

## Methods

### Japan Clinical Oncology Group 9501 trial

Patients younger than 75 years of age with histologically proven gastric adenocarcinoma considered potentially curable were enrolled in the JCOG9501 trial<sup>2,3</sup>. Additional eligibility criteria derived from intraoperative findings were T2b or higher, no gross metastases to para-aortic nodes, and negative cytology by peritoneal lavage. The surgeon confirmed the eligibility criteria during surgery and telephoned the JCOG Data Centre to register patients. Patients were then randomized to either standard D2 or extended D2 plus PAND using the minimization method according to clinical T category, Borrmann macroscopic type and institution. The surgeon then performed the allocated operation as described in the protocol.

The surgical procedures used in each group have been described previously<sup>2,3</sup>. In short, in the D2 group gastrectomy with D2 lymphadenectomy was carried out according to the 12th edition of the Japanese Classification of Gastric Carcinoma<sup>5</sup>. In the D2 plus PAND group the para-aortic lymph nodes were also dissected. The spleen was removed in patients having total or proximal subtotal gastrectomy. Pancreatectomy was confined to patients in whom the pancreas was involved by tumour. The reconstruction method was not prespecified. Adjuvant or neoadjuvant therapy was not allowed. This study was registered with ClinicalTrials.gov (no. NCT00149279).

### Japan Clinical Oncology Group 9502 trial

The eligibility criteria for the JCOG9502 trial were: histologically proven adenocarcinoma of the gastric cardia or body with oesophageal invasion of 3 cm or less, clinically T2–4, patient no more than 75 years old, no distant metastasis, and no bulky node category (N) 3 or N4 metastasis<sup>3</sup>. Patients were randomized to either standard TH or extended LTA treatment using the minimization method according to clinical T stage, Borrmann macroscopic type and institution.

The surgical procedures used in each group have been described previously<sup>4</sup>. In short, a total gastrectomy with D2 and additional dissection of the left upper para-aortic nodes was performed in the TH group. The lower mediastinum was accessed through the oesophageal hiatus extended by a longitudinal incision of the median part of the diaphragm. In the LTA group a long oblique incision over the seventh intercostal space was extended into the right abdomen. In the abdominal cavity, the same procedure as that performed in the TH group was carried out and thorough mediastinal lymph node dissection below the inferior pulmonary

vein was performed. The reconstruction method was not prespecified. Adjuvant or neoadjuvant therapy was not allowed. This study was registered with ClinicalTrials.gov (no. NCT00149266).

### Subjective symptom-related scores

The primary endpoint of these trials was overall survival. Postoperative changes in bodyweight and symptoms (JCOG 9501 and 9502) and also in respiratory function (JCOG9502 only) were assessed prospectively as secondary endpoints. Bodyweight was measured before surgery, and at 6 months, 1 year and 3 years after operation.

Surgeons evaluated patient symptoms during outpatient clinic visits at 6 months, 1 year and 3 years after surgery, without being blinded to the procedure performed. Symptoms included appetite, meal volume, bowel habit, sleep and occurrence of pneumonia (JCOG 9501 and 9502), and also incisional pain and dyspnoea for JCOG9502. As a surrogate for total physical strength, the proportion of patients who were able regularly to leave their homes to perform daily activities and those who returned to their former work were evaluated. All items were dichotomized, and scoring was performed as shown in *Table 1*.

Respiratory function, including vital capacity, forced expiratory volume in 1 s (FEV1) and arterial partial pressure of oxygen ( $PaO_2$ ) in room air, were also measured before, and at 1 and 6 months after surgery.

### Statistical analysis

The group means of bodyweight, vital capacity, FEV1 and  $PaO_2$  were determined using a mixed-effect model with pretreatment value, treatment arms, time and treatment–time interaction as co-variables. Items related to symptoms and respiratory function were dichotomized

**Table 1** Nine symptom items evaluated in this study

	Score 0	Score 1
Appetite	Poor	Good
Meal volume	$< \frac{1}{2}$ preoperative amount	$\geq \frac{1}{2}$ preoperative amount
Bowel habit	Irregular, diarrhoea	Daily, normal
Sleep	Disturbed	Good
Leaving home	Seldom	Regularly
Return to work	No	Yes
Pneumonia	Experienced	Never
Incisional pain*	Always, often	Seldom, none
Dyspnoea*	Yes	No

\*These parameters were evaluated only in the Japan Clinical Oncology Group 9502 trial.

and these group means were evaluated by marginal models fit via generalized estimating equations (GEEs), with treatment arms, time and treatment–time interaction as co-variables. All group means were compared at each time point between two groups. According to these models, point estimates with least-squares means, their confidence intervals and *P* value were calculated and compared at each time point between two groups. GEE is used to take into account the within-patient correlation that is inevitable when outcomes are measured repeatedly from the same patients<sup>6</sup>.

Measurements were missing for those who were still in hospital as a result of major complications and those who developed recurrence, and these data points were excluded from the analysis. Because of the exploratory nature of between-group comparisons, the test results are reported with two-sided *P* values without multiplicity adjustment of type I error.

All statistical analyses were carried out with SAS<sup>®</sup> software release 9.1 (SAS Institute, Cary, North Carolina, USA).

## Results

In the JCOG9501 trial, 523 patients were assigned randomly to either the D2 group (263 patients) or

**Table 2** Postoperative change in bodyweight between groups in Japan Clinical Oncology Group 9501 and 9502 trials

	Group	No. of patients	Bodyweight (kg)*	<i>P</i>
<b>JCOG9501</b>				
Before operation	D2	263	57.5 (56.3, 58.7)	—
	D2 + PAND	259	56.9 (55.7, 58.2)	
After 6 months	D2	255	51.1 (50.6, 51.6)	0.030†
	D2 + PAND	252	50.3 (49.8, 50.8)	
After 1 year	D2	242	51.1 (50.5, 51.7)	0.241†
	D2 + PAND	233	50.6 (49.9, 51.2)	
After 3 years	D2	192	51.1 (50.4, 51.8)	0.381†
	D2 + PAND	190	50.7 (50.0, 51.4)	
<b>JCOG9502</b>				
Before operation	TH	82	58.5 (56.4, 60.5)	—
	LTA	82	57.6 (55.6, 59.7)	
After 6 months	TH	75	49.7 (48.7, 50.6)	0.115‡
	LTA	71	48.5 (47.5, 49.6)	
After 1 year	TH	68	50.0 (49.0, 51.0)	0.031‡
	LTA	56	48.2 (47.0, 49.5)	
After 3 years	TH	47	50.7 (49.7, 51.7)	0.046‡
	LTA	40	49.0 (47.6, 50.3)	

\*Values are mean (95 per cent confidence interval), crude mean for preoperative values and least-squares mean for the others. JCOG, Japan Clinical Oncology Group; PAND, para-aortic nodal dissection; TH, abdominal–transhiatal; LTA, left thoracoabdominal. †*Versus* D2 + PAND, ‡*Versus* LTA (mixed-effect model).

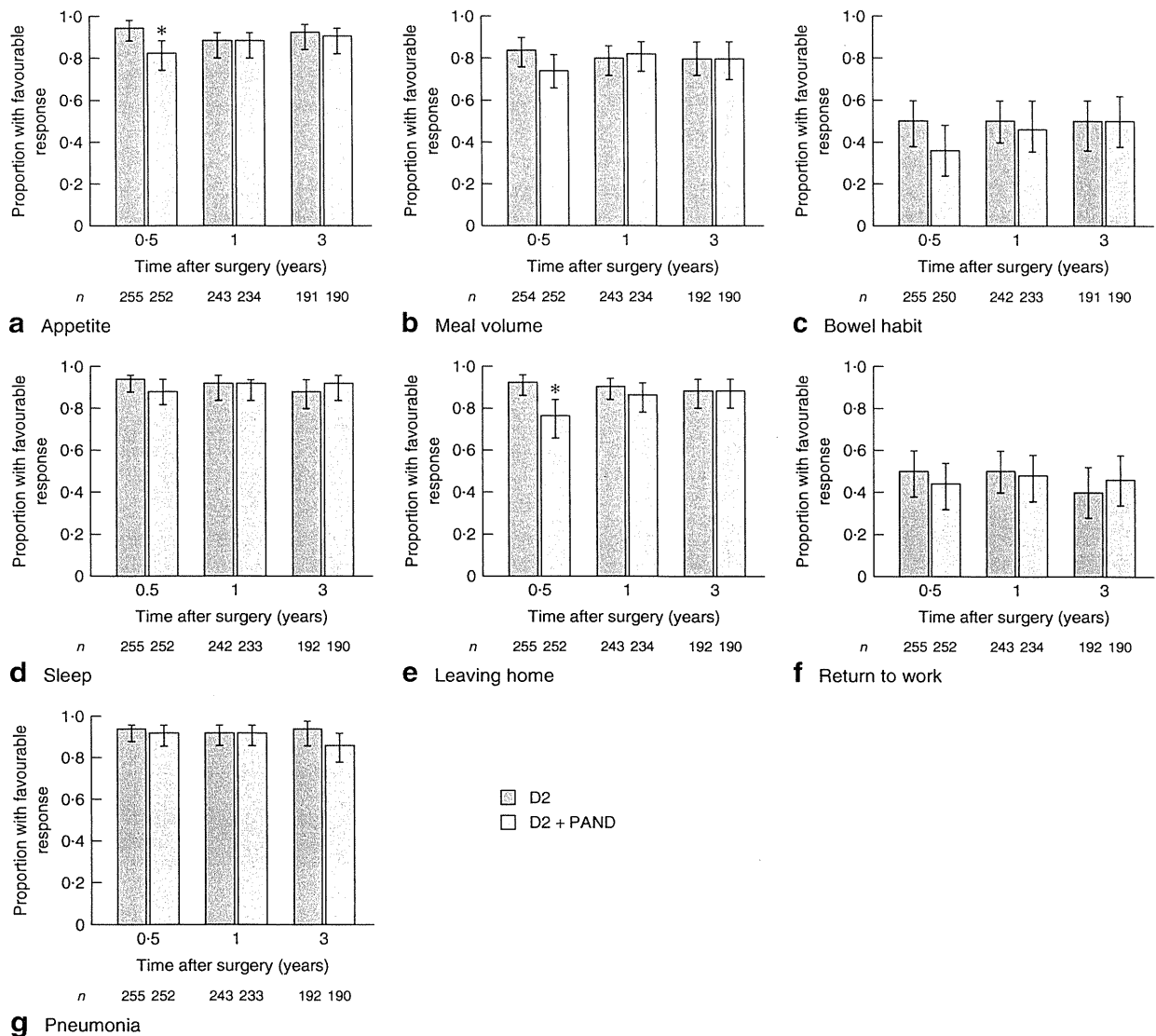
the D2 plus PAND group (260) in 24 Japanese hospitals between July 1995 and April 2001 (*Fig. S1*, supporting information). Patient characteristics have been published previously<sup>3</sup>. Total gastrectomy was performed in 102 patients (38.8 per cent) in the D2 group and 97 (37.3 per cent) in the D2 plus PAND group. The most common method of reconstruction was the Roux-en-Y procedure in both groups (D2, 59.7 per cent; D2 plus PAND, 60.8 per cent). Splenectomy was performed in 98 (37.3 per cent) and 93 (35.8 per cent) patients in the D2 and D2 plus PAND groups respectively; only nine (3.4 per cent) and 12 (4.6 per cent) patients respectively underwent distal pancreatectomy.

In the JCOG9502 trial, 167 patients were randomly assigned to either the TH (82 patients) or LTA (85) approach in 27 Japanese hospitals between July 1995 and December 2003 (*Fig. S1*, supporting information). Details of patient and tumour characteristics have already been published<sup>4</sup>. Most patients in both TH and LTA groups underwent total gastrectomy with splenectomy. Distal pancreatectomy was performed in 22 patients (27 per cent) in the TH group and 13 (15 per cent) in the LTA group.

**Table 3** Postoperative change in respiratory function between abdominal–transhiatal and left thoracoabdominal groups

	Group	No. of patients	Mean	<i>P</i> *
<b>Vital capacity (ml)</b>				
Before operation	TH	82	3573 (3416, 3731)	—
	LTA	82	3421 (3225, 3617)	
After 1 month	TH	80	2944 (2855, 3034)	<0.001
	LTA	74	2427 (2327, 2528)	
After 6 months	TH	73	3193 (3089, 3297)	<0.001
	LTA	68	2658 (2552, 2764)	
<b>FEV1 (%)</b>				
Before operation	TH	82	80.2 (78.3, 82.1)	—
	LTA	82	80.4 (78.3, 82.5)	
After 1 month	TH	80	84.4 (82.7, 86.2)	0.416
	LTA	74	83.3 (81.1, 85.4)	
After 6 months	TH	73	84.7 (82.6, 86.7)	0.985
	LTA	68	84.7 (81.8, 87.6)	
<b>PaO<sub>2</sub> in room air (mmHg)</b>				
Before operation	TH	80	86.6 (84.5, 88.8)	—
	LTA	81	87.1 (85.1, 89.1)	
After 1 month	TH	72	87.6 (85.5, 89.8)	0.004
	LTA	69	82.8 (80.3, 85.2)	
After 6 months	TH	73	90.3 (87.9, 92.8)	0.057
	LTA	68	87.0 (84.7, 89.4)	

Values in parentheses are 95 per cent confidence intervals. TH, abdominal–transhiatal; LTA, left thoracoabdominal; FEV1, forced expiratory volume in 1 s; PaO<sub>2</sub>, arterial partial pressure of oxygen. \**Versus* LTA (mixed-effect model).



**Fig. 1** Comparison of proportion of patients with a favourable response regarding seven symptoms between D2 and D2 + para-aortic nodal dissection (PAND) groups: **a** appetite, **b** meal volume, **c** bowel habit, **d** sleep, **e** leaving home, **f** return to work and **g** pneumonia. Group means are shown with 95 per cent confidence intervals. \* $P < 0.050$  versus D2 (generalized estimating equations model)

**Bodyweight**

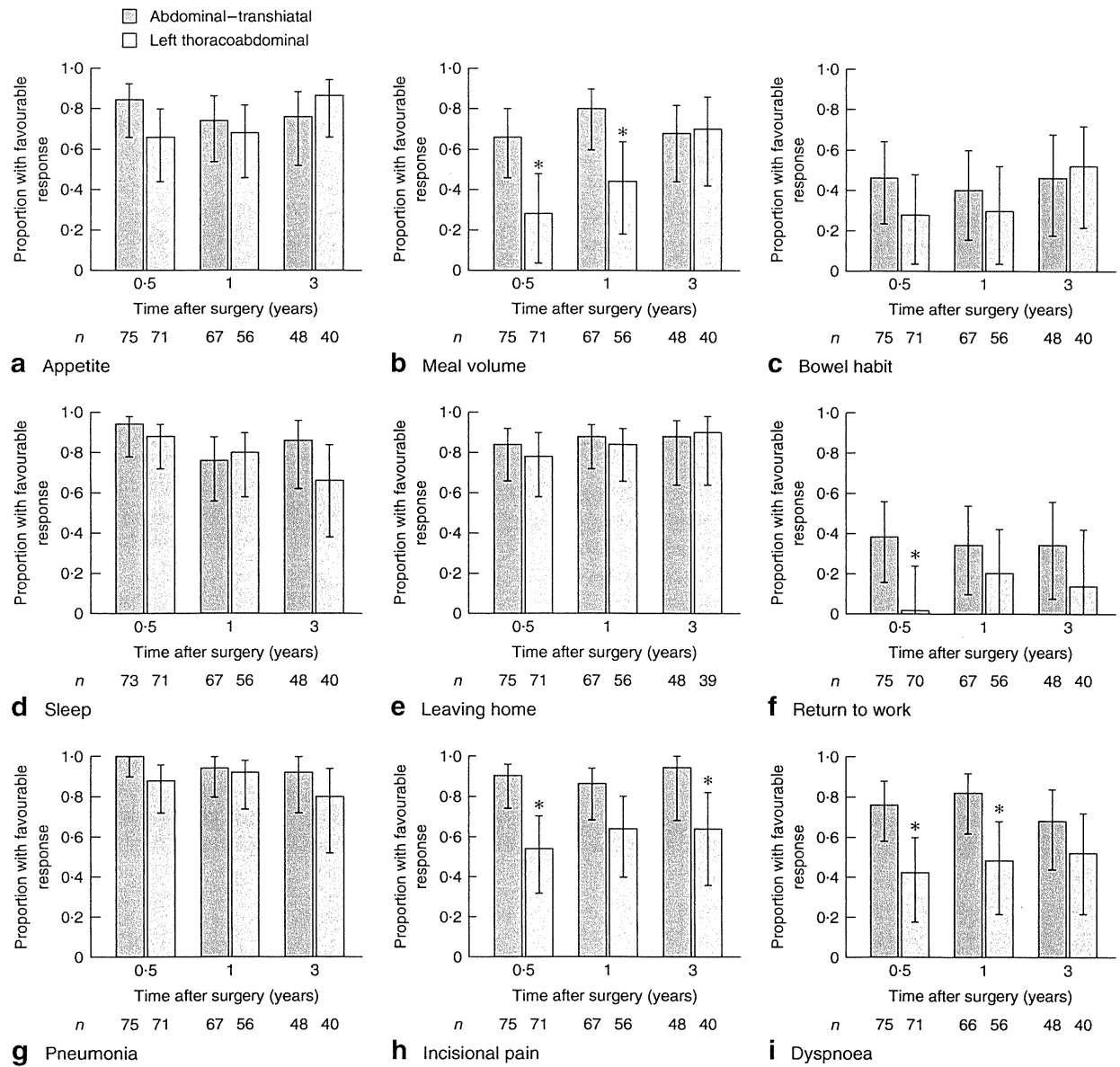
In the JCOG9501 trial, the decrease in mean bodyweight at 6 months was 6.4 kg in the D2 group and 6.6 kg in the D2 plus PAND group (Table 2). Postoperative bodyweight remained unchanged thereafter in both groups. Bodyweights were comparable between groups at 1 and 3 years' follow-up.

In the JCOG9502 trial, the decrease in mean bodyweight was 8.8 kg in the TH group and 9.1 kg in the LTA group at

6 months after surgery (Table 2). At 1 and 3 years' follow-up mean bodyweight was higher after a TH than a LTA procedure ( $P = 0.031$  and  $P = 0.046$  respectively).

**Postoperative symptoms**

Symptom scores after surgery are shown in Figs 1 and 2. In the JCOG9501 trial, appetite and the proportion of patients able to leave their home almost every day were significantly higher in the D2 group than in the D2



**Fig. 2** Comparison of proportion of patients with a favourable response regarding nine symptoms between abdominal-transhiatal (TH) and left thoracoabdominal (LTA) groups: **a** appetite, **b** meal volume, **c** bowel habit, **d** sleep, **e** leaving home, **f** return to work, **g** pneumonia, **h** incisional pain and **i** dyspnoea. Group means are shown with 95 per cent confidence intervals. \* $P < 0.050$  versus TH (generalized estimating equations model)

plus PAND group at 6 months. At 1- and 3-year follow-up symptom scores were comparable between the two groups.

In the JCOG9502 trial, meal volume and respiratory status (dyspnoea) were better in the TH group than in the LTA group up to 1 year after surgery. The proportion of patients with incisional pain was significantly higher in

the LTA group than in the TH group until the end of follow-up at 3 years.

### Respiratory function in Japan Clinical Oncology Group 9502 trial

The LTA group showed a significantly greater decrease in vital capacity than the TH group at 1 and 6 months after

surgery (Table 3). There was no deterioration in FEV1 after surgery in either group.  $PaO_2$  in the TH group did not change in the 6 months after surgery, whereas there was a transient decrease in the LTA group.

## Discussion

The first randomized controlled trial compared two types of lymphadenectomy within the same surgical approach for gastric cancer, whereas the second trial compared two completely different surgical approaches, namely with and without thoracotomy. In the present study, secondary outcomes of patients without recurrence after gastrectomy were evaluated. Bodyweight was comparable after D2 and D2 plus PAND, whereas the difference in bodyweight between the TH and the LTA groups widened gradually owing to recovery in the TH group. This means that bodyweight change after gastrectomy is more dependent on surgical approach than on the extent of lymphadenectomy. Some of the clinical symptoms were particularly negatively affected by a LTA compared with a TH approach, whereas D2 and D2 plus PAND had comparable scores. The decrease in vital capacity was significantly greater after a LTA than a TH procedure.

Clinical symptoms in the D2 plus PAND group were limited to a short time after operation, and mostly related to changes in bowel habit. This may be due either to autonomic nerve damage or to lymphoedema of the jejunum caused by PAND. However, limited autonomic nerve dissection in PAND may not cause long-term impairment of intestinal function. A small-scale randomized controlled trial of PAND in patients with pancreatic cancer showed that dissection of such nodes frequently caused diarrhoea for up to 4 months after surgery<sup>7</sup>. Although changes in bowel habit may be the biggest disadvantage of PAND, these negative effects were limited to the early postoperative period and seemed to be acceptable clinically. Wu *et al.*<sup>8</sup> compared postoperative symptoms between D1 alone and D2 plus retropancreatic lymph node dissection in a single-institution randomized controlled trial<sup>8</sup>. They reported no significant difference in symptoms between the two groups and concluded that postoperative changes in symptoms were related largely to the scope of gastric resection, disease status and combined resection of the pancreas or spleen rather than the extent of lymph node dissection.

Pain and dyspnoea are well known sequelae of intercostal thoracotomy<sup>9,10</sup>. The negative impact of the thoracotomy procedure on symptoms within the first year agreed with the results of previous studies<sup>11,12</sup>. The difference in meal volume might arise from the location of the anastomosis,

in the open thoracic cavity in LTA procedures *versus* the mediastinum in TH operations.

Although quality of life and symptoms are distinct entities, symptoms usually affect patients' quality of life quite strongly. Quality of life is usually assessed by questionnaire and is evaluated by the patients themselves to minimize information bias<sup>13,14</sup>. However, the Japanese versions of validated questionnaires such as the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) or the Functional Assessment of Cancer Therapy – General (FACT-G) were not available when these randomized controlled trials were conducted<sup>14,15</sup>. In the present study, the Gastric Cancer Surgical Study Group/JCOG Symptom Questionnaire, which consisted of only seven or nine queries, was used, because the more complicated the survey, the lower the compliance would have been. Moreover, this questionnaire evaluating patient-centred outcome such as symptom scores was completed by the doctor not the patient, which might have introduced observer bias.

The decrease in bodyweight and worsening of post-operative symptom scores following PAND was limited compared with D2 without PAND. Therefore, D2 plus PAND might be one option when R0 resection is impossible without dissection of such nodes. The LTA approach worsened both symptoms and respiratory function to a greater extent than the TH approach. Surgeons are advised to avoid the LTA approach based not only on previously published survival-related evidence but also on other parameters such as those evaluated in this study.

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### Supporting information

Additional supporting information may be found in the online version of this article.

**Fig. S1** CONSORT diagrams for a Japan Clinical Oncology Group (JCOG) 9501 and b JCOG9502 trials. PAND, para-aortic nodal dissection; TH, abdominal–transhiatal; LTA, left thoracoabdominal (Word file)

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## Commentary

### Functional outcomes after extended surgery for gastric cancer (*Br J Surg* 2011; 98: 239–245)

'Optimal' surgical treatment remains essential in offering the highest chance of cure to patients with advanced gastric cancer. Extending the degree of surgery not always allows better survival results, while it may impair short- and long-term quality of life. Nonetheless, the main factor affecting prognosis as well as quality of life after gastric cancer surgery is actually disease recurrence.

The study by Kurokawa and colleagues reports important data on quality of life from two well known randomized trials from Japan: Japan Clinical Oncology Group (JCOG) 9501, which evaluated D2 plus para-aortic nodal dissection (PAND) with D2 lymphadenectomy in advanced gastric cancer, and JCOG9502, which compared the left thoracoabdominal with the transhiatal approach for treatment of proximal gastric cancer with oesophageal infiltration, mainly type II and III according to the Siewert classification. As correctly noted by the authors, JCOG9501 compared a different extent of lymphadenectomy within the same surgical approach, whereas JCOG9502 compared two completely different surgical approaches, namely with and without thoracotomy.

Transhiatal resection represents the preferred approach for type III tumours. However, more debate exists for type II tumours where thoracotomy is more frequently accomplished in order to achieve adequate proximal resection margins and mediastinal lymph node dissection. As a consequence, the best approach for Siewert type II tumours has not yet been defined completely. Several clinical studies analysing lymph node involvement in adenocarcinoma of the gastro-oesophageal junction seem to demonstrate that nodal involvement in the mediastinum is infrequent in type III as well as type II tumours and, when present, always indicative of poor prognosis<sup>1,2</sup>. These data together with those presented by Kurokawa and colleagues should make transhiatal resection preferable. In this context one should note that total gastrectomy was always performed together with distal resection of the oesophagus in the JCOG9502 trial. Conversely, in Western countries oesophagogastrectomy with gastric tube reconstruction is usually preferred when a thoracotomy is performed. Hence, these results should be considered not completely reproducible in the latter setting.

Regarding PAND, no survival benefit has been demonstrated in a prophylactic setting in the JCOG9501 trial. Patients with positive para-aortic lymph node involvement at frozen-section examination were excluded from the analysis. Interestingly, some chances of survival have been noted for patients with positive para-aortic involvement in some Japanese as well as Western experiences. Furthermore, high 5-year survival rates were recorded in certain subsets of patients after D3 lymphadenectomy in a recent series published by the Italian Research Group for Gastric Cancer<sup>3</sup>. Such findings seem to reflect the *post hoc* analysis of the Japanese trial where a potential benefit was observed for tumours without serosal invasion. These results, together with the data presented by Kurokawa and colleagues, may justify the adoption of such an extended procedure in specialized centres in order to achieve R0 resection, and better analysis of its potential role in subgroups of patients in the context of a clinical trial.

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## Review Article

# Lymph Node Dissection in Curative Gastrectomy for Advanced Gastric Cancer

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Gastric cancer is one of the most common causes of cancer-related death worldwide. Surgical resection with lymph node dissection is the only potentially curative therapy for gastric cancer. However, the appropriate extent of lymph node dissection accompanied by gastrectomy for cancer remains controversial. In East Asian countries, especially in Japan and Korea, D2 lymph node dissection has been regularly performed as a standard procedure. In Western countries, surgeons perform gastrectomy with D1 dissection only because D2 is associated with high mortality and morbidity compared to those associated with D1 alone but does not improve the 5-year survival rate. However, more recent studies have demonstrated that western surgeons can be trained to perform D2 lymphadenectomies on western patients with a lower morbidity and mortality. When extensive D2 lymph node dissection is performed safely, there may be some benefit to D2 dissection even in western countries. In this paper, we present an update on the current literature regarding the extent of lymphadenectomy for advanced gastric cancer.

## 1. Introduction

Gastric cancer is one of the most common causes of death worldwide [1]. Although the prognosis of patients with advanced gastric cancer has improved with the introduction of effective chemotherapy [2] or adjuvant radiotherapy [3], surgical resection remains the primary therapeutic modality for curable advanced cancer. With regard to surgical procedure, dissection of regional LN is regarded an important part of en bloc resection for gastric cancer. However, there are significant differences in the extent of lymphadenectomy performed by surgeons in different countries.

In Japan, D2 dissection has been recommended as standard practice since the 1960s [4]. East Asian surgeons, especially Japanese and Korean surgeons, routinely performed gastrectomy with D2 dissection. However, most Western surgeons perform gastrectomy with only D1 dissection, because D1 was associated with less mortality and morbidity than D2 in prospective randomized trials performed in the Netherland and the UK concluded that there was no survival benefit for D2 over D1 lymph node dissection [5, 6]. However, there were significant problems with these

studies, including a high morbidity and mortality rate in the D2 group associated with inadequate surgical training, with inadequate dissection of D2 and with the frequent performance of distal pancreatectomy and splenectomy in the D2 group, which is now considered unnecessary [7].

More recent studies have demonstrated that western surgeons at experienced centers can be trained to perform D2 gastrectomy for selected western patients with low morbidity and mortality [8–10]. There may be some benefits to D2 gastrectomy when performed safely, but this assertion requires further validation to establish the global standard in gastrectomy.

In this paper, we describe an update on the current literature regarding the extent of lymphadenectomy for advanced gastric cancer.

## 2. Grouping of Lymph Nodes

The lymph nodes of the stomach have been arranged into a very useful classification by the Japanese Gastric Cancer Association (JGCA) [11, 12] (Table 1, Figure 1).



TABLE 1: Regional lymph nodes.

No. 1	Right paracardial LN
No. 2	Left paracardial LN
No. 3a	LN along the left gastric vessels
No. 3b	LN along the right gastric vessels
No. 4sa	LN along the short gastric vessels
No. 4sb	LN along the left gastroepiploic vessels
No. 4d	LN along the right gastroepiploic vessels
No. 5	Suprapyloric LN
No. 6	Infrapyloric LN
No. 7	LN along the left gastric artery
No. 8a	LN along the common hepatic artery (anterosuperior group)
No. 8b	LN along the common hepatic artery (posterior group)
No. 9	LN along the celiac artery
No. 10	LN at the splenic hilum
No. 11p	LN along the proximal splenic artery
No. 11d	LN along the distal splenic artery
No. 12a	LN in the hepatoduodenal ligament (along the hepatic artery)
No. 12b	LN in the hepatoduodenal ligament (along the bile duct)
No. 12p	LN in the hepatoduodenal ligament (behind the portal vein)
No. 13	LN on the posterior surface of the pancreatic head
No. 14v	LN along the superior mesenteric vein
No. 14a	LN along the superior mesenteric artery
No. 15	LN along the middle colic vessels
No. 16a1	LN in the aortic hiatus
No. 16a2	LN around the abdominal aorta (from the upper margin of the celiac trunk to the lower margin of the left renal vein)
No. 16b1	LN around the abdominal aorta (from the lower margin of the left renal vein to the upper margin of the inferior mesenteric artery)
No. 16b2	LN around the abdominal aorta (from the upper margin of the inferior mesenteric artery to the aortic bifurcation)
No. 17	LN on the anterior surface of the pancreas head
No. 18	LN along the inferior margin on the pancreas
No. 19	Infradiaphragmatic LN
No. 20	LN in the esophageal hiatus of the diaphragm
No. 110	Paraesophageal LN in the lower thorax
No. 111	Supradiaphragmatic LN
No. 112	Posterior mediastinal LN

According to this classification, lymph nodes surrounding stomach are divided into 20 stations and these are classified into three groups depending upon the location of the primary tumor. This grouping system is based on the results of studies of lymphatic flow at various tumor sites, together with the observed survival associated with metastasis to each nodal station [13]. In this grouping

TABLE 2: Depth of tumor invasion (T)—Japanese classification and TNN.

Depth of tumor invasion (T)	Japanese classification (JC: 13th edition)	TNM classification (6th edition)	JC (14th edition)/TNM (7th edition)
Mucosa and/or muscularis mucosa (M)	T1 (M)	Tis/T1	Tis/T1a
Submucosa (SM)	T1 (SM)	T1	T1b
Muscularis propria (MP)	T2 (MP)	T2a	T2
Subserosa (SS)	T2 (SS)	T2b	T3
Penetration of serosa (SE)	T3	T3	T4a
Invasion of adjacent structures (SI)	T4	T4	T4b

TABLE 3: Extent of lymph node metastasis (N)—Japanese classification and TNN classification.

N category	Japanese classification (JC: 13th edition)	TNM classification (6th edition)	JC (14th edition)/TNM (7th edition)
N <sub>0</sub>	No evidence of LN metastasis	No evidence of LN metastasis	No evidence of LN metastasis
N <sub>1</sub>	Metastasis to only Group 1 LN	Metastasis in 1 to 6 regional LNs	Metastasis in 1 to 2 regional LNs
N <sub>2</sub>	Metastasis to Group 2 LN, but no metastasis to Group 3 LN	7–15 nodes	3–6 nodes
N <sub>3</sub>	Metastasis to Group 3 LN	16 or more nodes	7 or more nodes N3a: 7–15 nodes N3b: 16 or more nodes

LN: lymph node.

system, the most perigastric LNs (stations nos. 1–6) are defined as group 1, whereas the nodes along the left gastric artery (station no. 7), common hepatic artery (station no. 8), celiac axis (station no. 9), splenic artery (station no. 11) and proper hepatic artery (station no. 12) are defined as group 2. Minor modifications of this grouping system are necessary according to the location of the primary tumor. D1 gastrectomy is defined as dissection of all the Group 1 nodes, and D2 is defined as dissection of all the Group 1 and Group 2 nodes.

Recently, new Japanese Classification of Gastric Carcinoma [12] and guideline for Diagnosis and Treatment of Carcinoma of the Stomach [14] edited by the Japanese Gastric Cancer Society were published in May and October, 2010 to match to the standard of TNM classification of UICC [15, 16] (Tables 2 and 3).



TABLE 4: Randomized controlled trials comparing D1 with D2/D3.

Study	Country	Comparison	Postoperative morbidity	Postoperative mortality	5-year survival
Dutch trial (1989–1993)	Netherlands	D1 ( <i>n</i> = 380) D2 ( <i>n</i> = 331)	25% 43% ( <i>P</i> < .001)	4% 10% ( <i>P</i> = .004)	45% 47% HR 1.00 (95% CI, 0.82–1.22)
MRC trial (1987–1994)	UK	D1 ( <i>n</i> = 200) D2 ( <i>n</i> = 200)	28% 46% ( <i>P</i> < .001)	6.5% 13% ( <i>P</i> = .04)	35% 33% HR 1.10 (95% CI, 0.87–1.39)
Taiwanese trial (1993–1999)	Taiwan	D1 ( <i>n</i> = 110) D3 ( <i>n</i> = 111)	7.3% 17.1% ( <i>P</i> < .012)	0% 0%	53.6% 59.5% HR 0.49 (95% CI, 0.32–0.77)
IGCSG trial (1999–2002)	Italy	D1 ( <i>n</i> = 76) D2 ( <i>n</i> = 86)	10.5% 16.3% ( <i>P</i> < .029)	0% 1.3% (N.S)	Under analysis

Recently, 15-year follow-up results of a randomized nationwide Dutch D1D2 trial were reported. The overall 15-year survival was 21% (82 patients) for the D1 group and 29% (92 patients) for the D2 group (*P* = .34). The gastric-cancer related death rate was significantly higher in the D1 group (48%, 182 patients) compared with that in the D2 group (37%, 123 patients), whereas death due to other diseases was similar in both groups [19].

The authors indicated in the interpretation that because a safer, spleen-preserving D2 resection technique had become available in high-volume centers, D2 lymphadenectomy should be the recommended surgical approach for patients with resectable (curable) gastric cancer.

In the British study, postoperative complications were significantly higher in the D2 group (46%) than in the D1 group (28%; *P* < .001), and the postoperative mortality was also significantly higher in the D2 group (13%) than in the D1 group (6.5%; *P* = .04) [6].

In this study, splenectomy was performed for many patients with distal gastrectomy and pancreaticosplenectomy was carried out in 56% of patients allocated to the D2 group and 4% of the D1 group. The high frequency of postoperative complications was influenced by the excessive surgery, which contributed to a misunderstanding of the definition of D2 gastrectomy defined by the Japanese Gastric Cancer Association. The 5-year survival rate was 33% in the D1 group and 35% in the D2 group, which did not significantly differ between the two groups [20].

Unlike these two large European trials, the Italian Gastric Cancer Study Group (IGCSG) has shown the safety of D2 dissection with pancreas preservation in a one-arm phase I-II trial [9]. Between 1994 and 1996, 191 eligible patients were entered in the study. The overall morbidity rate was 20.9%. Surgical complications were observed in 16.7% of patients and reoperation was necessary in six patients and was successful in all cases. The overall hospital mortality rate was 3.1%; it was higher after total gastrectomy (7.46%) than after distal gastrectomy (0.8%). This study concluded that postoperative morbidity and mortality rates were favorably

comparable to those reported after the standard Western gastrectomy and that the more extensive Japanese procedure with pancreas preservation can be regarded as a safe radical treatment for gastric cancer in selected Western patients treated at experienced centers.

A small-scale RCT comparing of the morbidity and mortality of D1 to D2 gastrectomy was performed by IGCSG [10].

Of 162 patients randomized, 76 were allocated to D1 and 86 to D2 gastrectomy. The overall postoperative 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* < .29). The overall postoperative mortality rate was 0.6% (one death); it was 1.3% after D1 and 0% after D2 gastrectomy. This study confirmed that, at very experienced centers, morbidity and mortality after extended gastrectomy could be as low as those after D1 gastrectomy.

Another single-institutional small-scale RCT has reported from Taiwan that there were no significant differences in the postoperative and mortality between patients undergoing D3 and D1 gastrectomy [21, 22]. This was the only trial that showed a significantly higher 5-year disease-specific survival in patients with D3 surgery than in those with D1 surgery (Table 4).

Therefore, D2 gastrectomy is becoming accepted as a safe treatment for gastric cancer at experienced centers, in western countries.

#### 4. D2 versus D3

In Japan, gastrectomy with more radical extended lymphadenectomy had been performed since 1980's at many specialized centers in order to improve the prognosis of patients with advanced gastric cancer [23–26]. The incidence of microscopic metastasis in the paraaortic nodes (section no. 16) in patients with gastrectomy undergoing D3 lymph node dissection ranged from 6% to 33%, and the 5-year

TABLE 5: Randomized controlled trials comparing D2 with D2 plus para-aortic lymph nodes.

Study	Country	Comparison	Postoperative morbidity	Postoperative mortality	5-year survival
JCOG trial (1995–2001)	Japan	D2 ( <i>n</i> = 263) D2+ PALN ( <i>n</i> = 260)	20.9% 28.1% ( <i>P</i> = .067)	0.8% 0.8% ( <i>P</i> = .99)	69.2% 70.3% HR 1.03 (95% CI, 0.77–1.37)
Polish trial (1999–2003)	Poland	D2 ( <i>n</i> = 141) D2+ PALN ( <i>n</i> = 134)	27.7% 21.6% ( <i>P</i> = .248)	4.9% 2.2% ( <i>P</i> = .37)	Under analysis
East Asian trial (1995–2002)	Japan, Korea, and Chinese Taiwan area	D2 ( <i>n</i> = 135) D2+ PALN ( <i>n</i> = 134)	26% 39% ( <i>P</i> = .023)	0.7% 3.7% ( <i>P</i> = .107)	52.6% 55.4% ( <i>P</i> = .801)

D2: gastrectomy with D2 lymph node dissection. PALN: para-aortic lymph node dissection.

survival rate had been reported to range from 12% to 23% in patients undergoing gastrectomy with D3 dissection. Extending these previous findings regarding the favorable results of D3 dissection, the Japanese Clinical Oncology Group (JCOG) conducted a randomized clinical trial between 1995 and 2001 to compare D2 gastrectomy alone with D2 plus paraaortic lymph node dissection (PAND) [27]. A total of 523 patients with T2b, T3, and T4 gastric cancer were registered and randomly assigned to D2 alone group (263 patients) or D2 plus PAND group (260 patients).

The rates of surgery-related complications among patients assigned to D2 lymphadenectomy alone and those assigned to D2 lymphadenectomy plus PAND were 20.9% and 28.1%, respectively (*P* = .07). There were no significant differences between the two groups in the frequencies of anastomotic leakage, pancreatic fistula, abdominal abscess, pneumonia, or death from any cause within 30 days after surgery (the mortality was 0.8% in each group). The 5-year overall survival rate was 69.2% for the group assigned to D2 lymphadenectomy alone and 70.3% for the group assigned to D2 lymphadenectomy plus PAND; the hazard ratio for death was 1.03. Moreover, there were no significant differences in recurrence-free survival between the two groups.

Recently, meta-analyses of D2 lymphadenectomy versus D2 with PAND were reported [28]. Three RCTs including the PGCSG study in Poland [29], EASOG study in Japan, Korea, and Chinese Taiwan area [30, 31], and JCOG-9501 study in Japan [27] were eligible (Table 5). Another analysis included 4 RCTs and 4 nonrandomized studies were identified [32]. These meta-analyses showed that D2+ PAND can be performed as safely as a standard D2 resection without increasing postoperative mortality but failed to benefit overall survival in patients with advanced gastric cancer.

Gastrectomy with D2 lymphadenectomy plus PAND cannot be recommended as a routine practice for the surgical treatment of gastric cancer.

## 5. Mediastinal Lymph Node Dissection for Gastric Cancer

For patients with esophageal invasion from gastric cancer, it is necessary to perform mediastinal resection included

the lower esophagus and the periesophageal lymph nodes and to confirm that the esophageal cut end is negative by performing histological examination using frozen section as necessary [33]. Conventionally, this mediastinal procedure was done through the left thoracoabdominal approach (LTA), because the frequency of lymph node metastasis was reported to be high with about 20–40% and an adequate margin from the tumor could be secured. However, a mediastinal procedure was enabled through the abdominal-transhiatal approach (TH) with advances in surgical methods using a circular stapler in recent years.

In Japan, an RCT comparing LTA versus TH for Siewert type II and III tumors with esophageal invasion of 3 cm or less was carried out by JCOG [34]. Between 1995 and 2003, 167 patients were enrolled from 27 Japanese hospitals and randomly assigned to TH (*n* = 82) or LTA (*n* = 85), although the projected sample size was 302. After the first interim analysis, the predicted probability of LTA having a significantly better overall survival than TH at the final analysis was only 3.65%; therefore, the trial was closed. The 5-year overall survival was 52.3% in the TH group and 37.9% in the LTA group. The hazard ratio of death for LTA compared with TH was 1.36 (0.89–2.08, *P* = .92). Three patients died in hospital after LTA but none after TH. Morbidity after LTA was worse than that after TH with rates of 49% and 34%, respectively.

This study concluded that LTA could not be performed for gastric cancer with esophageal invasion of 3 cm or less, because LTA did not improve survival compared to TH and resulted in increased morbidity.

## 6. Splenectomy or Pancreaticosplenectomy in the Treatment of Cancer of the Upper Third of the Stomach

In Japan, pancreaticosplenectomy for LN dissection around the splenic artery (station no. 11) and splenic hilus (station no. 10) had been widely performed, because this procedure was proposed as a radical dissection of metastatic LN along the splenic artery [35, 36]. However, Japanese retrospective analyses proved that there was no survival benefit of these

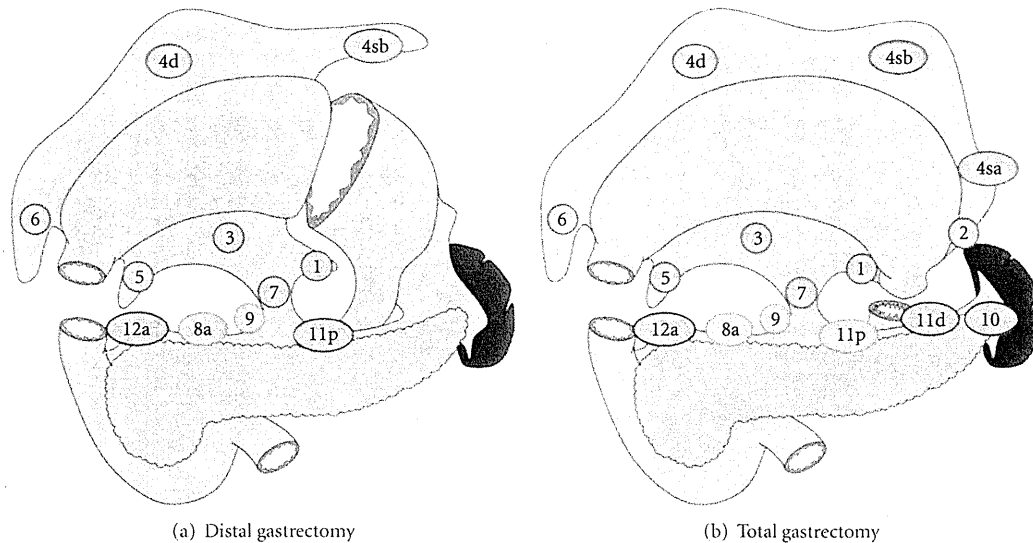


FIGURE 2: Lymph node dissection according to the Japanese gastric cancer treatment guideline 2010 of the 3rd edition reproduced from [14] with permission. D1 distal gastrectomy consists of LN dissection of station nos. 1, 3, 4sb, 4d, 5, 6, and 7 and D1 total gastrectomy consists of station nos. 1–6 and 7 (blue circle). Yellow circles indicate the lymph nodes that belong to D1+, and red circles indicate those to D2.

procedures [37, 38]. Recently, pancreas-preserving splenectomy has been considered a safe and effective procedure without decreasing surgical curability [39, 40].

In the JCOG 9501 study, pancreas-preserving splenectomy was generally performed with low surgical mortality [27, 41]. In this study, only 22 of 523 patients underwent pancreaticosplenectomy and 59% of patients (13 of 22 cases) developed postoperative complications.

In this pancreas-preserving procedure, the splenic artery is generally divided at the distal site after branching-off of the great pancreatic artery in Sasako's modification and the splenic vein is preserved as distal as possible in order to prevent pancreatic fistula and pancreatic atrophy and consequent glucose intolerance [42].

In Western countries as well, pancreaticosplenectomy had a marked adverse effect on both mortality and morbidity in two RCTs [5, 6].

Currently, pancreaticosplenectomy is considered beneficial only when the primary tumor or metastatic LN directly invades the pancreas, but is not performed for prophylactic dissection of lymph nodes around the splenic artery (station no. 11).

According to the Japanese experience with LN dissection at the splenic hilus with splenectomy, the incidence of hilar node metastasis ranged 15–21% for tumors located at or infiltrate to the proximal third of the stomach. About 20–25% of patients with LN metastasis have survived over 5 years following LN dissection with splenectomy [35]. However, hilar nodal metastasis was reported to be not found in the early gastric cancer base on retrospective data [43, 44]. Splenectomy is recommended for curative resection of the proximal advanced gastric cancer with infiltration to the greater curvature in the Gastric Cancer Treatment Guidelines 2010 [14].

Two RCTs compared gastrectomy with splenectomy and gastrectomy alone in patients with gastric cancer were reported with regard to the effectiveness and safety [45, 46].

Csendes et al. reported 187 patients who underwent total gastrectomy between 1985 and 1992; these patients were randomized into two groups, gastrectomy with splenectomy and gastrectomy alone. Postoperative complications were more frequent in the splenectomy group than in the surgery alone group, including postoperative fever over 38°C (50% versus 39%:  $P < .04$ ), pulmonary complications (39% versus 24%:  $P < .008$ ), and subphrenic abscess (11% versus 4%:  $P < .05$ ). There were no significant differences between the groups in hospital mortality (4.4% for splenectomy versus 3.1% for gastrectomy alone) or in the 5-year survival rate (42% for splenectomy versus 36% for gastrectomy alone) [45].

The other trial reported by Yu et al. was carried out in Korea between 1995 and 1999. Two hundred seven patients with gastric cancer were divided randomly into two groups, total gastrectomy (103 patients) and total gastrectomy plus splenectomy (104 patients). Postoperative mortality was 8.7% in total gastrectomy alone group and 15.4% in total gastrectomy plus splenectomy group, but there was no significant difference between the groups. Hospital mortality was 1.0% in total gastrectomy alone and 1.9% in total gastrectomy plus splenectomy group; there was no significant difference between the two groups.

The 5-year survival rates did not differ statistically between the gastrectomy alone group (48.8%) and gastrectomy plus splenectomy group (54.8%). There was no 5-year survivor among patients with lymph node metastasis at the splenic hilum in either group [46].

Therefore, these results did not support the effectiveness of prophylactic dissection at the splenic hilum during

splenectomy in patients undergoing total gastrectomy for proximal gastric cancer.

## 7. Future Perspectives

In Japan and Korea, gastrectomy with D2 LN dissection is the gold standard of treatment for advanced gastric cancer. In order to improve the prognosis of these patients, adjuvant chemotherapy after D2 gastrectomy is thought to be effective and several studies have been reported [47, 48]. Recently, a meta-analysis based on the individual data of 3838 patients from 17 different trials with median follow-up 7 years was reported and indicated a modest but statistically significant benefit associated with adjuvant chemotherapy after curative resection of gastric cancer [49]. In Japan, adjuvant chemotherapy with S-1 is a standard treatment for patients with stage II/III gastric cancer after curative gastrectomy with D2 LN dissection [48]. Moreover, to improve the survival of patients with advanced gastric cancer, neoadjuvant chemotherapy and/or chemotherapy with combination setting or new agents, such as molecular targeting agents, are thought to be necessary in addition to performing D2 gastrectomy with safety and reliability [50].

Last year, the Japanese Classification of Gastric Carcinoma was revised to conform with the TNM classification of UICC in many respects. In the new guidelines for the Diagnosis and Treatment of Carcinoma of the Stomach, D1, D1+, and D2 gastrectomy were described according to the type of gastrectomy, making the guidelines easier to understand. A global study using unified criteria is necessary to establish a safe and effective worldwide treatment standard including gastrectomy with LN dissection.

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## Phase II Feasibility Study of Adjuvant S-1 plus Docetaxel for Stage III Gastric Cancer Patients after Curative D2 Gastrectomy

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### Key Words

Gastric cancer · Adjuvant chemotherapy · S-1 · Docetaxel · Gastrectomy · D2 lymph node dissection

### Abstract

**Objective:** The aim of this prospective study was to evaluate the feasibility and safety of adjuvant S-1 plus docetaxel in patients with stage III gastric cancer. **Methods:** We enrolled 53 patients with pathological stage III gastric cancer who underwent D2 gastrectomy. They received oral S-1 (80 mg/m<sup>2</sup>/day) administration for 2 consecutive weeks and intravenous docetaxel (40 mg/m<sup>2</sup>) on day 1, repeated every 3 weeks (1 cycle). The treatment was started within 45 days after surgery and repeated for 4 cycles, followed by S-1 monotherapy (4 weeks on, 2 weeks off) until 1 year after surgery. The feasibility of the 4 cycles of chemotherapy, followed by S-1 administration, was evaluated. **Results:** A total of 42 patients (79.2%, 95% CI 65.9–82.9) tolerated the planned 4 cycles of treatment with S-1 and docetaxel, and 34 patients (64.2%, 95% CI 49.8–76.9) completed subsequent S-1 monotherapy for 1 year. Grade 4 neutropenia was observed in 28% and grade 3 febrile neutropenia in 9% of the patients, while grade 3 nonhematological toxicities were relatively low.

**Conclusions:** Adjuvant S-1 plus docetaxel therapy is feasible and has only moderate toxicity in stage III gastric cancer patients. We believe that this regimen will be a candidate for future phase III trials seeking the optimal adjuvant chemotherapy for stage III gastric cancer patients.

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### Introduction

The principal aims of adjuvant chemotherapy for curatively resected gastric cancer are to prevent distant or local recurrence and improve the survival of patients. In Japan, several studies concerning postoperative adjuvant chemotherapy for patients with gastric cancer have been performed since 1960, but none of these studies demonstrated therapeutic benefits of adjuvant chemotherapy [1–6].

The National Surgical Adjuvant Study Group for Gastric Cancer study evaluated postoperative chemotherapy for patients with T2, N1–2 gastric cancer from 1998 using uracil-tegafur (an oral fluoropyrimidine prodrug) for 18 months, excluding stage I gastric cancer, based on an analysis of previous studies. Although this study was interrupted because of the introduction of S-1 and the start

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of a new large-scale trial – the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) – using S-1 for stage II and III gastric cancer from 2001, the results of this study showed that adjuvant chemotherapy with uracil-tegafur was effective for T2, N1–2 gastric cancer [7].

In an ACTS-GC study, adjuvant chemotherapy using S-1 has been reported to be effective for Japanese stage II and III gastric cancer patients who have undergone a D2 dissection. This trial was stopped on the recommendation of the independent data and safety monitoring committee, because the first interim analysis, performed 1 year after completion of enrollment, showed that the 3-year overall survival (OS) rate of 80.1% in the S-1 group was higher than that of 70.1% in the surgery-only group. However, in stage III gastric cancer patients, the difference in the 3-year OS rate between the S-1 group and the surgery-alone group was less than that in stage II [8].

Therefore, to improve the prognosis for patients with advanced gastric cancer after curative resection, more effective chemotherapy is required for patients with stage III gastric cancer.

Recently, several combination chemotherapeutic regimens involving S-1 and other anticancer drugs such as cisplatin, taxanes and irinotecan (CPT-11) have been reported to yield and increased overall response rates and prolonged median survival time [9–12].

In these studies, in patients with advanced gastric cancer, S-1 plus docetaxel has shown that the response rate and median OS was 56% and 14.3 months, respectively. Moreover, gastrointestinal toxicities of this combination regimen were reported to be comparatively few and low grade: anorexia (6.3%), stomatitis (10.4%) and nausea (6.3%), which was considered to be advantageous for the postoperative patients [10].

Therefore, S-1 plus docetaxel may be a promising regimen for stage III advanced gastric cancer after curative resection, as well as being a candidate for an experimental arm in the next adjuvant chemotherapy trial.

The aim of this phase II study was to evaluate the feasibility and safety of adjuvant chemotherapy of S-1 plus docetaxel for stage III gastric cancer patients.

## Patients and Methods

### Eligibility Criteria

The eligibility criteria of this study were: (1) histologically proven gastric cancer of stage IIIA or IIIB after R0 surgery with D2 lymph node dissection; (2) age 20–80 years; (3) Eastern Cooperative Oncology Group performance status 0–1; (4) no previous treatment for cancer except for the initial gastric resection for the

primary lesion; (5) adequate digestive function; (6) duration of the period from surgery <6 weeks, and (7) adequate organ function, including a leukocyte count between 4,000 and 12,000 mm<sup>3</sup>, a neutrophil count >2,000 mm<sup>3</sup>, a platelet count >100,000 mm<sup>3</sup>, a hemoglobin count >9.0 g/dl, aspartate aminotransferase and alanine aminotransferase levels within 2.5 times the upper limit of the normal range, a serum bilirubin level <1.5 mg/dl, a serum creatinine level <1.2 mg/dl, and creatinine clearance of at least 60 ml/min. Moreover, absence of other severe medical conditions and an absence of synchronous or metachronous malignancy were needed for this study.

Exclusion criteria were as follows: infection or suspected infection with fever; congestive heart failure; uncontrolled diabetes or hypertension; interstitial pneumonia or lung fibrosis; symptomatic brain metastasis; liver cirrhosis or active hepatitis, and pregnancy. Patients with a history of prior chemotherapy were also excluded.

Written informed consent was obtained from each patient before enrollment and the protocol was approved by the institutional ethics committees of the participation centers.

The eligibility criteria for stage classification was judged in accordance with the guidelines of the Japanese Gastric Cancer Association [13] and all patients were additionally staged using the 6th edition of UICC TNM staging system [14].

### Study Design

In this feasibility study, oral S-1 (80 mg/m<sup>2</sup>/day) was administered for 2 consecutive weeks and intravenous docetaxel (40 mg/m<sup>2</sup>) on day 1, repeated every 3 weeks (1 cycle). The treatment was started within 45 days after surgery and repeated for 4 cycles. After 4 cycles of this treatment, S-1 was administered as daily monotherapy according to the schedule of the ACTS-GC study until 1 year after surgery. Namely, patients received 2 oral doses of 40 mg/m<sup>2</sup> of S-1 per day, for 4 weeks, followed by 2 weeks of no chemotherapy. If patients had hematological toxic effects of grade 3 or 4 or nonhematologic toxic effects of grade >2, their dose of docetaxel was reduced from 40 to 35 mg/m<sup>2</sup>, and at the same time, the dose of S-1 was reduced from 120 to 100 mg, or from 100 to 80 mg or from 80 to 50 mg per day.

The primary endpoint was the feasibility of completing 4 cycles of S-1 plus docetaxel; the secondary endpoints were safety, disease-free survival, OS and feasibility of S-1 administration until 1 year after surgery. The definition of feasibility of administration was 'treatment completion rate >75% at 4 cycles of S-1 plus docetaxel therapy' and the completion of treatment rate was defined as follows: (full analysis set – number of discontinued patients by adverse events)/number of all patients × 100.

We adopted the combination chemotherapy method reported by Yoshida et al. [10], using the same schedule. Although it is difficult to decide how many cycles of S-1 plus docetaxel should be performed in an adjuvant setting, we decided to carry out this study with 4 cycles of S-1 plus docetaxel based on the results of a study using an average of 4 courses reported by Yoshida et al. [10], which was performed for patients with advanced and recurrent gastric cancer.

### Follow-Up

Patients underwent hematologic tests and assessments of clinical symptoms at least once during every course of chemotherapy. The presence of a relapse was determined by means of imaging

**Table 1.** Patient characteristics

Patients (n = 53)		
Age, years	Median	65
	Range	43–78
Gender	Male	42
	Female	11
ECOG PS	0	31
	1	22
Pathological type	Intestinal	23
	Diffuse	29
	Others	1
Stage <sup>1</sup>	IIIA	36
	IIIB	17
T stage <sup>2</sup>	pT2	21
	pT3	30
	pT4	2
N stage <sup>2</sup>	pN0	1
	pN1	22
	pN2	30
M stage <sup>2</sup>	M0	53
	M1	0
Stage <sup>2</sup>	IIIA	36
	IIIB	16
	IV (T4, N1)	1

ECOG PS = Eastern Cooperative Oncology Group performance status.

<sup>1</sup> Japanese classification. <sup>2</sup> TNM classification.

studies, including ultrasonography, computed tomography and gastrointestinal endoscopy. Patients underwent abdominal computed tomography at 6-month intervals during the first 2 years after surgery, at 1-year intervals thereafter until 5 years after surgery, and also underwent gastrointestinal endoscopy at 1-year intervals.

#### Statistical Analysis

The calculation of the sample size for the study was based on an expected feasibility rate of 75% and a threshold feasibility rate of 50%, using a 2-sided  $\alpha$  error of 0.05 and a statistical power of 90%. The planned sample size was 50 patients, allowing for a 20% dropout rate. The feasibility rate was evaluated by exact binomial test. Statistical analysis was done using R software version 2.12.1 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Patient Characteristics

We enrolled 53 patients from 13 institutions for this study, 42 men and 11 women with a median age of 65 years (range 43–78), between May 2007 and August 2008.

**Table 2.** Adverse events of 4 cycles of chemotherapy with S-1 plus docetaxel (n = 53)

	G1	G2	G3	G4	≥G3, %
<b>Hematologic</b>					
Anemia	20	11	2	0	3.3
Leukopenia	7	17	7	3	18.9
Neutropenia	4	4	11	15	49.1
Thrombocytopenia	7	0	0	0	3.8
Febrile neutropenia	-	-	5	0	9.4
<b>Nonhematologic</b>					
AST/ALT	7	0	0	0	0
Total bilirubin	4	3	0	0	0
Nausea	9	3	3	0	5.7
Vomiting	2	2	0	0	0
Anorexia	16	7	5	0	9.4
Fatigue	12	8	3	0	5.7
Stomatitis	5	1	1	0	1.9
Diarrhea	6	3	0	0	0
Alopecia	5	3	-	-	0

National Cancer Institute Common Toxicity Criteria, version 3.0. AST = Aspartate aminotransferase; ALT = alanine aminotransferase.

Thirty-six patients had stage IIIA disease and 17 patients had stage IIIB disease. The demographic and clinicopathological characteristics of these patients are listed in table 1.

### Toxicity

The most frequent grade 3–4 hematological toxicity during 4 cycles of this regimen was neutropenia, which was observed in 26 of 53 patients (49.1%) (table 2). Grade 3 febrile neutropenia was observed in 5 patients (9%). Additional grade 3–4 hematological toxicities consisted of leukopenia in 10 patients (18.9%) and anemia in 2 patients (3.8%). Nonhematological toxicities of grade  $\geq 3$  involved nausea in 5.7%, anorexia in 9.4% and fatigue in 5.7%. There was no grade 4 nonhematological toxicity in any patient.

No treatment-related deaths occurred within 30 days after completion of this regimen.

### Feasibility

The feasibility of the planned 4 cycles of treatment was 79.2% (95% CI 65.9–89.2;  $p < 0.001$  under the null hypothesis) with 42 out of 53 patients (table 3). Reasons for discontinuation of this regimen were adverse events in 9 patients, by physician's decision in 1 patient, and 1 patient postponed the treatment schedule due to personal rea-

**Table 3.** Feasibility of protocol treatment

	S-1 plus docetaxel for 4 cycles	S-1 plus docetaxel and S-1 monotherapy for 1 year
Patients	53	53
Completed	42	34
Not completed	11	19
Treatment completing rate	79.2% (65.9–89.2)	64.2% (49.8–76.9)

Figures in parentheses are 95% CIs.

sions. A total of 42 patients completed 4 cycles of S-1 and docetaxel, but 8 patients did not follow the planned S-1 monotherapy: 3 due to recurrent cancer, 2 due to toxicity, 1 due to patient refusal, 1 due to the physician's decision, and 1 due to personal reasons.

The relative performance of S-1 and docetaxel for 4 cycles of chemotherapy was 79.6 and 87.8%, respectively. Moreover, the compliance rates of S-1 patients were 84.9, 73.6, 69.8 and 64.2% (95% CI 49.8–76.95) at 3, 6, 9 and 12 months after surgery, respectively.

### Discussion

This phase II study demonstrated that postoperative adjuvant S-1 plus docetaxel therapy of 4 cycles is feasible, with a feasibility rate of 79.2%. Moreover, the compliance of S-1 treatment was similar to those of the ACTS-GC study up to 1 year after surgery: 84.9 versus 87.4% at 3 months, 73.6 versus 77.9% at 6 months, 69.8 versus 70.8% at 9 months and 64.2 versus 65.8% at 12 months, respectively [8].

Since there were few gastrointestinal toxicities during an additional 4 courses of docetaxel, this combination regimen seemed to be highly tolerable. These results may have important implications for future adjuvant treatment strategies for stage III gastric cancer.

In Japan, for metastatic or recurrent gastric cancer, S-1 plus cisplatin is now considered to be one of the standard regimens based on a phase III trial (SPIRITS study) [16].

The results of the SPIRITS study (S-1 vs. S-1 plus cisplatin) established the superiority of the S-1 plus cisplatin combination over S-1 monotherapy [15]. The rate of response to combination therapy versus monotherapy was 54 versus 31% ( $p = 0.0018$ ), and the median survival time was 13.0 versus 11.0 months ( $p = 0.0366$ ).

Therefore, S-1 plus cisplatin is considered to be a candidate for an experimental arm in the next adjuvant chemotherapy trial.

More recently, adjuvant chemotherapy studies using S-1 plus cisplatin have been reported for patients with resected gastric cancer [16, 17]. Five courses of S-1 plus cisplatin appear to be too toxic as postgastrectomy treatment for clinical stage II/III patients who underwent gastrectomy but turned out to be stage IV gastric cancer, so that the median relative dose intensities of S-1 and cisplatin were only 37 and 40%, respectively [16]. Moreover, a feasibility study of adjuvant chemotherapy with 3 courses of S-1 plus cisplatin followed by S-1 monotherapy until 1 year after surgery demonstrated that 3 courses of combined chemotherapy were not feasible because of the high incidence of grade 3–4 toxicities including neutropenia (40%), anorexia (28%) and nausea (8%) [17]. In this clinical trial, they suggested the modified protocol, the first chemotherapy cycle of which consisted of S-1 monotherapy; then, cisplatin was added to cycles 2, 3 and 4, followed by S-1 monotherapy up to 1 year after surgery. This amended protocol is more feasible than the original protocol, because of relatively few grade 3–4 toxicities including neutropenia (37%), anorexia (8%) and nausea (3%) and should be considered as a feasible experimental arm for the next postoperative adjuvant phase III trial [17].

Nausea and anorexia are commonly observed adverse reactions after the administration of cisplatin, and dehydration due to impaired oral food intake could increase the renal toxicity of cisplatin, especially in patients immediately after gastrectomy.

On the other hand, preclinical pharmacokinetic studies on docetaxel have shown that its hepatobiliary excretion is the major route of elimination, while renal excretion is minimal (<5%) [18–20]. Thus, it seems that docetaxel is a suitable anticancer agent for patients immediately after surgery. Moreover, S-1 plus docetaxel can be given in outpatient clinics, while S-1 plus cisplatin usually requires hospitalization to ensure hydration; thus, the former reduces the inconvenience to both patients and clinicians.

In both Japan and Korea, phase III studies of S-1 alone versus S-1 and docetaxel (JACCRO GC03 study) as chemotherapy for advanced gastric cancer are ongoing and the results should be reported soon [21].

If the results of the JACCRO GC03 study are favorable, it seems that the present regimen will become a promising candidate for adjuvant chemotherapy in stage III gastric cancer.

In conclusion, postoperative adjuvant chemotherapy with S-1 and docetaxel of 4 cycles and S-1 monotherapy afterwards until 1 year after surgery is considered to be feasible for patients who have undergone gastrectomy for gastric cancer.

This should be regarded as a potential experimental arm together with S-1 plus cisplatin for the next adjuvant phase III study comparing S-1 plus other drug combination chemotherapy and S-1 alone as adjuvant chemotherapy for patients who have undergone curative resection with D2 lymph node dissection for stage III gastric cancer.

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