after D2 and 2.6% after D1 resection. Post-operative mortality rate was 0.6% (one death); it was 1.3% after D1 and 0% after D2 gastrectomy.

☆ For the IGCSG (T. Allone, D. Andreone, M. Calgaro, F. Calvo, L. Capussotti, M. Degiuli, G. R. Fronda, M. Garino, L. Locatelli, P. Mello Teggia, M. Morino, A. Ponti, F. Robecchi, D. Scaglione)

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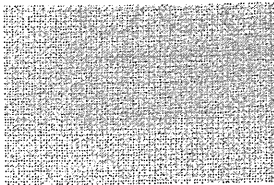

Interpretation. Our preliminary data confirm that in very experienced centres morbidity and mortality after extended gastrectomy can be as low as those showed by Japanese authors. They also suggest that D2 gastrectomies with pancreas preservation are not followed by significantly higher morbidity and mortality than D1 resections.
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Introduction

Large retrospective Japanese series have shown impressive survival results after D2 gastrectomy (gastric resection together with the removal of level-2 lymph nodes as standardized by the Japanese Society for Research in Gastric Cancer—JSRGC) for potentially curable gastric cancer.[1,2]

Although some non-Japanese series have also reported favourably,[3,4] these extended lymphadenectomies are still mostly avoided in western countries due to the related increase of postoperative morbidity and mortality.

During the last decade, two European prospective randomised trials have reported that D2 gastric resections are followed by higher morbidity and mortality than D1 resections, and offer no survival benefit over D1 procedures.[5,6]

The disadvantages of D2 resections have been mostly related to pancreatico-splenectomy, which had been described as an integral part of D2 gastrectomy for all proximal tumours by the JRSGC until the 1990s, and consequently was routinely adopted for middle and upper third tumours in the D2 arm of European trials.[7]

Unlike these two European trials, we have recently shown that D2 dissection with pancreas preservation is safe in a one-arm phase I-II trial with a very strict quality control system.[8]

There is not yet evidence from randomised controlled trials that D2 resections give better long-term survival results than standard D1. For this reason our new IGCSG phase III multicentre randomised trial was set up involving the same centres that had already participated into the previous phase 1-2 trial, in order to maintain a homogeneous level of experience among all surgeons.

Patients and methods

Design of the Italian gastric cancer trial

Goals of the trial

- To evaluate whether extending the lymph node dissection to N2 level can improve the survival rate.
- To evaluate whether extending the lymph node dissection to N2 level can decrease the recurrence rate.
- To evaluate morbidity and mortality rates after surgery in both groups of patients.
- To determine the prognostic value of D2 dissection.

Patient selection

Patients less than 80-year-old with histologically proven and potentially curable gastric cancer were eligible for enrolment in the IGCSG trial. Patients undergoing emergency surgery or with severe cardio respiratory, renal or metabolic disease (ASA ≥ 4) precluding extended resections were excluded, as were those with a co-existing cancer or distant metastases at preoperative staging. ASA assessment was performed by an experienced consultant anaesthetist in all cases.
Written informed consent was required.
Criteria of curability at laparotomy included:

- Absence of macroscopic involvement of liver and peritoneum (H0, P0).
- Absence of macroscopic involvement of adjacent organs ($T < 4$).
- Absence of macroscopic massive involvement of N2 nodes (enlarged nodes at celiac area).
- Absence of malignant cells in para-aortic nodes (16B1) at biopsy and frozen section.
- Absence of malignant cells in peritoneal washing fluid, during intraoperative fresh examination.
- Absence of macroscopic residual tumour (R0).
- No involvement of the oesophagus, cardia or duodenum.

Surgical definitions

The study was performed according to the rules of the JRGC as regards the extent of stomach removal and the technique of lymph-node dissection,[9] and to the Japanese Classification of Gastric Carcinoma—second English Edition by the Japanese Gastric Cancer Association,[12] particularly as concern the definitions of classifications and grouping of regional lymph nodes, the extent of lymph node metastasis (N) and the curative potential of gastric resection (Resection A, B or C). In this new classification the regional lymph nodes are

classified into three groups (compartments or levels 1-3), depending upon the location of the primary tumour.

Treatment details

The operative details of the two procedures respected the general rules for gastric cancer study, as described by the Japanese Research Society for Gastric Cancer in 1981. D1 resection entailed removal of the nodes usually defined as perigastric nodes 'en bloc' with the specimen, according to the JGCA. In the D2 arm, during total gastrectomy, the pancreas was removed only when it was suspected to be involved by the tumour. When required (clinical $T > 1$ on the greater curvature of the proximal and middle thirds of the stomach), splenectomy was performed with the pancreas preservation technique as described by Maruyama.[10]

Quality control

Only surgeons who participated in the previous one-arm phase 1-2 study on D2 gastrectomy were allowed to participate in this new randomised trial. This restriction permitted maintenance of an homogeneous level of acquired experience among all participating surgeons, as in our previous trial a strict system for quality control had been set up and documented.[8] Since there is evidence that the learning curve for D2 gastrectomy may be between 20 and 25 cases,[11] the randomised part of the study was restricted to the five centres at which more than 25 D2 dissections had been performed during the earlier study. A minimum number of 25 retrieved nodes were required for definition of proper D2 dissection.

Data about post-operative course (hospital stay, blood transfusions, bowel transit, drainage) and early or late morbidity (< or >30 days) and treatment were reported on patient-cards. Hospital mortality (not 30 days mortality) was reported.

Registration and treatment data were regularly collected and sent to the Reference Centre within 30 days of compilation. Follow-up data were sent every 6 months.

Registration and randomisation

Centralised randomisation was performed from the Department of Oncology, Division of Surgery, San Giovanni Antica Sede Hospital, Turin.

The randomisation was performed using random permuted blocks, stratified according to the different operative units. Patients who fulfilled the eligibility criteria during laparotomy were registered by phone call to the randomisation centre. The operator at the randomisation centre completed the patient-form data on the patient operative unit, time and date of randomisation, then opened the envelope with the randomisation code and immediately communicated it to the operative unit.

In order to document strict adhesion to the recruitment procedures, and to prove the absence of selection bias, all patients with a gastric cancer undergoing surgery in each operative unit (eligible or non-eligible) were registered.

Size of the study

The size of the study was calculated on the basis of the effects D1 and D2 surgery on 5 year survival rate. To detect an increase in survival of 15% (from 30% after D1 to 45% of D2 group) 5 years after curative surgery, 160 patients will have to be randomised to each arm (alpha = 0.05 one-sided, power = 0.80).

Results

From January 1999 to December 2002, 296 patients were registered from five participating centres out of the nine centres which participated in our previous trial. Of these, 134 were found not to be eligible for randomisation. Causes of non-eligibility are shown in Table 1. One hundred and sixty-two patients were randomised either to D1 (76) or D2 (86). The two groups were comparable with respect to median age, sex and location of the tumour, as reported in Table 2. They were also similar as regard the extent of gastric resection and stage of disease. Early gastric cancer accounted for 33 per cent of the tumours. The spleen was removed in only 16 patients, four times during a D1 and 12 times during a D2 gastrectomy. A distal pancreatectomy was required in only four patients, when the pancreas was suspected of being involved by the

Table 1 Reasons for exclusion

	No. of patients (%)
Total patients registered	296 (100)
Patients randomised	162 (54.7)
Patients non-eligible	134 (46.3)
No informed consense	8 (6.0)
Metastases/secons tumour	14 (10.4)
Nodal spread (N2, N3)	34 (25.2)
Peritoneal spread	26 (19.3)
T4	25 (18.4)
Physical conditions/age	26 (19.3)
No adenocarcinoma (lymphoma)	1(1.4)

Table 2 Patient characteristics

	D1	D2	Total
No. of patients	76	86	162
Median age (range)	64 (34-81)	61.46 (25-80)	62.01 (29-81)
≥70	22	18	40
Sex (m/f)	39/37	48/38	87/75
Location			
Upper	9	11	20
Medium	18	22	40
Distal	49	52	101
Diffuse	-	1	1
Tumour stage			
pT1	27	27	54
pT2	23	28	51
pT3	26	31	57
Type of resection			
Total gastrectomy	19	22	41
Distal gastrectomy	57	64	121
Splenectomy (S)	3	9	12
Distal pancr. + S	1	3	4

tumour. The mean number of nodes removed was 27.0 during a D1 gastrectomy and 36.6 during a D2.

Post-operative course

Table 3 gives data on post-operative course. Overall, the post-operative hospital morbidity was 13.6%. The rate was higher in the D2 group (16.3%) than in D1 group (10.5%), but this difference was not statistically significant. In both groups there were more complications after total than after distal gastrectomy, but again this difference was not significant.

As regards major abdominal infections, no anastomotic dehiscence occurred and only one case of duodenal stump leakage was registered, while two pancreatic leakages and two cases of acute pancreatitis were observed.

Reoperation was necessary after five major surgical complications (Table 3). The overall hospitality mortality was 1/163. This death occurred after a D1 gastrectomy (1/76) and was due to an intraoperative stroke; obviously no significant difference could be observed between D1 and D2 group as concerns mortality.

Post-operative hospital stay

The data on hospital stay excluded the early death (intraoperative), and consequently were based upon 161 patients. The median time of hospital stay was 12 days for D1 groups (mean 13.75, range 8-78) and 12 days for D2 group (mean 13.15, range 8-27). The effect of splenectomy on duration of hospital stay was not clear: patients having received splenectomy stayed in hospital half-a-day more (12.5 days, mean 13.49, range 9-17) than patients without splenectomy 12 days, (mean 12.87, range 8-78, see Table 4).

Discussion

Despite its recent decline, gastric cancer is still a common lethal disease in western countries. For apparently resectable cancers, surgery offers the best loco regional control; but unfortunately, average 5-year survival rates for treated patients remain low in the western world, ranging from 15 to 30%.[11,13] Over the years, Japanese surgeons have performed radical procedures involving extended lymphadenectomy, and have reported impressive survival figures with extremely low morbidity and mortality.[1,2,14] Two recent European randomised trials, however, failed to demonstrate a significant

Table 3 Post-operative complications and mortality

	D1 (76)	D2 (86)	Global (162)
Non-surgical complications	4 (5.26%) Cardiac 2 Pulmonary 2	7 (8.13%) Pulmonary 4 Pleural 3	11 (6.79%)
Surgical complications	4 (5.26%) Pancreatic leakage 1 Intraperit. haemorrhage 2 Colonic perforation 1[a]	7 (8.13%) Pancreatic leakage 1 Intraperit. haemorrhage 1[a] Duodenal leakage 1[a] Acute pancreatitis 2[a] Abdominal abscess 2	11 (6.79%)
Total morbidity	8 (10.52%)	14 (16.27%)	22 (13.58%)
Mortality	1 (1.31%)	-	1 (0.61%)

[a] Requiring reoperation.

Table 4 Lengths of hospital stay

	D1	D2	S0	S+
Days median (range)	12 (8-78)	12 (8-27)	12 (8-78)	12.5 (9-17)
Days mean	13.75	13.15	12.87	13.49

S0, splenectomy not performed; S+, splenectomy performed.

survival benefit of radical D2 gastrectomy over standard D1 resection.[5,6] The benefit of D2 gastrectomy's potential for reducing loco regional recurrence may be nullified by the significant increase of post-operative morbidity and mortality. These unfavourable results have been attributed to many factors, including the lack of technical experience of surgeons dealing with extended gastrectomy, the large number of elderly patients presenting with associated vascular and cardio respiratory diseases, the large number of centres involved in randomised trials with consequent low quality control, and particularly the distal pancreatico-splenectomy routinely performed during total gastrectomy in the D2 arms of randomised trials. Subset analysis of the MRC and Dutch randomised trials has recently indicated that the poorer outcomes in D2 resections are largely due to pancreas and spleen removal.[7,15]

We performed a previous prospective multicentre phase 1-2 study on feasibility and safety of D2 gastrectomy with pancreas preserving technique, involving only a few surgeons. In this study, distal pancreatico-splenectomy was not performed unless the pancreas was suspected of being involved by the tumour. We observed that, when performed in specialized centres, with a strict quality control system, by experienced surgeons, D2 gastrectomy with pancreas preservation could be safe in Western countries. Our morbidity and mortality rates were not only absolutely comparable to those observed after standard resections but also very close to those shown by Japanese surgeons.[8]

Compared to the patients in the Dutch and British trials our patients were younger, and had a higher proportion of early and distal cancers, and these factors may help to partially explain the striking difference between our morbidity and mortality results and those in these trials.

Having reached a good standard of experience in D2 procedures, we planned a new trial, randomising patient to either D1 or D2 gastrectomy.

To maintain a homogenous level of acquired technical experience in D2 procedures, only surgeons already involved in our previous study were allowed to participate in this new trial; this should avoid bias associated with new surgeons who have not yet completed their learning curve. After careful review of the safety results obtained in the first trial, four out of the nine surgical teams did not join this new randomised trial because completion of their learning curve could not be proven (see above).

These preliminary data seem to confirm our previous reports. Overall morbidity is around 14%; although this figure is a slight underestimate due to the fact that the majority of centres have registered in their database major and minor non-surgical but only major surgical complications, it is very low, and comparable to the best results shown by Japanese authors.[14] The overall morbidity is higher in D2 gastrectomy, but the difference between the two groups of patients is not statistically significant. Moreover, the rate of complications after D2 gastrectomy (16.35%) is considerably better than the rates of both arms (D1 and D2) in the English and Dutch trials.[5,6]

The ASA grade is a fairly crude and subjective measure of patient fitness, and it is not possible to make realistic comparisons of comorbid pathology and organ functional reserve between our patients and those in the Dutch and British trials. We cannot exclude the possibility that difference between these populations contributed to the difference in morbidity and mortality results. In support of our belief that proper surgical training and quality control played the leading part in our low morbidity, we observed very few 'technical' complications requiring re-operation, such as anastomotic leakage (seen in only one duodenal stump leak).

The importance of pancreatic complications after extended gastric surgery, was confirmed by our data. Although the pancreas was not removed routinely during D2 total gastrectomies, three out of the seven complications registered after a D2 procedure were related to the pancreas (two acute pancreatitis and one pancreatic leakage), and two of these required a reoperation.

Overall mortality was very low, at 0.6%. This rate is comparable to those shown by eastern authors in series from experienced centres, and is strikingly different from the rates of both arms reported in MRC and Dutch trials. Our study was powered to detect a difference in 5 year survival between D1 and D2 surgery: detecting a morbidity or mortality difference would require a larger number of

patients, and it is therefore, possible that a small difference exists. Our preliminary results are sufficient to indicate that any such difference is likely to be too small to be clinically important.

These preliminary results confirm that the radical technique of extended lymph node removal can be performed in Western centres without an increase in post-operative morbidity and mortality, if some conditions are respected. First, surgeons involved in these procedures should have completed their learning curve under strict quality control, possibly by a Japanese instructor; second, this procedure should be performed only in selected patients, suitable for extended surgery and with a potentially curable cancer; third, a policy of removing the spleen only when oncologically necessary, with preservation of the tail of the pancreas is associated with low morbidity and mortality, and routine pancreatico-splenectomy is absolutely to be avoided during total gastrectomy.

We found that after an adequate learning period, D2 gastrectomy can offer morbidity and mortality results comparable to those reported in Japanese series.

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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

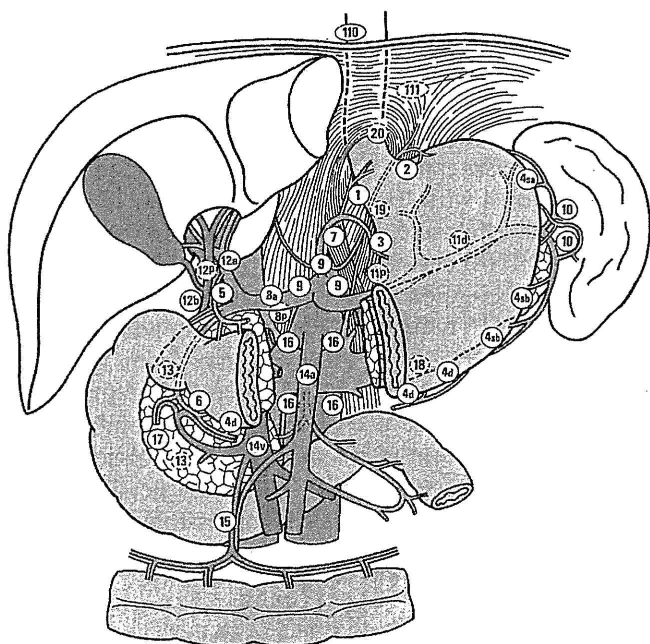

Fig. 1. Lymph node station numbers (*circled*) in the Japanese classification of gastric carcinoma [3]. These stations are further classified into N1/N2/N3 according the location of the primary tumor

changed from the S-stage to a T-stage system, which was equivalent to the T-staging of the UICC system.

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		
	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-

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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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FROM THE ASCO-JSCO JOINT SYMPOSIUM

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Role of surgery in multidisciplinary treatment for solid cancers

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Abstract In the evolution of solid cancer, there are four steps: noninvasive tumor, local invasive cancer without metastasis, local invasive cancer with lymph node metastasis, and eventually systemic disease. For the first three phases, local treatment, including lymph node dissection, may cure the disease. The choice of local treatment depends on the tumor characteristics, but surgery remains important in many of these cancers. Gastric cancer is one of the typical tumors which remain locally invasive, with or without nodal metastasis, but without systemic metastasis for a rather long period. Metastasis to lymph nodes occurs, frequently even in T1 tumors, but seldom to other sites until the late stage. Thus, the target of local control is the regional lymph nodes. The Intergroup study IT-0116 proved the effect of chemoradiotherapy (CRT) for curable gastric cancer, and thus proved the insufficiency of limited surgery (D0/1). The conventional method of local control for gastric cancer is surgery, including regional lymph node dissection (D2). However, the superiority of D2 has not been proven by randomized controlled trials (RCTs). But all RCTs so far have a crucial problem in the quality of treatment given in the D2 arm. D2 is not a dangerous procedure if done by specialists in large-volume hospitals. D0/1 plus CRT is better than D0/1 alone, but it may be worse than D2 alone. The survival benefit of CRT after D2 is an open question. Establishing standard adjuvant chemotherapy after D2 is a more urgent clinical issue, and there is no reason to abandon D2 gastrectomy for curable gastric cancer in Japan.

Key words Role of surgery · Gastric cancer · Chemoradiotherapy · Local control

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The role of surgery in multidisciplinary treatment for cancer

We believe that solid cancers evolve as follows: lesions without invasion, then locally invasive cancer, which will soon metastasize to regional lymph nodes and then to other organs as systemic disease. The initial lesion of cancer is sometimes noninvasive, and is therefore called dysplasia, in spite of cellular or structural atypia, in the West. There are many arguments about dysplasia and early noninvasive cancer between the West and Japan, including, recently, lung cancer. Due to the development of helical computed tomography (CT), very early cancers, i.e., possible noninvasive cancers, are now being diagnosed in many countries, including the United States and Japan. For a long time, in Japan, we have diagnosed these lesions (which are called dysplasia in the West) in the stomach or in the colon, as cancer. It is well known that many of these dysplastic lesions will invade in a rather short time, at which time they are locally invasive cancers (at this point, a diagnosis of cancer is made in the West). The lesions then start to show metastasis to the regional lymph nodes, and then finally, become systemic disease, with metastases in many distant organs. For noninvasive cancer or dysplasia, just observation or limited resection, such as endoscopic mucosal resection (EMR), is the best way to manage them. For locally invasive cancer, just a wide excision could be sufficient. However, as it is impossible to discriminate exactly between locally invasive lesions with and without regional lymph node metastasis, these lesions are often treated by a wide excision plus lymph node dissection. Recently, sentinel-node biopsy has been used to discriminate those lesions with or without nodal metastasis and to minimize the level of aggressive surgery for these tumors. If the tumor becomes systemic disease, local control plus systemic treatment is mandatory if we aim to cure the disease. As the weapon for local treatment, surgery is most frequently used, but radiation can also be used, depending on the tumor characteristics. Different cancers have different patterns of tumor development or evolution. For example, small-cell