Preoperative and neoadjuvant chemotherapy represent investigational options. The rationale of preoperative chemotherapy is based on the difficulty of performing an R0 resection in patients with initially unresectable locally advanced tumors and the high risk of micrometastatic disease in these patients. Neoadjuvant chemotherapy has potential for resectable gastric cancer for the purpose of treating micrometastases.

Intensive chemotherapy is necessary for the improvement of the R0 resection rate and complete elimination of the micrometastases. However, it is difficult for patients who undergo gastrectomy to tolerate intensive chemotherapy. Because weight decreases by gastrectomy, it is necessary to reduce the dose of chemotherapy. The tolerance to chemotherapeutic agents with digestive organ toxicity was often reduced by gastrectomy-related gastrointestinal effects.

S-1 (TS-1, Taiho Pharmaceutical, Tokyo, Japan) is an orally active combination of tegafur (a prodrug that is converted by cells to fluorouracil), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the gastrointestinal toxic effects of fluorouracil) at a molar ratio of 1:0.4:1. The response rate of S-1 alone exceeded 40% in two phase 2 trials involving patients with metastatic gastric cancer.[5,6] The combination chemotherapy of S-1 plus cisplatin (CDDP) achieved a high response rate (74%, 95%CI: 54.9–90.6) in a previous phase I/II study of patients with metastatic gastric cancer.[7]

These factors led us to perform the current phase II trial to investigate the use of an active preoperative chemotherapy regimen. The primary objectives of the trial were to investigate tolerance to the preoperative regimen, its effects on operative morbidity and mortality, and the response rate. Secondary objectives included evaluation of the R0 resection rate, disease-free and overall survival, and failure pattern.

Patients and methods

Patients

The study was conducted as a prospective multi-institutional phase II trial by the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) in Japan. All patients had histologically confirmed adenocarcinoma of the stomach. They also had to have initially unresectable locally advanced tumors because of invasion to adjacent structures or severe lymph node metastases, staged by contrast-enhanced CT as T2-3N2-3M0 or T4NanyM0, according to the Japanese Classification of Gastric Carcinoma (2nd English Edition).[8] They also had to have lymph node metastases that were measurable according to the RECIST$^{1.0}$ guidelines.[9] We did not require laparoscopic staging as an entry criterion for this study. Any sites of suspected M1 disease had to be ruled out prior to entrance into the study. No prior chemotherapy or radiation was allowed. The age range was 20–75 years. The performance status (ECOG) was 0 from 1.

Because of the worse prognosis of type IV gastric cancer, also known as scirrhous or linitis plastica, we excluded such cases.[10] Acceptable hematologic profile (WBC $\geqq$ 4000 cells/mm^3, hemoglobin $\geqq$ 8.0 g/dl, platelets $\geqq$ 100,000 cells/mm^3), and renal (BUN $\leqq$ 25 mg/dl, creatinine $\leqq$ 1.2 mg/dl and/or creatinine clearance $>$ 60 ml/min) and hepatic function (total serum bilirubin $<$ 1.5 mg/dl) were required. In addition, certain respiratory function test results (ratio of the forced expiratory volume in one second $\geqq$ 50%, PaO2 in room air $\geqq$ 70 mmHg) were required criteria. No clinically significant auditory impairment was allowed. Patients with prior cancer diagnosed during the previous 5-year period (except for colon carcinoma *in situ*) were excluded. Other exclusion criteria included significant cardiac disease, pregnancy or serious infections. The protocol was reviewed and approved by the Institutional Review Board of each institution. All patients gave written informed consent.

Preoperative chemotherapy

Patients found to have locally advanced gastric cancer as defined above, received two cycles of S-1 plus cisplatin every 35 days. Preoperative chemotherapy consisted of S-1 at 80 mg/m^2 divided in two daily doses for 21 days and cisplatin at 60 mg/m^2 intravenously on day 8. Physical examination, abdominal CT scan and assessment of toxicity were performed prior to each cycle. The response measurement of the preoperative chemotherapy was carried out according to the RECIST$^{1.0}$ guidelines. Because it was preoperative chemotherapy, response was not confirmed at least 4 weeks apart. Toxicity was recorded and graded according to the National Cancer Institution Common Toxicity Criteria (NCI-CTC) version 2.0 scale. Operative complication was graded according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE v4.0). If a tumor decreased in size, according to protocol criteria, we added 1 or 2 more courses. If curative resection was considered possible after planned chemotherapy, the patient had surgery. If curative resection was considered difficult, a further course of chemotherapy was added. The doses of both agents were attenuated for grade $\geqq$3 toxicities, using standard reduction criteria.

Surgery

The surgery was planned for 3–6 weeks from the day of last administration of chemotherapy. Surgery involved a radical resection, the extent of which (total or distal gastrectomy) depended on the site of the primary tumor, with a D2 lymphadenectomy. We performed D2 or more dissection in patients with metastasis to N3 lymph nodes before chemotherapy. Spleen preservation in total gastrectomy procedure was entrusted to the decision of each clinician.

Patients in whom curative resection was impossible underwent palliative operation. The postoperative treatment was left to the decision of each physician.

Biostatistical considerations

The 3 primary end points of the study were as follows; 1) tolerance to preoperative chemotherapy, 2) operative morbidity and mortality, and 3) objective response rate (ORR). Secondary end points were R0 resection rate, failure pattern, and disease-free and overall survival. One of the primary end points was ORR. The number of patients to be enrolled was calculated at 24, which was required given the assumption that the 95% confidence interval (CI) would be ±20%, assuming an expected response rate of 60%. Finally, we set the number as 30 patients in consideration of disqualified patients. The early stopping criterion of the trial was 3 treatment related deaths. Analogous samples were used to estimate the response rate, R0 resection rate, operative morbidity and mortality, and incidence of treatment related grade 3–4 toxicity. Overall survival (OS) of all patients was calculated from the day of registration in the trial. OS and disease-free survival (DFS) of the patients who underwent R0 resections were calculated from the day of surgery. Survival distributions were estimated using the Kaplan–Meier method.

Follow-up

Following completion of chemotherapy and surgery, patients were followed at 3- monthly intervals until year 3. Thereafter, 6-month follow-up visits were performed. CT scans and appropriate blood studies were performed on the occasion of each evaluation.

Results

Patient population

Between December 2000 and December 2007, 27 patients with initially unresectable local advanced gastric cancer were enrolled into the study from 9 institutions. As shown in Table 1, the male to female ratio was 20:7. The median age was 63 years. As for the histologic type, 15 cases were undifferentiated (including signet ring cell carcinoma) and 11 cases were differentiated type. One case was classified as mucinous carcinoma. There were 3 cStage IIIa (11.1%) preoperatively, 8 cStage IIIb (29.6%), and 16 cStage IV (59.3%).

Preoperative chemotherapy

The median number of preoperative chemotherapy regimens was 3 courses. Grade 3–4 toxicities associated with preoperative S-1/CDDP are described in Table 2. Hematologic toxicity (Grade 3/4) was 7.4% and non-hematologic toxicity (Grade 3/4) was 3.7%. Treatment was generally well tolerated and no chemotherapy-related deaths were observed. While there was no CR, there were 17 cases of PR and the response rate was 63.0% [95%CI: 42.4–80.6] (Table 2).

Table 1
Patient characteristics ($n = 27$).

		Number	%
Age, years	Median (range)	63	(48–75)
Gender	Male	20	74.1
	Female	7	25.9
Histology	Differentiated	11	40.7
	Undifferentiated	15	55.6
	Other	1	3.7
Pretreatment cStage	T2N2M0 (IIIA)	3	11.1
	T3N2M0 (IIIB)	7	25.9
	T4N1M0 (IIIB)	1	3.7
	T2N3M0 (IV)	5	18.5
	T3N3M0 (IV)	6	22.2
	T4N2M0 (IV)	3	11.1
	T4N3M0 (IV)	2	7.4

Operative outcome

All patients who were entered into this trial had initially unresectable tumors. Nine patients were diagnosed as being unresectable when chemotherapy was completed and did not undergo surgery. Eighteen patients (66.7%) underwent laparotomy (Table 3). Thirteen patients (48.1%) had R0 resections. Three patients (11.1%) underwent R1 surgery, because of positive results of peritoneal washing cytology. Two patients underwent simple laparotomy because of peritoneal metastases or unresectable local extension of metastatic lymph nodes. Postoperative complications are described in Table 3. The incidence of complications was 22.2%. One patient underwent operative intervention because of pancreatic leakage; however, there were no surgery-related deaths.

Table 2
Courses, responses and toxicities of preoperative chemotherapy.

				n	%
Courses	Median (range)			3	(1–9)
Response	CR			0	0.0
	PR			17	63.0
	SD			6	22.2
	PD			4	14.8
Toxicities		Grade1/2		Grade3/4	
		n	%	*n*	%
	Neutropenia	10	37.0	2	7.4
	Thrombocytopenia	3	11.1	1	3.7
	Hemoglobin	21	77.8	1	3.7
	Vomiting	7	25.9	1	3.7
	Nausea	13	48.1	1	3.7
	Diarrhea	4	14.8	1	3.7
	Anorexia	17	63.0	1	3.7
	Cerebral infarction	0	0	1	3.7
Treatment related death				0	0.0

Table 3
Operative outcome ($n = 27$).

		Number	%
No operation		9	33.3
Operation		18	66.7
	R0 resection	13	48.1
	R1 resection	3	11.1
	R2 resection	0	0
	Simple Laparotomy	2	22.2
Complications			
	None	14	77.8
	Pancreatic leak	3 (Grade 1: 2, Grade 4: 1)	16.7
	Lymphorrhea	1 (Grade 1)	5.6
	Anastomotic leak	0	0.0
Re-operation		1	5.6
Mortality		0	0.0

Seven of 9 patients who did not undergo surgery received 2nd-line chemotherapy (S-1: 3 patients, S-1/CPT-11: 2 patients, CPT-11/CDDP: 1 patient, Paclitaxel: 1 patient). Four of 5 patients who underwent R1-2 surgery received further chemotherapy (S-1/Paclitaxel: 2 patients, S-1: 1 patient, CPT-11/CDDP: 1 patient).

Overall survival of all patients

Only one patient was lost to follow-up at 8 months from the first day of preoperative chemotherapy, but all other patients were followed more than three years. The median overall survival time and the 3-year overall survival rate of all patients were 31.4 months and 31.0% [95%CI: 17.5–55.1], respectively.

DFS, OS, and first relapse site of patients who underwent R0 resection

Thirteen patients underwent R0 resection. The details of these patients are shown in Table 4. Twelve of these 13 patients (92.3%) achieved PR after preoperative chemotherapy. The median number of course of chemotherapy of these patients was 3 (2–5). Of these patients, only 2 patients (15.4%) underwent D2 plus para-aortic lymph node dissection (D3). Downstaging was observed in 11 patients (84.6%). Seven of 13 patients received postoperative adjuvant chemotherapy (S-1: 4 patients, S-1 plus CDDP: 1 patient, CPT-11: 1 patient, CPT-11/CDDP: 1 patient). To date, recurrence has been diagnosed in 10 patients. First relapse site of five of ten patients was para-aortic lymph nodes. The median disease-free survival time and the 3-year disease-free survival rate of the 13 patients were 17.4 months and 23.1% [95%CI: 8.6–62.3], respectively (Fig. 1A). The median overall survival time and the 3-year overall survival rate of the 13 patients were 50.1 months and 53.8% [95% CI: 32.6–89.1], respectively (Fig. 1B).

Discussion

The combination chemotherapy of S-1 plus cisplatin was chosen because it had achieved a high response rate of 74% (95%CI: 54.9–90.6) in previous phase I/II study of patients with metastatic gastric cancer. The incidences of severe (Grade 3/4) hematological and non-hematological toxicities were 15.8 and 26.3%, respectively.[7] A randomized controlled trial in Japan showed the superiority of S-1/cisplatin compared with S-1 monotherapy according to the response rate and survival for metastatic gastric cancer.[11] Therefore, S-1/cisplatin therapy is now the standard treatment for metastatic gastric cancer in Japan.

This multi-institutional phase II prospective trial of preoperative chemotherapy in initially unresectable locally advanced gastric cancer showed that preoperative chemotherapy using S-1/cisplatin was not only feasible but also achieved a high response rate. The overall response rate was 63.0% [95%CI: 42.4–80.6]. The incidence of grade 3/4 toxicities was less than 10% and treatment related

Table 4
Patients who underwent R0 resection.

No.	cStage	Course	Response	Gastrectomy	D	Combined resection	fStage	Nodes	First relapse
1	T3N2M0 (IIIB)	2	PR	Distal	D3	Liver, Gallbladder	T2N2M0 (IIIA)	4	None
2	T3N3M0 (IV)	3	PR	Total	D2	Spleen, Panc. (tail) Gallbladder	T2N2M0 (IIIA)	6	Brain
3	T3N2M0 (IIIB)	2	PR	Total	D2	Spleen	T2N2M0 (IIIA)	10	Lymph (para AO)
4	T3N2M0 (IIIB)	2	PR	Distal	D3	None	T2N2M0 (IIIA)	3	None
5	T3N2M0 (IIIB)	3	PR	Total	D1*	Liver	T2N0M0 (IB)	0	None
6	T2N2M0 (IIIA)	2	SD	Distal	D2	Panc. (head)	T4N3M0 (IV)	7	Peritoneum
7	T4N2M0 (IV)	3	PR	Total	D2	Spleen, Panc. (tail)	T3N2M0 (IIIB)	10	Lymph (para AO)
8	T2N3M0 (IV)	4	PR	Distal	D2	Gallbladder	T2N2M0 (IIIA)	1	Bone
9	T4N3M0 (IV)	3	PR	Distal	D2	None	T1N0M0 (IA)	0	Lung
10	T4N1M0 (IIIB)	3	PR	Total	D2	Spleen	T2N2M0 (IIIA)	4	Lymph (hepatic)
11	T2N3M0 (IV)	5	PR	Total	D1*	None	T2N3M0 (IV)	2	Lymph (para AO)
12	T2N2M0 (IIIA)	3	PR	Total	D1*	None	T2N0M0 (IB)	0	Lymph (para AO)
13	T3N2M0 (IIIB)	3	PR	Total	D1*	None	T2N2M0 (IIIA)	13	Lymph (para AO)

D1*: we performed almost D2 dissection, but it classified D1 dissection according to the Japanese classification of gastric carcinoma (2nd English edition), because of preserving spleen.

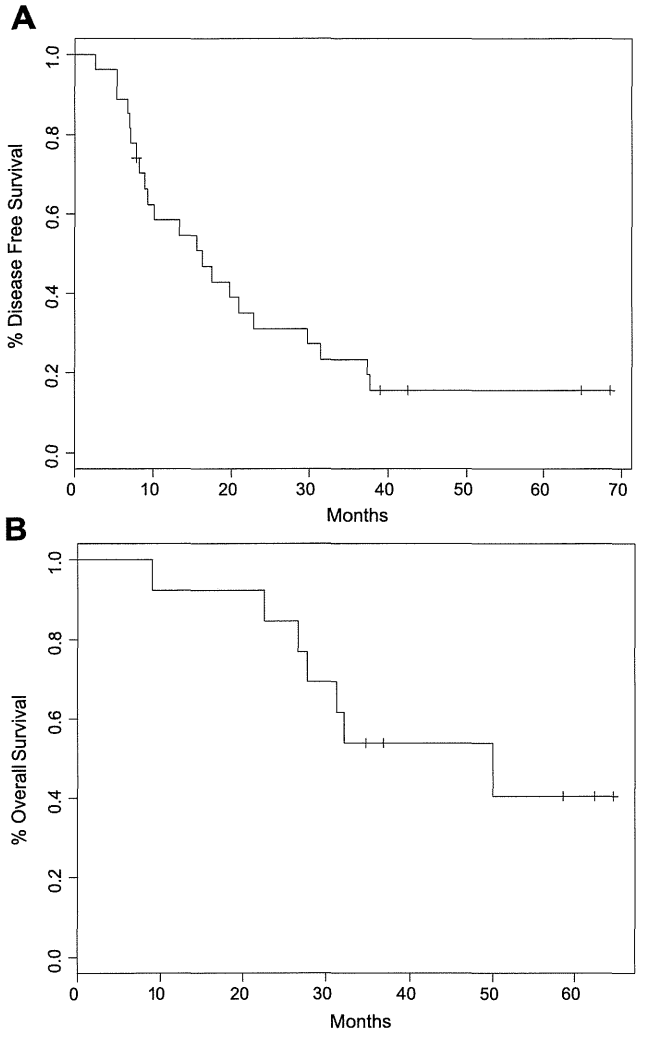

Figure 1. Disease-free and overall survival of the patients who underwent R0 surgery ($n = 13$).

mortality was 0.0%. Similar results were reported in other studies.[12,13] These results encourage the use of S-1/cisplatin combination chemotherapy as neoadjuvant treatment for patients who have resectable gastric cancer. Such trials are currently under way in Japan.[14,15]

The recently completed MAGIC trial constitutes a larger study regarding neoadjuvant chemotherapy in gastric cancer. In this study, 503 patients were randomized to three cycles of pre- and three cycles of postoperative epirubicin/cisplatin/5-FU (ECF) chemotherapy or surgery alone. Neoadjuvant chemotherapy was tolerable and was completed in 88% of patients. Significant downsizing (5.0 versus 3.1 cm median tumor size, $P < 0.001$), downstaging (54% versus 36% T1–T2 tumors, $P = 0.01$) and enhanced resectability (79% versus 69%, $P = 0.02$) were noted. Improved progression-free survival and survival were demonstrated, with an overall 5-year survival of 36% versus 23% for those undergoing surgery alone.[16] We should conduct phase III clinical trials of the neoadjuvant chemotherapy of S-1/cisplatin therapy for resectable gastric cancer.

In Japan, the ACTS-GC trail demonstrated a survival advantage of postoperative adjuvant chemotherapy after R0 resection. R0 patients were randomized to adjuvant chemotherapy using S-1 (529 patients) versus surgery alone (530 patients); improved survival (3-year overall survival rates of 80.1% versus 70.1%, $P = 0.003$) was noted.[17] Adjuvant chemotherapy, as reported by the ACTS-GC Group, is now considered a standard treatment for R0 patients. However, of the 283 patients who had stage III disease and received S-1 adjuvant chemotherapy, 73 patients died. The hazard ratio of the adjuvant chemotherapy group worsened with an increasingly advanced stage. These results suggest that S-1 monotherapy is insufficient for patients who have stage III or more. However, for patients who have initially unresectable gastric cancer like the patients enrolled in this trial, S-1/cisplatin chemotherapy is insufficient because of the high relapse rate of patients who underwent R0 resection.

For the patients immediately after gastrectomy, highly toxic chemotherapy is difficult because of overlaps between chemotherapy-induced gastrointestinal toxicity and digestive symptoms due to gastrectomy.[18] Therefore, further improvements in preoperative therapy will require development of more effective chemotherapeutic regimens. During the last decade, several new agents with promising activity against gastric cancer were identified. These include paclitaxel, docetaxel, irinotecan and trastuzumab. These agents are now undergoing phase II and III trials, as part of combination regimens.[19–22] If improved outcome is seen in metastatic disease, these agents will undergo extensive testing in the preoperative setting.

The absence of laparoscopic staging might have allowed inclusion of patients with positive peritoneal cytology or small peritoneal implants that could have disappeared with the chemotherapy; these patients have a worse prognosis, which could have impacted on the final results. Actually, there were 3 cases of positive cytology at exploration after chemotherapy. Laparoscopic staging should be mandatorily included in future similar projects.

An interesting point is that there were many para-aortic lymph node recurrences in the patients who underwent R0 resection. Among 13 patients who underwent curative resection, initial recurrence in 5 patients was in a para-aortic lymph node. These patients had not undergone para-aortic lymph node dissection. The prognostic improvement effect of the para-aortic lymph node dissection was refuted by two clinical trials.[23,24] In the JCOG 9501 trial, 523 patients with resectable gastric cancer were enrolled, and 263 were assigned to D2 group and 260 were assigned to D2 plus para-aortic nodal dissection. The 5-year overall survival rate was 69.2% for D2 lymphadenectomy group and 70.3% for the D2 lymphadenectomy plus para-aortic nodal dissection group; the hazard ratio for death was 1.03 (95%CI, 0.77 to 1.37; $P = 0.85$). There were also no significant differences in recurrence-free

survival and the pattern of recurrence between the two groups.[23] In the East Asian Surgical Oncology Group trial, 269 patients with resectable gastric cancer were enrolled, and 135 were assigned to the D2 group and 134 were assigned to the D2 plus para-aortic nodal dissection. The 5-year overall survival rates were 52.6% for the D2 lymphadenectomy group and 55.0% for the D2 lymphadenectomy plus para-aortic nodal dissection group. There was no significant difference in survival between the two groups ($P = 0.801$).[24] It was concluded that the D2 lymphadenectomy plus para-aortic nodal dissection did not improve prognosis regarding D2 lymph node dissection in the resectable gastric cancer.

However, in these trials, patients who had gross metastases to the para-aortic nodes were excluded. The incidence of metastases in the para-aortic nodes was lower than expected in 8.5% and 9.7%, respectively. The median number of metastatic nodes was only 2 nodes among the patients who underwent D2 plus para-aortic nodal dissection in the JCOG 9501. In the East Asian Surgical Oncology Group trial, the mean number of metastatic nodes was 5.9 in the para-aortic lymph node dissection group.

Recently, 15-year follow-up results of a randomized nationwide Dutch D1D2 trial were published. 711 patients underwent randomly assigned treatment with curative intent (380 in the D1 group and 331 in the D2 group). Overall 15-year survival was 21% for the D1 group and 29% for the D2 group. Gastric cancer-related death rate was significantly higher in the D1 group (48%, 182 patients) than that in the D2 group (37%, 123 patients). Local recurrence was 22% (82 patients) in the D1 group versus 12% (40 patients) in D2, and regional recurrence was 19% (73 patients) in D1 versus 13% (43 patients) in D2. After a median follow-up of 15 years, D2 lymphadenectomy was associated with lower locoregional recurrence and gastric cancer-related death rates than D1 surgery.[25] This difference was greater in the patients with lymph node metastases from 7 to 15.[26]

The observation period was shorter in the clinical trials of JCOG and East Asian Surgical Oncology Group than in the Dutch trail, and fewer mortality events occurred and also fewer metastases to lymph nodes. Therefore, para-aortic lymph node dissection might have better prognosis in patients with severe lymph node metastases like the patients enrolled in our trial.

In summary, preoperative S-1/cisplatin can be safely delivered to patients undergoing radical gastrectomy. The response rate was high, with no increase in operative morbidity and mortality compared with those upon surgery without preoperative chemotherapy.[27] Controlled trials of neoadjuvant chemotherapy using this regimen with the postoperative S-1 monotherapy for resectable gastric cancer are necessary. For initially unresectable locally advanced gastric cancer, the rate of recurrence was high, and the most common initial recurrent site was para-aortic lymph node. New trials, using a more effective regimen along with extended lymph node dissection are necessary.

Conflict of interest statement

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Macroscopic tumor size as an independent prognostic factor for stage II/III gastric cancer patients who underwent D2 gastrectomy followed by adjuvant chemotherapy with S-1

Toru Aoyama · Takaki Yoshikawa · Takafumi Watanabe · Tsutomu Hayashi · Takashi Ogata · Haruhiko Cho · Akira Tsuburaya

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Abstract
Background In patients with stage II/III gastric cancer, tumors often recur even after curative D2 gastrectomy followed by adjuvant S-1 chemotherapy. The objective of this retrospective study was to clarify the prognostic factors in these patients that might be useful for future patients.
Methods Overall survival (OS) was examined in 82 gastric cancer patients who underwent curative D2 surgery; were diagnosed with stage IIA, IIB, IIIA, IIIB, or IIIC pathologically; and received adjuvant S-1 after surgery between June 2002 and March 2010.
Results When length of OS was evaluated by the log-rank test, significant differences were observed with regard to macroscopic tumor diameter and the depth of tumor invasion. A macroscopic tumor diameter >70 mm was regarded as a critical point of classification considering survival. Univariate and multivariate Cox's proportional hazard analyses demonstrated that macroscopic tumor diameter was the only significant independent prognosticator. The 5-year survival was 64.9% in patients with a macroscopic tumor diameter <70 mm, and 33.1% in patients with a macroscopic tumor diameter ≥70 mm ($P = 0.022$).
Conclusions The macroscopic tumor diameter was the most important prognostic factor for survival in patients with stage II/III gastric cancer who underwent D2 gastrectomy followed by adjuvant S-1 chemotherapy. Prognostic factors can be affected by adjuvant chemotherapy.

T. Aoyama · T. Yoshikawa (✉) · T. Watanabe · T. Hayashi · T. Ogata · H. Cho · A. Tsuburaya
Department of Gastrointestinal Surgery, Kanagawa Cancer Center, 1-1-2 Nakao, Asahi-ku, Yokohama 241-0815, Japan
e-mail: yoshikawat@kcch.jp

Keywords Gastric cancer · Adjuvant chemotherapy · S-1 · Prognostic factor

Introduction

Every year, more than 934,000 people develop gastric cancer worldwide. Gastric cancer is the second most frequent cancer-related cause of death after lung cancer [1]. Complete resection is essential for the cure of gastric cancer. Stage IV cancers are unresectable, and these patients have a poor prognosis. Stage I cancers, in which the tumor is limited to T1N0–1 and T2N0, rarely develop a recurrence, and patients have an excellent prognosis. On the other hand, patients with stage II/III gastric cancer often develop tumor recurrence even after complete curative resection. Therefore, it is important to identify prognostic factors for patients with stage II and III gastric cancer in order to select patients for more aggressive treatment. Previously, lymph node metastasis [2, 3] and the depth of tumor invasion [4, 5] were reported to be significant prognostic factors that could be used to predict survival. However, these reports only analyzed patients who were treated with surgery alone or with surgery followed by adjuvant chemotherapy of unknown efficacy, because effective adjuvant chemotherapy had not been verified in these patients.

In 2007, the adjuvant chemotherapy trial of TS-1 for gastric cancer (ACTS-GC) trial demonstrated that S-1 was effective as adjuvant chemotherapy for Japanese patients who had undergone a D2 curative gastrectomy for locally advanced gastric cancer and had been diagnosed with pathological stage II or III disease [6]. Based on the ACTS-GC trial, S-1 adjuvant chemotherapy became the standard treatment for patients with stage II and III gastric cancer.

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This trial suggested that S-1 could improve patient survival by inhibiting peritoneal metastases. Therefore, it seems that prognostic factors might be altered following effective S-1 adjuvant chemotherapy.

In this study, we investigated the prognostic factors for patients with stage II and III gastric cancer who underwent D2 gastrectomy followed by adjuvant chemotherapy with S-1.

Patients and methods

Patients

The patients were selected from the prospective database of the Kanagawa Cancer Center, Department of Gastrointestinal Surgery, Yokohama, Japan, according to the following criteria: (1) histologically proven gastric adenocarcinoma; (2) patients underwent a curative D2 resection for gastric cancer as a primary treatment between June 2002 and March 2010; (3) stage IIA, IIB, IIIA, IIIB, or IIIC disease was diagnosed pathologically according to the Japanese classification of gastric carcinoma 14th edition published by the Japanese Gastric Cancer Association [7]; (4) patients received adjuvant S-1 chemotherapy after surgery at a starting dose of 80 mg/m^2/day.

Following the rule defined by the protocol of the ACTS-GC trial, patients received S-1 chemotherapy and were followed at outpatient clinics [6]. Written informed consent was obtained from each patient prior to treatment initiation. Survival data were obtained from hospital records or from the city registry system.

Measurement of tumor diameter

Tumor diameter was measured according to the Japanese classification of gastric carcinoma, 14th edition published by the Japanese Gastric Cancer Association [7]. The resected specimen was opened along the greater curvature to observe the mucosal surface clearly. The opened stomach was placed on a flat board, and the longest tumor diameter was measured and used in the analysis.

Evaluation and statistical analyses

The overall survival (OS) was evaluated by univariate and multivariate analyses. The survival curves were calculated using the Kaplan–Meier method and compared by the log-rank test. Cox's proportional hazard model was used to perform univariate and multivariate survival analyses. A P value of <0.05 was defined to be statistically significant.

An SPSS software package (v11.0J Win; SPSS, Chicago, IL, USA) was used for all statistical analyses.

Results

A total of 240 patients underwent surgical resection and were diagnosed with stage IIA, IIB, IIIA, IIIB, or IIIC disease pathologically. Among them, 82 patients were eligible for the present study. All patients had received S-1 as the standard therapy after 2007, when the results of the ACTS-GC trial were presented, or as the test treatment in clinical trials of ACTS-GC or the stomach cancer adjuvant multi-institutional trial group (SAMIT) study. Patients who had received other chemotherapy in other clinical trials and those who did not receive adjuvant chemotherapy were excluded. The patients' ages ranged between 36 and 80 years (mean 62.0). Fifty-six patients were male, and 26 were female. The pathological stage was IIA in 1 patient, IIB in 23 patients, IIIA in 10 patients, IIIB in 23 patients, and IIIC in 25 patients. The median follow-up period was 24.2 months (range 2.8–76.5 months). The median duration of adjuvant S-1 administration was 7.6 months (range 0.2–34.8 months). The S-1 treatment was continued for 1–3 months in 74 patients, 3–6 months in 61 patients, and 6–12 months in 47 patients. Three patients continued treatment for more than 13 months at the patient's request. When OS, stratified by clinical factors, was compared by the log-rank test, a significant difference was observed in regard to macroscopic tumor diameter and the depth of tumor invasion (Table 1). Lymph node metastasis was marginally significant. A macroscopic tumor diameter of 70 mm was regarded as the optimal critical point of classification, considering the 3-year survival rate, which was regarded as more reliable than the 5-year survival rate because median follow-up was only 24.2 months. Each clinicopathological factor was categorized, as shown in Table 2, and was analyzed for prognostic significance. Univariate analyses for OS demonstrated that macroscopic tumor diameter was a significant prognostic factor, but that tumor depth and nodal metastasis were only marginally significant (Table 2). Macroscopic tumor diameter was selected for the final model to be analyzed by multivariate analysis (Table 3). The 5-year survival was 64.9% in patients with a macroscopic tumor diameter <70 mm, and it was 33.1% in those with a macroscopic tumor diameter ≥ 70 mm (Fig. 1).

Discussion

In this report, we first evaluated the potential prognostic factors in stage II/III gastric cancer patients who underwent D2 gastrectomy followed by adjuvant S-1 chemotherapy, and clarified that macroscopic tumor diameter was the most important prognostic factor, based on the hazard ratio and p values.

Table 1 Comparison of survival rates stratified by patient characteristics

Characteristics	3-Year survival rate (%)	5-Year survival rate (%)	*P* value
Age (years)			0.5451
<70	70.4	52.5	
≥70	70.9	70.9	
Performance status (ECOG)			0.2743
0	73.7	59.9	
1	54.3	40.7	
Site of tumor			0.2228
Entire	33.3	0	
Upper third	83.6	65.0	
Middle third	67.6	67.6	
Lower third	70.9	56.8	
Macroscopic tumor diameter (mm)			0.0390
<30	85.7	68.6	
≥30 to <50	78.6	78.6	
≥50 to <70	79.4	54.4	
≥70 to <90	67.0	50.2	
≥90	17.9	17.9	
Histological type			0.1874
Differentiated	76.7	68.2	
Undifferentiated	68.6	49.2	
Depth of invasion			0.0415
pT2, pT3	85.7	85.7	
pT4a, pT4b	66.4	47.7	
Lymph node metastasis			0.0997
pN0	57.1	38.1	
pN1	–	–	
pN2	72.7	72.7	
pN3	64.3	33.1	
Lymphatic invasion			0.5798
Negative	75.2	58.5	
Positive	68.1	54.5	
Vascular invasion			0.3664
Negative	52.1	52.1	
Positive	75.6	58.5	

ECOG Eastern Cooperative Oncology Group

Table 2 Univariate Cox proportional hazards analysis of clinicopathological factors

Factors (category)	No. of patients	HR	95% CI	*P* value
Age (years)				0.547
<70	56	1.000		
≥70	26	0.712	0.235–2.157	
Performance status (ECOG)				0.281
0	70	1.000		
1	12	1.599	0.631–4.885	
Site of tumor				0.275
Entire	4	1.000		
Upper third	25	0.062	0.058–1.075	
Middle third	35	0.104	0.083–1.262	
Lower third	18	0.124	0.069–1.380	
Macroscopic tumor diameter (mm)				0.028
<70	55	1.000		
≥70	27	2.776	1.116–6.857	
Histological type				0.198
Differentiated	28	1.000		
Undifferentiated	54	2.068	0.685–6.246	
Depth of invasion				0.075
pT2, pT3	21	1.000		
pT4a, pT4b	61	6.222	0.830–46.638	
Lymph node metastasis				0.072
pN0–pN2	53	1.000		
pN3	29	2.295	0.929–5.671	
Lymphatic invasion				0.371
Negative	20	1.000		
Positive	62	0.621	0.218–1.766	
Vascular invasion				0.581
Negative	26	1.000		
Positive	56	1.315	0.497–3.475	

HR hazard ratio, *CI* confidence interval, *ECOG* Eastern Cooperative Oncology Group

Table 3 Stepwise multivariate Cox proportional hazards analysis of clinicopathological factors

Factor (category)	No. of patients	*P* value	HR	95% CI
Macroscopic tumor diameter (<70 vs. ≥70 mm)	55 and 27	0.028	2.766	1.116–6.857

Some authors have reported the significance of the macroscopic tumor diameter in the prognosis of gastric cancer patients. For example, Kunisaki et al. [8] examined 1215 patients with gastric cancer and classified them into groups with smaller tumors and those with larger tumors, by setting 100 mm as the cutoff value for the maximal tumor diameter. They found that OS was markedly different between stage II/III patients with smaller and larger tumors. Saito et al. [9] evaluated 1473 patients with gastric cancer and divided them into two groups using a cutoff value of 80 mm for the tumor size. They found that the prognosis of patients with the large tumors was significantly worse than the prognosis for those with the small tumors. However, these reports only examined patients

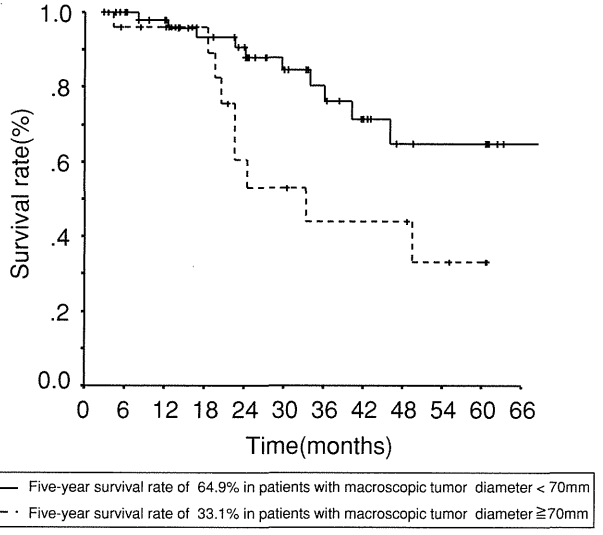

Fig. 1 Survival curves of patients with macroscopic tumor diameters of <70 and ≥70 mm

who had undergone surgery only, or those who had undergone surgery with adjuvant therapy of unproven efficacy. In the present study, evaluating patients who received S-1 adjuvant chemotherapy, we set the cutoff value for tumor size at 70 mm, considering the 3-year survival rate, and found that tumor size was a strong independent prognostic factor. The optimal cutoff value was different between the previous reports and the present one, which may be explained by the use of S-1 adjuvant chemotherapy in our study; by differences in the durations of the follow-up periods and the numbers of patients; and by inter-institutional variability.

Previously, the depth of tumor invasion had been considered to be the key prognostic factor in gastric cancer patients who underwent curative resection [4, 5]. Several authors indicated that serosal invasion correlated with peritoneal recurrence and a poorer prognosis. In the ACTS-GC trial, the incidence of peritoneal recurrence was 11.2% in the S-1 group and 15.8% in the surgery-only group ($P = 0.009$) [6]. On the other hand, the incidence of hematogenous recurrence was 10.2% in the S-1 group and 11.3% in the surgery-only group. These results suggest that S-1 was more effective in reducing peritoneal recurrence than in reducing hematogenous recurrence. The depth of tumor invasion might no longer be a useful prognostic factor, because S-1 can reduce the incidence of peritoneal recurrence.

Lymph node metastasis has also been considered as a strong prognostic factor in gastric cancer patients [2, 3]. The ACTS-GC trial demonstrated that hazard ratios for death were better in N0 and N1 than in N2 patients. In the present study, nodal metastasis was found to be a marginally significant factor according to our univariate analysis, and it remained in the final model, but did not reach statistical significance by multivariate analysis. Our results suggest that nodal metastasis may be an inferior prognostic factor compared to the tumor size when the examination is limited to patients who receive S-1 chemotherapy. However, the marginal significance might become more important if the number of patients is increased or if there is longer-term follow-up.

There were many limitations in this study. First, this was a retrospective single-center study with a small sample size. Our findings in this series may have been observed by chance only. Second, the median follow-up period was only 24.2 months, which is not enough to lead to a definite conclusion. Third, the optimal tumor size cutoff value is unclear. In our study, the cutoff value was set at 70 mm by considering the 3-year survival rate. However, regardless of whether the cutoff value was 70, 80, or 90 mm, tumor size remained an independent significant prognosticator (data not shown). Thus, large tumors seemed to have a poor prognosis. An appropriate cutoff value should be determined in other validation studies. Fourth, the depth of tumor invasion and nodal metastasis had prognostic impact in the ACTS-GC study although the tumor size was not examined. When comparing the ACTS-GC trial and our present study, there are some differences in the backgrounds of the patients. The depth of invasion was deeper in the present study (pT4a, pT4b, 61/82; 74.3%) than in the ACTS-GC trial (pT4a, pT4b, 239/529; 45.1%). The incidence of nodal metastases was higher in the ACTS-GC trial (478/529; 90.4%) than in the present study (68/82; 82.9%), while that of TNM-N3 was higher in the present study (29/82; 35.%) than in the ACTS-GC trial (147/529; 27.8%). Because many patients in the present series received S-1 adjuvant chemotherapy as a test arm of the SAMIT trial (a 2 × 2 phase III trial for surgical serosa-positive disease), the incidence of T4a and N3 may be high in this series. Also, differences in background factors could affect prognosticators in stage II/III disease. Considering these limitations, our results should be validated in different series with large sample sizes and sufficient follow-up periods.

In conclusion, the macroscopic tumor diameter was found to be the only significant independent prognostic factor in patients who underwent D2 gastrectomy followed by adjuvant S-1 chemotherapy. Therefore, it appears that the value of prognostic factors can be altered by the use of effective adjuvant chemotherapy.

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Conflict of interest None declared.

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ORIGINAL ARTICLE

Survival and prognosticators of gastric cancer that recurs after adjuvant chemotherapy with S-1

Toru Aoyama · Takaki Yoshikawa · Takafumi Watanabe · Tsutomu Hayashi · Takashi Ogata · Haruhiko Cho · Akira Tsuburaya

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Abstract
Background Some patients experience a recurrence of cancer even after curative D2 gastrectomy followed by adjuvant S-1 chemotherapy. The objective of this retrospective study was to clarify the survival and prognosticators in these patients.
Methods The study selected patients who underwent curative D2 surgery, were diagnosed with stage II, IIIA, or IIIB cancer, received adjuvant S-1 for more than 4 weeks, and experienced recurrence confirmed by an imaging study.
Results A total of 34 patients were evaluated. The median overall survival (OS) was significantly longer in the 26 patients who received palliative chemotherapy than that in the 8 who did not (8.5 vs. 2.5 months, $P = 0.002$). Only 1 patient received S-1, 21 received taxane-containing regimens, and 4 received irinotecan plus cisplatin as the first-line chemotherapy. Univariate and multivariate analyses showed that the histological type was only independent significant prognosticator.
Conclusions These results suggested that the survival did not reach the level expected for first-line chemotherapy. The histological type was a significant prognosticator in patients who experienced recurrence after adjuvant S-1 therapy and thereafter received palliative chemotherapy.

Keywords Gastric cancer · Adjuvant chemotherapy · Recurrence · S-1

T. Aoyama · T. Yoshikawa (✉) · T. Watanabe · T. Hayashi · T. Ogata · H. Cho · A. Tsuburaya
Department of Gastrointestinal Surgery, Kanagawa Cancer Center, 1-1-2 Nakao, Asahi-ku, Yokohama 241-0815, Japan
e-mail: yoshikawat@kcch.jp

Introduction

5-Fluorouracil (5-FU)-based chemotherapy is widely used for unresectable advanced or recurrent gastric cancer and has a survival benefit in comparison to the best supportive care [1]. Two phase III studies to evaluate chemotherapy regimens for gastric cancer were recently reported from Japan [2, 3]. The JCOG9912 trial compared 5-FU to S-1 alone or cisplatin (CDDP) plus irinotecan (CPT-11), and found S-1 alone to be comparable to 5-FU alone, but CDDP plus CPT-11 therapy failed to demonstrate superiority to 5-FU alone in overall survival (OS; 11.4 vs. 12.3 vs. 10.8 months). The SPIRITS trial compared the efficacy of S-1 plus CDDP to that of S-1 alone, and found that S-1 plus CDDP showed a significantly longer overall survival (OS; 13 vs. 11 months; $P = 0.037$). These trials included patients with recurrent gastric cancer who did not receive adjuvant chemotherapy or those who received an oral fluoropyrimidine other than S-1. However, prior to these studies, no drugs had been confirmed to be effective as adjuvant chemotherapy after curative surgery.

The ACTS-GC trial first demonstrated that S-1 was effective as adjuvant chemotherapy for Japanese patients who underwent curative gastrectomy for locally advanced gastric cancer and were diagnosed as pathological stage II or III [4]. Therefore, adjuvant S-1 chemotherapy has been established as the standard therapy for stage II or III gastric cancer in Japan. However, about 30% of the patients still develop recurrence after a curative resection followed by adjuvant S-1. The survival of patients who experience recurrence after adjuvant S-1 has not been fully clarified. It is unclear whether these patients should be treated as candidates for first-line chemotherapy.

The present study investigated the survival, and the factors that could predict the survival, in gastric cancer

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patients who experienced recurrence after adjuvant chemotherapy with S-1 and thereafter received palliative chemotherapy.

Patients and methods

Patients

Patients were selected from the database of the Kanagawa Cancer Center, Department of Gastrointestinal Surgery, Yokohama, Japan, according to the following criteria: (1) histologically proven gastric adenocarcinoma, (2) patients who underwent a curative surgical resection for gastric cancer as a primary treatment between June 2002 and December 2009, (3) stage II, IIIA, or IIIB determined pathologically according to the guidelines of the Japanese Gastric Cancer Association[5], (4) patients who received adjuvant S-1 chemotherapy after surgery for more than 4 weeks at a starting dose of 80 mg/m^2, (5) recurrence was confirmed by computed tomography (CT), magnetic resonance imaging (MRI), barium enema, laparoscopy, or bone scintigraphy.

Evaluation and statistical analyses

The overall survival (OS) was calculated from the date of the imaging study that confirmed the recurrence to the date of any cause of death or last follow-up. Unpaired Student's *t*-test or the χ^2 method was used to compare two groups. Survival curves were calculated using the Kaplan–Meier method and compared by the log-rank test. Cox's proportional hazard model was used to perform univariate and stepwise multivariate survival analyses. A P value of <0.05 was defined to be statistically significant, and the data were expressed as medians ± ranges.

An SPSS software package (v11.0 J Win; SPSS, Chicago, IL, USA) was used for all statistical analyses.

Results

A total of 233 patients underwent surgical resection and were pathologically diagnosed as stage II, IIIa, or IIIb. Among them, 92 patients received adjuvant chemotherapy with S-1. Thirty-four patients were eligible for the present study. The median follow-up was 21.5 months (range from 4.3 to 57.2 months). The median OS was 7.3 months (95% confidence interval [CI], 5–9.6 months). Twenty-six patients received palliative chemotherapy after recurrence, while 8 did not, due to renal dysfunction in 2, liver dysfunction in 1, mechanical intestinal obstruction in 1, and patient's refusal in 4. The median OS was 8.5 months (95% CI, 4.4–12.5 months) in the patients who received chemotherapy and 2.5 months (95% CI, 0.7–4.3 months) in those who did not, and the difference was statistically significant ($P = 0.0022$; Fig. 1).

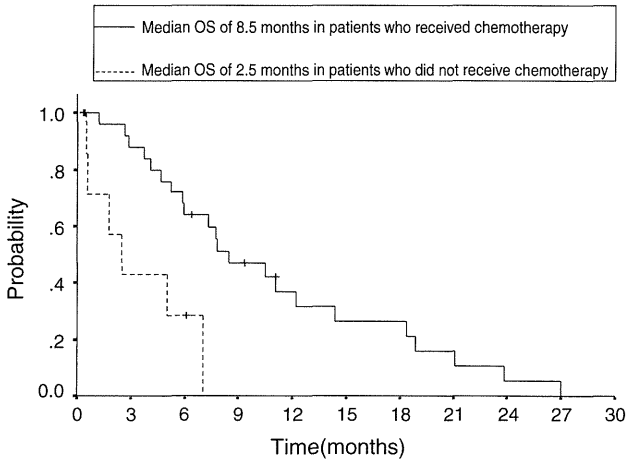

Fig. 1 Kaplan–Meier curves for overall survival (*OS*) showed a significant difference between patients who received chemotherapy (*solid line*) and those who did not receive chemotherapy (*broken line*; $P = 0.0022$)

The backgrounds of the 26 patients who received chemotherapy are shown in Table 1. None of the 26 patients received any other therapies, such as a surgical resection or radiological treatment, in addition to chemotherapy during the clinical course.

Prognosticators in these patients were analyzed by univariate and multivariate analyses. The median duration of adjuvant S-1 administration was 6.2 months, with a range from 1 to 19.9 months. Six patients stop S-1 for ≦3 months due to toxicity. The treatment was withdrawn in 8 of the remaining patients before 6 months, due to recurrence in 5, toxicity in 2, and for other reasons in 1. The treatment was withdrawn in 6 of the remaining patients before 9 months, due to recurrence in 3 and for other reasons in 3. As a result, 8 patients discontinued S1 due to recurrence and 12 patients discontinued S1 due to toxicity or other reasons. The chemotherapy regimens after recurrence were individually selected by the patient's physician. One patient received S-1, 21 received taxane-containing regimens [taxane group (i.e., paclitaxel and docetaxel)], and 4 received irinotecan plus cisplatin (CPT-11 group).

A univariate analysis of factors affecting OS demonstrated that histological type was the only significant factor (Table 2). The OS of the differentiated type was significantly better than that of the undifferentiated type ($P = 0.009$; Fig. 2). The multivariate analysis revealed that histological type remained the only independent significant prognosticator (Table 3). However, the duration of

Table 1 Background of patients who received chemotherapy

Age (years)	58.6 ± 11.6
Gender	
Male	16
Female	10
PS (ECOG) at recurrence	
0	18
1	8
Histological type	
Differentiated	9
Undifferentiated	17
Pathological stage	
Stage II	4
Stage III A	9
Stage III B	13
Site of recurrence	
Peritoneum	14
Liver	5
Lymph node	5
Other	2
Disease-free interval, months median (range)	13.1 (3.9–38.9)
Duration of adjuvant S-1	
<3 Months	6
≧3 Months	20
Treatment-free interval (since last S-1)	
<6 Months	13
≧6 Months	13
Disease-free interval (since surgery)	
<12 Months	12
≧12 Months	14
First-line chemotherapy after recurrence	
Taxane group	21
CPT-11 group	4
S-1	1
Second-line chemotherapy after recurrence	
Taxane group	5
CPT-11 group	6

PS performance status, *ECOG* Eastern Cooperative Oncology Group, *CPT* irinotecan

Table 2 Univariate Cox proportional hazards analysis of clinicopathologic factors

Factor (category)	No. of patients	OR	95% CI	*P* value
Age				0.164
<65 Years	17	1.000		
≧65 Years	9	2.204	0.724–6.716	
PS (ECOG)				0.136
0	18	1.000		
1	8	2.315	0.768–6.975	
Histological type				0.009
Differentiated	9	1.000		
Undifferentiated	17	4.117	1.420–11.931	
Duration of adjuvant S-1				0.173
<3 Months	6	1.000		
≧3 Months	20	0.477	0.164–1.384	
Treatment-free interval (since last S-1)				0.161
<6 Months	13	1.000		
≧6 Months	13	2.026	0.755–5.433	
Recurrence-free interval (since surgery)				0.242
<12 Months	12	1.000		
≧12 Months	14	1.737	0.689–4.383	
Site of recurrence				0.412
Peritoneum	14	1.000		
Other	12	0.688	0.282–1.682	
First-line chemotherapy after recurrence				0.483
S-1	1	1.000		
CPT-11 group	4	0.590	0.076–4.545	
Taxane group	21	0.427	0.097–1.886	

OR odds ratio, *CI* confidence interval, *PS* performance status, *ECOG* Eastern Cooperative Oncology Group

chemotherapy tended to be significant according to the univariate analysis, but not based on the multivariate analysis.

Figure 3 shows details of the regimens of the first- and second-line chemotherapy in 9 patients with the differentiated type and 17 with the undifferentiated type. Most patients received taxane-containing regimens as the first-line chemotherapy. The proportion of patients who received both taxanes and irinotecan was higher in those with the differentiated type (6 of 9 patients, 66.7%) than in those with the undifferentiated type (3 of 17 patients, 17.6%), and the difference was statistically significant ($P = 0.012$).

Discussion

Only Shitara et al. [6] retrospectively examined the efficacy and survival of the treatment in patients who developed recurrence after adjuvant S-1 chemotherapy. The response rate to S-1-containing chemotherapy was 0%. They recommended other chemotherapeutic regimens in this setting. Most patients in the present study received taxane-containing regimens. Only 1 patient received palliative S-1 after recurrence. Despite the use of taxanes in most patients, the median OS of the 26 patients who received chemotherapy after recurrence was only 8.5 months, which did not reach the level expected for

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.

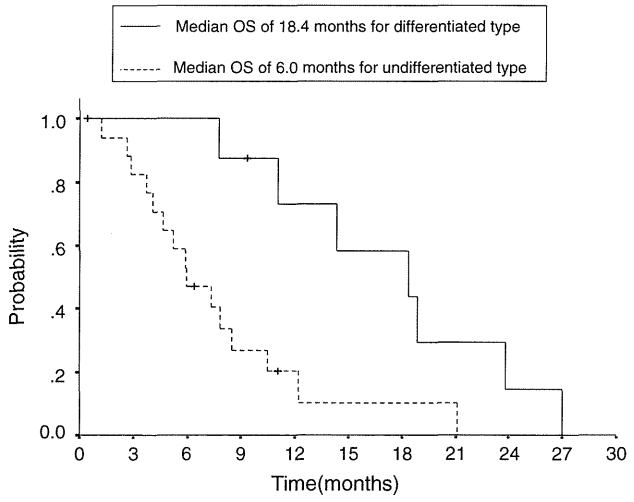

Fig. 2 Kaplan–Meier curves for overall survival (*OS*) showed a significant difference between patients with the differentiated type (*solid line*) and those with the undifferentiated type (*broken line*; $P = 0.009$)

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

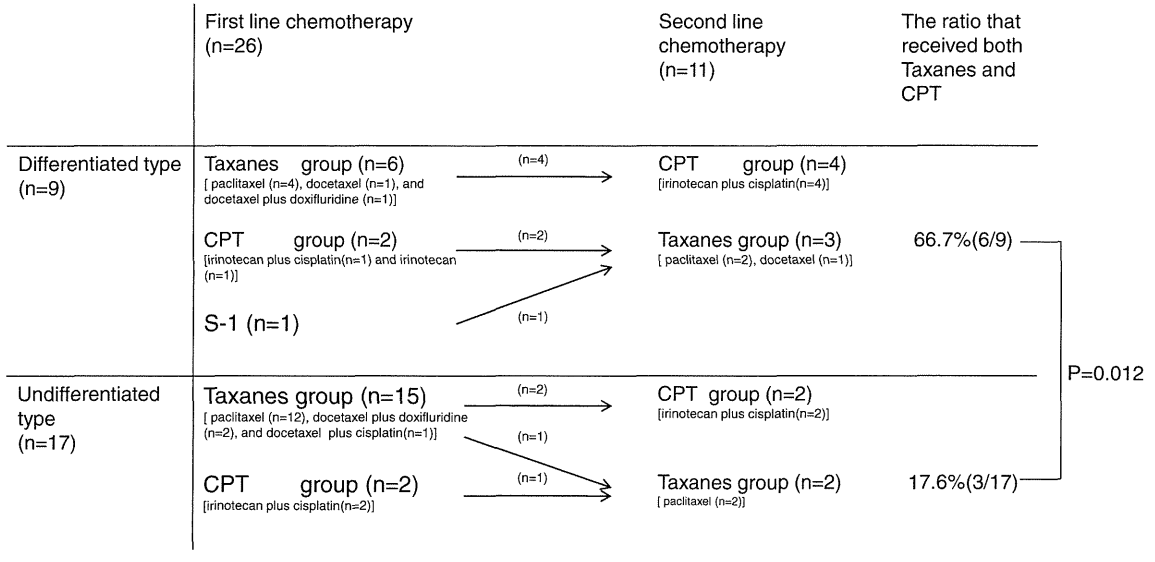

Fig. 3 Details of the first line- and second-line chemotherapy regimens in 9 patients with the differentiated type and 17 with the undifferentiated type

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.

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Conflict of interest None declared.

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胃癌の外科治療に関する臨床試験

Problem and perspective of surgical clinical trials for gastric cancer in Japan

大阪大学大学院医学系研究科消化器外科学[1]　兵庫医科大学上部消化管外科[2]
黒川幸典[1]　土岐祐一郎[1]　笹子三津留[2]

【ポイント】

◆ 胃癌に対するリンパ節郭清のRCTの結果，欧米ではD1が標準，アジアではD2が標準となった．

◆ わが国において現在進行中の3つの大規模RCT（脾摘，網嚢切除，腹腔鏡下手術）の結果が待たれている．

◆ 手術の臨床試験の成功には，JCOGのような組織による試験の質と手術手技の質の管理が不可欠である．

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胃癌手術における長年の課題

1881年にTheodor Billrothが胃癌に対する幽門側胃切除術を世界ではじめて成功させて以来，徐々に胃癌手術の短期成績は向上してきた．術後の長期成績を向上させるためには，胃と一緒にリンパ節を郭清することが重要であることが認識されるようになり，より広範囲のリンパ節まで郭清する拡大手術がわが国を中心に広まっていった．近年までの長い歴史の間，どの範囲のリンパ節まで郭清すればよいのかというのは最も重要な課題であったが，経験豊富な外科医の経験論，あるいは限られた過去のデータのなかから治療成績を検討するといった「後向き研究」によって，郭清範囲が決定されることがほとんどであった．

しかし，これらの方法は「バイアス」といわれるような様々な因子の影響が入るために好ましくないということが認識されるようになり，正しいエビデンスに基づいた医療の実践が望まれるようになった．正しいエビデンスを得るためには「前向き研究」，なかでもランダム化比較試験（randomized controlled trial：RCT）という無作為に治療方法を分けて比較する研究が必要であり，適切な統計手法を用いた解析が不可欠である．1990年代からは手術法同士を比較するRCTが徐々に世界中で実施されるようになり，最も適切な手術法，すなわち標準手術といわれる手技が確立されるようになってきた．

欧米での標準的リンパ節郭清

胃のすぐ近傍にあるリンパ節のみを郭清するD1手術に比べて，胃の基幹動脈の周囲にあるリンパ節まで郭清するD2手術を適切に行うためには，より高い技術の習得が必要である（図1a）．

胃癌患者が非常に少ない英国とオランダでD1とD2を比較する2つのRCTが1980年代から1990年代前半にかけて行われた．その結果，英国の試験ではD1の5年生存率が35%，D2が33%，オランダの試験ではD1の5年生存率が45%，D2が47%と，両試験ともにD2の優越性を示すことができなかったばかりか，両試験ともに術後合併症や在院死の割合がきわめて高いことが問題視された（表1）[1,2]．D2手術手技の教育がほとんど行われることなく実施された英国の試験では，D2の術後合併症発生割合が46%，在院死割合が13%に達し，最低限のD2手術手技の教育が行われたオランダの試験においても，D2の術後合併症発生割合が43%，在院死割合が10%であった．これらのRCTの結果から，欧州における胃癌の標準手術はD1であり，D2は臨床試験を除いて通常は行うべきではない

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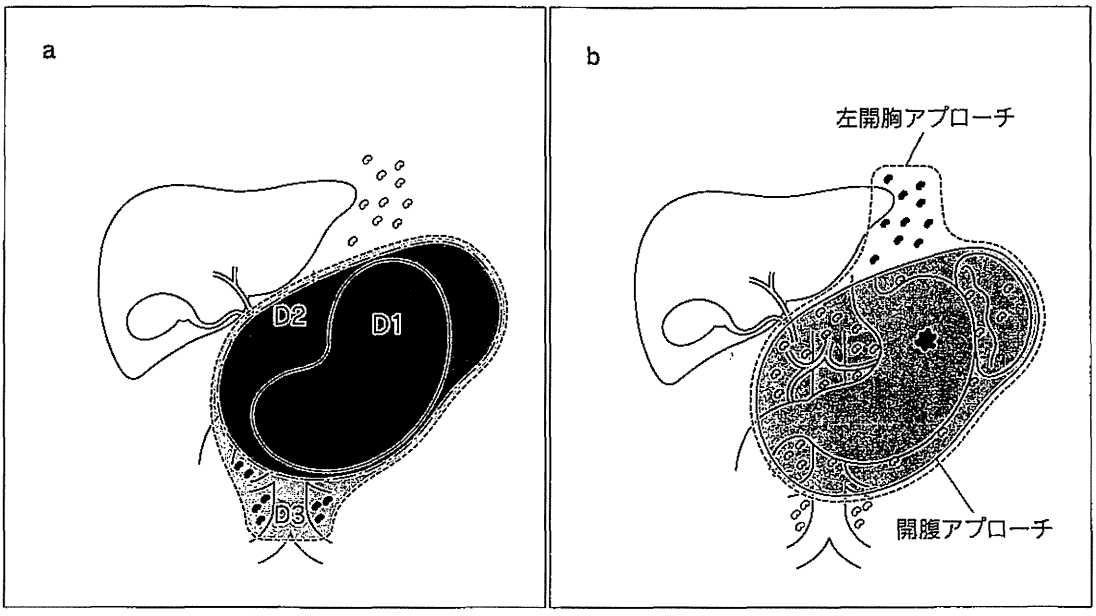

図1　胃癌手術におけるD1/D2/D3のリンパ節郭清範囲（a）と，食道浸潤胃癌に対する開腹アプローチと左開胸アプローチのリンパ節郭清範囲（b）

表1　胃癌リンパ節郭清に関するRCTの成績

	英国	オランダ	台湾	日本
群	D1 vs. D2	D1 vs. D2	D1 vs. D2	D2 vs. D3
総患者数	400	711	221	523
合併症発生割合	D1：28% D2：46%	D1：25% D2：43%	D1：7% D2：17%	D2：21% D3：28%
在院死割合	D1：7% D2：13%	D1：4% D2：10%	D1：0% D2：0%	D2：0.8% D3：0.8%
5年生存率	D1：35% D2：33%	D1：45% D2：47%	D1：54% D2：60%	D2：69% D3：70%

という結論に至った．

また，米国では胃癌術後の補助化学放射線療法の有無に関するRCTが実施され（INT0116），根治切除後に45 Gyの放射線治療と5-FU＋ロイコボリンによる化学療法を受けた群では，手術単独群に比べて有意に生存率の改善効果が認められるという結果が得られた[3]．驚くべきことに，この試験の登録患者の54%が胃のすぐ近傍にあるリンパ節すらも十分に郭清しない手術（D0）を受けており，D1とD2の手術を受けた割合はそれぞれ36%，10%であった．郭清度のサブグループ別に生存曲線を比較すると，D0とD1のサブグループでは両群間の差が大きかったのに対し，D2では両群間の差はまったく認められなかった．全登録患者の85%で病理学的リンパ節転移陽性だったことから，D0やD1の手術しか受けなかった場合には多くの症例で局所リンパ節転移が遺残したため，術後の化学放射線療法によって生存率の改善が得られたと考えられる．

以上から，進行胃癌に対する局所制御が不十分なD0やD1の手術しか実施されない米国では術後の化学放射線療法が不可欠であることが証明された．

アジアでの標準的リンパ節郭清

胃癌の罹患率が欧米よりも極端に高い日本においては，1970年頃からD2が標準的なリンパ節郭清となっていた．日本と同じく胃癌罹患率の高い台湾において，欧州の試験と同様にD1とD2（「胃癌取扱い規約」（第12版）[4]におけるD3に相当する）を比較するRCTが実施された．この試験では1993年から1999年の間に221例の胃癌患者が登録され，D2手術の経験が豊富な3人の外科医によって実施された．その結果，術後合併症発生割合はD1が7%，D2が17%，在院死は両群

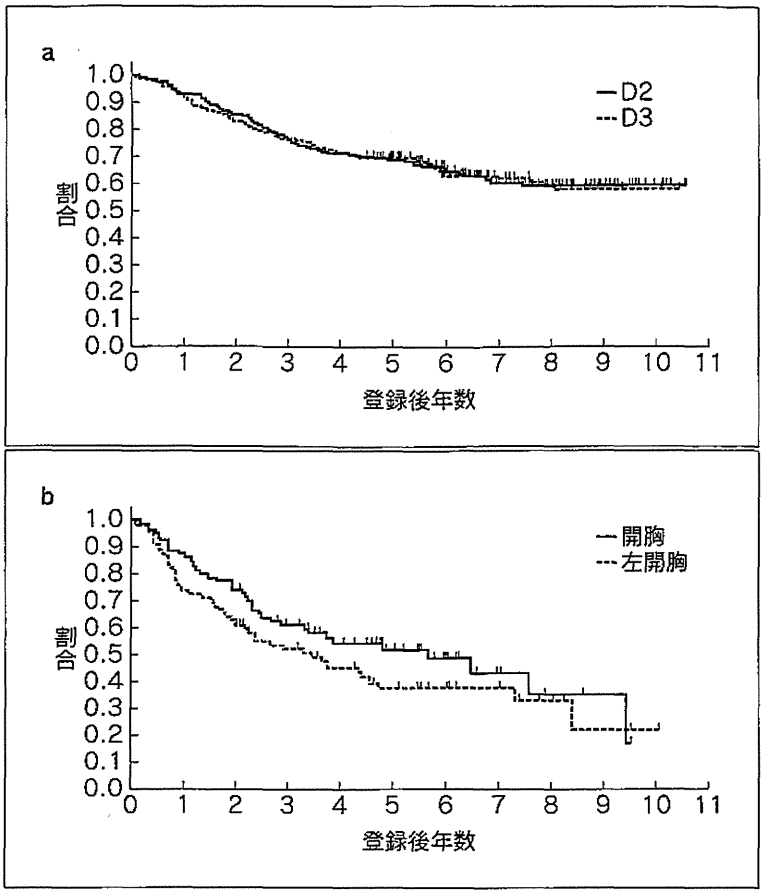

図2　D2群とD3群の全生存曲線（a：JCOG9501）と，開腹群と左開胸群の全生存曲線（b：JCOG9502）

ともに0であり，D2手術に慣れた外科医が行えば安全にできることが確認された（表1）[5]．さらに，5年生存率はD1が54%であったのに対しD2は60%であり，統計学的有意差（p=0.04）をもってD2の生存率改善効果が証明された．つまり，胃癌手術の技術および術後管理の優れた施設においては，標準手術はあくまでもD2であると証明されたわけである．

一方わが国では，1980年代に入って通常のD2よりもさらにリンパ節郭清範囲を広げる試みがなされるようになった．たとえば，胃の漿膜下層以深にまで浸潤したような胃癌の場合には，腹部大動脈周囲のリンパ節に転移する可能性が高くなるため，予防的な大動脈周囲リンパ節郭清（本稿ではD3と定義する）が行われるようになっていたのである（図1a）．そこで，日本臨床腫瘍研究グループ（JCOG）において，標準手術であるD2と拡大手術であるD3とを比較するRCT（JCOG9501）が1995年から実施され，2001年までに523例の胃癌患者が登録された．この試験では，100例以上のD2手術の経験のある外科医，もしくは年間80例以上の胃切除症例を有する24施設のみで実施され，定期的に手術ビデオの供覧を行って手術手技の統一化がはかられた．その結果，D2とD3の合併症発生割合はそれぞれ21%と28%，在院死割合は両群ともに0.8%という比較的良好な成績を示すことができたものの（表1），D3の5年生存率は70%と，D2の69%と比べてほぼ同等であり（図2a），統計学的有意差を認めなかった（p=0.85）[6]．以上から，漿膜下層以深に浸潤した胃癌に対する予防的D3の臨床的意義は否定され，標準手術は引き続きD2であることが確認された．

JCOG9501以外にリンパ節郭清範囲を広げる手術の有用性を調べたRCTとしては，食道に浸潤した胃癌に対して左開胸による下縦隔リンパ節郭清を行うべきか否かを調べたRCT（JCOG9502）がある．標準手術である開腹からのアプローチに比べて，左開胸からのアプローチを行うことは侵襲的ではあるものの，下縦隔のリンパ節を十分に郭清することで生存率が改善することが期待された（図1b）．1995年から2003年までに167例の胃癌患者が登録され，2003年に第1回目の中間解析が実施されたが，拡大手術である左開胸群

が標準手術である開腹群に比べて合併症が多いのにもかかわらず，生存率においてむしろ悪い傾向を示したため，試験が中止された．その後の追跡調査においても，開腹群の5年生存率52.3%に対して左開胸群は37.9%と悪く（図2b），食道浸潤胃癌に対して左開胸アプローチによる下縦隔リンパ節郭清の臨床的意義は否定された[7]．

わが国で進行中の重要なRCT

このように，わが国において開発されてきた拡大手術の臨床的意義が2つのRCTにおいて否定される結果となった．このほかにも，胃癌外科領域において標準手術と拡大手術を比較する重要なRCTが2つ進行中である．

1つ目は，胃上部の進行胃癌手術において脾臓を合併切除することの意義を調べたRCT（JCOG0110）である．胃上部の進行胃癌ではリンパ節転移がしばしば脾動脈周囲および脾門部に及ぶことから，これを郭清する目的で，胃全摘に加えて脾を合併切除する術式が古くから行われてきた．一方で，脾門リンパ節に転移がある症例では他部位のリンパ節にも広範に転移があることが多いため，これを郭清しても生存への寄与は小さく，さらに脾臓を合併切除することによって合併症や後遺症が明らかに増加するといった否定的な意見も多い．そこで，脾臓を切除するか否かのRCTが2002年から2009年にかけて実施され，計505例の胃癌患者が登録されて現在，追跡中である．もし，この試験で生存率における脾温存群の非劣性が証明されれば，今後は胃上部の進行胃癌に対して脾臓を温存することが新たな標準治療となるものと思われる．

2つ目のRCTは，漿膜下層以深に浸潤した胃癌の胃切除術に際して，網嚢腔表面を覆う腹膜を合併切除するという「網嚢切除」の意義を調べたRCT（JCOG1001）である．漿膜に達した胃癌細胞はまず網嚢腔内に散布され，網嚢腔の腹膜表面に微小転移や微小浸潤をきたすと考えられていることから，網嚢腔表面を覆う腹膜を広範囲に切除することによって腹膜再発の予防を狙った術式が1980-1990年代にはわが国で広く行われていた．しかし，網嚢切除は煩雑かつ高度の技術を要するため術後の合併症が増加することが懸念され，さらに，これまでに網嚢切除の有用性に関する臨床試験のエビデンスがないこともあり，最近では網嚢切除を併施する施設は減少の一途をたどり，現在ではむしろ少数派となっている．そうしたなか，網嚢切除の生存率改善効果を示唆する小規模なRCTの中間解析結果が発表され[8,9]，廃れつつあったわが国の伝統技術である網嚢切除が再び注目を浴びてきている．この網嚢切除の意義を検証するため，JCOGにおいて2010年よりRCTが開始され，1,000例の患者が登録される予定である．

縮小手術・低侵襲手術の普及

胃癌に限らず，癌はある程度以上進行すると全身に広がり，いくら大きな手術をしても手術の領域外に再発することも多い．もし手術成績が同じなのであれば，より体の負担の少ない手術のほうが望ましいといえる．また，わが国の胃癌の約半数は早期胃癌であり，Stage Ⅰの胃癌であれば90%以上の人が手術によって治癒する時代である．つまり，今や癌は不治の病ではなくなったため，術後の後遺症軽減を目的とした幽門保存胃切除や噴門側胃切除といった縮小手術が考案され，実施されることが増えてきた．

さらに，低侵襲手術として近年急速に普及しているのが腹腔鏡下手術である．腹腔鏡下手術は導入当初は胆石症などの良性疾患で実施されることが主であったが，手術機器や手術手技の進歩とともに，現在では様々な癌の手術に利用されるようになってきた．欧米では大腸癌に対する開腹手術と腹腔鏡下手術を比較するRCTが行われ，両者の間の生存期間に差はないと報告されている[10]．早期大腸癌に対しては，日本においても腹腔鏡下手術が標準手術とみなされるようになってきた．胃癌は大腸癌に比べると手術手技の難易度が高いため，腹腔鏡下手術の普及は遅れていたものの，近年では胃癌に対する腹腔鏡下胃切除の実施数は急速に増加している．現在，早期胃癌に対する開腹手術と腹腔鏡下手術を比較するRCT（JCOG0912）が進行中であり，この試験において生存率における腹腔鏡下手術群の非劣性が証明されれば，腹腔鏡下手術は開腹手術と並んで早期胃癌に対する標準手術になるものと思われる．

手術に関する臨床試験の推進

わが国で実施されている臨床試験の数自体は増加の一途をたどっているが，その質は様々である．生物統計学や臨床試験方法論の専門家が関与したRCTはま