Table 2 Operative data from patients undergoing palliative gastrectomy ($n = 18$)

Characteristics	
Surgical procedure	
Total gastrectomy	14 (78%)
Distal gastrectomy	3 (17%)
Proximal gastrectomy	1 (6%)
Lymph node dissection	
≤D1	18 (100%)
>D1	0
Sites of positive margin	
Proximal only	12 (67%)
Proximal and distal	6 (33%)
Residual tumor	
R1	4 (22%)
R2	14 (78%)
Complications	
Anastomotic leakage	2 (11%)
Anastomotic hemorrhage	1 (6%)
Intra-abdominal abscess	1 (6%)
Pneumonia	1 (6%)

was not margin-positive after Roux-en-Y reconstruction. In these patients with anastomotic leakage, oral intake was not resumed up to the time of death. Anastomotic hemorrhage, intra-abdominal abscess, and pneumonia occurred in 1 patient each. These 3 patients recovered with conservative treatment and maintained oral intake during their remaining survival time. Of the 5 patients who developed a postoperative complication, 4 had undergone total gastrectomy, and 1 had undergone distal gastrectomy. The complication in 1 patient who underwent distal gastrectomy was duodenal stump leakage that was not margin-positive after Roux-en-Y reconstruction. To achieve a negative proximal margin, the risk of surgery is considered to differ between distal gastrectomy and total gastrectomy. All 18 patients presented with cancer progression and died during follow-up. The median overall survival was 7.5 months (Fig. 1). The median time from operation to decrease in oral intake was 5.5 months (Fig. 2). Anastomotic recurrence developed in 3 patients, and all of whom had anastomotic stricture 2–3 months after gastrectomy (Table 3). Of these 3 patients, 2 had undergone total gastrectomy, and 1 had undergone distal gastrectomy. Anastomotic stricture due to anastomotic recurrence occurred in the patients after palliative distal gastrectomy. One of these three patients was treated by endoscopic balloon dilatation and maintained oral intake for 2 months after balloon dilatation. This patient had undergone total gastrectomy. The other 2 patients had peritonitis carcinomatosa when anastomotic recurrence was found. Balloon dilatation was not performed for these 2 patients, because we considered that oral intake could not be resumed even with anastomotic stricture dilatation. One patient after distal gastrectomy did not undergo balloon dilatation because of poor general condition owing to peritonitis carcinomatosa.

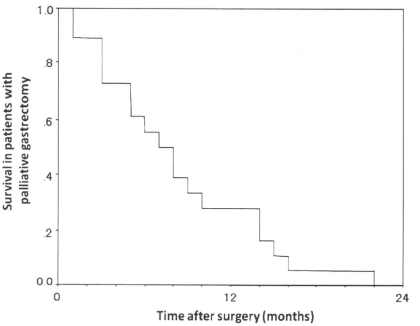

Fig. 1 Survival in patients with palliative gastrectomy

In all 18 patients, the status of the proximal margin was negative on macroscopic examination, because the goal of all surgeries, even palliative, was to obtain a macroscopic negative margin. Therefore, patients with a microscopic-positive margin cannot be compared with those with a macroscopic-positive margin.

In 46 patients with a negative proximal margin, the median overall survival was 8.5 months, and the median time from operation to a decrease in oral intake was 7 months. There was no significant difference between proximal margin-positive and proximal margin-negative patients in the time between gastrectomy and death ($p = 0.26$) and a decrease in oral intake ($p = 0.12$).

Discussion

Radical resection is the primary treatment for gastric cancer, but the benefit of noncurative gastrectomy for metastatic gastric cancer patients is still debatable. The prognosis of patients who undergo noncurative gastrectomy is extremely poor [7, 19, 20]. Palliative gastrectomy is not the same as noncurative gastrectomy. Noncurative gastrectomies have been classified as either palliative or nonpalliative. Palliative care has been defined by the World Health Organization as "the total active care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social, and spiritual problems is paramount. The goal of palliative care is the achievement of the best quality of life

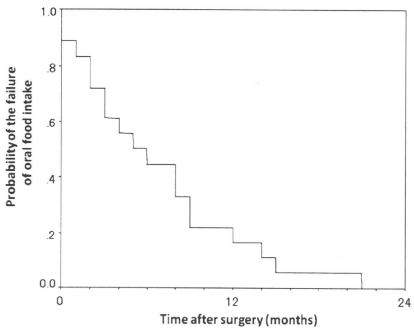

Fig. 2 Cumulative incidence of failure of oral food intake. Kaplan–Meier curve showing the time to failure of oral food intake after operation

for patients and their families" [21]. Palliative gastrectomy should concentrate on relieving symptoms such as gastric outlet obstruction, perforation, or tumor bleeding. Therefore, in the present study, patients without symptoms were excluded, even if a noncurative operation was performed. The morbidity was high after palliative gastrectomy for far advanced gastric cancer with urgent symptoms that needed to be controlled. For patients with short life expectancy, complications of surgery ruin the rest of their lives. In the present study, anastomotic leakage dealt a crushing blow. It is difficult and risky to perform highly placed intramediastinal anastomosis for far advanced gastric cancer with severe esophageal invasion to achieve a negative proximal margin. Palliative resection does not seek to offer cure options, and resection margin involvement was not considered to affect the clinical course after gastrectomy. However, in general, a positive resection margin induces anastomotic recurrence and anastomotic stenosis. Anastomotic stenosis caused by recurrence might lead to decreasing oral intake. Actually, it is unclear whether a positive proximal margin in palliative gastrectomy affects the amount of oral intake after surgery. In this study, anastomotic recurrence occurred in 3 of 18 patients (16.7%), and recurrence was found at 2 months after gastrectomy. Lee et al. [22] reported that anastomotic recurrence was found in 4.3% of patients who underwent gastrectomy for advanced gastric cancer, and anastomotic strictures were observed at a median interval of 11.9 months. Cho et al. [23] reported that resection margin involvement occurred in 1.8% of gastrectomies with curative intent, and that anastomotic recurrence occurred in 14.3% of patients with positive resection margins. Jakl et al. [24] reported that anastomotic recurrence was found at a median interval of 11 months. The present study showed that a positive proximal margin resulted in a high incidence of early recurrence at the site of anastomosis. In 2 patients, anastomotic stenosis caused by tumor recurrence did not affect their quality of life, because their condition was poor due to peritonitis carcinomatosa. For another patient with anastomotic stricture caused by recurrence, who was in good general condition, endoscopic balloon dilatation was effective in maintaining a reasonable quality of life. We performed endoscopic balloon dilatation for anastomotic stricture as salvage therapy, which was effective for benign esophagojejunal anastomotic stricture [25, 26], but there are other salvage treatments available. Some studies have shown that a self-expandable metal stent provides safe and effective palliation of anastomotic recurrence of gastric cancer [27–30]. If long-term survival is possible, stent insertion is worthwhile, because the effect of balloon dilatation is temporary. At any rate, patients with anastomotic stricture due to tumor recurrence after palliative gastrectomy, if they are in good general condition, can maintain oral intake with balloon bougie or stenting therapy. Therefore, we concluded that it is not

Table 3 Patients with anastomotic stenosis caused by local recurrence

Case	Noncurable factor	Surgical procedure	Interval between operation and AS caused by local recurrence	Recurrent site except anastomosis	Interval between operation and non-local recurrence	Intervention for AS	Outcome	
1	P, CY	Total gastrectomy	2 months	Peritoneal dissemination	4 months	Balloon dilatation	6 months	Death
2	P, CY	Distal gastrectomy	2 months	Peritoneal dissemination	2 months	None	3 months	Death
3	P, CY, M(LYM)	Total gastrectomy	3 months	Peritoneal dissemination	3 months	None	5 months	Death

AS anastomotic stenosis, *P* peritoneal metastasis, *CY* peritoneal lavage cytology, *M(LYM)* nonregional lymph node metastasis

necessary for palliative gastrectomy to achieve a negative proximal margin, because salvage therapies resulted in maintenance of a tolerable oral intake.

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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

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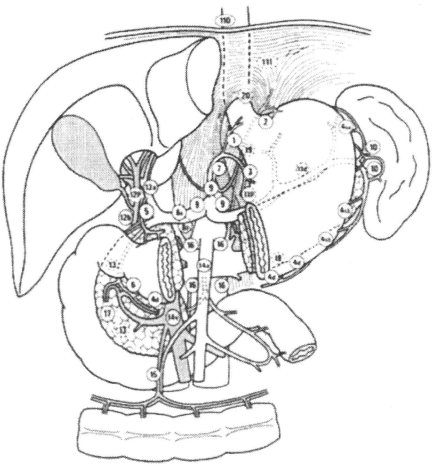

Station. 1	Rightparacardial LN
Station. 2	Leftparacardial LN
Station. 3	LN along the lesser curvature
Station. 4sa	LN along the short gastric vessels
Station. 4sb	LN along the left gastroepiploic vessels
Station. 4d	LN along the right gastroepiploic vessels
Station. 5	Suprapyloric LN
Station. 6	Infrapyloric 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 (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	D2	263	20.9%	0.8%	69.2%
(1995–2001)	D2+PAND	260	28.1%	0.8%	70.3%
[30, 31]			($P = 0.067$)	($P = 0.99$)	HR 1.03 (95% CI, 0.77–1.37)
Polish trial	D2	141	27.7%	4.9%	Under analysis
(1999–2003)	D2+PAND	134	21.6%	2.2%	
[32]			($P = 0.248$)	($P = 0.37$)	
East Asian trial	D2	135	26%	0.7%	52.6%
(1995–2002)	D2+PAND	134	39%	3.7%	55.4%
[33, 34]			($P = 0.023$)	($P = 0.107$)	($P = 0.801$)

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%	39%	11%	4.4%	42%
				($P < 0.04$)	($P < 0.008$)	($P < 0.05$)	($P > 0.7$)	
Korean trial (1995–1999) [48]	TG	103	8.7%	Not stated	Not stated	Not stated	1.0%	48.8%
	TG + S	104	15.4%				1.0%	54.8%
			($P = 0.142$)				($P = 1.000$)	($P = 0.503$)

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.

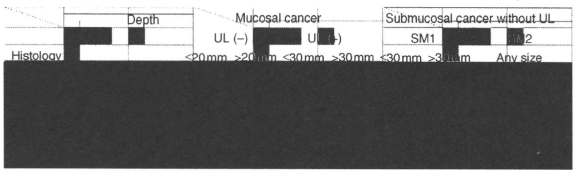

Fig. 2. Japanese guideline criteria for endoscopic resection. Size is shown in mm. *Black area*, Guideline criteria for endoscopic resection; *gray area*, criteria for extended endoscopic resection; *white area*, no indication for endoscopic resection. *UL*, With ulcerated lesion; *SM1*, submucosal level 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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●特 集●

抗がん剤の腔内投与の現状と問題点
—エビデンス不足，しかし日常診療では常に悩むこと—

腹腔内（IP）化学療法のエビデンスと標準化への問題点

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Evidence and Issues in Standardization of Intraperitoneal Chemotherapy: Akira Tsuburaya, Haruhiko Cho and Takaki Yoshikawa (*Gastrointestinal Surgery, Kanagawa Cancer Center*)

Summary

Intraperitoneal (IP) chemotherapy targets IP regional metastasis by maintenance of high-dose intensity. Thus, it is applied for cancers in which IP lesions limit the prognosis or QOL of patients. In ovarian cancer, ample evidence to support survival benefit of IP chemotherapy has been established, however, its standardization has not yet been accomplished. NCI has made efforts for the dissemination of and education in IP therapy, and GOG's research focuses on a less toxic IP regimen. In gastric cancer, the advantage of IP therapy has not been proved, and for its approval, phase Ⅰ-Ⅲ trial of IP with or without cytoreduction surgery should be initiated. **Key words**: Intraperitoneal chemotherapy, Ovarian cancer, Gastric cancer, Cytoreduction, **Corresponding author**: Akira Tsuburaya, Gastrointestinal Surgery, Kanagawa Cancer Center, 1-1-2 Nakao, Asahi-ku, Yokohama 241-0815, Japan

要旨 抗癌剤の腹腔内（IP）投与は，腹膜転移に対して，非常に高い dose intensity を保つことで局所（regional）効果を期待する。よって，IP病変が予後規定因子である場合，または同病変による合併症がQOLを最も損なう癌腫に対して適応となる。卵巣癌においては，IP化療のエビデンスが最も豊富であるが，同時に標準化が進んだとはいい難く，NCIによる普及・教育とGOGなどによるより毒性の低いIP投与法が研究されている。胃癌におけるIPの優位性を示すエビデンスは少なく，cytoreductionの意義も同時に検討するような，治験レベルによる第Ⅰ相から第Ⅲ相比較試験を行う必要がある。

はじめに

抗癌剤の腹腔内（IP）投与は，腹膜転移あるいは腹腔内のリンパ節転移に対して，非常に高い IP dose intensity を保つことで局所（regional）効果を期待する。よって，IP病変が予後規定因子である場合，または同病変による合併症がQOLを最も損なう癌腫に対して適応となる。多くの固型癌では腹腔内病変と前後して，遠隔転移を伴いかつ予後規定因子となる場合が多いためにⅣ化学療法（化療）が適応となる。

IP投与の理論的な根拠としては，1．高濃度，2．長期にわたる薬剤の滞留と組織あるいは血中移行，があるが，前者1．の高濃度による機序に関しては，否定的なエビデンスもある。2007年に報告されたAGO-Ovar/AIOとEBMTの共同試験では，stage Ⅱ～Ⅳ卵巣癌の減量手術後に対する高用量化療の優位性は証明されなかった[1]。同試験では，標準的なⅣ化療としてcarboplatin AUC 5+paclitaxel 175 mg/m^{2}に対して，高用量群の末梢血幹細胞移植+carboplatin AUC 20+paclitaxel 200～250 mg/m^{2}とを比較したが，無再発生存，全生存率ともに有意差はなかった。IPのメカニズムとしては，後者2．を生かしたデザインが必要かもしれない。

本稿では，IP治療の要件に見合う可能性の高い癌腫として卵巣癌と胃癌について取りあげ，これまでのIPに関するエビデンスのレビューと，今後実地医療に導入してゆくために必要な臨床試験や標準化のありかたについての考察を行った。

Ⅰ．IP化療の特殊性とその対象

実地医療に還元されるエビデンスの多くはランダム化比較試験（RCT）によるが，モダリティが異なる比較（手術対化学放射線など）は困難な場合が多い。これは試験治療のリスク/ベネフィットを比較する際に，ベネフィットの基本となる生存の比較は容易であるのに対して，リ

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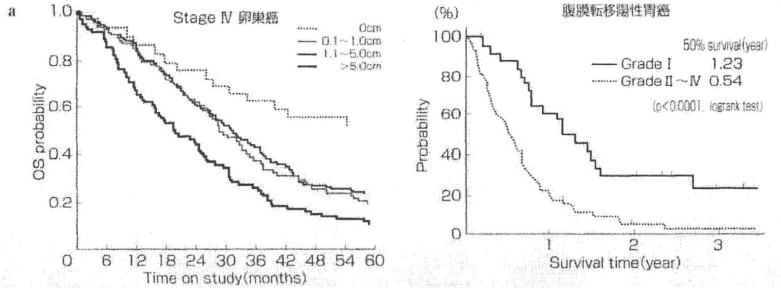

図 1 腹腔内残存腫瘍径と全生存[3,5]

スクの部分でまったく異なった系統の有害事象が共通の尺度で比較できないことと，治療の選択に患者の好みが大きく関与するためである。IP も単なる IV の投与経路の variation としてではなく，まったく異なるモダリティとして治療開発する必要がある。

一方，対象の選定も重要になる。腹腔からの diffusion による薬剤の移行は数 mm が限界と考えられ，血管新生の乏しい結節への薬剤移行は望めないため[2]，IP 化療の適応は残存腫瘍の大きさと薬剤のクリアランスにより規定される。たとえば，骨盤外にも腹膜転移を有する stage Ⅲ卵巣癌においては，術後の腹腔内残存腫瘍の大きさが予後を規定すると考えられているため，安全にできる最大限の cytoreduction（減量手術）が推奨されている。同様に遠隔転移を有する stage Ⅳにおいても，腹腔内残存病変の大きさが重要な予後規定因子にあげられている（図 1a）[3]。この研究は後ろ向き解析ではあるが，GOG の前向きな試験の個別データを一定の基準で抽出して用いており，また Cox の多変量解析では年齢，PS に加え，組織型，遠隔転移部位，残存腫瘍径の予後因子で調整している。しかしながら，手術による介入（cytoreduction）が容易な症例は予後がよいだけという selection bias をみている可能性も否定はできない[4]。また optimal cytoreduction を達成するために，腸管，肝臓，脾臓や横隔膜などの病変を切除することは，GOG の施設などの限られた施設の専門医により行われ，一般病院や本邦では日常的には行われていない。ガイドライン上は，手術手技について“安全にできる最大限の”切除と謳ってはいるが，安全性と根治性は相反する因子であり，高リスクの治療を標準化するにはエビデンスの確立と教育システムが急務である。現在，国内外の前向きな試験，EORTC55971 や JCOG0602 がそれぞれ登録終了と登録中であり，これら試験の結果が待たれる。いずれにしても，卵巣癌の進展は IP 病変が主で，Ⅳ期に至っても予後規定因子と考えられ，IP 化療のよい研究対象と思われる。

一方，Ⅳ期の胃癌においては，原発巣を切除する意義も IP 病変に対する cytoreduction の効果も不明で，ガイドライン上も臨床研究としてあげられている。後ろ向き研究では，胃癌でも腹膜転移の量によって予後が異なることが示されているが[5]，Fujimura らの報告を Winter らの卵巣癌の生存と単純比較すると，bulky でかつ切除不能と思われる 5 cm 以上の IP 病変をもつ胃癌と卵巣癌の MST が，それぞれ約 7 か月と 19 か月，また比較的腫瘍の少ない 5 cm 未満ではそれぞれ約 15 か月と約 30 か月以上と，両者間には腫瘍の doubling time（TDT）や化療への感受性などの biology に大きな差がある（図 1）。すなわち卵巣癌においては，TDT が比較的長く，減量手術によって腫瘍の増殖曲線をリセットあるいは巻き戻せる可能性があるが，胃癌では TDT も短く手術による介入効果は乏しいと思われる。また，胃癌では腹膜転移による合併症として腸管狭窄や閉塞を来しやすく，経口摂取の障害や腹水貯留による PS の低下も早い[6]。切除不能胃癌に対する多くの臨床試験は，経口摂取不能例と中等度以上の腹水貯留例を対象から除外してあり，卵巣癌におけるような surgical staging も一般的ではないために，腫瘍量が多い腹膜転移に対する化療の効果やリスク・ベネフィットは明らかではなく，標準治療はないといわざるを得ない。

一方，胃癌の再発形式として腹膜転移は最も頻度が高いために，IP 化療が根治切除後の補助化学療法として，欧米では 1980 年代から研究されたが，そのほとんどで有意差が示されず，また有害事象が IP 群に多かったために[7]，近年は臨床研究としてもあまり行われていない。本邦での RCT としては，JCOG9206-2 が T3 の根治手術後を対象に，JCOG9701 が細胞診のみ陽性で，それ以外は根治切除後を対象に行われ[8]，近年は切除不能な腹膜

転移例を対象に，新規抗癌剤による臨床試験が行われている。

Ⅱ．IP化療のエビデンス

婦人科領域ではstage Ⅲ卵巣癌に対してoptimal cytoreductionした後の一次治療において，GOGの三つの試験をはじめ[9-11]，多くの第Ⅲ相試験によりIP化療のエビデンス（生存の延長）が確立した（図2）[12]。メタアナリシスの結果では約12%のリスク低下を示しているが，GOG172においては生存期間中央値の延長にして約16か月にも達する。また不完全切除後（残存腫瘍1 cm以下）と肉眼的な完全切除後（microscopic residual tumor）では，やや後者においてリスク低下が大きい傾向があった（表1）。しかしながら，IP治療の完遂率は低く，予定された6コースを行えたのは42%で，IVの90%に比して有意に低かった。その原因として，有害事象の発現率が高いことと（約2倍），IPに関連する痛みや代謝性の合併症も多いことがあげられる[12]。

表1　GOG172における残存腫瘍径別生存期間[11]

	IV	IP	RR	p value
PFS	18.3 m	23.8 m	0.80	0.05
Visible	15.4 m	18.3 m	0.81	
Micro	35.2 m	37.4 m	0.80	
OS	49.4 m	65.6 m	0.75	0.03
Visible	39.1 m	52.6 m	0.77	0.72
Micro	78.2 m	NA	0.69	

胃癌においては，術後補助化学療法としてIP化療と手術単独との比較試験のほとんどで有意差が示されなかった（表2）。Rosenらはカーボンに吸着させたmitomycin CのIP化療の効果をRCTで検証したが生存に差はなく，また60日以内の合併症と治療関連死亡がIP群で有意に多かった[7]。本邦でのJCOG9206-2では，T3-4（漿膜浸潤または他臓器浸潤）胃癌根治切除直後のIP cisplatinとその後のIV cisplatin＋IV 5-FU＋PO UFT療法の効果を手術単独群と比較したが差は認めず，また有意に手術合併症の頻度が高かった[8]。

表2　胃癌に対するIP化療の第Ⅲ相試験

Author	Regimen	Number of patients	Median survival **5-year survival	p value (%)	Morbidity (%)
Hajiwara	Mitomycin C	24	>3 y	0.01	
[1992]	Control	25	1.2 y		
Rosen	Mitomycin C	46	738 d	0.44	35%
[1998]	Control	45	515 d		16%
Schiessel	Cisplatin	31	15 mo	NS	
[1989]	Control	33	12 mo		
Sautner	Cisplatin	33	17 mo	0.6	
[1994]	Control	34	16 mo		
Yu	Mitomycin-FU	125	38.7%**	0.2	
[1998]	Control	123	29.3%**		
Miyashiro	Cisplatin	134	61.6%**	0.48	43%
[1998]	Control	133	62.7%**		28%

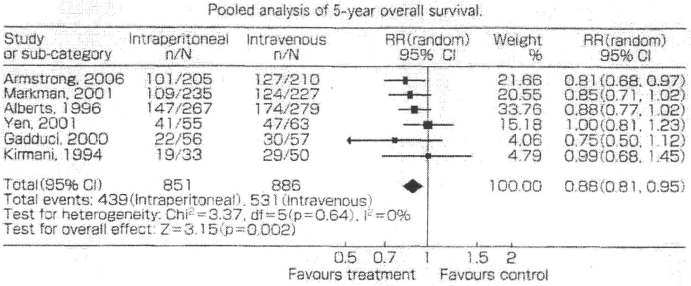

図2　卵巣癌に対するIP化療のメタアナリシス[12]
RR: relative risk, 95% CI: 95% confidence interval, Chi²: chi-square test, df: degrees of freedom

Ⅲ．IP 化療の標準化と今後

卵巣癌においては，IP 化療のエビデンスが最も豊富であるが，同時に標準化が進んだとはいい難く，実地医療ではⅣ投与がいまだに標準的である。これは，Ⅳのベストレジメン（paclitaxel Ⅳ＋carboplatin Ⅳ）との比較が済んでいないことのみが原因ではなく，IP の前提となる optimal cytoreduction や IP 投与法の標準化が進まなかったことに原因がある[13]。これに対して NCI（米国国立癌研究所）では，Clinical Announcement を発効して，stage Ⅲ卵巣癌に対する IP 治療の普及・教育を行い[14,15]，GOG においてはより毒性の低い IP 投与法に関するランダム化第Ⅰ～Ⅱ相試験を計画しているが，本邦における Fujiwara らによる carboplatin の IP 投与もその候補となっていて[16]，方向性はほぼ定まっている。胃癌においては S-1 の経口投与に，タキサン系の薬剤の IP 投与を併用したパイロット試験が行われているが，エビデンスは少ない。近年，高リスクの治療ほどエビデンスやガイドラインの拠り所が必要となり，"toxic new" と考えられる IP も保険適応外のまま臨床試験としてのみ続けてゆくのは限界がある。本邦の胃癌の保険適応に際しては，治験による第Ⅰ相から第Ⅲ相比較試験までが要件となっているので，相応の戦略のもとで治療開発する必要がある。対象としては，卵巣癌を参考にすれば，CY1 や P1 で肉眼的に切除できた microscopic な病変が最も効果が期待されるものの，対象が限定されるため腫瘍量の少ない非治癒切除例を対象に，第Ⅱ相の段階から残存腫瘍量で層別した試験が望ましい。この場合は，Ⅳまたは経口の化学療法を主治療として先行させるのが標準と考えられるので，cytoreduction の意義も検討するような 2×2 の factorial のデザインとなる。また，投与法の標準化を[15]，早い段階から進めるのと同時に，NCI で推奨しているような太径の単孔カテーテルの適応取得も同時に行う必要がある。

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ORIGINAL ARTICLE

A phase I study of palliative chemoradiation therapy with paclitaxel and cisplatin for local symptoms due to an unresectable primary advanced or locally recurrent gastric adenocarcinoma

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Abstract
Purpose To establish the maximum tolerated dose and dose-limiting toxicity of chemoradiation with paclitaxel (PTX) and cisplatin (CDDP) for patients with local symptoms due to unresectable primary advanced or locally recurrent gastric adenocarcinoma located at left-upper abdomen.
Methods Chemotherapy consisted of PTX at escalating doses of 40–80 mg/m^2 per day and CDDP at escalating doses of 20–25 mg/m^2 per day on days 1, 15, and 29. Concurrent radiation was administered up to a dose of 45 Gy for 5 weeks.
Results A total of nine patients were enrolled, of which six were into level 1 (PTX 60 mg/m^2 and CDDP 20 mg/m^2) and three into level −1 (PTX 50 mg/m^2 and CDDP 20 mg/m^2). At level 1, one patient developed grade 3 fatigue, and the other experienced grade 5 DIC, grade 5 pneumonia, grade 4 thrombocytopenia, grade 3 hyponatremia, and grade 3 esophagitis as dose-limiting toxicities. A palliative effect was observed in eight of nine patients; six of six patients at level 1 and two of three at level −1.
Conclusion PTX 50 mg/m^2 and CDDP 20 mg/m^2 given biweekly with concurrent radiation therapy of 45 Gy were well tolerated.

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