In conclusion, extended D2 lymphadenectomy plus PAND should not be used to treat curable stage T2b, T3, or T4 gastric cancer. D2 gastrectomy is associated with low mortality and reasonable survival times when performed in selected institutions that have had sufficient experience with the operation and with postoperative management.

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REVIEW ARTICLE

Yukinori Kurokawa · Mitsuru Sasako

Recent advances in chemotherapy and chemoradiotherapy for gastrointestinal tract cancers: adjuvant chemoradiotherapy for gastric cancer

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Abstract Chemoradiotherapy (CRT) is one of the effective modalities for the local control of gastric cancer. Advances in CRT as an adjuvant treatment have been made in the West. The INT0116 trial demonstrated that postoperative chemotherapy with 5-fluorouracil (FU) plus leucovorin and concomitant 45-Gy radiation significantly improved the survival of gastric cancer patients who received gastrectomy with D0 or D1 lymph node dissection. As the result of this trial, the standard treatment for curable gastric cancer in the United States has been considered as a combination of surgery and postoperative CRT. The great interest in CRT in the adjuvant setting for gastric cancer has induced oncologists, particularly in the West, to conduct new clinical trials using various kinds of anticancer drugs. However, there is no rationale for adjuvant CRT after D2 dissection. Large-scale randomized controlled trials in Japanese patients have shown significant improvement of overall survival brought about by postoperative adjuvant chemotherapy with S-1. The results of these studies have suggested that even D2 surgery alone brings about much better survival for patients than limited surgery plus adjuvant CRT. Thus, strategies for the postoperative treatment of gastric cancers should be classified according to the degree of surgery.

Key words Chemoradiation · Radiation · Stomach · INT0116

Introduction

The primary role of radiotherapy or chemoradiotherapy (CRT) for patients with malignancies is local control of the tumor. A combination of radiotherapy plus a fluoropyrimidine (5-fluorouracil [5-FU]) used as a radiation sensitizer, could result in the good control of small amounts of residual or recurrent gastric cancer.[1] In the early 1980s, a randomized controlled trial (RCT) examining the effect of postoperative CRT for gastric cancer patients was conducted in the United States.[2] The CRT regimen was 37.5 Gray with combination chemotherapy using 5-FU (three courses of rapid intravenous infusion). The results showed 5-year overall survival (OS) rates and local recurrence rates of 4% and 54%, respectively, in the surgery-alone group and 23% and 39%, respectively, in the CRT group. Although only 62 patients were registered in this study, it was the first RCT to show that postoperative CRT might be a promising modality after surgery for gastric cancer patients.

In the early 1990s, a British RCT was conducted to evaluate the efficacy and the safety of postoperative radiotherapy and postoperative chemotherapy.[3] A total of 436 gastric cancer patients were randomized to either a surgery-alone group, a postoperative radiotherapy group, or a postoperative chemotherapy group. In the radiotherapy group, a midline dose of 45 Gy was given over 35 days, with the option of a further 5-Gy boost to a reduced field. In the chemotherapy group, 4 mg/m^2 mitomycin, 30 mg/m^2 doxorubicin, and 600 mg/m^2 5-FU were given on a 3-weekly basis for eight cycles. Neither the radiation group nor the chemotherapy group demonstrated a survival benefit when compared to the surgery-alone group; 5-year OS rates in the surgery-alone group, the radiation group, and the chemotherapy group were 20%, 12%, and 19%, respectively. This negative result triggered the acceleration of the use of postoperative CRT or preoperative chemotherapy for gastric cancer patients in the West.

Intergroup (INT) 0116 trial

In the late 1990s, an American RCT (INT0116) was conducted to evaluate the survival benefit of adjuvant CRT for gastric cancer.[4] A total of 556 patients with resected

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adenocarcinoma of the stomach or gastroesophageal junction were randomly assigned to either a surgery-alone group or a CRT group. In this trial, the treatment in the CRT group consisted of 425 mg/m^2 bolus 5-FU per day and 20 mg/m^2 leucovorin for 5 days, followed by 45-Gy radiation at 1.8 Gy per day, 5 days per week for 5 weeks, with a 400 mg/m^2 5-FU bolus and 20 mg/m^2 leucovorin per day on the first 4 and the last 3 days of radiotherapy. One month after the completion of radiotherapy, two 5-day cycles of 5-FU and leucovorin were given. Radiation was focused on the level-2 lymph node stations and both the proximal and distal resection margins. As a result, the CRT group showed a significant improvement in OS ($P = 0.005$) with the hazard ratio for death of 1.35 (95% confidence interval, 1.09 to 1.66). Local recurrence occurred in 29% of the patients in the surgery-alone group and in 19% of those in the CRT group. Grade 4 adverse events occurred in 32% of the patients in the CRT group, and 3 patients (1%) died from toxic effects of the CRT. The proportion of patients who completed the CRT was 64%. Since the reporting of this result, the standard treatment for curable gastric cancer in the United States has been considered as a combination of surgery and postoperative CRT.

However, most surgeons and oncologists who were familiar with D2 lymph node dissection could not accept the result of the INT0116 trial, because the surgical quality in this trial was an important issue. A detailed analysis of the type of surgery revealed that 54% and 36% of the patients, respectively, underwent D0 and D1 dissection, while only 10% underwent D2 dissection. In the subgroup analyses, the survival benefit of adjuvant CRT was not observed in the patients who received D2 dissection.[5] Recently, a Taiwanese RCT comparing D2 with D1 dissection without adjuvant therapy demonstrated the survival benefit of D2 dissection over D1; the 5-year survival rates of patients who received D2 and D1 dissections were 59.5% and 53.6%, respectively (log-rank; $P = 0.04$).[6] Furthermore, the latest Japanese RCT (Japan Clinical Oncology Group [JCOG] 9501),[7] which compared D2 with D2 plus paraaortic nodal dissection for stage T2b-T4 gastric cancer, demonstrated that there was no significant difference in survival between the two groups and that D2 dissection without adjuvant therapy brought about much better long-term survival than that in previous reports from outside eastern Asia. These Asian studies[6,7] indicated that D1 dissection was insufficient treatment for local control in patients with curable gastric cancer.

Of interest, the patient population enrolled in the CRT group in the INT0116 trial was quite similar to that enrolled in another Japanese RCT (JCOG9206-2),[8] which compared surgery alone with surgery followed by adjuvant chemotherapy with cisplatin, 5-FU, and uracil-tegafur (Table 1). The 5-year OS rates in the CRT group in the INT0116 trial and in the surgery-alone group in the JCOG9206-2 trial were 42% and 61%, respectively. Although a direct comparison of results from two different trials needs careful consideration in the interpretation, this suggests that D2 dissection without adjuvant therapy might produce better survival than D0/D1 dissection followed by CRT. Thus, the result of the INT0116 trial[4] can be generalized only to gastric cancer patients who received D0 or D1 lymph node dissection.

Table 1. Comparison between the INT0116 and the JCOG9206-2 trials

	INT0116[4]	JCOG9206-2[8]
Country	United States	Japan
Number of patients	281 (tested group)	133 (control group)
Treatment	Surgery plus adjuvant CRT	Surgery-alone
Proportion of patients with D2 or greater lymph node dissection	10%	99%
Proportion of pathological T3/4 cases	69%	69%
Proportion of pathological node-positive cases	86%	76%
Overall survival rate	3-Year: 50% 5-Year: 42%	3-Year: 66% 5-Year: 61%

Table 2. Comparison between Korean nonrandomized study and Japanese randomized studies

	Korean study[9]	JCOG9501[7]	ACTS-GC[10]
Country	Korea	Japan	Japan
Study design	Non-RCT	RCT	RCT
Number of patients	281 (tested group)	263 (control group)	529 (tested group)
Treatment	Surgery (D2) plus adjuvant CRT	Surgery alone (D2)	Surgery (D2) plus adjuvant chemotherapy (S-1)
Proportion of pathological T3/4 cases	48%	49%	45%
Proportion of pathological node-positive cases	51%	70%	90%
Overall survival rate	3-Year: 66% 5-Year: 57%	3-Year: 76% 5-Year: 69%	3-Year: 80%

Table 3. Ongoing studies of adjuvant chemoradiotherapy for gastric cancer

ClinicalTrials.gov identifier	NCT00052910 (CALGB80101)	NCT00323830	NCT00011960	NCT00123318	NCT00718913	NCT01839911
Country	United States	Korea	United States	Australia	Greece	United States
Study design	RCT	RCT	RCT	Non-RCT	Non-RCT	Non-RCT
Estimated number of patients	824	490	94	52	49	25
Target gastric cancer population	Stage IB-IV (M0)	Stage IB-IV (M0)	Stage IB-III	T3–4, N1–2, M0	T2–3, Any N, M0	Stage IB-IV (M0)
Chemotherapy regimen	5-FU + leucovorin vs epirubicin + cisplatin + 5-FU	Capecitabine + cisplatin	Paclitaxel + cisplatin, with vs without 5-FU	Epirubicin + cisplatin + 5-FU	Docetaxel + cisplatin + capecitabine	Floxuridine (intraperitoneal) + 5-FU + leucovorin
Radiation dose	45 Gy	With vs without 45 Gy	45 Gy	45 Gy	45 Gy	45 Gy
Degree of lymph node dissection	Any	D2	Any	D2	Any	Any

Adjuvant chemoradiotherapy after D2 lymph node dissection

The benefit of adjuvant CRT after curative gastrectomy with D2 lymph node dissection is controversial. A Korean nonrandomized study examined the survival benefit of adjuvant CRT after D2 dissection.[9] A total of 544 patients with curatively resected gastric cancer received adjuvant CRT (the same as that used for the INT0116 trial), while a total of 446 patients received surgery alone. The OS in patients with CRT was significantly better than that in patients without CRT (5-year OS rates, 57% vs 51%). The hazard ratio for death was 0.80 (95% confidence interval, 0.67 to 0.97), and the log-rank *P* value was 0.02. The proportion of patients with local recurrence within the radiation field was significantly lower in the CRT group (15%) when compared with that in the surgery-alone group (22%). In the CRT group, 75% of the enrolled patients completed treatment as planned, and only 1 patient (0.2%) died of toxicity. The authors concluded that adjuvant CRT was feasible even after D2 surgery and could improve survival. However, the survival in the CRT group reported in this Korean study was much worse than that in the surgery-alone group in the Japanese JCOG9501 trial[7] (Table 2). The proportion of patients with pathological T3/4 stage was similar in both studies, but the proportion of pathological node-positive cases in the Korean study was lower than that in the JCOG9501 trial. Of note, a large-scale RCT (ACTS-GC),[10] which compared surgery alone with adjuvant chemotherapy using S-1 for 1 year after D2 dissection, was conducted in patients with stage II/III gastric cancer in Japan. It demonstrated that there was a significant survival benefit of adjuvant chemotherapy, which led to the establishment of new standard treatment for stage II/III gastric cancer in Japan. The background of the patients in the Korean study[9] was very similar to that in the Japanese ACTS-GC trial regarding pathological T stage, but the ACTS-GC trial included many more pathological node-positive cases than the Korean study. Nevertheless, the 3-year OS rate in the adjuvant chemotherapy group was 80% in the ACTS-GC trial, while the 3-year OS rate in the adjuvant CRT group was 66% in the Korean study. This suggests either that the D2 dissection at this Korean institute may not have been sufficient as local control, or that chemotherapy without radiation was more effective than chemotherapy with radiation when patients underwent D2 dissection. Besides the Korean study, two feasibility studies of CRT based on the INT0116 trial were reported from Singapore and Hong Kong,[11,12] but the long-term outcomes in these retrospective studies were inferior to those in the Japanese randomized studies[7,8,10] noted above.

Ongoing studies of adjuvant CRT

Reflecting the great interest in the adjuvant setting of CRT for gastric cancer patients, there are many ongoing studies in Western countries and in Eastern Asia (Table 3). Among

them, only the Korean study and the Australian study limited the inclusion criteria to patients who received D2 surgery. The largest trial, CALGB80101, was planned to compare 5-FU plus leucovorin with ECF (epirubicin, cisplatin, 5-FU) in combination with radiation therapy. Because the ECF regimen as pre- and postoperative chemotherapy is one of the standard treatments for resectable gastric cancers in Europe, according to the positive result of the MAGIC trial,[13] the CALGB80101 trial should show which is the better chemotherapy regimen to be combined with radiation for gastric cancer patients who receive D0 or D1 surgery. In Korea, capecitabine, an oral fluoropyrimidine, is frequently used for the treatment of gastric cancers, so that an RCT is planned to compare capecitabine plus cisplatin with and without radiation, which may prove the significance of radiation after D2 surgery.

Conclusion

CRT has a certain benefit for gastric cancer due to its good local control, so that it is important to consider how to utilize this modality. The results of the INT0116 trial[4] led to adjuvant CRT for gastric cancer patients becoming one of the standard treatments after gastrectomy with D0 or D1 lymph node dissection. However, there is no rationale for employing CRT in patients after D2 surgery. The Japanese RCTs[7,8,10] have suggested that D2 surgery alone or D2 surgery plus adjuvant chemotherapy using S-1 brings about much better survival than D0/D1 surgery plus adjuvant CRT. Therefore, it seems reasonable that the target population for adjuvant CRT should be limited to gastric cancer patients who have received D0 or D1 surgery.

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Review article

Adjuvant chemotherapy with 5-FU or regimens including oral fluoropyrimidine for curable gastric cancer

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Abstract
Since 2000, several studies have reported positive results in reasonable-size randomized controlled trials of adjuvant treatment for potentially curable gastric cancer. At present, postoperative adjuvant chemoradiotherapy and perioperative chemotherapy are the standard of care in the United States and Europe (including Great Britain), respectively, while postoperative S-1 monotherapy is the standard of care in Japan. The effect of adjuvant treatment varies according to the type of surgery, and the best results so far have been observed in the adjuvant chemotherapy of TS-1 for gastric cancer (ACTS-GC) trial, in which D2 surgery followed by S-1 monotherapy was tested. The role of radiotherapy after D2 dissection remains unclear.

Key words Adjuvant treatment · Fluorouracil · Chemoradiotherapy · Gastric cancer

Introduction

A meta-analysis of the randomized controlled trials (RCTs) on adjuvant chemotherapy for curable gastric cancer reported the efficacy of the treatment in 2000 [1], although there had been no pivotal study showing the benefit of adjuvant treatment before 2000. In this century, however, several reports have presented the efficacy of adjuvant treatment for gastric cancer.

Results of Western trials

Intergroup study of adjuvant chemoradiotherapy [2]

Macdonald et al. [2] reported the results of the Intergroup 0116/South West Oncology Group (SWOG) 9008 study in 2001; the study was performed to evaluate the efficacy of adjuvant treatment comprising the administration of 45-Gy radiotherapy and five courses of chemotherapy consisting of 5-fluorouracil (5-FU) and leucovorin. Postoperative adjuvant chemoradiotherapy (CRT) showed a statistically significant improvement of relapse-free survival (RFS) and overall survival (OS) for patients with gastric cancer undergoing curative surgery, compared with surgery alone as control. The 3-year OS after CRT was 50%, while that of the surgery-alone group was 41% (hazard ratio [HR], 1.35; 95% confidence interval [CI], 1.09–1.66; $P = 0.005$). The chemotherapy used in this study, 5-FU and leucovorin, was a slightly-out-of-date regimen, but the low toxicity and high compliance of this treatment could have been the key to this successful study.

The study had two major weak points. First, only 10% of patients underwent D2 dissection in spite of the recommendation of D2 dissection in the protocol, suggesting that poor local control by surgery was salvaged by radiotherapy. Secondly, 35 % of the irradiation plans had major or minor deviations, most of which could be revised before actual treatment by the central quality controller. The eventual rate of major deviation was 6.5%. This happened in the United States, where the standard level of radiotherapy seems to be much higher than that in most other countries, including Japan. This fact should be taken into consideration when this treatment is adopted in other countries.

After this result came out, the standard treatment after potentially curative surgery for node-positive patients in the United States has been postoperative CRT. At present, we cannot see any United States clinical phase III trial of adjuvant treatment for potentially curable gastric cancer in the registry of the NCI (http://www.clinicaltrial.gov.)

MAGIC trial [3]

Cunningham et al. [3] reported the results of the MAGIC trial, which was performed to evaluate the efficacy of

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Table 1. List of reviewed trials

Author	Accrual period	No. of patients analyzed	Chemotherapy	3-Year OS (%)		5-Year OS (%)		HR	*P* value
				ACT	Surgery	ACT	Surgery		
Nakajima T [11]	1988–1992	579	MMC+5FU, UFT			85.8	82.9	0.738	0.17
Macdonald [2]	1991–1998	556	5-FU+Leu, Rad (45 Gy)	50	41			0.74	0.005
Nashimoto [12]	1993–1994	252	MMC+5FU+AraC, UFT			91.2	86.1	NA	0.14
Neri [4]	1989–1991	137	Epirubicin+5FU+Leu			30.2	12.6	0.51	<0.01
Bajetta [6]	1992–1997	271	Etopo+Adria+CDDP			52	48	0.93	0.87
Chipponi [7]	1989–1997	199	CDDP+5FU+Leu			39.0	38.7	NA	NA
Bouche [8]	1989–1997	260	5FU+CDDP			46.6	41.9	0.74	0.063
Nitti [9]	1990–1998	191+206	FAMTX+Leu, FEMTX+Leu			43	44	0.98	0.86
De Vita [10]	1996–2001	225	Epirubicin+Leu+5FU+Etopo			48.0	43.5	0.91	0.61
Nakajima [14]	1997–2001	190	UFT			86	73	0.48	0.017
Cunningham [3]	1994–2002	503	Epirubicin+CDDP+5FU			36.3	23.0	0.75	0.009
Sakuramoto [15]	2001–2003	1059	S-1	80.1	70.1			0.68	0.003

ACT, adjuvant chemotherapy; HR, hazard ratio; MMC, mitomycin C; 5FU, 5-fluorouracil; Leu, leucovorin; Rad, radiation; AraC, cytarabine; Etopo, etoposide; Adria, adriamycin; CDDP, cisplatin; UFT, uracil-tegafur; FAMTX, 5-fluorouracil + adriamycin + methotrexate; FEMTX, 5-fluorouracil + epirubicin + methotrexate; NA, not available

perioperative chemotherapy (three cycles each before and after surgery). The chemotherapy (ECF) used for this trial was a combination of epirubicin (50 mg/m^2; day 1), cisplatin (60 mg/m^2; day 1), and 5-FU [200 mg/m^2/day; continuous intravenous administration (civ) days 1–21]. This treatment showed statistically significant improvement of both PFS and OS compared with surgery alone as control. The 5-year OS was 36.3% in the chemotherapy group and 23.0% in the surgery-alone group. There were 100 participating hospitals with no active quality control of surgery. Therefore, only about 53% of curable patients underwent D2 dissection. Secondly, 14.5% of the patients had adenocarcinoma of the esophagus, requiring a different type of surgery. Thirdly, shortly after randomization, 9 of 253 patients allocated to surgery alone did not undergo surgery or no information about surgery was available for them. If the quality of eligibility assessment had been reasonable, it would have been impossible that so many of the randomized patients did not undergo surgery. Fourthly, among 198 patients who underwent surgical resection, the pathological T stage was unknown in 5 patients and the pathological nodal stage was unknown in 42 patients. These facts strongly suggest that the quality of this trial was much poorer than those of the Intergroup 0116/SWOG 9008 study and Japanese studies. In the MAGIC trial, as the OS of curable patients in the surgery-alone group was not reported separately, comparison of results with those of other clinical trials which included only curable patients is almost impossible. However, the tumors resected in the control group were not more advanced than those included in the Intergroup 0116/SWOG 9008 study or in Japan Clinical Oncology Group (JCOG) studies.

Other clinical phase III trials with surgery alone as the control arm

In this century, six other articles reporting the results of RCTs of adjuvant chemotherapy with surgery alone as a control could be found. All but one included 5-FU as a component of the regimen. In 2001, Neri et al. [4] reported the results of a small RCT including 137 patients in total. The chemotherapy used was a combination of epirubicin, 5-FU, and leucovorin (EFL). In this paper, they reported a statistically significant survival benefit for chemotherapy over surgery alone ($P < 0.01$) [4]. However, the number reported in the interim analysis of the same trial published in 1996 [5] was different from the report of their final analysis [4], suggesting a low quality of this trial. None of the other five studies showed statistically significant differences between treatment and observation after surgery [6–10]. Table 1 shows the results of these trials. One of them was a combined analysis of two trials including 191 and 206 patients. The common aspect of these six trials is the limited number of patients enrolled in each study, fewer than 300 if combined analysis is divided by trial. None of these studies showed a statistically significant difference between the arms, which might have been reached if they had had 500 patients in one arm.

Results of Japanese clinical trials

JCOG 8801 [11]

Nakajima et al. [11] reported the results of an RCT comparing adjuvant chemotherapy using a combination of mitomycin (MMC; 1.4 mg/m^2) + 5-FU (166.7 mg/m^2),

twice weekly for 3 weeks, followed by oral administration of uracil-tegafur (UFT; 300 mg daily) for 18 months, with surgery alone as control. They enrolled 579 patients with exclusively serosa-negative gastric cancer in the study. The 5- year survival rates of the treatment and control arms were 85.8% and 82.9%, respectively. This difference was not statistically significant ($P = 0.17$; HR, 0.74; 95% CI, 0.50–1.09). In the subgroup analysis of this study, it was suggested that this kind of adjuvant chemotherapy trial should exclude patients with T1 tumors, regardless of the pathological node positivity.

JCOG 9206-1 [12]

Nashimoto et al. [12] reported the results of an RCT comparing adjuvant chemotherapy consisting of a combination of i.v. infusion of MMC (1.33 mg/m^2), 5-FU (166.7 mg/m^2), and cytarabine (13.3 mg/m^2) twice weekly for the first 3 weeks, followed by oral UFT (134 mg/m^2) for 18 months, with surgery alone as the control arm. In total, 252 patients were enrolled during 2 years. There was no significant difference between the two arms for either RFS or OS. The 5-year OS values in the test and control arms were 91.2% and 86.1%, respectively. The survival curves for both RFS and OS showed a small but clear separation between the groups. Comparison of these two curves suggests that the results of this study were negative due to a too-small sample size, which had low power to detect a difference. A clinical significance of 5% superiority for this stage of gastric cancer (the patients had serosa-negative gastric cancer) should be considered in relation to the adverse events and cost of this treatment. The JCOG did not carry any out any further confirmatory study of this regimen.

JCOG 9206-2 [13]

Miyashiro et al. [13] reported the results of an RCT comparing adjuvant chemotherapy (comprising the intraperitoneal administration of cisplatin [CDDP]) and combination i.v. chemotherapy, with CDDP (70 mg/m^2) and 5-FU (700 mg/m^2), followed by oral administration of UFT (266.7 mg/m^2 daily) for 12 months. There was no difference in OS or RFS (only 1% difference in 5-year OS). At the time when this study was planned, CDDP intraperitoneal and 5-FU + CDDP i.v. therapies were some of the most attractive ones that were thought to have the potential to improve OS and RFS. However, mainly due to the high toxicity of the intraperitoneal administration of CDDP, low compliance was a large problem in this study.

National Surgical Adjuvant Study of Gastric Cancer (N-SAS-GC) [14]

In the 1980s and 1990s, many Japanese surgeons used UFT in clinical practice without sufficient evidence that it improved OS and RFS after curative surgery. The Japanese government initiated an RCT to re-evaluate the efficacy of this drug and ordered the pharmaceutical company that produced UFT to take over this trial as a sponsored one to compare UFT (360 mg/m^2, 5 days on and 2 days off) versus surgery alone for pT2, pN1/2 patients. The target population of this study was selected based on the subgroup analysis of the JCOG 8801 study. Due to very slow accrual, the sponsor and the investigators decided to stop accrual after only 190 patients had been randomized. As the original projected sample size was 500, less than half of the expected number was registered. Without any expectation, these enrolled patients were followed up, but the second interim analysis showed statistically significant differences of OS and RFS between the arms in this study. Later, with full follow up, the final survival results were reported. Five-year OS values after adjuvant treatment and surgery alone were 86% and 73%, respectively ($P = 0.017$). The HR for OS in the chemotherapy group was 0.48 (95% CI, 0.26–0.89). However, there are several criticisms of this study. The number of enrolled patients was less than half of the expected sample size. The survival rate of the control arm (surgery alone) was much lower than that in the JCOG 9201-1 study, which had been carried out in almost the same period. The 5-year RFS of the surgery-alone arm in the N-SAS-GC trial was 68%, while the pT2pN1-4 subpopulation in the JCOG 9206-1 study showed a 5-year RFS of 80%.

Adjuvant Chemotherapy of TS-1 for Gastric Cancer (ACTS-GC) [15]

The ACTS-GC trial was also a sponsor-led RCT, carried out to evaluate the efficacy of S-1 monotherapy as adjuvant chemotherapy after curative D2 surgery. Pathological stage II, IIIA, and IIIB patients were randomized within 6 weeks after surgery either to S-1 administration or surgery alone. The treatment regimen comprised 6-week cycles, in which S-1 at 80 mg/m^2 per day was given for 4 weeks, with no chemotherapy for the following 2 weeks. This trial showed good patient accrual of 1059 patients within 38 months. At the first planned interim analysis, the difference between the two arms was so large that the independent data and safety monitoring committee recommended to the investigators to stop the trial and open the results. The final analysis, carried out using the updated data of 6 months later, was reported in the *New England Journal of Medicine*. The most frequent grade 3/4 toxicity was anorexia (6%),

followed by nausea (3.7%) and diarrhea (3.1%). Compliance at 6 months and at 1 year was 78% and 66%, respectively. The primary endpoint, OS at 3 years, was 80.1% in the S-1 group and 70.1% in the surgery-alone group, with an HR of 0.68 (95% CI, 0.52–0.87). The HR of the RFS was even smaller, 0.62 (95% CI, 0.50–0.77; $P < 0.001$). It was also reported that S-1 significantly reduced lymph nodal ($P = 0.01$) and peritoneal ($P = 0.009$) recurrence. Subgroup analysis showed a consistent HR of less than 1.0 in any subgroup, suggesting the applicability of the results to all subpopulations included in this study. This has been the first positive large high-quality Japanese phase III study of adjuvant chemotherapy for curable gastric cancer to have had a strong impact on clinical practice.

Comparison of Western and Japanese trials

There have been longstanding arguments regarding the large differences in OS or RFS between Western and Japanese studies. It was often mentioned that Western and Japanese studies were treating different diseases. This is true in some aspects, but not in the majority of aspects. To date, there has been no high-quality study that has reported biological differences in gastric cancer between Western and Japanese patients. Moreover, some studies report the similarity of gastric cancers in Western and Japanese patients [16, 17]. Stage migration, due to more accurate nodal staging in Japan, can explain some part of the large differences in OS and RFS[18]. To carry out fair comparison and avoid stage migration, comparison by T stage seems the most reliable method.

The two populations in the Intergroup 0116/SWOG 9008 study [2] and the JCOG 9206-2 trial [13] were by chance very similar in most aspects, suggesting that almost the same patient populations were treated in these two different studies. Table 2 shows the baseline characteristics of the randomized patients in these two trials. Unlike the actual features of gastric cancer patients in the United States, the majority of patients in the Intergroup 0116/SWOG 9008 study [2] had classic-type antral cancer of intestinal histology. There were more patients with nodal metastasis in the United States study but there were more with diffuse cancer and more with linitis plastica in the Japanese study, resulting in a good balance in terms of prognosis. The OS in the test arm of the Intergroup 0116/SWOG 9008 study [2] was 40%, while that for the entire patient cohort, including the surgery-alone group, was 61%. This large difference can be explained only by a difference in treatment, i.e., D2 dissection or D1 + radiotherapy.

Quality of surgery

Subgroup analysis of the Intergroup 0116/SWOG 9008 study suggested that no benefit of the treatment was

Table 2. Comparison of Intergroup 0116/SWOG 9008, JCOG 9206-2, and MAGIC trials

	Intergroup 0116 SWOG 9008 [2]	JCOG 9206-2 [13]	MAGIC [3]
No. of patients	281 (CRT arm)	268	253 (Surgery alone)
Tumor location			
Antrum	53%	31%	NA
Body	24%	32%	NA
Cardia	21%	28%	12%+ Eso14%
Multiple	2%		NA
All sites		9%	NA
Histological type			
Diffuse	92	162	NA
Intestinal	135	93	NA
pT stage			
T1	14	5	16
T2	75	87	55
T3	174	165	106
T4	18	18	16
T3+4	68%	65%	63%
Node-positive	85%	72%	73%
Tumor size; cm (median)		6.0	5.0
Surgery			
D0	54%	0%	0%
D1	36%	1%	28%*
D2	19%	99%	53%*
Adjuvant	5FU+Leu+Rad	5FU+CDDP+UFT	None-surgery alone
5-Year Survival	42%	61%	23% (32%**)

Eso, esophageal cancer

* % among those undergoing curative resection; ** 5-year survival rate among curable patients

observed in those who underwent D2 dissection [19]. Hundahl et al. [20] made an ad-hoc analysis of the prognostic impact of hypothetical residual nodal disease, calculated using a computer program based on a large database accumulated at the National Cancer Center Hospital in Tokyo, and found that the limited dissection which had high probability of residual disease undermined the prognosis. In other words, this study clearly demonstrated that the effect of chemoradiotherapy depended on the type of surgery.

In the ACTS-GC study [15], all patients underwent D2 dissection, while only 10% and 40% of the enrolled patients underwent D2 dissection in the Intergroup 0116/SWOG 9008 study [2] and the MAGIC trial [3], respectively. It is also possible to make a comparison between the types of surgery in the MAGIC trial and the ACTS-GC study [15] or the JCOG 9206-1 study [12]. Looking at the baseline characteristics of the patients and tumors, it is hardly acceptable that the MAGIC trial has shown good results. For Japanese standards, the results of the control arm of the MAGIC trial were extremely poor, and this could have been the reason for the positive results of this study.

Is radiation needed?

The Intergroup 0116/SWOG 9008 study [2] showed a clear benefit of CRT in those who underwent less than D2 dissection. However, there remain two clinical questions. The first question is whether D1 + CRT can replace D2 + chemotherapy alone. The second one is whether CRT can improve the results of D2 dissection. The second issue is more relevant for Japanese physicians and patients, because D2 + chemotherapy is the standard of care in Japan. There is only one study, by Kim et al. [21], reporting the results of a retrospective comparison of OS between patients who underwent D2 + postoperative CRT and those with D2 surgery alone. These authors selected 446 patients as the surgery-alone group out of 3447 patients who underwent potentially curative resection. These patients fulfilled the eligibility criteria for CRT in their institution. One of the reasons for exclusion was palliative resection, which is not consistent with the description of "curative resection" for the entire group. The results of such kinds of retrospective analysis are usually far less reliable than the results of a prospective study. There were several important differences between the two groups, D2 + CRT and D2 alone, including the age of the patients, which is known to be one of the most important prognostic factors in gastric cancer patients. We should keep in mind also that this comparison was not between D2 + CRT versus D2 + chemotherapy. The OS obtained for D2 + CRT did not seem to be superior to the OS observed in the patients who underwent D2 + chemotherapy in the ACTS-GC study [15]. In other words, the OS of those who underwent surgery alone in the study by Kim et al. [21] was far poorer than the stage-specific OS reported in the ACTS-GC study [15]. Kim and colleagues are now carrying out a single-institutional prospective RCT comparing D2 + CRT versus D2. We should wait for the results of this study. If this study shows remarkable results, Japanese physicians would have to consider the benefit of the addition of radiotherapy over D2 + chemotherapy.

Future directions

Through this review, it appears that the achievement of the ACTS-GC study [15] should be highly appreciated, and for the moment the standard of care for stage II/III gastric cancer is D2 surgery followed by postoperative adjuvant chemotherapy with S-1 for 1 year. As the results of surgery alone in Japan are acceptably good for stage II patients, the next question might be whether we can reduce the total dose and period of adjuvant treatment with S-1 for these patients. An RCT of noninferiority design to compare 6 months' and 12 months' administration of S-1 might be an interesting trial, because the standard length of adjuvant chemotherapy for other cancers in Western countries is usually 6 months. For more advanced stages, more effective chemotherapy is expected. Careful selection of the next candidate treatment for the test arm of an adjuvant phase III trial for curable stage III gastric cancer is now ongoing; this is being done by carrying out feasibility studies using some regimens that show better OS than S-1 alone for advanced or metastatic gastric cancer. If such regimens cannot be given postoperatively, preoperative administration might be another way to go.

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The Number of Metastatic Lymph Nodes is a Significant Risk Factor for Bone Metastasis and Poor Outcome After Surgery for Linitis Plastica-type Gastric Carcinoma

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Abstract

Background Linitis plastica-type gastric carcinoma remains a disease with poor prognosis despite an aggressive surgical approach. Although a prominent pattern of disease failure is peritoneal carcinomatosis, some patients experience rapid disease progression without signs of the peritoneal disease.

Methods Clinicopathologic data from 178 patients with linitis plastica-type gastric cancer operated on between 1991 and 2000 were analyzed. Survival stratified by curability of surgery, pN stage, and patterns of failure were evaluated by using the Kaplan-Meier method, and χ^2 test was used to evaluate correlation between the number of metastatic lymph nodes in terms of pN categories and the incidence of various patterns of metastasis and recurrence. Cox regression hazard model was used to identify independent prognostic factors.

Results R0 resection was performed only among 82 patients (46% of those who underwent laparotomy). Node metastasis was frequent with only 22 patients classified as pN0. Peritoneal carcinomatosis was observed in 131 patients and was the commonest pattern of recurrence. Bone metastasis, found in 13 patients, was associated with poor outcome, and its incidence was significantly correlated with the number of metastatic nodes. pT4 status and pN3 status were identified as significant independent prognostic determinants.

Conclusion Treatment strategy for the linitis plastica should in general combine surgery with aggressive treatment directed toward peritoneal disease. However, patients with >16 metastatic nodes more often are associated with bone metastasis than those with modest nodal involvement and suffer from poor prognosis.

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Introduction

Linitis plastica-type gastric carcinoma is found in 12–14% of all cases of advanced gastric carcinoma in leading institutions in Japan and western countries [1]. It is diffusely infiltrative by nature and has a propensity toward involvement of the entire stomach, invasion of the gastric serosa, peritoneal seeding, and gross lymph node metastases [2]. In Japan, radical surgery with systemic extended lymphadenectomy has been considered effective in the management of gastric carcinoma in general [3, 4]. Authors, along with others, have shown some encouraging data, indicating that the advantageous effect of the extended surgery that has been suggested for gastric cancer in general in Japan also applies to the linitis plastica type [5–7], provided curative (R0) resection was performed. However, prognosis of the patients with this type of cancer, whose common pattern of failure is peritoneal dissemination, remains outstandingly poor in comparison with other types [8]. Given that free disseminated cancer cells are detected from the peritoneal washing by reverse-transcriptase polymerase chain reaction in up to 70–80% of patients who undergo surgery for the linitis plastica, all

efforts to cure the disease by surgery may begin to seem futile.

More recently, the authors and others have found that chemotherapy with modern cytotoxic agents exerts some promising effect on patients with free cancer cells in the peritoneal cavity. Two-year survival rate of the patients who were positive for peritoneal washing cytology treated with S-1 monotherapy was 47%, whereas <20% of similar patients in the historical control survived that far [9]. Intraperitoneal drug delivery of anticancer drugs also is a rational option to treat the disseminated cancer, and a high level of evidence in support of intraperitoneal administration of cisplatin and paclitaxel was reported for optimally debulked ovarian cancer [10], another cancer type that is frequently associated with the peritoneal disease. The authors also have begun to accumulate favorable in vivo [11] and pharmacokinetic data [12], suggesting that intraperitoneal administration of paclitaxel could be effective to combat peritoneal metastases derived from gastric cancer. It seems adequate to combine surgery with chemotherapy directed toward peritoneal disease when considering a multimodal treatment strategy for the linitis plastica. In practice, however, a certain population with this type of cancer are found to die early without any signs of peritoneal disease. To explore whether it is possible to customize perioperative therapy against patients with the linitis plastica, the authors analyzed pooled data of linitis plastica patients treated with the conventional policy of radical surgery alone or surgery followed by chemotherapy, and searched for clinicopathologic characteristics that predicts early disease failure.

Patients and methods

Between 1991 and 2000, a total of 2,244 patients with gastric carcinoma were identified in the prospective data file at Department of Surgery II, Nagoya University Graduate School of Medicine and Department of Gastroenterological Surgery, Aichi Cancer Center. Among them, 192 patients (8.6%) had gastric cancer of the linitis plastica type and fulfilled the following criteria to be included for analyses in the current study: 1)patients with primary gastric carcinoma who were preoperatively diagnosed as linitis plastica type by barium meal and endoscopy; 2) patients who were not given neoadjuvant chemotherapy; 3) patients with no signs of ascites, distant metastasis, or bulky paraaortic nodes metastases after the preoperative evaluation with physical examination and computerized tomography. This database allows for accurate storage and retrieval of patients based on the Japanese Classification of Gastric Carcinoma [13] and tumor-node-metastasis [14]. Fourteen of the 192 patients were lost to follow-up, and the remaining 178 patients form the basis of current study. Of these, patterns of disease failure are unknown in 6 patients. Of 150 patients who were treated with gastrectomy, details of the number of metastatic lymph nodes were unavailable in 2 patients.

Surgical procedure

Indication for gastrectomy was decided based on surgical findings at laparotomy, except in four patients who underwent staging laparoscopy. After laparotomy, abdominal cavity was thoroughly examined for tumor metastasis and peritoneal deposits in particular. A sample of peritoneal deposits was taken whenever they were detected and diagnosis of cancer metastasis was histologically confirmed by frozen sections. Gastrectomy was performed and chemotherapy given at the discretion of the surgeons for the patient who was diagnosed at laparotomy to have a small number of peritoneal deposits (P1–P2 by the Japanese Classification for Gastric Carcinoma [13]). Gastrectomy was avoided for those with extensive invasion to the retroperitoneum and for those with extensive peritoneal dissemination graded as P3 by the Japanese Classification of Gastric Carcinoma. When potentially curative R0 resection [14] was considered possible, total gastrectomy with splenectomy and D2 lymphadenectomy as proposed by Maruyama [15] had been the treatment of choice. Efforts were made to avoid distal pancreatectomy unless direct invasion to the pancreas was observed.

Histopathological evaluation of the resected specimens

The resected specimens were examined by the pathologists after hematoxylin and eosin staining, depth of cancer invasion (pT categories), and the number of metastatic lymph nodes (pN categories) were evaluated for clinical staging according to the Tumor-Node-Metastasis classification [14]. The nodal status was not evaluated histopathologically in 30 patients with disseminated or locally advanced disease, including 28 patients who did not undergo gastrectomy.

Follow-up program

The patients were followed for a median of 3,509 (range, 1,825–5,295) days or until death. Follow-up program consisted of interim history, physical examination, hematology, and blood chemistry panels, including serum CEA and CA19-9 values, which were performed every 3 months for the first postoperative year, and every 6 months

thereafter. Abdominal ultrasonography or computerized tomography was performed every 6 months. Autopsy or second-look surgery was not always performed, and failure analysis is based primarily on clinical observations and information obtained through computerized tomography, bone scintigram, physical examination, and clinical symptoms.

Statistical analysis

Survival analysis stratified by curability of surgery was performed with all 178 patients. Survival analysis with reference to the number of nodal metastasis was performed with 148 patients who underwent gastrectomy and had detailed data regarding the number of lymph nodes removed. Failure analyses were performed in 172 patients whose patterns of disease failure had been recognized. The Kaplan-Meier method was used to plot the survival curves. The Student's t test was used to evaluate the difference in the number of metastatic lymph nodes between a group of patients who developed bone metastasis and a group who did not. χ^2 test was performed to evaluate correlation between the number of metastatic lymph nodes and the incidence of bone, liver, or distant lymph node metastasis. Cox regression hazard model was used for multivariate analysis to find a significant independent prognostic factor.

Results

Patient demographics

Mean age of the patients was 59 ± 11.5 years (male:female ratio, 90:88). A total of 150 patients were treated with gastrectomy (115 total, 1 proximal, and 34 distal gastrectomies), and the remaining 28 underwent exploratory laparotomy or laparoscopy. Extended lymphadenectomy of D2 or more had been performed in 101 patients. R0 resection was performed only for 82 patients (46% of those who underwent laparotomy). Serosal invasion was found in 158 patients (89%), of which 54 had invasion to the adjacent structures (pT4). Node metastasis also was frequent, and only 22 patients were found after systemic lymphadenectomy to have no lymph node metastasis. The mean number of metastatic nodes was 15 among those who underwent gastrectomy and 10.2 among those treated by R0 resection. Despite the preoperative diagnosis through conventional imaging studies that these patients have no distant metastasis, peritoneal deposits were found at laparotomy in as many as 78 patients (44%), confirming the well-documented fact that laparoscopic examination is mandatory for accurate staging of advanced gastric cancer.

Operative mortality

Only seven patients died of causes other than cancer, of which two patients had recurrent disease at the time of death. One patient died on the 3rd postoperative day as a result of heart failure, and another on the 245th postoperative day after a prolonged effort to control the surgical complication. No other perioperative death was observed, and postoperative mortality rate was 1.1%.

Survival of the patients according to residual tumor classification, respectability, and the number of metastatic lymph nodes

The prognosis of 178 patients with linitis plastica in this study was poor, with a 50% survival time of 13.8 months. Median survival time of patients treated with R0 resection was 30.2 months, those treated with palliative resection was 8.2 months, and those who did not undergo a gastrectomy was 7.8 months, with no difference in survival between the latter two groups (Fig. 1). Survival analysis of the patients stratified by the pN categories according to the TNM classification revealed that only a subset with metastatic lymph nodes >16 (pN3) exhibited remarkably poor prognosis (Fig. 2). On the other hand, patients without nodal metastasis (pN0) did not survive any longer than the node-positive patients.

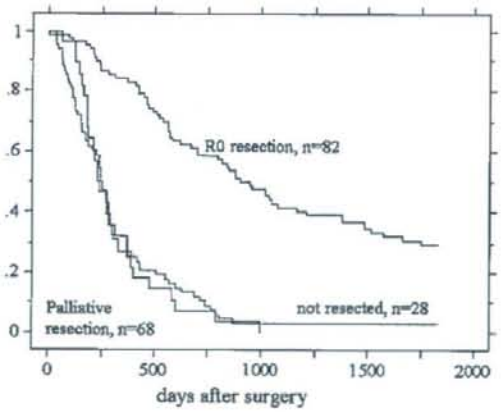

Fig. 1 Survival of patients with linitis plastica-type gastric carcinoma ($n = 178$) stratified according to the surgery performed: R0 resection ($n = 82$), palliative resection ($n = 68$), and exploratory laparotomy or laparoscopy ($n = 28$)

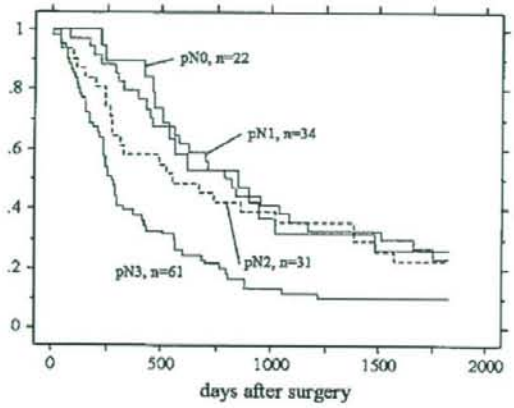

Fig. 2 Survival of patients with linitis plastica-type gastric carcinoma who underwent gastrectomy with systemic lymphadenectomy ($n = 148$) stratified according to the number of metastatic lymph nodes: pN0 = no metastatic lymph nodes ($n = 22$); pN1 = 1–6 metastatic nodes ($n = 34$); pN2 = 7–15 metastatic nodes ($n = 31$); pN3 = ≥16 metastatic nodes ($n = 61$)

Patterns of disease failure: the association with pN stage and prognosis

Clinically observed patterns of disease failure were peritoneal carcinomatosis in 131, distant lymph nodes in 17, bone or bone marrow metastasis sometimes leading to disseminated intravascular coagulation in 13, hepatic in 11, local in 6, and other sites in 8. Twenty-eight patients suffered from multiple patterns of metastasis, including eight patients with metastatic disease in three distinct sites. Survival of patients with metastases and recurrences to the bone, liver, and distant nodes were invariably brief, whereas a fraction of patients with peritoneal carcinomatosis survived longer (Fig. 3). χ^2 analysis showed a remarkable and statistically significant trend of patients with > 16 metastatic lymph nodes suffering from bone metastasis (Table 1), whereas there were only weak correlations between a high pN stage and hepatic metastasis or recurrences in the distant nodes (data not shown). The number of metastatic nodes among patients with bone metastasis was 26.7 ± 7.7 and was significantly greater than the number among other patients (14 ± 13.6; $p = 0.0026$). Peritoneal carcinomatosis occurred commonly and regardless of the nodal status in patients with linitis plastica-type gastric cancer.

Independent prognostic factors to predict and long-term survival

Univariate analyses identified sex, invasion to the adjacent structures (T4 status), finding of the peritoneal seeding (positive versus negative), hepatic metastasis and presence > 16 metastatic nodes (pN3 versus others), and R-classification (R0 versus R1 and R2) as significant prognostic factors. Of these, R-classification, pN3 status,

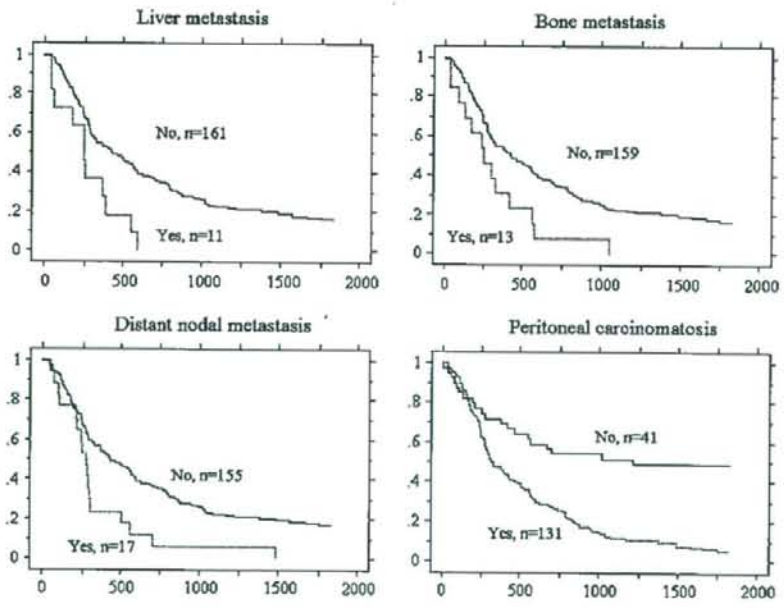

Fig. 3 Survival of patients with linitis plastica-type gastric carcinoma stratified by whether they suffered from a specific type of metastasis or recurrence. Although patients rarely had hepatic or bone metastasis, patients with these metastases had extremely poor prognosis

Table 1 Bone metastasis among patients with a greater number of metastatic lymph nodes

	Bone metastasis		
	No	Yes	
pN0 (no. of metastatic nodes 0)	19	0	19
pN1 (no. of metastatic nodes 1–6)	34	0	34
pN2 (no. of metastatic nodes 7–15)	30	1	31
pN3 (no. of metastatic nodes ≥16)	51	10	61
	134	11	145

$p = 0.009$

Of 150 patients who underwent gastrectomy, 3 patients with no information regarding patterns of disease failure and 2 in whom the number of metastatic lymph nodes had been unavailable were excluded

and sex were independent significant prognostic factors (Table 2).

Discussion

Prognosis of linitis plastica type gastric cancer remains dismal compared with other types of gastric carcinoma [8]. More radical approach with super-extended lymphadenectomies has been proposed in Japan several years ago [6, 7], but the current consensus derived from recent data is that patients with peritoneal deposits do not benefit from surgical treatments, as observed in the current study in which patients treated by palliative resection did not live longer than those who did not undergo gastrectomy. Furthermore, the authors have shown through molecular detection using CEA RT-PCR that free cancer cells can be found scattered in the peritoneal cavity of 70–80% of patients with the linitis plastica [16]. Although these findings are discouraging, some evidence pointing to the efficacy against peritoneal carcinomatosis through the use of recent cytotoxic agents, such as S-1 and paclitaxel have began to emerge [17, 18]. Clinical trials testing more intensive strategy to eliminate the intraperitoneal minimal disease, such as intraperitoneal chemotherapy [10, 12] or chemohyperthermia in combination with surgery [19–21], could now be seriously considered.

One drawback to this approach is the possibility that some patients may die due to rapid progression—particularly due to the pattern of failure other than the peritoneal metastasis. It is now clear that the risk factors for the early death are the invasion to the adjacent structure and a large number of metastatic lymph nodes. Bone metastasis, often leading to disseminated intravascular coagulation, was observed in 13 of 178 patients (7.3%) and was associated with a particularly poor prognosis. This pattern of failure is mostly observed among patients with pN3-stage disease (>16 metastatic nodes). A small proportion of patients with no nodal disease did not show favorable prognosis compared with those with node-positive disease. Thus, biology of node-negative cancer does not seem utterly different from that of node-positive cancer in terms of survival time and tendency to develop into peritoneal carcinomatosis. It remains clear, however, that a great number of metastatic nodes do reflect a particularly aggressive biology.

Our data delineated the well-documented fact that accurate preoperative staging for advanced gastric cancer cannot be obtained without laparoscopic exploration [22, 23]. Despite this knowledge, the authors have not been able to offer this procedure to all patients with potentially operable gastric cancer due to limited capacity of the operating facility. However, patients with linitis plastica now receive laparoscopy immediately before surgery to rule out extensive peritoneal disease, because the risk of finding peritoneal deposits has been repeatedly shown to be substantial for this type of gastric cancer [16]. Nevertheless, those with minimal metastatic disease may still be offered a multimodal treatment strategy, including surgical resection, in which case gastrectomy is performed immediately after the exploratory laparoscopy.

Conclusion

Although peritoneal carcinomatosis remains the most feared pattern of disease failure in the linitis plastica-type cancer, bone metastasis leading to early death is observed

Table 2 Multivariate analysis of relevant prognostic factors among patients with linitis plastica who were treated with gastrectomy and had data regarding the number of metastatic lymph nodes available ($n = 148$)

Variable		Hazard ratio	95% confidence interval	p value
R classification	R1 and R2	3.16	1.74–5.75	0.0002
No. of metastatic LNs	≥16	1.64	1.12–2.41	0.0112
Gender	Male	1.64	1.12–2.41	0.0112
Invasion to the surroundings	Positive	1.71	1.08–2.7	0.0213
Peritoneal deposits	Positive	1.04	0.62–1.74	0.8901
Hepatic metastasis	Positive	0.97	0.44–2.11	0.9464

in 7.3% of patients, and these patients were found to have extensive nodal disease. pN3 stage (>16 metastatic lymph nodes) is an adverse prognostic determinant, possibly resulting in early recurrences outside the peritoneal cavity. These patients may be candidates for aggressive systemic therapies rather than locoregional intraperitoneal therapies.

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Operation

D2リンパ節郭清：適応と手技

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D2リンパ節郭清：適応と手技

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I. 適　応

現行のガイドラインでは，治癒切除可能な進行胃癌のすべてと早期胃癌の一部にD2リンパ節郭清を行うように記載されている。しかし，早期胃癌の術式に関しては，組織型，術中のリンパ節所見（sN）および術前の病巣の大きさを加味して，郭清範囲を決定するようになっており，実際のところ，組織型を除いた他の2因子が的中する確率は良くて2/3と予想できる。したがって，結果的にD2郭清の適応ではなかった症例にD2を実施することは日常的に起こるし，その逆もしかりである。

実際D2郭清がD1＋βに比べて，どれだけ侵襲が大きいか，あるいは術後の合併症を増やすかということについては，明確な比較はされていないし，比較したとしても大きな差があるとは思えない。D1のみとD2には，ことにBMI 30以上の患者などでは，合併症発生率に差があることは想定できるが，幽門側胃切除でD2とD1＋βに差があるとは思われない。胃全摘では，脾摘や膵脾合併切除をD2の一部に含めれば話は別であるが，脾摘もしない不完全なD2とD1＋βとでどれだけの差があるかは疑わしい。縮小手術を行い，術後の病理がわかってから，再手術を行って追加郭清することを考えれば，少しでも不安がある場合にはD2を行うべきである。現行のガイドラインは，術中のリンパ節の迅速診断を多用する癌研のデータを元に作られたもので，一般病院では，やりそこねを避けることのほうが重要であり，SMであれば積極的にD2郭清を行う方針が無難と筆者は考えている。病変の部位による適応は取扱い規約を参照していただきたい。

結論としては，D2は術前にSMと診断されるすべての早期胃癌と治癒切除可能な進行胃癌のすべてに適応してよいと思われる。ただし，脾摘の適応と患者のリスク要因はこの議論と別に考える必要がある。

II. 手　技

1. 胃全摘・幽門側胃切除に共通の部分

a) 大網切除とbursectomy

適応補足：bursectomyについては，癌の浸潤を認めないBursa Omentalis切除の意義を示す明確なエビデンスはないので，絶対適応は後壁の腫瘍が浸潤もしくは炎症性に癒着する場合となる。相対適応は後壁に存在する進行癌でT4の可能性を否定できない症例。大網切除も同じであるが，大網付着部に浸潤している進行胃癌では，bursectomyはこだわらないとしても，完全な大網切除は行うほうがいいと思っている。しかし，No.6郭清を行うすべての症例

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