first-line chemotherapy for gastric cancer. Shitara [6] reported the median OS was only 9.1 months with S-1-containing chemotherapy and 10.1 months with a non-S-1-containing regimen. These results suggest that, in patients who have recurrence after adjuvant S-1 chemotherapy, the disease may have to be treated as refractory to S-1.

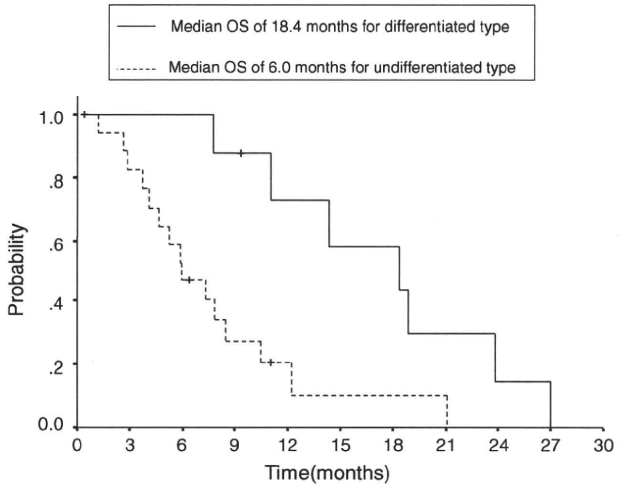

Fig. 2 Kaplan–Meier curves for overall survival (*OS*) showed a significant difference between patients with the differentiated type (*solid line*) and those with the undifferentiated type (*broken line*; $P = 0.009$)

Table 3 Stepwise multivariate Cox proportional hazards analysis of clinicopathologic factors

Factor (category)	No. of patients	*P* value	Hazard ratio	95% CI
Histological type (Differentiated versus undifferentiated)	9 and 17	0.009	4.117	1.420–11.931

Histological type is not known as a prognosticator in first-line chemotherapy for gastric cancer. The present study is the first to demonstrate that histological type was the only significant prognosticator by univariate and multivariate analyses in patients with recurrence after adjuvant S-1. On the other hand, some authors have reported the significance of the histological type in the survival of preoperative patients or in sensitivity to chemotherapy. Adachi et al. [7] evaluated 504 preoperative patients with gastric cancer that was classified as well-differentiated and poorly differentiated types. They found the 5-year survival rate to be higher in patients with well-differentiated gastric carcinoma than that in patients with poorly differentiated gastric carcinoma. Futatsuki et al. [8] reported a late phase II study of CPT-11 in advanced gastric cancer that found that the response rate was higher in patients with differentiated types than those with undifferentiated types (30.0 vs. 14.3%). On the other hand, Mai et al. [9] reported a late phase II study of docetaxel in advanced gastric cancer and found that the response rate was similar in patients with differentiated-type cancer and those with undifferentiated type (20.0 vs. 26.3%). In addition, two phase II studies of paclitaxel in advanced gastric cancer showed that the response rates for diffuse- and intestinal-types were 29 and 17%, and 36 and 24%, respectively [10, 11]. These reports may suggest that the histological type is important for chemosensitivity. which determines survival especially in S-1-refractory tumors. Patients with a differentiated type may have a greater chance of responding to both taxanes and CPT-11

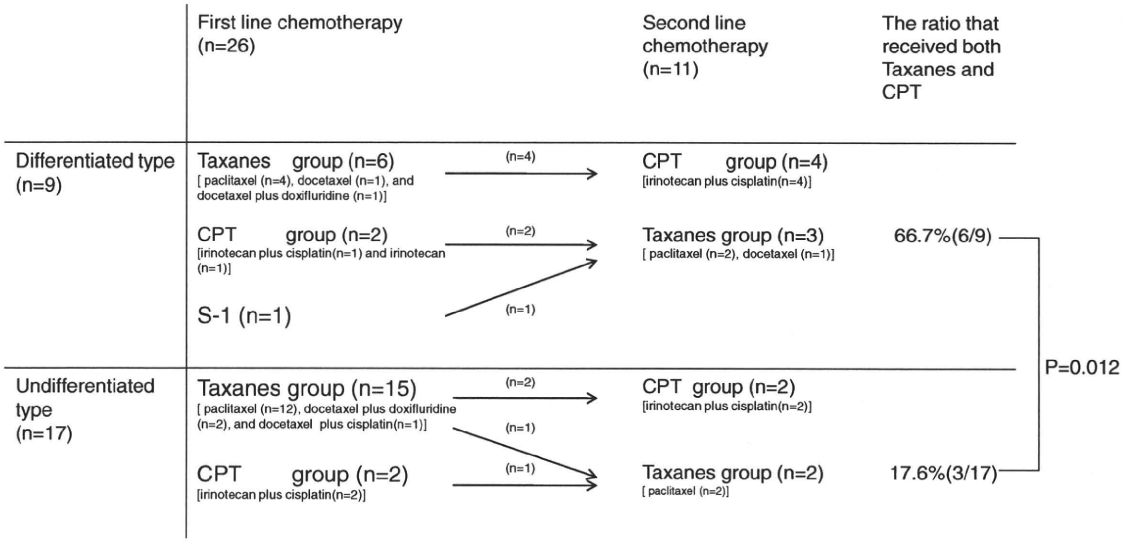

Fig. 3 Details of the first line- and second-line chemotherapy regimens in 9 patients with the differentiated type and 17 with the undifferentiated type

in comparison to those with an undifferentiated type, which would thereby contribute to the survival.

The present study found that 66.7% of patients with the differentiated type received both taxanes and CPT-11, in comparison to 17.6% of those with the undifferentiated type. This difference may have affected the difference in the survival between the two types. In particular, only 2 patients received CPT-11 as second-line chemotherapy among 15 patients with the undifferentiated type who had received taxanes as first-line chemotherapy, which decreased the rate of the entry into the second-line chemotherapy and may have shortened the survival. However, the undifferentiated type has more chance of responding to taxanes than CPT-11, as mentioned above. It is unclear whether or not the survival of the undifferentiated type is improved by selecting CPT-11 as the first-line chemotherapy.

Of note, the duration of the S-1 adjuvant chemotherapy did not have a significant prognostic impact in our study. Although a group who received S-1 for 3 months or longer tended to have a lower risk of recurrence compared with a group who received S-1 for <3 months, the difference did not reach statistical significance. Moreover, multivariate analysis identified the histological type as the only independent significant prognostic factor. Nevertheless, the duration of S-1 chemotherapy could, in theory, be relevant, and there is a possibility that the small number of patients analyzed might have adversely affected our results. The reasons for discontinuation of S-1 should also be taken into consideration when discussing the prognostic impact of the treatment duration. Again, given the small sample size, it was not practical at this time to analyze survival by further subdividing the patients into those who discontinued treatment due to toxicity and those whose treatment was terminated due to recurrence. In addition to the issue of sample size, the retrospective nature of the study and diversity of the drugs used after S-1 failure are weaknesses that need to be borne in mind when interpreting results from the present study.

In summary, the present study revealed that survival after failing the standard adjuvant chemotherapy did not reach the expected 12 months as observed in recent phase III trials for untreated advanced/metastatic gastric cancer. Undifferentiated phenotype was a significant indicator of poor prognosis in these patients.

Acknowledgments This work was supported, in part, by Kanagawa Health Foundation.

Conflict of interest None declared.

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Gastric Cancer (2010) 13: 137–148
DOI 10.1007/s10120-010-0560-5

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.

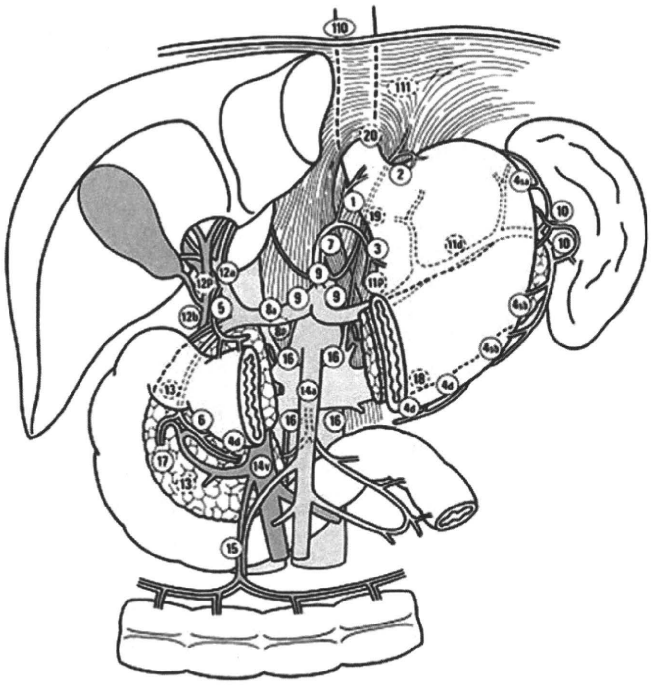
In this review, we first discuss the current status of the extent of LN dissection for advanced gastric cancer and offer an optimal management approach in view of the results of recent clinical trials.

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

Offprint requests to: M. Terashima
Received: February 13, 2010 / Accepted: May 21, 2010



Station. 1	Right paracardial LN
Station. 2	Left paracardial 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 (1989–1993) [10, 15–17]	D1	380	25%	4%	45%
	D2	331	43% ($P < 0.001$)	10% ($P = 0.004$)	47% HR 1.00 (95% CI, 0.82–1.22)
MRC trial (1987–1994) [11, 18]	D1	200	28%	6.5%	35%
	D2	200	46% ($P < 0.001$)	13% ($P = 0.04$)	33% HR 1.10 (95% CI, 0.87–1.39)
IGCSG trial (1999–2002) [15]	D1	76	10.5%	0%	Under analysis
	D2	86	16.3% ($P < 0.29$)	1.3% (N.S)	
Taiwanese trial [14, 19]	D1	110	7.3%	0%	53.6%
	D3	111	17.1% ($P = 0.012$)	0%	59.5% 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 adenocarcinoma 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	263	20.9%	0.8%	69.2%
	D2+PAND	260	28.1% ($P = 0.067$)	0.8% ($P = 0.99$)	70.3% HR 1.03 (95% CI, 0.77–1.37)
Polish trial (1999–2003) [32]	D2	141	27.7%	4.9%	Under analysis
	D2+PAND	134	21.6% ($P = 0.248$)	2.2% ($P = 0.37$)	
East Asian trial (1995–2002) [33, 34]	D2	135	26%	0.7%	52.6%
	D2+PAND	134	39% ($P = 0.023$)	3.7% ($P = 0.107$)	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 (1985–1992) [47]	TG	97	Not stated	39%	24%	4%	3.1%	36%
	TG+S	90		50% ($P < 0.04$)	39% ($P < 0.008$)	11% ($P < 0.05$)	4.4% ($P > 0.7$)	42%
Korean trial (1995–1999) [48]	TG	103	8.7%	Not stated	Not stated	Not stated	1.0%	48.8%
	TG + S	104	15.4% ($P = 0.142$)				1.0% ($P = 1.000$)	54.8% ($P = 0.503$)

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.

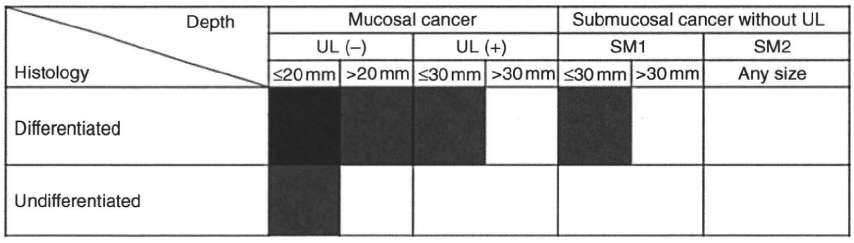


Fig. 2. Japanese guideline criteria for endoscopic resection. Size is shown in mm. *Black area*, Guideline criteria for endoscopic resection; *gray area*, criteria for extended endoscopic resection; *white area*, no indication for endoscopic resection. *UL*, With ulcerated lesion; *SM1*, submucosal level 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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胃癌成績向上を目指した集学的治療と個別化
―手術と周術期化学療法をめぐる話題

1　エビデンスのある手術手技の確立

日本の胃癌手術は近年大きく進歩してきました．1970年代には2群リンパ節郭清（D2）を伴う胃切除が定着し，その後，手術は拡大の方向に進みました．その中で大動脈周囲リンパ節郭清（D3）も行われていましたが，ランダム化臨床試験JCOG9501で，D2郭清とD3郭清の5年生存率は差がなく，残念ながら拡大郭清の意義は否定されました．

開胸開腹手術についても，80年代後半には「これをやってこそ専門家」という状況でした．ところが食道浸潤胃癌において比較試験JCOG9502を行った結果，開腹のみの手術のほうが予後は良かったのです．

これらの試験はいずれもネガティブな結果となりましたが，試験によるエビデンス構築の重要性が認識され，その後の脾摘と脾温存を比較するJCOG0110試験や，腹腔鏡下手術と開腹手術の比較試験JCOG0912などに結びついていきます．

JCOG0110試験は，上部進行胃癌を対象に，胃全摘をしたうえで脾摘と脾温存を比較する非劣性試験です．D2郭清を伴う胃全摘手術では脾摘がスタンダードであり，海外の小規模試験では有意差はないものの，脾摘のほうが脾温存よりも予後は良いと報告されています．一方で，脾摘による生存へのメリットはそれほど大きくないという報告もあります．JCOG0110試験には505人が登録し，第1回中間解析では差が認められなかったため，現在は経過観察中ですが，2年後には第2回中間解析が報告されるでしょう（表1）．

2　高度進行胃癌に対する外科手術の挑戦

治癒切除不能の進行胃癌に対し，腫瘍量を減らすための減量手術を検証する試験（JCOG0705/REGATTA）も進行しています．胃切除＋術後化学療法（TS-1＋CDDP）と化学療法（TS-1＋CDDP）のみを比較する

表1　胃癌手術に関するJCOG試験

Study No.	試験名	デザイン	現状および結果	Ref.
JCOG0912	臨床病期Ⅰ期胃癌に対する腹腔鏡下幽門側胃切除術の開腹幽門側胃切除に対する非劣性を検証するランダム化比較試験	PhaseⅢ	登録中	—
JCOG0705	治癒切除不能進行胃癌に対する胃切除術の意義に関するランダム化比較第Ⅲ相試験	PhaseⅢ	登録中	—
JCOG0703	臨床病期Ⅰ期胃癌に対する腹腔鏡下幽門側胃切除術の安全性に関する第Ⅱ相試験	PhaseⅡ	腹腔鏡下幽門側胃切除術の安全性が確認された．	Kurokawa Y et al, Jpn J Clin Oncol 2008, 38：501-503
JCOG0110	上部進行胃癌に対する胃全摘術における脾合併切除の意義に関するランダム化比較試験	PhaseⅢ	登録終了，フォローアップ中	Sano T et al, Jpn J Clin Oncol 2002, 32：363-364
JCOG9502	食道浸潤胃癌の外科治療に関する比較臨床試験	PhaseⅢ	食道浸潤胃癌に対する左開胸開腹法は予後改善に寄与しない．	Sasako M et al, Lancet Oncol 2006, 7：644-651
JCOG9501	大動脈周囲リンパ節郭清の臨床的意義に関する研究	PhaseⅢ	治癒切除可能な胃癌に対する大動脈リンパ節郭清は予後改善に寄与しない．	Sasako M et al, N Engl J Med 2008, 359：453-462

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日韓共同のランダム化試験です．肝転移，腹膜播種，遠隔リンパ節転移のいずれか1つを有する患者さんが対象であり，登録条件は厳しいのですが，各国で110人以上，全体で330人を目標にしています．

良い成績が出ていた手技を変更するときは，エビデンスをもって変えないと理解が得られません．そういった意味で重要なのが，胃後壁漿膜浸潤例に対する網嚢切除の意義を検証する試験です．昔は当たり前に網嚢切除が行われていましたが，有用ではないとする意見があり，試験でそれを検証します．最近プロトコールが承認され，間もなく試験が開始される見込みです．

腹腔鏡下胃切除術では，第Ⅱ相試験JCOG0703でStage Ⅰの早期癌に限り，その安全性が示され，開腹手術と比較する第Ⅲ相試験JCOG0912の登録がスタートしました．手術は，触った感じや剝いだ感じなど，さまざまな情報を補い修正していきます．癌が進行すればするほど，その修正が必要になってくるわけですが，腹腔鏡下手術は開腹手術に比べはるかに情報が少ない手技です．この試験で非劣性が証明されれば，ようやくオプションの1つになるわけです．進行癌でも腹腔鏡下胃切除術が行われつつありますが，この試験結果を待つべきでしょう．

JCOGではこのほか，ESD（内視鏡的粘膜下層剝離術）の拡大適応に関する試験JCOG0607も消化器がん内科グループにより開始されています．

3 集学的治療における術後補助化学療法の役割

術後補助化学療法は，N･SAS-GC試験やACTS-GC試験を経て，TS-1レジメンが標準となりました．80年代半ば，日常臨床としてすでに術後補助化学療法が行われ，90年代には全国的に術後経口フッ化ピリミジン投与による治療が行われていました．その状況を危惧し，厚生省（現厚生労働省）の指導で，1997年にN･SAS-GC試験が実施されたのです．手術単独と手術＋高用量UFTが比較され，中間解析で有意差が出ましたが，症例数が190例と少ないため，UFTの有用性はさらなる検証が必要とされました．

しかしN･SAS-GC試験は，手術単独を対照群とするスタンスの意義を再認識する契機となり，またJCOG以外にも参加施設を広げることが可能であることを示したといえます．その経験もあり，ACTS-GC試験には1,000例以上が集まりました．胃癌治療で初めて大規模な臨床試験によって有効な治療法が開発でき，rationaleに基づいた臨床試験ができたという意義は大きいと考えます．またオールジャパンで結集するとこれだけのことができるという手ごたえもわかりました．ACTS-GC試験は日本中から参加した外科医が誇りに思うべき臨床試験です．

現在，UFTの位置づけを明らかにするためのSAMIT試験が進行中です．TS-1は確かに臨床効果もfeasibilityもありますが，胃全摘の患者さんへの投与はそう簡単ではありません．そこで最初の3カ月は自覚症状のある有害事象が少ないタキサン系抗癌剤を使い，その後UFTあるいはTS-1をシークエンシャルに使うというのがSAMIT試験のコンセプトです．漿膜浸潤胃癌を対象にした2×2のFactorial Designによるランダム化比較試験で，TS-1単剤に対するUFT単剤の非劣性と，パクリタキセル→UFTあるいはTS-1の優越性が検証されます．

実は術後補助化学療法の開発はいま大きな問題を抱えています．昔は抗癌剤として認可されれば，進行癌でも術後補助化学療法でも使うことができましたが，現在は違います．HER2陽性の進行胃癌でトラスツズマブの有効性が示されましたが，術後補助化学療法と

表2　術前化学療法（JCOG試験）

Study No.	試験名	デザイン	現状および結果	Ref.
JCOG0501	根治切除可能な大型3型・4型胃癌に対する術前TS-1＋CDDP併用療法による第Ⅲ相試験	PhaseⅢ	登録中	—
JCOG0405	高度リンパ節転移を伴う進行胃癌に対する術前TS-1＋CDDP併用療法＋外科切除の第Ⅱ相試験	PhaseⅡ	TS-1＋CDDP療法は，R0切除率82.4%でありbulky N2/3症例に対し有望な治療.	Kawashima Y et al, GI Cancers Symposium 2008
JCOG0210	根治切除可能な大型3型・4型胃癌に対する術前TS-1＋CDDP併用療法の安全性確認試験	PhaseⅡ	TS-1＋CDDP療法は，完遂率73%，3年生存率26%であり，大型3型および4型胃癌に対し安全かつ有望.	Fujitani K et al, GI Cancers Symposium 2007 Iwasaki Y et al, JGCA 2008
JCOG0002	4型胃癌に対する術前TS-1単独療法の第Ⅱ相試験	PhaseⅡ	TS-1単独療法は安全で有効だが2年生存率は59%で，期待生存率60%に到達せず.	Kinoshita T et al, Gastric Cancer 2009, 12：37-42
JCOG0001	高度リンパ節転移を伴う進行胃癌に対する術前CPT-11＋CDDP併用療法＋外科切除の第Ⅱ相試験	PhaseⅡ	CPT-11＋CDDPは予想どおり従来の治療成績を改善したが，毒性に十分注意が必要.	Yoshikawa T et al, Br J Surg 2009, 96：1015-1022

して使うには新たに試験をしなくてはなりません．どうやって術後補助化学療法を開発していくか，今後の課題といえます．

4　進行胃癌に対する術前補助化学療法の可能性

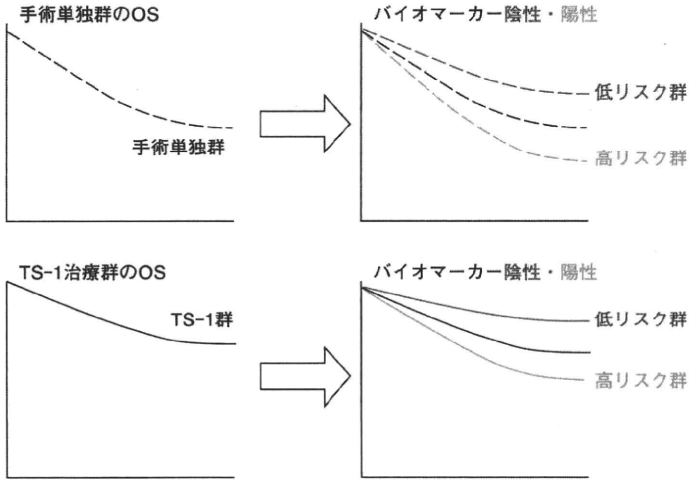
TS-1による術後補助化学療法で効果不十分と思われる群に対しては，術前補助化学療法（NAC）が検討されています．NACの適応は大きく2つに分けられます．1つは切除可能だが再発の危険性が高いグループ，もう1つは切除不能の可能性が高く，NACをしないと完全切除R0を行える可能性が小さくなるグループです．

大型3型・4型胃癌を対象に，腹腔鏡で治癒切除できることを確認したうえで，NAC（TS-1＋CDDP）＋手術＋術後補助化学療法（TS-1単剤）と手術＋術後補助化学療法（TS-1単剤）を比較する試験が行われています（JCOG0501試験）．一方，治癒切除が難しい高度リンパ節転移例などに対しては，第Ⅱ相試験の結果から，TS-1＋CDDPが暫定的に標準となっています（**表2**）．

さらに今，ドセタキセルを加えるDCS療法の試験が検討されており，手術と化学療法による集学的治療は今後さらに発展すると考えられます．

5　個別化治療と今後の胃癌治療への期待

個別化治療は，腫瘍細胞の遺伝子変異などのバイオマーカーを用いて，患者さんをサブグループに分けることによって可能となります．現在，ACTS-GC試験に登録した患者さんから手術時に摘出され保存されていた腫瘍組織病理標本を用いて，このバイオマーカー研究を進めています（**図1**）．治療効果を予測する因子はもちろんのこと，登録者の半分は手術単独ですから，癌の遺伝子変異が予後因子として有用かどうかも明らかになるでしょう．試験後の探索研究ではあり



検討するバイオマーカー

①63種の遺伝子発現量（mRNA）

- TS，DPD，OPRT，TP（5-FUの感受性規定因子）
- ERCC1（プラチナ系抗癌剤の感受性規定因子）
- Topo Ⅰ（イリノテカンの感受性規定因子）
- HER2，VEGF，EGFR（分子標的薬の感受性規定因子）
- 胃癌の予後に関連する遺伝子など

②7種の蛋白発現（免疫染色）

- TS，DPD，OPRT，TP，HER2，ERCC1，EGFR

③K-ras変異の検討

●予後因子の検討（上図）
手術切除後の低リスク群・高リスク群を判別できるマーカーの探索
●効果予測因子の検討（下図）
TS-1および他薬剤の効果予測因子を検討し，TS-1単独を上回る治療法開発に活用

図1　ACTS-GC試験バイオマーカー研究の意義

ますが，手術単独を対照群とすることが許されなくなっている今，この研究は大変貴重で重要な研究です．800を超えるサンプル数が集まると見込んでおり，信頼性の高いデータになると思います．来年にも、今後の胃癌の試験デザインに大いに参考になる情報が得られることが期待されます．

大腸癌がそうであるように，薬物療法が大幅に進歩すると，肝転移や腹膜播種など，手術の適応が増えることで，さらに治る人が増えていくでしょう．しかし抗癌剤が良くなったからといって，いい加減な手術で治ると考えてはいけません．抗癌剤が進歩したからこそ，手術に求められるものも増えています．求められたときに的確に手術ができる技術をもった外科医となるよう，若い人に伝えるべき技量は伝えていかなくてはいけないと考えているところです．

2010年12月号(Vol. 33 No. 13)

わが国と欧米のリンパ節郭清の考え方

Principles and philosophy of lymph node dissection for soild cancers in Japan and the West

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●要旨●欧米ではリンパ節転移は癌が全身病化している証しであると考え，本邦ではそれは癌の急激な広がりを防ぐ局所のバリアーと考えていた二極化した時代は終わり，局所コントロールと全身治療をどう組み合わせるかの重みの違いを癌腫ごとに見出す時代を迎えている。cancer stem cellあるいはNicheという概念が提唱され，ある程度実体が捕まりかけているが，リンパ節転移を含めて転移形成のメカニズムにはまだまだ未知のことも多い。

● key words：リンパ節転移，cancer stem cell，転移能，stage migration

はじめに

今から約10年前の1999年に同じ企画の特集号を本誌が出している[1]。この10年間に研究の進歩，臨床試験による明確なデータとしての証拠などが積み重ねられ，少しだけ進歩した見地に立つことができているのは事実である。しかし，いまだに“想定”や“説”の域を出ない内容も多く残っている。今後cancer stem cell[2]やNiche[3]といった新しい概念が実証を伴って，明確なリンパ節転移のメカニズムと臨床的意義をわれわれに教える日はそう遠くはないと思われる。

癌のとらえ方：局所疾患か全身疾患か

癌のリンパ節転移の治療対象としての存在にこだわりつづけてきたわが国の考え方と，1970年代頃より癌が全身疾患であり，リンパ節転移をコントロールすることの意義を軽視する傾向の強くなった欧米の癌治療に対する考え方は途中で大きく離れた時期もあったが，今徐々に1つの考え方で合意されようとしている。

癌は局所で発生し，浸潤能と転移能を徐々に備えていき，局所浸潤癌から領域転移を伴う領域癌，そして他臓器への血行性転移を伴う全身疾患へと進むものが一般的である。癌を局所疾患ととらえることも全身疾患と初めからとらえてしまうことも間違いであろう。固形癌の治療で手術の役割をきわめて重視してきたわが国でも，欧米に多い癌における治療体系のあり方は浸透してきたし，手術一点張りできた胃癌においても化学療法と組み合わせてこそより多くの患者が治癒することが臨床試験により実証され[4]，全身化した癌を想定した補助化学療法が定着した。

以前の特集号で筆者は，胃癌では癌細胞は最初にリンパ節経路で徐々に転移を起こしていき，大循環に入るのは相当ステージが進んでからであると記載している。すなわち，門脈循環系に存在する肝臓やリンパ節は癌が全身化することを防ぐバリアーとして機能しているのではないか，したがって胃癌では郭清の効果が十分に上がると記載している。しかし，その後1,000例近い胃癌患者の骨髄や末梢血をいただいて研究をする機会を得たが，その結果ではステージ1ですら多くの患者の末梢血や骨髄中に癌細胞が存在することが判明し，初期癌でリンパ節転移も全身転移も少ないのは癌細胞が局所で釘付けにされているからではないことがわかった[5]。すなわち，癌が全身に回っていることと転移が成立することの間には，いくつものステップ

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があり，局所リンパ節を郭清して患者が治癒するのは，他部位に癌細胞が行っていないからではないということである。ここから先の研究が今後の癌治療の有効性を大きく変える鍵を握るであろうと想像している。

転移の形成に関する新しい考え方

転移が成立するには血管新生を含めたいくつかの条件が必要であることは理解されてきた。癌細胞自身がさまざまな形のサイトカインを産生し，それらが骨髄を含めた間質系細胞に働きかけて転移に必要な条件を転移先で生み出すようなメカニズムも想定されている[6]。Nicheというコンセプトはまさにその1つであり，いくつかの断片的な事実が理解されはじめているが，全体の確固たる説明には至っていない。欧米では，アングロサクソン系に多い乳癌や悪性黒色腫などの基礎的・臨床研究から固形癌の普遍的な理解を推し進めてきたので，多くの研究がされている。消化器の固形癌での研究はそれらの分野を追随する形で行われている。現在間違いなくいえることは，癌細胞が存在すれば遠隔部位においても転移に直結するということではなく，転移形成能をもつ癌細胞だけが，そして転移が成立する環境でのみ転移を形成できるという考えである。このような能力をもつ癌細胞を即，cancer stem cellとする考えと，stem cellに限らず転移能をもつことは可能であるという考えもあり[7]，まだまだ多くの疑問点が残っている。

リンパ節転移の存在は何を意味するか

リンパ節転移は予後の指標であり，その摘出が予後を改善するものではないという基本的な考えは依然多くの固形癌治療の分野で支持されているのが欧米の実情である[8]。乳癌の研究に大変な貢献をしたBlake Cadyの“lymph nodes, indicator but not governors of cancer”という強烈なメッセージは今もその土台にある[9]。実際ごく少数の癌腫を除くと6～7個以上のリンパ節転移の存在はきわめて予後不良の証しにしかすぎず，外科手術の貢献はわずかであり，十分な全身療法を補助療法として加えるのが常識である。ただし，有効な全身療法が存在しない癌腫では，局所コントロールがたまたま成功して，なんらかの腫瘍免疫が自然に発現したようなケースでまれに治るのであろうと推測されている。しかし，中には胃癌のように，17個以上のリンパ節転移が存在しても治癒するケースが7～8％あるような癌腫もあり，当然6～7個程度の転移を有する場合には30～40％程度の患者は治癒する[10]。このような癌腫と食道癌，乳癌，大腸癌など5個以上の転移があると極端に予後が不良となる癌腫との差がどこにあるのかも仮説の域を出ない。しかし，全身疾患ととらえて用いる薬剤治療がきわめて有効な乳癌のようなケースでは局所コントロールの重みは著しく軽くなってしまう。他方，治療において局所コントロールの必要性がもっとも広く受け入れられているのが胃癌であり，次いで大腸癌であろう。10年前では，欧米ではすべての癌に対して乳癌と同じ考え方がされようとしていたが，胃癌における多くの臨床試験の結果で局所コントロールが胃癌の治癒においては欠かせず，治療成績の改善に役立つことが欧米でも明確に認識されるようになってきている[11)～17)]。欧米と日本がすべての癌腫においてリンパ節転移の考え方で対立していた時代は終わろうとしている。

全身疾患のマーカーとしてのリンパ節転移

乳癌や大腸癌ではリンパ節転移の有無により，治療方針が変わることはガイドラインなどに記載されている。乳癌，大腸癌，食道癌などでは，転移個数が4～5個以上ある場合は急激な予後の悪化を意味し，転移を有するすべての症例が補助療法の適応になるとされている。これらの癌腫ではリンパ節転移の存在が腫瘍細胞の転移能を示していると考えられ，全身化の指標と考える。一方，胃癌のようにリンパ節転移があっても，手術単独でも相当な確率で癌が治癒する癌腫ではすべての症例が補助療法の対象とはなっていない。具体的にいえば，リンパ節転移のあるT1はステージにかかわらず，補助療法を行わずとも90％以上の5年生存率で，補助化学療法の適応からは除外されている[18]。

リンパ節転移の不思議

リンパ節に限らず転移が成立するには，まず癌細胞が原発巣から抜け出して，血管，リンパ管に進入する，あるいは自由腔（腹腔や胸腔）に遊離し飛散することが必要である。次にこれらの遊離癌細胞から転移性腫瘍の形成に至る過程が起こることとなる。腹膜播種な