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Phase II Clinical Trial of Postoperative S-1 Monotherapy for Gastric Cancer Patients with Free Intraperitoneal Cancer Cells Detected by Real-Time RT-PCR

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Abstract

Background We have previously reported the molecular detection of peritoneal micrometastases in patients with gastric cancer by quantifying carcinoembryonic antigen (CEA) mRNA in the peritoneal washes. Patients with CEA mRNA exceeding a cutoff value have a significant risk for developing peritoneal carcinomatosis, but optimal treatment for this population remains unknown.

Methods CEA mRNA (+) patients with gastric cancer were treated postoperatively with S-1 monotherapy. Overall survival, the primary endpoint of this phase II trial, was compared with the historical control, which is comprised of CEA mRNA (+) patients who were not given postoperative chemotherapy.

Results A total of 32 patients with CEA mRNA (+) gastric cancer were enrolled. Twelve patients (37.5%) relapsed; ten showed peritoneal relapse. Three-year survival was similar between the study population and the historical control (67.3% vs. 67.1%, respectively).

Conclusions S-1 monotherapy, which significantly reduced risk for recurrence in stage II/III gastric carcinoma in another phase III trial, seems not to be as effective in eradicating free cancer cells in the abdominal cavity.

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Gastric cancer is the second-most common cause of cancer death worldwide, and peritoneal carcinomatosis represents the most common route of tumor dissemination in patients with this disease [1–3]. This pathology is most likely caused by the presence of metastatic free cancer cells exfoliated from serosal surfaces of the primary cancer. We previously reported the detection of peritoneal micrometastases by reverse-transcriptase polymerase chain reaction (RT-PCR) analysis of peritoneal wash samples using carcinoembryonic antigen (CEA) mRNA as a target [3–7]. In these studies, CEA mRNA values correlated with depth of tumor invasion (pT category), and both overall survival and survival free from peritoneal relapse were significantly inferior among the CEA mRNA (+) patients. Several experimental studies have shown that micrometastases are more sensitive to chemotherapy compared with macrometastases [8–10]. Accordingly, micrometastasis detected by CEA RT-PCR could represent an important target of therapy.

Meta-analyses have suggested that adjuvant chemotherapy is effective in treating gastric cancer, but no definitive conclusion had been reached in the early 2000s regarding the efficacy of postoperative adjuvant chemotherapy for gastric-cancer patients treated with D2-lymphadenectomy [11]. S-1 (Taiho Pharmaceutical, Tokyo, Japan) is an orally active combination of tegafur (a prodrug converted by cells into fluorouracil), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (which inhibits phosphorylation of

fluorouracil in the gastrointestinal tract, thereby reducing gastrointestinal toxic effects of fluorouracil) in a molar ratio of 1:0.4:1 [12]. Response rates for S-1 monotherapy exceeded 40% in two late phase II trials, which involved patients with advanced or recurrent gastric cancer [13, 14]. Toxicity profile was moderate, and use in the postoperative adjuvant setting was considered feasible [15]. We therefore initiated a phase II trial of postoperative S-1 therapy for patients with CEA mRNA (+) gastric cancer.

A total of 32 patients with CEA mRNA(+) gastric cancer had been enrolled by the middle of 2006, when postoperative S-1 therapy was shown to improve significantly the prognosis for patients with stage II/III gastric cancer compared with observation alone in a pivotal phase III study [16]. Because most CEA mRNA (+) patients would have been categorized as stage II/III if RT-PCR had not been performed and would thus be treated by S-1 anyway, the trial was closed and survival data were analyzed after all patients had been followed for 12 months or more.

Patients and methods

Eligibility criteria

Patients entered into this study were required to fulfill the following eligibility criteria: (1) previously untreated patients with histologically proven adenocarcinoma; (2) between 20 and 80 years old; (3) Eastern Cooperative Oncology Group performance status (PS) of 2 or less; (4) treated with R0 resection of the primary lesion, and showing no distant or peritoneal metastases on preoperative imaging or at laparotomy; (5) no tumor cells in peritoneal fluid on routine cytological examination through Papanicolaou staining; (6) positive free cancer cells in the abdominal cavity detected through CEA RT-PCR; (7) adequate organ function (leukocyte count 3,000/mm^3; platelet count 100,000/mm^3; hemoglobin 8.0 g/dl; total bilirubin 1.5 mg/dl; aspartate aminotransferase and alanine aminotransferase levels 2.5 times the upper limit of the normal range; and serum creatinine no greater than the upper limit of the normal range); and (8) life expectancy >3 months. Written informed consent was obtained from all patients, and the study protocol was approved by the institutional review board.

Peritoneal washing

Aliquots of 100–200 ml of saline were introduced into the Douglas cavity and left subphrenic space at the beginning of each operation and aspirated shortly after gentle agitation. Half of each wash was sent for routine cytopathology with conventional Papanicolaou staining and the other half

was used to measure CEA mRNA levels. Intact cells collected from washes by centrifugation at 1,800 rpm for 5 min were rinsed with phosphate-buffered saline (PBS), dissolved in ISOGEN-LS RNA extraction buffer (Nippon Gene, Tokyo, Japan), and stored at −80°C.

Real-time quantitative RT-PCR

Frozen samples in ISOGEN-LS were thawed and total RNA was extracted using guanidinium isothiocyanate–phenol–chloroform, then cDNA was synthesized from total RNA using SuperScript II RNase H$^-$ reverse transcriptase (Invitrogen, Carlsbad, CA, USA) according to the instructions of the manufacturer. The resultant first-strand cDNA was stored at −80°C until analysis. Single-step real-time RT-PCR for CEA mRNA was performed using CEA-specific oligonucleotide primers and two fluorescent hybridization probes on a LightCycler instrument (Roche Diagnostics, Mannheim, Germany), as described previously [5, 7]. To quantify and confirm the integrity of the isolated RNA, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) also was analyzed by real-time RT-PCR using the appropriate primers and hybridization probes. All primers and probes were synthesized and purified by reverse-phase high-performance liquid chromatography at Nihon Gene Research Laboratories (Sendai, Japan). Six external CEA mRNA standards were prepared by tenfold serial dilution (1–10^5 cells) of cDNA equivalent to 1 × 10^6 COLM-2 cells (a colon cancer cell line that expresses large amounts of CEA) spiked into 1 × 10^7 peripheral blood leukocyte. Each run comprised six external standards, a negative control without a template, and patient samples with unknown mRNA concentrations. The amount of mRNA in each sample was then automatically measured by reference to the standard curve constructed each time on the LightCycler software. CEA mRNA was quantified in each patient using the peritoneal washing samples from Douglas cavity and subphrenic space. If at least one CEA mRNA value from the two washes was above the cutoff value (>0.1), the patient was considered as CEA mRNA (+). The cutoff value had been selected by the authors to maximize the sensitivity for detection of peritoneal micrometastasis. This cutoff value was then validated using an independent set of patients in the previous study [4].

Study design and treatment

The primary endpoint of the trial was overall survival, and secondary endpoints were peritoneal recurrence-free survival and the safety profile of S-1. Patients were to receive two oral doses of S-1 at 40 mg/m^2 per day for 4 weeks, followed by 2 weeks of no chemotherapy. This 6-week cycle was to be repeated throughout the first year after

surgery and was to be evaluated as effective if 3-year survival was shown to be higher than that of historical controls. The historical control was comprised of 58 patients who had CEA mRNA >0.1 at Aichi Cancer Center between 1995 and 2000 and were given no postoperative adjuvant chemotherapy. The sample size was calculated as 40 to confirm that the lower limit of the 95% confidence interval (CI) for 3-year survival among the study population exceed 65%, which is the 3-year survival proportion for historical control. The survival curve was estimated using Kaplan–Meier methods. Patients were to be followed up for 3 years postoperatively. Differences between curves were evaluated by log-rank testing. Adverse events were assessed according to the Common Toxicity Criteria of the National Cancer Institute (version 2.0).

Postoperative surveillance

The follow-up program consisted of interim history, physical examination, hematology, and blood chemistry panels including tests for CEA and CA19-9, performed every 3 months for 2 years. Computed tomography was performed every 6 months. Peritoneal recurrence, evident on the basis of clinical symptoms, digital examination, and physical and radiologic findings of bowel obstruction and ascites, was confirmed by paracentesis, laparotomy, and autopsy performed at the discretion of the surgeon.

Results

Patient demographics

Thirty-two patients with gastric cancer with CEA mRNA (+) status (23 men, 9 women) who underwent R0 surgery were registered between September 2003 and April 2006 at Aichi Cancer Center Hospital. Median duration of follow-up was 31.5 months after surgery (minimum 16.2 months, and maximum 51.4 months). Characteristics of the 32 patients with CEA mRNA (+) gastric cancer are summarized in Table 1. Mean age was 57.8 years (minimum 35 years, and maximum 75 years). Serosal invasion and lymph node metastasis was observed in 24 patients (75%) and 23 patients (71.9%), respectively. T1-stage patients and macroscopic type 0 (gross finding suggestive of early stage cancer) were more frequent among the control group, but other characteristics showed similar distributions.

Overall survival and peritoneal recurrence-free survival

No significant difference in survival curves was identified between the study population and the historical control ($P = 0.46$; Fig. 1). Twelve patients (37.5%) relapsed,

Table 1 Baseline characteristics of the patients

	S-1 adjuvant ($n = 32$)	Control ($n = 58$)	P value
Age (year)	57.8	58.4	0.83
Gender			
M	23	39	0.81
F	9	19	
Location			
L	11	16	0.07
M	18	24	
U	3	18	
Macroscopic type			
0	1	15	0.01
1	2	0	
2	5	12	
3	19	19	
4	5	12	
Operative procedure			
Total	9	25	0.23
Proximal	0	1	
Distal	23	32	
Lymph node dissection			
≤D1	2	3	NS
≥D2	30	55	
Depth of invasion			
T1	1	15	<0.01
T2	7	13	
T3	23	20	
T4	1	10	
Lymph node metastases			
N0	9	18	0.25
N1	11	11	
N2	12	29	
Histological type			
pap	0	1	0.10
tub1	2	1	
tub2	5	16	
por1	3	5	
por2	20	27	
sig	0	7	
muc	0	1	
Other	2	0	

NS not significant, *pap* papillary adenocarcinoma, *tub1* well differentiated tubular adenocarcinoma, *tub2* moderately differentiated tubular adenocarcinoma, *por1* poorly differentiated adenocarcinoma solid type, *por2* poorly differentiated adenocarcinoma non-solid type, *sig* signet-ring cell carcinoma, *muc* mucinous adenocarcinoma

including 10 patients with peritoneal relapse (Table 2). Two-year survival proportion was 93.5% in the S-1 adjuvant chemotherapy group as opposed to 77.6% in the
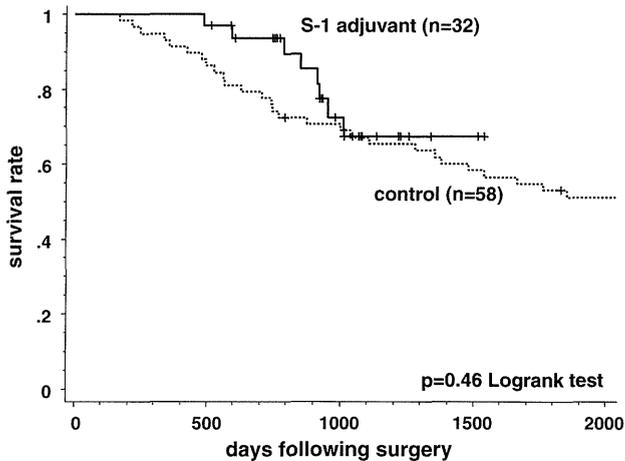
Fig. 1 Overall survival curve of patients with S-1 adjuvant therapy and historical controls. Three-year survival rates were comparable between groups. The difference in survival curves was not significant ($P = 0.46$; log-rank test)

Table 2 Site of first relapse, according to treatment group

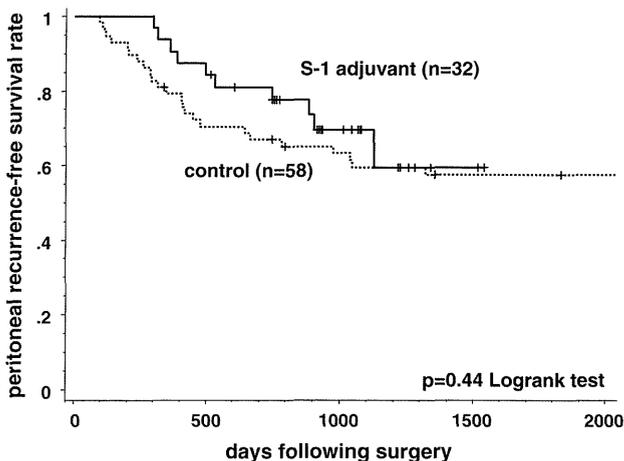| Site	S-1 adjuvant ($n = 32$)		Control ($n = 58$)	
No. of relapses	12	(37.5%)	31	(53.4%)
Local	0	(0.0%)	4	(6.9%)
Lymph nodes	2	(6.3%)	14	(24.1%)
Peritoneum	10	(31.3%)	24	(41.4%)
Hematogenous	2	(6.3%)	7	(12.1%)

Fig. 2 Peritoneal recurrence-free survival curve of patients with S-1 adjuvant treatment and historical controls. Survival of the S-1 adjuvant group tended to be slightly favorable, but this was not significant ($P = 0.44$; log-rank test)

historical control group, but the difference was nullified by 3 years after surgery (67.3% vs. 67.1%, respectively). The difference in peritoneal recurrence-free survival curves was not significant ($P = 0.44$; Fig. 2).

Discussion

A significant survival benefit of postoperative adjuvant chemotherapy with S-1 was demonstrated for stage II/III gastric cancer in the ACTS-GC study [16]—a pivotal phase III trial comparing surgery followed by 1 year of S-1 monotherapy with surgery alone. In that study, peritoneal relapse was observed in 143 of 1,059 patients enrolled, representing the most frequent site of relapse. Peritoneal dissemination is considered to arise from free cancer cells in the peritoneal cavity exfoliated from the serosal surface of the stomach after penetration by the primary tumor. Patients with free cancer cells detectable through conventional cytological examination (CY1) had not been eligible for that trial. This suggests that conventional cytological examination lacks sensitivity and fails to detect minute quantities of free cancer cells. Our previous study revealed that RT-PCR mediated detection of CEA mRNA in the peritoneal washes offers a more sensitive tool to detect subgroups of patients at high risk for peritoneal relapse [3–5, 7, 17] and could be a powerful tool in selecting patients for postoperative adjuvant therapy.

There are several reports describing the detection of minimal residual disease in gastric cancer using peritoneal washes and other body fluids, using both RT-PCR based and other techniques [18]. Of these, studies using peritoneal washes had been the most successful. CEA had been the commonest target, but false-positive cases have often been an issue, given that the expression of CEA is not confined to cancer cells. Use of multiple markers combining highly specific molecules and use of microarray tips would eventually minimize this problem [19]. Analysis of other samples, such as peripheral blood and bone marrow aspirates, have led to inconsistent results and had been less convincing as prognostic markers for gastric cancer [20, 21]. We have shown again in the current study that a CEA mRNA (+) population who are negative for conventional cytology (CY0) exists and has a risk for peritoneal carcinomatosis. Survival of our 32 patients was shown not to be dismal compared with CY1 patients [22] or those with stage IV disease in general, however. The notion that CEA RT-PCR may be useful to identify patients who are not indicated for surgery [23] could be challenged by the opinion that the CY0/CEA mRNA(+) population may benefit from adequate multimodal treatments.

Needless to say, a one-arm phase II study comparing survival data with a historical control is seriously flawed. Because the study involved CEA RT-PCR, which is not commercially available, a single institutional study was the only feasible option. Given the low incidence of CY0/CEA mRNA (+) patients, a more sophisticated study design had been considered unrealistic. Of note is that S-1, irinotecan, and taxanes were available by the time patients in the

historical control group relapsed. Thus, most patients in the control group were treated by essentially the same anticancer drugs in the same sequence, and the major difference between the current phase II patients and the historical control was whether chemotherapy had been started immediately after surgery or after relapse. Whereas the current trial was ongoing, CEA mRNA in the peritoneal washes also had been quantified in several patients outside of the trial as referent data. Some of CEA mRNA (+) patients were not treated with S-1 because they were allocated to the surgery alone group in another trial or did not wish to be registered to the present study. The 3-year survival proportion of these 11 cases was 63.6%, equivalent to the historical control of our study.

In the recent phase III trial, postoperative S-1 led to significant improvements in overall and relapse-free survival over observation alone at the first interim analysis and became a standard of care for stage II/III gastric cancer in Japan. Because the CY0/CEA mRNA(+) population, the target of the current study, mostly fall into the same stage II/III category, exploring the efficacy of identical treatment in this particular population seemed to have lost meaning, and we decided to close the trial. However, it remains unclear whether the improved survival of the interventional group as observed in the interim analysis eventually leads to cure of the corresponding number of patients or just a delay in relapse. In the present study, although more patients were alive at an earlier phase of follow-up compared with historical controls, the fates of patients at 3 years after surgery were basically identical. This suggests that gastric cancer relapse, at least in a high-risk population identified through CEA RT-PCR, is only delayed by S-1 monotherapy; not cured.

The specificity of CEA RT-PCR in detecting peritoneal relapse was 81.6% and occasional false-positive results were deemed unavoidable [24]. In the current analysis, 15 pathologically T1-stage cancers were included in the control group and 1 T1 cancer was identified in the treatment group. This difference is due to characteristics of patients between the control and treatment groups. We rarely examined lavage cytology nor CEA mRNA test in surgically T1 patients after the time of treatment group, because our previous analysis showed uselessness of CEA mRNA detection in pT1 patients. After analyzing only surgical T3 patients, no significant difference in survival curves was identified between the study population and the historical control ($P = 0.18$; Fig. 3). The difference in peritoneal recurrence-free survival curves was not significant ($P = 0.27$; Fig. 4). Considering that the rate of risk reduction was lower among stage IIIB than among stage II in the ACTS-GC trial, there is a potential need for more powerful chemotherapy than S-1 for high-risk populations among those who are eligible for postoperative adjuvant
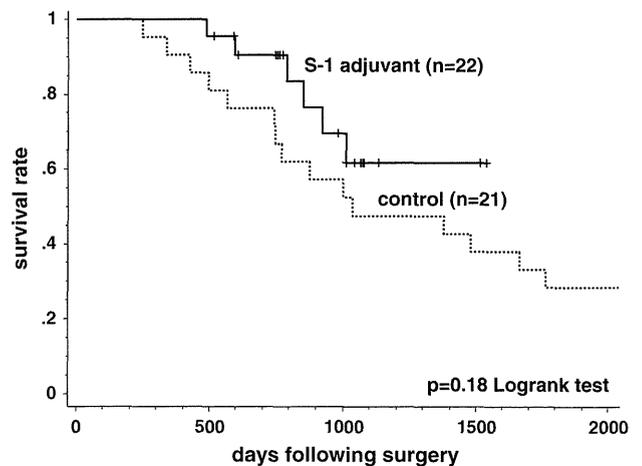

Fig. 3 Overall survival curve of surgical T3 patients with S-1 adjuvant treatment and historical controls. Survival of the S-1 adjuvant group tended to be slightly favorable, but this was not significant ($P = 0.18$; log-rank test)
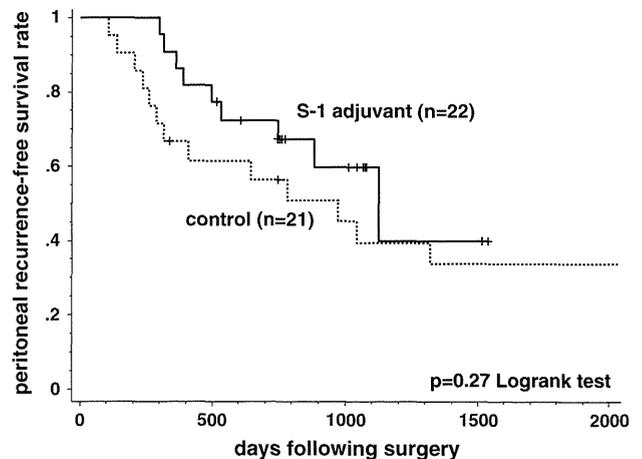

Fig. 4 Peritoneal recurrence-free survival curve for surgical T3 patients with S-1 adjuvant therapy and historical controls. Survival of the S-1 adjuvant group tended to be slightly favorable, but was not significant ($P = 0.27$; log-rank test)

therapy. Results of the current study reinforce the notion that S-1 monotherapy may be insufficient for some high-risk patients.

To combat peritoneal micrometastasis, sequential use of paclitaxel and S-1 or UFT (tegafur and uracil) is currently being explored in another pivotal phase III trial using a 2 × 2 factorial design with S-1 or UFT monotherapy as active controls [25]. Furthermore, the feasibility of S-1 combined with cisplatin or taxotere has been tested in the postoperative adjuvant setting. However, addition of cytotoxic agents to S-1 may lead to increased frequencies of adverse events, leading to poor compliance. Conversely, intraperitoneal administration of anticancer drugs has the theoretical advantage of exposing higher levels of

anticancer agents with lower systemic doses [26]. Indeed, a recent study [27] showed that adjuvant chemotherapy containing intraperitoneal cisplatin significantly improved RFS and OS in patients with grossly serosa-positive advanced gastric cancer. The pharmacokinetic and therapeutic advantages of paclitaxel when administered intraperitoneally have been well documented for gastric cancer as well [28, 29]. Studies to improve the cure rate among high-risk subsets of stage II/III patients using a combination of S-1 with other drugs or modalities are warranted.

Conclusions

Adjuvant chemotherapy with S-1 may delay cancer relapse but does not always eradicate micrometastases in the abdominal cavity. More effective treatments, possibly directed toward peritoneal micrometastasis, could be proposed to treat high-risk subsets of curatively resected gastric cancer, and CEA RT-PCR might be used to identify these high-risk patients.

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Review article

Lymph node dissection in the resection of gastric cancer: review of existing evidence

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Abstract
Gastric cancer is one of the leading causes of cancer-related death worldwide. Surgery is the only curative therapy for localized gastric cancer, but the extent of regional lymphadenectomy has been a matter of considerable debate. Extended resections that are regarded as standard procedures in some Asian countries, including Japan and Korea, have not been shown to be as effective in Western countries. The extent of lymphadenectomy for advanced gastric cancer has been studied in many prospective randomized controlled trials. On the other hand, patients with early gastric cancer have an excellent survival rate (>90%) after radical surgery. Lymph node metastasis from early gastric cancer is relatively infrequent. Therefore, it might be practical to perform less invasive surgery for early gastric cancer. In this review article, we examine the evidence for lymph node dissection as radical surgery in advanced gastric cancer and the possibility of limited resection for early gastric cancer.

Key words Gastric cancer · Lymph nodes · Surgery

Introduction

Gastric cancer is a very common disease worldwide and is the second most frequent cause of cancer death, affecting about one million people per year [1]. Surgery is the most effective and successful method of treatment for gastric cancer, and there is no doubt that systematic lymph node (LN) dissection is the most effective procedure to treat LN metastases of gastric cancer. However, the optimal extent of surgical intervention remains unresolved. Japanese and other Asian surgeons routinely perform an extended (D2) dissection to remove the nodes along the main branches of the celiac axis [2, 3], while many Western surgeons perform more limited (D1) dissection–which removes only the nodal groups

adjacent to the parts of the stomach removed–because of the absence of randomized controlled trials (RCTs) that favor D2 gastrectomy [4]. Theoretically, the removal of a wider range of LNs by extended LN dissection increases the chances for cure. In fact, the pattern of recurrence after extended surgery is completely different from that after limited surgery and involves locoregional recurrence in the majority of cases [5]. An extended LN dissection might have an influence on the locoregional recurrence rate. However, if the patients have already developed micrometastases or if no LNs are affected, such resection might be irrelevant and harmful, in terms of increased morbidity and mortality.

In this review, we first discuss the current status of the extent of LN dissection for advanced gastric cancer and offer an optimal management approach in view of the results of recent clinical trials.

In contrast with results in patients with advanced gastric cancer, patients with early gastric cancer (EGC) have an excellent survival rate (>90%) after radical surgery [6, 7]. Lymph node metastases from EGC are relatively infrequent, and metastases to group N2 are even rarer [8]. Therefore, it might be appropriate to perform less invasive surgery for EGC. In the latter part of this article, we review limited gastrectomy for EGC.

Surgical anatomy of the gastric lymphatics

Knowledge of LN node staging is mandatory for understanding the ongoing debate regarding LN dissection. The very complex LNs of the stomach have been arranged into a very useful classification by the Japanese Gastric Cancer Association (JGCA) [9]. According to this classification, 16 different LN compartments (stations) are identified surrounding the stomach. These LN stations are classified into three groups that correspond to the location of the primary tumor and reflect the likelihood of harboring metastases. Most perigastric LNs (stations 1–6) are defined as group N1, whereas the nodes along the left gastric (station 7), common hepatic
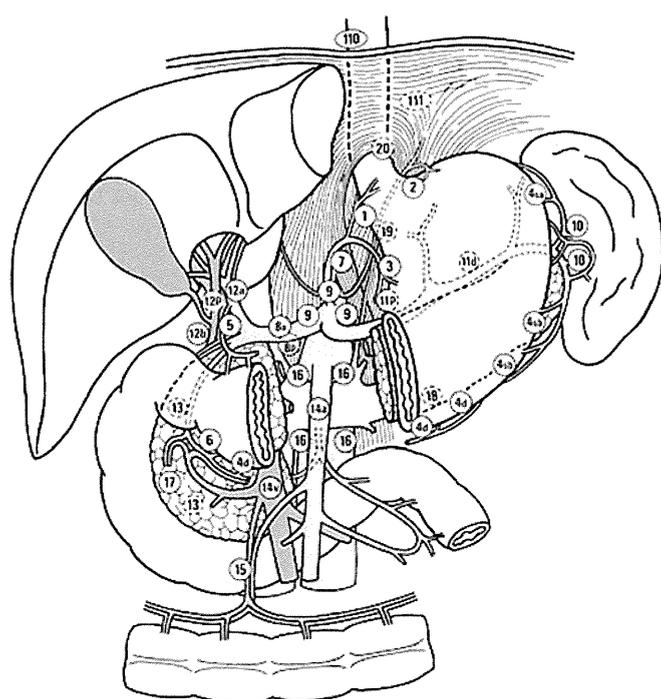
Station. 1	Rightparacardial LN
Station. 2	Leftparacardial LN
Station. 3	LN along the lesser curvature
Station. 4sa	LN along the short gastric vessels
Station. 4sb	LN along the left gastroepiploic vessels
Station. 4d	LN along the right gastroepiploic vessels
Station. 5	Suprapyloric LN
Station. 6	Infrapyloric LN
Station. 7	LN along the left gastric artery
Station. 8a	LN along the common hepatic artery (Anterosuperior group)
Station. 8p	LN along the common hepatic artery (Posterior group)
Station. 9	LN around the celiac artery
Station. 10	LN at the splenic hilum
Station 11p	LN along the proximal splenic artery
Station. 11d	LN along the distal splenic artery
Station. 12a	LN in the hepatoduodenal ligament (along the hepatic artery)
Station. 12b	LN in the hepatoduodenal ligament (along the bile duct)
Station. 12p	LN in the hepatoduodenal ligament (behind the portal vein)
Station. 13	LN on the posterior surface of the pancreatic head
Station. 14v	LN along the superior mesenteric vein
Station. 14a	LN along the superior mesenteric artery
Station. 15	LN along the middle colic vessels
Station. 16a1	LN in the aortic hiatus
Station. 16a2	LN around the abdominal aorta (from the upper margin of the celiac trunk to the lower margin of the left renal vein)
Station 16b1	LN around the abdominal aorta (from the lower margin of the left renal vein to the upper margin of the inferior mesenteric artery)
Station. 16b2	LN around the abdominal aorta (from the upper margin of the inferior mesenteric artery to the aortic bifurcation)
Station. 17	LN on the anterior surface of the pancreatic head
Station. 18	LN along the inferior margin of the pancreas
Station. 19	Infradiaphragmatic LN
Station. 20	LN in the esophageal hiatus of the diaphragm
Station. 110	Paraesophageal LN in the lower thorax
Station. 111	Supradiaphragmatic LN
Station. 112	Posterior mediastinal LN

Fig. 1. Lymph node station numbers according to the *Japanese classification of gastric carcinoma 2nd English edition* reproduced from [9], with permission. *LN*, Lymph node

(station 8), splenic (station 11), and proper hepatic (station 12) arteries and along the celiac axis (station 9) are defined as group N2. Minor modifications of this schedule occur depending on the location of the primary tumor (Fig. 1). For example, the LNs at the splenic hilum (station 10) also belong to group N2 when the tumor is located in the proximal stomach. The paraaortic LNs (station 16) are defined as group N3.

D1 versus D2 or D3 trials

Five RCTs comparing D1 and D2/D3 dissection have been performed. There have been two large-scale RCTs [10, 11], two small-scale RCTs [12, 13], and 1 small-institution trial [14]. Three major RCTs and one ongoing RCT [15] are summarized in Table 1.

Dutch Gastric Cancer Group trial

The Dutch Gastric Cancer Study Group, involving 80 Dutch hospitals, conducted a large-scale, RCT in the Netherlands between 1989 and 1993 [10]. In this trial,

996 patients were centrally randomized; 711 patients (380 in the D1 group and 331 in the D2 group) underwent the allocated treatment with curative intent, and 285 patients required palliative treatment. D2 patients had higher postoperative mortality (10% vs 4% for D1; $P = 0.004$); they also had significantly more complications (43% vs 25% for D1; $P < 0.001$), which led to a significantly prolonged hospital stay for patients with a D2 dissection. Overall 5-year survival rates were similar in the D1 and D2 groups (45% for D1 and 47% for D2). The hazard ratio (HR) comparing the risk of death within 5 years after D2 surgery with that within 5 years after D1 surgery was 1.00 (95% confidence interval [95% CI], 0.82–1.22). At a median follow-up of 11 years, 68% of the patients were deceased, 35% without and 65% with recurrent disease. At 11 years, survival rates were 30% for D1 and 35% for D2 ($P = 0.53$), with a risk of relapse of 70% for D1 and 65% for D2 ($P = 0.43$) [16]. Interestingly, when hospital deaths were excluded, survival rates were 32% for D1 ($n = 365$) and 39% for D2 ($n = 299$, $P = 0.10$), and the relapse risk of these patients ($n = 664$) was in favor of the D2 dissection group ($P = 0.07$). Furthermore, in the subset analysis,

Table 1. Major randomized controlled trials comparing D1 with D2/D3

Study	Intervention	Patients	Postoperative morbidity	Postoperative mortality	5-Year survival
Dutch trial	D1	380	25%	4%	45%
(1989–1993)	D2	331	43%	10%	47%
[10, 15–17]			($P < 0.001$)	($P = 0.004$)	HR 1.00
					(95% CI, 0.82–1.22)
MRC trial	D1	200	28%	6.5%	35%
(1987–1994)	D2	200	46%	13%	33%
[11, 18]			($P < 0.001$)	($P = 0.04$)	HR 1.10
					(95% CI, 0.87–1.39)
IGCSG trial	D1	76	10.5%	0%	Under analysis
(1999–2002)	D2	86	16.3%	1.3%	
[15]			($P < 0.29$)	(N.S)	
Taiwanese trial	D1	110	7.3%	0%	53.6%
[14, 19]	D3	111	17.1%	0%	59.5%
			($P = 0.012$)		HR 0.49
					(95% CI, 0.32–0.77)

MRC, Medical Research Council; IGCSG, Italian Gastric Cancer Study Group; HR, hazard ratio; 95% CI, 95% confidence interval

when hospital deaths were excluded, there was a significant survival and relapse advantage for patients with International Union Against Cancer (UICC) pN2 disease who had a D2 dissection ($P = 0.01$). Other stages showed no significant differences (N0 $P = 0.42$; N1 $P = 0.31$; N3 $P = 0.24$).

This trial showed an extremely high hospital mortality after D2 dissection [17]. Such a high mortality was caused by a very low hospital volume. Lack of experience in dealing with major surgical complications after D2 dissection; namely, anastomotic leakage, pancreatic fistula, and intraabdominal abscess, led to the high mortality. Low-quality surgery with high mortality immediately after operation could explain why D2 dissection was not found to be beneficial. Furthermore, in this study, there was a high rate of protocol violations in terms of lymph node dissection [18]. If lymph nodes were harvested from stations that were not supposed to be included according to the protocol, this was called contamination. If lymph nodes were not harvested from stations that should have been harvested, this was called noncompliance. Contamination occurred in 6% of the D1 dissection group, and noncompliance occurred in 51% of the D2 group. Contamination in the D1 dissection group and noncompliance in the D2 group could have led to the small difference between the trial arms.

Medical Research Council Gastric Cancer Surgical Group Trial

In 1986, the Medical Research Council of Great Britain initiated a nationwide, multi-institutional, RCT comparing D1 dissection with D2 dissection in that country [11].

Central randomization followed a staging laparotomy. Of 737 patients with histologically proven gastric adeno-

carcinoma registered, 337 patients were ineligible by staging laparotomy because of advanced disease. Thus, 400 patients were randomized, with 200 patients receiving D1 dissection and 200 patients receiving D2 dissection. Postoperative mortality was significantly higher in the D2 group (13%) than in the D1 group (6.5%; $P = 0.04$) [19]. Postoperative complications were also significantly higher in the D2 group (46%) than in the D1 group (28%; $P < 0.001$), with the most frequent complications being anastomotic leakage (26% for D2 vs 11% for D1; $P < 0.015$), cardiac complications (8% for D2 vs 2% for D1; no significant difference [NS]), and respiratory complications (8% vs 5% for D1; NS). In this trial, many surgeons thought that D2 distal gastrectomy included splenectomy, and splenectomy was carried out in many distal gastrectomy cases. Pancreatico-splenectomy was carried out in 56% of patients allocated to the D2 group and 4% of the D1 group. This was based on a misunderstanding of the definition of D2 gastrectomy by the JGCA. In Japan, splenectomy is included in D2 dissection only when a total gastrectomy is carried out. Together with thorough lymph node dissection of the lesser curvature, splenectomy causes serious ischemia of the remnant stomach, necrosis of the remnant stomach, or anastomotic leakage. Hospital death in the D2 dissection group was 13%; such a high mortality is no longer accepted for any cancer surgery. In fact, there was no difference in 5-year survival between the two arms (33% vs 35% for D1; HR, 1.10; 95%CI, 0.87–1.39).

Taiwanese trial

This study was a single-institutional trial that was carried out between 1993 and 1999. This is the only trial that showed a statistically significant survival benefit of D3

over D1 gastrectomy [14, 20]. Of 221 patients, 110 patients were randomly assigned to D1 surgery and 111 patients were randomly assigned to D3 surgery between 1993 and 1999. Overall 5-year survival was significantly higher in patients assigned to D3 surgery than in those assigned to D1 surgery (59.5% vs 53.6%; $P = 0.041$). The HR comparing the risk of death within 5 years after D3 with that within 5 years after D1 surgery was 0.49 (95% CI, 0.32–0.77). Overall, 215 patients who had R0 resection had recurrence at 5 years (50.6% for D1 surgery and 40.3% for D3 surgery; $P = 0.197$). Five-year disease-specific survival was significantly higher in patients assigned to D3 surgery than in those assigned to D1 surgery (64.9% vs 58.5%; $P = 0.044$; HR, 0.69).

Small-scale RCT in South Africa

Between 1982 and 1986, a small-scale RCT was performed in South Africa, involving 43 patients who were randomized to D1 or D2 resection [12]. Although there were no hospital deaths, D2 gastrectomy was associated with longer operating time, more blood loss, longer hospital stays, and a higher reoperation rate, but there was no detailed analysis of complications. There was no survival difference at a median follow-up of 3.1 years.

Small-scale RCT in Hong Kong

Between 1987 and 1991, another RCT was conducted in Hong Kong [13]. This study randomized 55 patients to either D1 or D3 gastrectomy; D3 patients had longer operative times, greater transfusion needs, longer hospital stays, and more subphrenic abscesses than D1 patients. There was no detailed statistical analysis of postoperative complications in the D1 group. One patient in the D3 group died from operative complications. Overall survival was better in the D1 group ($P = 0.07$).

It is obvious that the two large-scale RCTs in the Netherlands and the United Kingdom showed the same tendency. The Dutch and MRC studies had extremely high hospital mortality after D2 dissection, 10% and 13%, respectively. Such a high mortality negated the survival benefits of D2 dissection. The critics of these trials have suggested that there was inadequate pretrial training of the surgeons; in particular, their lack of experience in treating major surgical complications led to the high hospital mortality. Morbidity and mortality are significantly related to hospital volume [21]. The learning curve for a D2 gastrectomy may be up to 25 cases [22, 23]. The number of patients per hospital per year was 1.0 in the Dutch trial and 1.5 in the MRC trial. After these two trials with miserable short-term results, the Italian Gastric Cancer Study Group (IGCSG) performed a phase II study between 1994 and 1996 to assess the safety of D2 gastrectomy [24]. In this study,

postoperative complications were seen in 20.9% of patients, with only 3.1% mortality. This trial was carried out in only nine hospitals, and only 18 surgeons participated in the trial. They avoided splenectomy in distal gastrectomy and the routine use of distal pancreatectomy in total gastrectomy. They also performed a phase III trial comparing D1 gastrectomy to D2 gastrectomy [15]. In that phase III trial, postoperative morbidity was 16.3% in D2 gastrectomy and 10.5% in D1 gastrectomy, and postoperative mortality was 1.3% after D1 but 0% after D2 gastrectomy. There were no significant differences in the postoperative morbidity and mortality between the two groups. Therefore, D2 gastrectomy was regarded as a safe treatment for gastric cancer in experienced centers. The lack of experience with the D2 gastrectomy and with postoperative care led to a poor outcome in patients with D2 gastrectomy in the Dutch and MRC trials. The results of the phase III study by the IGCSG are awaited.

D2 versus D3 trial

In Japan, D2 gastrectomy is regarded as a safe operation, and D2 gastrectomy is a common practice in ordinary general hospitals. Therefore, in Japan, conducting a D1 versus D2 trial was considered unethical. Japanese surgeons first introduced the D2 gastrectomy in the 1960s [25]. Since the 1980s, gastrectomy with more radical extended lymphadenectomy (D3; super-extended lymphadenectomy) has been practiced at many specialized centers in Japan [26–29]. In advanced gastric cancer, the incidence of microscopic metastases in the paraaortic nodes was 6% to 33% [29]. The 5-year survival for these patients has reached 12% to 23% after gastrectomy with super-extended lymph node dissection. In Japan, between 1995 and 2001, the Japanese Clinical Oncology Group (JCOG) conducted a randomized trial comparing D2 gastrectomy alone with D2 plus paraaortic node dissection (PAND) [30]. A total of 523 patients with curable T2b, T3, or T4 gastric cancer were randomly assigned to D2 lymphadenectomy alone (263 patients) or to D2 plus PAND (260 patients). The overall operative morbidity rate was 24.5%. The morbidity for the D2+PAND group was higher than that for the D2 alone group (28.1% and 20.9%, respectively), but there was no significant difference between the groups ($P = 0.067$) [31]. There were four hospital deaths (0.8%), 2 patients in each group ($P = 0.99$). The 5-year overall survival rates after D2 plus PAND were not significantly better than those after D2 alone (D2, 69.2% and D2+PAND, 70.3%; HR, 1.03; 95% CI, 0.77–1.37). The two survival curves were almost overlapping, while D2 plus PAND showed longer operation time and more blood loss than D2. This study concluded that

prophylactic D2+PAND should not be carried out for curable gastric cancer.

Another phase III trial compared D2 to D2 plus PAND in Poland [32]. Of 275 patients enrolled, 141 patients were allocated to D2 alone and 134 patients were allocated to D2+PAND. The morbidity rates were 27.7% for D2 and 21.6% for D2 plus PAND ($P = 0.248$). The postoperative mortality rates were 4.9% for D2 and 2.2% for D2 plus PAND ($P = 0.375$). In this study, PAND did not result in increased morbidity and mortality, but the survival benefits remain to be analyzed.

In East Asia, another RCT comparing D2 with D2 plus PAND was carried out between 1995 and 2002 [33, 34]. A total of 269 patients were randomized, with 135 patients receiving D2 dissection and 134 patients receiving D2 plus PAND dissection. Postoperative morbidity was significantly higher in the D2 plus PAND group (39%) than in the D2 group (26%; $P = 0.023$). Hospital mortality was 0.7% in the D2 group and 3.7% in the D2 plus PAND group ($P = 0.12$). The overall 5-year survival was 52.6% for the D2 group and 55.4% for the D2 plus PAND group; there was no survival benefit of PAND over standard D2 lymphadenectomy ($P = 0.801$).

These three trials demonstrated that both D2 and D3 gastrectomy are safe treatments. However, at the present time, D3 dissection should not be performed for curable gastric cancer, because evidence of survival benefits is lacking (Table 2).

Should splenectomy or pancreatico-splenectomy be carried out routinely in the treatment of cancer of the upper third of the stomach?

Pancreatico-splenectomy should not be carried out routinely

No RCT has proven the survival benefits of pancreatico-splenectomy (PS) with total gastrectomy. In Japan, PS for lymph node dissection around the splenic artery and splenic hilum had been widely performed [35, 36], because this has been proposed as a radical procedure for complete removal of metastatic lymph nodes along the splenic artery. However, a Japanese retrospective analysis showed no survival benefit from these procedures [37, 38], and PS was proven to be dangerous in RCTs [16, 18]. In the MRC trial, PS was performed in 56% of patients allocated to the D2 gastrectomy group, and PS had a marked adverse effect on both morbidity (58% for D2+PS and 30% for D2 without PS; $P < 0.001$) and mortality (16% for D2+PS and 9% for D2 without PS; $P = 0.01$). In the Dutch trial, PS was performed for 108 patients in the D1 and D2 groups, and the morbidity and mortality rates were 40% and 12%, respectively (relative risk, 3.43; 95% CI, 2.49–4.72) [15]. In the JCOG 9501 trial, PS was identified as a significant independent risk factor for complications [31]. PS was performed in only 22 of the 523 registered patients, and complications were identified in 13 patients (59%). There is no doubt that PS results in a high incidence of complications. In the Dutch trial, in a subgroup analysis of patients who did not have a PS ($n = 603$), morbidity and mortality were significantly higher in the D2 group, but the 11-year survival rate was significantly better in the D2 group than in the D1 group (31% vs 42%; $P = 0.02$) [39]. There appears to be a survival benefit of D2 gastrectomy if procedures that increase morbidity and mortality, such as PS, can be avoided.

Therefore, PS is considered to be beneficial only when there is direct tumor invasion to the pancreas.

Is splenectomy indeed effective treatment?

In the JCOG 9501 trial and the IGCSG phase III trial, a low incidence of hospital deaths was achieved because a pancreas-preserving splenectomy was generally used [15, 31]. Pancreas-preserving splenectomy is considered to be a safe procedure that does not decrease surgical

Table 2. Randomized controlled trials comparing D2 with D2 + PAND

Study	Intervention	Patients	Postoperative morbidity	Postoperative mortality	5-Year survival
JCOG trial (1995–2001) [30, 31]	D2 D2+PAND	263 260	20.9% 28.1% ($P = 0.067$)	0.8% 0.8% ($P = 0.99$)	69.2% 70.3% HR 1.03 (95% CI, 0.77–1.37)
Polish trial (1999–2003) [32]	D2 D2+PAND	141 134	27.7% 21.6% ($P = 0.248$)	4.9% 2.2% ($P = 0.37$)	Under analysis
East Asian trial (1995–2002) [33, 34]	D2 D2+PAND	135 134	26% 39% ($P = 0.023$)	0.7% 3.7% ($P = 0.107$)	52.6% 55.4% ($P = 0.801$)

JCOG, Japan Clinical Oncology Group; PAND, paraaortic node dissection; HR, hazard ratio; 95% CI, 95% confidence interval

Table 3. Randomized controlled trials related to splenectomy for gastric cancer

Study	Intervention	Patients	Postoperative morbidity				Postoperative mortality	5-Year survival
			Any	Fever > 38°C	Pulmonary	Subphrenic abscess		
Chilean trial	TG	97	Not stated	39%	24%	4%	3.1%	36%
(1985–1992)	TG+S	90		50%	39%	11%	4.4%	42%
[47]				(P < 0.04)	(P < 0.008)	(P < 0.05)	(P > 0.7)	
Korean trial	TG	103	8.7%	Not stated	Not stated	Not stated	1.0%	48.8%
(1995–1999)	TG + S	104	15.4%				1.0%	54.8%
[48]			(P = 0.142)				(P = 1.000)	(P = 0.503)

TG, total gastrectomy; TG+S, total gastrectomy with splenectomy

curability [40–42]. However, it is not known whether splenectomy contributes to survival.

From the Japanese experience with splenectomy, the incidence of hilar nodal metastasis ranged from 0–2% for distal and middle-third gastric cancer, to 15% for proximal-third tumors, and 21% for tumors that infiltrate the entire stomach. Based on retrospective data, hilar nodal metastasis was not found in EGC [43–46]. These data suggested that splenectomy was crucial for the curative resection of proximal advanced gastric cancer and might improve the prognosis.

Two RCTs compared the effectiveness and safety of gastrectomy with splenectomy to gastrectomy alone in patients with gastric cancer (Table 3). One of these RCTs was carried out in Chile [47], and the other was carried out in Korea [48]. Both studies were performed in single institutions. In Chile, between 1985 and 1992, 187 patients with gastric cancer, including early-stage cases, were randomized. However, this study did not state how the patients were randomized. Total gastrectomy was performed for all patients. The frequency of septic complications, including postoperative fever higher than 38°C, pulmonary complications, and subphrenic abscess, was significantly higher in the splenectomy group than in the gastrectomy-alone group (fever, 50% vs 39%; $P < 0.04$; pulmonary, 39% vs 24%, $P < 0.008$; subphrenic abscess, 11% vs 4%, $P < 0.05$, respectively). There was no significant difference between the groups in the hospital mortality rate (4.4% for splenectomy vs 3.1% for gastrectomy alone; $P > 0.7$). In this study, the survival statistics excluded the operative mortality rate. The 5-year survival rates were 42% for splenectomy and 36% for gastrectomy alone; there was no significant difference between the groups ($P > 0.5$). In subgroup analysis, there was no survival benefit for stage II, IIIA, and IIIB cancer.

In the other trial, carried out in Korea between 1995 and 1999, 207 patients with gastric cancer were randomized to either total gastrectomy or total gastrectomy plus splenectomy for lymph node dissection at the splenic hilum and along the splenic artery. Overall, 103

patients had the spleen-preserving procedure, and 104 had splenectomy. Postoperative morbidity was 8.7% in the spleen-preserving group and 15.4% in the splenectomy group, but there was no significant difference between the groups ($P = 0.142$). One patient (1.0%) in the spleen-preserving group and 2 patients (1.9%) in the splenectomy group died from postoperative complications, but this difference was not significant ($P = 1.000$). The incidence of metastasis at the splenic hilum and along the splenic artery was 10.6% and 17.3%, respectively. The 5-year survival rate was 48.8% for patients in the spleen-preserving group and 54.8% in the splenectomy group; there was no significant difference ($P = 0.503$). The 5-year survival rate of patients with lymph node metastasis at the splenic hilum was 0%, with or without splenectomy. In the subgroup with lymph node metastasis along the splenic artery, the 5-year survival rate was 20.0% in the spleen-preserving group and 23.4% in the splenectomy group ($P = 0.753$). Therefore, these results did not support the use of prophylactic splenectomy to remove macroscopically negative lymph nodes near the spleen in patients undergoing total gastrectomy for proximal gastric cancer.

In Japan, an RCT to evaluate splenectomy for upper-third advanced gastric cancer is ongoing [49]. This trial includes the evaluation of long-term survival, postoperative morbidity, mortality, and quality of life. Registration of about 500 patients has been completed, and the results of this study are awaited.

Mediastinal lymph node dissection for gastric cancer with esophageal invasion

Siewert and Stein [50] developed a now widely used classification of carcinomas involving the stomach and esophagus into three types: adenocarcinoma of the distal esophagus, which may infiltrate the esophagogastric junction from above (type I); true cardia carcinoma arising from the esophagogastric junction (type II); and subcardial gastric carcinoma that infiltrates the esopha-

gogastric junction and distal esophagus from below (type III). According to the Siewert classification, gastric cancer with esophageal invasion is classified as type II or type III. In Japan, an RCT comparing left thoraco-abdominal esophagogastrectomy (LTE) versus transhiatal esophagogastrectomy (THE) for Siewert type II and III tumors with esophageal invasion of 3 cm or less was carried out [51] (Table 4). Between 1995 and 2003, 167 patients were enrolled and randomly assigned to LTE ($n = 85$) or THE ($n = 82$); 95 tumors were classified as Siewert type II and 63 as type III. Nine tumors could not be classified using the Siewert classification because they were large or because data were missing. The postoperative morbidity rate was 49% in the LTE group and 34% in the THE group ($P = 0.06$). Three patients in the LTE group died in hospital, but there was no mortality in the THE group ($P = 0.25$); 5-year survival was 37.9% in the LTE group and 52.3% in the THE group ($P = 0.93$). The HR of death for LTE compared to THE was 1.30 (95% CI, 0.83–2.02; $P = 0.92$). This trial concluded that LTE could not be justified to treat cancer of the cardia or subcardia because LTE did not improve survival over THE, and it increased morbidity.

Another RCT that compared THE with transthoracic esophagogastrectomy (TTE) for adenocarcinoma of the esophagogastric junction or esophagus was performed in The Netherlands between 1994 and 2000 [52, 53]. In this trial, 220 patients with Siewert type I and type II tumors were enrolled; 106 patients were assigned to THE, and 114 were assigned to TTE. THE was associated with fewer pulmonary complications, a shorter duration of mechanical ventilation, and shorter stays in the intensive care unit (ICU) and in the hospital. Two patients in the THE group and 5 patients in the TTE group died in hospital; there difference in hospital mortality between the two groups was not significant ($P = 0.45$). The 5-year survival rate was 34% for the THE group and 36% for the TTE group ($P = 0.71$). According to the Siewert classification, 90 patients (43 patients in THE group and 47 patients in the TTE group) were classified as having type I tumors, and 115 patients (52 patients in the THE group and 63 patients in the TTE group) were classified as having type II tumors. The difference in overall 5-year survival was as large as 14% (37% for THE vs 51% for TTE; $P = 0.33$) for type I tumors, while it was negligible for type II tumors (31% for THE and 27% for TTE; 5-year survival difference,-4%; $P = 0.81$). The results of this study strongly suggested that thorough mediastinal dissection via right thoracotomy is needed for type I tumors but not for type II tumors, although there was no significant difference in survival.

In view of the results of these two trials, the transhiatal approach is regarded as the standard treatment for patients with Siewert type II and III tumors.

Table 4. Randomized controlled trials for adenocarcinoma of the esophago-gastric junction

Study	Intervention	Patients	Postoperative morbidity					Postoperative mortality	5-Year survival
			Any	Pulmonary	Cardiac	Anastomotic leakage	Chylous leakage		
Dutch trial (1994–2000) [52, 53]	THE	106	Not stated	57%	16%	14%	2%	2%	34%
	TTE	114		27%	26%	16%	10%	4%	36%
	For Siewert type I or II			($P < 0.001$)	($P = 0.10$)	($P = 0.85$)	($P = 0.02$)	($P = 0.45$)	($P = 0.71$)
JCOG trial (1995–2003) [51]	THE	82	34%	4%[a]	Not stated	6%	Not stated	0%	52.3%
	LTE	85	49%	13%		8%		3.5%	37.9%
	For Siewert type II or III (esophageal invasion ≤3 cm)		($P = 0.06$)	($P = 0.05$)		($P = 0.77$)		($P = 0.25$)	HR 1.30 (95% CI, 0.83–2.02)

THE, transhiatal esophagogastrectomy; TTE, transthoracic esophagogastrectomy; LTE, left thoraco-abdominal approach for esophagogastrectomy; HR, hazard ratio; 95% CI, 95% confidence interval
[a] Pneumonia

Table 5. Japanese guidelines for surgical treatment (curative intention) by stage

	N0	N1	N2	N3
T1 (M)	IA A) ER (differentiated type, ≤2 cm, UL(-)) B) MGA (remainder)	IB A) MGB (≤2 cm) B) D2 (>2 cm)	II D2	IV D3
T1 (SM)	IA A) MGA (differentiated type, ≤1.5 cm) B) MGB (remainder)	IB A) MGB (≤2 cm) B) D2 (>2 cm)	II D2	IV D3
T2	IB D2	II D2	IIIA D2	IV D3
T3	II D2	IIIA D2	IIIB D2	IV D3
T4	IIIA D2 with combined resection	IIIB D2 with combined resection	IV D2 with combined resection	IV D3 with combined resection

ER, endoscopic resection; MGA, modified gastrectomy A; MGB, modified gastrectomy B; UL, with ulcerated lesion

The treatment of early gastric cancer

There is a major difference in the proportion of EGCs in Japan and Korea compared to the rest of the world. EGCs now account for nearly 50% of all gastric cancers treated at major institutions in Japan and Korea [54, 55]. However, in Western countries, the frequency of EGC was only 10%–20% [56, 57]. Therefore, the majority of reports on EGC have been published from Japan. However, there are a few reports of RCTs dealing with the extent of lymphadenectomy for EGC.

The JGCA issued a set of treatment guidelines to help standardize treatment (Table 5) [2]. In Japan, resection of at least two-thirds of the stomach with D2 lymphadenectomy has been conventional surgical treatment for gastric cancer, including EGC, though conservative treatments such as endoscopic mucosal resection or function-preserving limited gastrectomy for EGC have recently been performed [58, 59].

The indications for endoscopic resection

Endoscopic resection is comparable in many respects to surgical therapy, with the advantages of being less invasive and more economical. The extremely low incidence of lymph node involvement in certain stages of EGC means that cure can be accomplished by such local treatment. Therefore, endoscopic resection is indicated for EGCs without lymph node metastasis. According to the guidelines, the accepted indications for endoscopic resection are: (1) well-differentiated elevated cancers less than 2 cm in diameter; and (2) small (≤1 cm) depressed lesions without ulceration. In addition, these lesions must be moderately or well-differentiated cancers confined to the mucosa and have no lymphatic or vascular involvement. These criteria for node-negative gastric cancer were defined using a large retrospective database of more than 5000 EGC patients who underwent gastrectomy with D2 lymphadenectomy [60]. The guidelines show the extended indications for which endoscopic resection may be appropriate, and these indications include: differentiated-type mucosal cancer without ulceration greater than 2 cm in diameter; differentiated-type mucosal cancer with ulceration up to 3 cm in diameter; undifferentiated-type mucosal cancer without ulceration up to 2 cm in diameter; and, in the absence of lymphovascular invasion, a tumor not deeper than submucosal level 1 (less than 500 μm; Fig. 2). However, extending the indications for endoscopic resection remains controversial, because of the lack of supportive clinical evidence. In Japan, a phase II trial of endoscopic resection for EGC, which is clinically diagnosed as belonging to the expanded indications, is ongoing [61].

Surgical treatment for EGC

According to the Japanese guidelines, modified gastrectomy (MG) should be performed for EGC (Table 6). MG is classified as MG A and MG B according to the extent of resection and lymph node dissection [2]. MG A involves the dissection of group N1 nodes, those in the left gastric artery (station 7), and those in the anterior wall of the common hepatic artery (station 8a). MG B involves dissection of the lymph nodes in the celiac axis (station 9), in addition to MG A. MG A is indicated for clinically observed mucosal cancers or differentiated-type submucosal cancers smaller than 1.5 cm in diameter, and MG B is indicated for submucosal cancers and EGCs smaller than 2 cm with clinical N1 disease.

Histology / Depth	Mucosal cancer				Submucosal cancer without UL		
	UL (−)		UL (+)		SM1		SM2
	≤20 mm	>20 mm	≤30 mm	>30 mm	≤30 mm	>30 mm	Any size
Differentiated	■	▨	▨		▨		
Undifferentiated	▨						

Fig. 2. Japanese guideline criteria for endoscopic resection. Size is shown in mm. *Black area*, Guideline criteria for endoscopic resection; *gray area*, criteria for extended endoscopic resection; *white area*, no indication for endoscopic resection. *UL*, With ulcerated lesion; *SM1*, submucosal level 1 (≤500 μm from lamina muscularis mucosae); *SM2*, submucosal level 2 (>500 μm from lamina muscularis mucosae)

Table 6. Areas of gastric resection and extent of LN dissection

Type of gastrectomy	Area of gastric resection	Extent of LN dissection
Modified gastrectomy A	<2/3	D1 + station 7[a]
Modified gastrectomy B	<2/3	D1 + station 7, 8a, 9
Standard	≥2/3	D2

LN, lymph node
[a] In lower-third cancer, station 8a nodes should be dissected

In cases of EGC in which endoscopic resection is not appropriate, though there is a low risk of lymph node metastasis, MG A is performed. Basically, MG A is indicated for apparent intramucosal cancers with no lymph node involvement in which endoscopic resection is not appropriate, or for differentiated submucosal cancers of about 1.5 cm diameter that are found to be node-negative during operation. MG B can be used for cases of apparent submucosal cancers that are diagnosed during the operation as being node-negative and it can be used for patients with tumors of less than 2 cm who are suspected of having metastasis to the group N1 lymph nodes for which dissection would result in cure. These criteria were established on the basis of retrospective data [8, 62–68]. However, pre- or intraoperative diagnosis is not always accurate, so it is inevitable that over-diagnosis occurs when surgeons decide whether limited resection is feasible.

Limited resection of the stomach for early gastric cancer

Recently, pylorus-preserving gastrectomy (PPG) or proximal gastrectomy has been performed for EGC when the tumor location is suitable for these limited resections. The purpose of these approaches is to preserve the gastric reservoir, and they have a favorable outcome. However, the extent of lymph node dissection in these approaches is also limited. Therefore, the surgeon must carefully judge whether these limited gastrectomies are appropriate.

Pylorus-preserving gastrectomy

PPG is currently indicated for EGC in the gastric body [69, 70]. PPG is a modification of distal gastrectomy, preserving 2–3 cm of the pyloric cuff, which maintains pyloric ring function. In a retrospective study, the incidences of dumping syndrome, biliary reflux, and gallbladder stone formation were lower, and body weight recovery was better following PPG than after Billroth I reconstruction [71–75]. In a prospective randomized trial, only dumping syndrome was reduced [76].

The indication for PPG is early cancer located in the middle third of the stomach without lymph node metastasis, excluding patients who are candidates for endoscopic resection. In PPG, all regional lymph nodes, except for the suprapyloric nodes, should be dissected, as in the standard D2 gastrectomy. It is unnecessary to dissect suprapyloric nodes (station 5) routinely, because metastases to suprapyloric nodes are extremely uncommon from cancer in the middle third of the stomach [69, 77, 78].

For preserving pyloric function, it is necessary that 2–3 cm of the pyloric cuff is preserved, so PPG is indicated for tumors more than 4 cm from the pyloric ring to maintain the distal margin.

Proximal gastrectomy

Proximal gastrectomy is currently indicated for EGC only when at least half of the stomach can be preserved to maintain both the curability of the operation and the functional capacity of the remnant stomach [79]. Splenectomy is not performed. Therefore, nodes of the

splenic hilum (station 10) and the distal splenic nodes (station 11d) are not dissected, and the dissection of the distal lesser curvature nodes (station 3) is complete because of the preservation of the distal stomach. There are retrospective data that support this procedure for EGC in the upper third of the stomach. There were no positive nodes along the right gastroepiploic vessels (station 4d), suprapyloric nodes (station 5), infrapyloric nodes (station 6), nodes in the splenic hilum (station 10), or nodes along the distal splenic artery (station 11d) in 258 EGCs of the upper third of the stomach in which total gastrectomy + D2 lymphadenectomy was performed [79]. Prospective studies have demonstrated that proximal gastrectomy for early upper-third gastric cancer can be performed safely with an excellent cure rate [80–82]. Some studies have shown improvement of postoperative absorption and body weight recovery to be better after proximal than after total gastrectomy [83, 84].

Future perspectives

There is no doubt that gastrectomy with regional lymph node dissection is the only treatment modality for advanced gastric cancer. In Japan and Korea, gastrectomy with D2 lymphadenectomy is the gold standard of treatment for advanced gastric cancer. However, several studies have revealed that more extended resection than D2 surgery has no impact on survival. In order to improve locoregional control of gastric cancer, multimodal treatment involving chemotherapy or radiotherapy in addition to surgery is thought to be a promising treatment strategy. Survival benefits from adjuvant chemotherapy or chemoradiotherapy have been demonstrated in some studies [85–87]. Moreover, molecular targeting agents, such as bevacizumab, cetuximab, and panitumumab, have been introduced to clinical practice for the treatment of gastric cancer [88, 89]. To improve the survival of patients with advanced gastric cancer it is necessary to use these active new agents effectively in addition to conventional cytotoxic agents before or after surgery.

On the other hand, for EGC, it is important to clarify the indications for limited resection, including endoscopic resection. The extent of the indications for endoscopic resection should be made clear, and for patients with EGC in whom endoscopic resection is not indicated, sentinel node navigation surgery might be considered. Sentinel node navigation surgery might be able to identify clinically undetectable lymph node metastases and provide essential information for performing individualized selective lymphadenectomy [90–92].

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