proportion of patients with nodal disease beyond the perigastric region, although this has not been confirmed in Western randomized trials[15,16]. Although long-term follow-up revealed significantly better disease-free survival for the D2 group in the subset with node-positive cancer[17], this difference did not extend to all patients in the trial, in part owing to the unacceptably high mortality rate associated with D2 resection[8]. JCOG 9501, a Japanese multi-institutional prospective randomized trial comparing D2 with more extended resection, has superior quality control of surgical procedures and reliability of data[13] than retrospective Japanese studies and Western prospective trials.

The most significant risk factor for both surgical and overall complications in the present study was pancreatic resection, although it should be noted that this was performed in only 4·2 per cent of patients, compared with 30·3 and 15·2 per cent in the UK Medical Research Council (MRC) and Dutch trials respectively[15,16]. The rate of pancreatectomy was lower in the present series because a pancreas-preserving technique[18,19] was generally used, whereas distal pancreatectomy and splenectomy were integral parts of D2 dissection in the Dutch trial unless cancer was located in the distal stomach. The low morbidity rate in the present study may well be related to pancreas preservation[18,19]. The success of this approach has also been reported in a multicentre phase II trial of D2 dissection in Northern Italy[20].

Splenectomy, on the other hand, was not an independent determinant of risk, possibly because it was never performed with distal gastrectomy in the present series. In the Dutch randomized trial a high mortality rate after distal gastrectomy was attributed in part to necrosis of the remnant stomach as a result of splenectomy and division of the short gastric arteries[21]. The survival benefit of splenectomy performed solely to facilitate dissection of lymph nodes close to the splenic hilum has been questioned, however, and a randomized trial to explore this issue is ongoing[22].

Age was not an independent risk factor for overall complications in this study, in contrast to the Dutch trial in which age over 65 years was a significant risk factor for hospital death and overall complications[21]. This discrepancy may be attributed to the fact that only patients aged 75 years or less were eligible for inclusion in the JCOG 9501[13], whereas other trials have included older patients[15,16]. Japanese patients were, on average, 8 years younger than Dutch patients[23]; consequently the proportion of patients over 65 years of age was 29·8 per cent in the present series as opposed to 51·3 per cent in the Dutch trial[16]. This age distribution may account for the very low incidence of perioperative cardiovascular events in the present series, another factor that may have influenced the low morbidity and mortality rates.

Extended lymph node dissection may be hampered by excess bodyweight[24–26] and in the present study BMI was a significant risk factor for major surgical complications. Caucasians in general have a higher BMI than Japanese and the incidence of morbid obesity is significant among patients in the USA and Europe. Only 14·7 per cent of the present patients had a BMI of 25 kg/m^2 or greater, whereas one-third of the US population is obese (BMI over 27 kg/m^2)[27]. These data suggest that the patients' physique favours Japanese patients when major gastric cancer surgery is performed.

The extent of lymph node dissection (D2 *versus* D3), surgical volume and the period in which the operation was performed had no impact, suggesting that there were no learning curve issues. Although D2 resection has long been a standard procedure in Japan, all surgeons in the trial were experts from specialized centres who had sufficient experience with D3 resection through numerous other studies. Of the variables reflecting difficulties encountered during surgery, prolonged operating time was identified as a significant independent risk factor for both overall and major surgical complications. However, amount of blood loss and blood transfusion were significant only in univariate analysis; this may be attributable to multicolinearity, as these two factors are closely related.

Gastrectomy with extended lymphadenectomy is feasible and safe in Japan, provided that older patients with co-morbidity are excluded and pancreatectomy is reserved for lesions with direct invasion to the pancreas. Obese patients should be treated with caution, however, as they have a significant risk of developing major surgical complications. Hopefully, with careful patient selection, appropriate surgical expertise and pancreas and spleen preservation[8] where possible, equally good results, rarely achieved previously[20,28], will be realized in the West.

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Participating institutions and chief participants: National Cancer Center Hospital (M. Sasako, T. Sano), Niigata Cancer Centre Hospital (A. Nashimoto, H. Yabuzaki), National Shikoku Cancer Centre (A. Kurita, Y. Kubo), Osaka Medical Center for Cancer and Cardiovascular Diseases (M. Hiratsuka, I. Miyashiro), Osaka National Hospital (K. Kobayashi, T. Tsujinaka), National Cancer Centre Hospital East (T. Kinoshita), Tokyo Metropolitan Komagome Hospital (K. Arai, Y. Iwasaki), Aichi Cancer Centre (T. Kito, Y. Yamamura), Osaka Medical College (K. Okajima, M. Tanigawa), International Medical Centre of Japan (O. Kobori, T. Shimizu), Sakai City Hospital, Kanagawa Cancer Centre (H. Furukawa, H. Imamura), Tokyo Metropolitan Bokuto Hospital (M. Kitamura, S. Inoue), Nagaoka Chuo General Hospital (T. Yoshikawa, T. Shimizu), Niigata City General Hospital (K. Aizawa), Cancer Institute Hospital (K. Ota, S. Oyama), Kyoto Second Red Cross Hospital (H. Tokuda, S. Takahashi), Saitama Cancer Centre, Hiroshima City Hospital (Y. Tanaka, K. Uchida), Kanazawa University (K. Miwa, T. Fujimura), Gifu Municipal Hospital (H. Tanemura, H. Oshita), Kagoshima University (T. Aiko, S. Hokita), Iwate Medical University (M. Terashima, K. Saito) and Okayama University (H. Isozaki).

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Seminars in Oncology

Overview of Adjuvant Therapy for Resected Gastric Cancer: Differences in Japan and the United States

Atsushi Ohtsu[a] and Mitsuru Sasako[b]

Survival in adjuvant chemotherapy following resected gastric cancer has been studied by both Japanese and Western investigators using varied chemotherapy regimens in different target patients. Gastrectomy with D2 lymphadenectomy is the standard in Japan, and trials of adjuvant therapy in these patients have shown no survival advantages over surgery alone. In the United States, where 5-year survival rates in patients with gastric cancer are much lower following potentially curative surgery, adjuvant therapy has shown a survival benefit. The differences observed in these trials may result from the additional experience that Japanese surgeons have gained because of the higher incidence of gastric cancer there, or because of this increased incidence, there are more stringent screening guidelines in place and these cancers are possibly being diagnosed at an earlier stage. The Japanese viewpoint on the use of adjuvant therapy in patients with gastric cancer following potentially curative resection is that the quality of surgery, including diagnostic and pathologic procedures, is a more important prognostic factor than adjuvant chemotherapy. Also, they have determined from previously conducted clinical trials that patients with stage 1–2 tumors should be excluded from the target populations of randomized trials. Until the results of INT-0116 became available, there had been no improvement, or only marginal improvement, in overall or disease-free survival for patients receiving adjuvant chemotherapy following gastric cancer resection in the United States and Europe.
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Gastric cancer is the fourth most common cancer worldwide and the second leading cause of cancer death, accounting for 10.4% of cancer deaths globally. In 2000, there were an estimated 865,000 new cases of gastric cancer.[1] Approximately 50% of patients with gastric cancer have metastasis at diagnosis, and of those without metastasis at diagnosis, only 50% are eligible for gastric resection. In fact, gastric cancer resection typically occurs in late-stage cancer, when the cancer has already spread to the peritoneal cavity, lymph nodes, or blood vessels.[2] The 5-year survival rate in the United States and most Western countries is between 5% and 15%.[3] Age-standardized incidence rates of gastric cancer are highest in Japan; however, because of mass screening that leads to earlier disease stage at diagnosis, the 5-year survival rate is approximately 52%.[1] Adjuvant therapy for gastric cancer after surgical resection has been investigated for many years. Its efficacy in gastric cancer remains questionable because no concrete evidence exists to show that adjuvant therapy for resected gastric cancer improves survival. Questions exist regarding the necessity, most useful chemotherapy combinations, worldwide standardization of lymph node dissection grade, eligibility for surgery based on tumor stage, and the benefit of individualization of therapy for adjuvant chemotherapy for gastric cancer.

Adjuvant Therapy for Resected Gastric Cancer

Early trials of adjuvant therapy for gastric cancer in Japan evaluated the use of mitomycin-C (MMC), and later, a combination of MMC and oral fluoropyrimidines. These studies showed a small survival benefit compared with surgery alone. Re-examination of these data led to additional studies of these agents. Pooled data showed borderline survival benefit for oral fluoropyrimidines compared with surgery alone.

Recent studies have shown either no differences or marginal improvement in overall survival (OS) with adjuvant chemotherapy compared with surgery alone.[4–6] Three meta-analyses of randomized, controlled clinical trials comparing surgery alone with adjuvant chemotherapy showed only

[a]National Cancer Center Hospital East, Kashiwa, Japan.
[b]National Cancer Center Hospital, Tokyo, Japan.
Dr Ohtsu has no significant financial relationships to disclose.
Address reprint requests to Astushi Ohtsu, MD, National Cancer Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chilea, 277-8577 Japan; e-mail: aohursu@east.ncc.go.jp

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Table 1 Meta-Analyses Randomized Clinical Trials in Patients With Resected Gastric Cancer (Adjuvant Chemotherapy *v* Surgery Alone)

Study	Trials Analyzed (No.)	HR	95% CI
Hermans et al (1993)[7]	11	0.82	0.68–0.97
Earle and Maroun (1999)[8]	13	0.80	0.66–0.97
Mari et al (2000)[6]	20	0.82	0.75–0.89

Abbreviations: CI, confidence interval; HR, hazard ratio.

marginal advantages of adjuvant chemotherapy (Table 1).[6–8] As a result of these meta-analyses, adjuvant chemotherapy following curative surgery for gastric cancer continues to be an investigational approach.[6] The use of meta-analysis has been the trend in determining benefits of adjuvant chemotherapy for resected gastric cancer, but recent studies suggest standardization of lymph node dissection protocols worldwide, tumor stage qualification for target populations of randomized trials, and surgery quality along with diagnostic procedures are all needed to qualify the results of these meta-analyses.

Adjuvant Therapy for Resected Gastric Cancer in Japan

Three randomized controlled clinical trials have been conducted or are currently underway in Japan comparing surgery with or without adjuvant chemotherapy (Table 2).[9,10]

Nashimoto et al[9] conducted a randomized, multicenter, phase III study ([Japan Clinical Oncology Group] JCOG-9206-1) to evaluate the survival benefit of adjuvant chemotherapy in patients with serosa-negative gastric cancer following curative resection. Patients were randomly assigned to observation or chemotherapy with MMC 1.33 mg/m^2, 5-fluorouracil (5-FU) 166.7 mg/m^2, and cytarabine 13.3 mg/m^2 twice weekly for the first 3 weeks after surgery, and oral 5-FU 134 mg/m^2 daily for the next 18 months. The primary endpoint was relapse-free survival. The 5-year relapse-free survival among patients who received chemotherapy in addition to surgery was 88.8% versus 83.7% in patients who underwent surgery alone; these differences were not statistically significant ($P = .14$). The 5-year survival in the chemotherapy plus surgery group was 91.2% versus 86.1% in patients who had surgery alone ($P = .13$). Fewer patients who received the combination of chemotherapy plus surgery experienced cancer recurrence (7.1%) than did patients who received surgery alone (13.8%). Because there was no relapse-free or OS benefit with this adjuvant chemotherapy regimen in patients with macroscopically serosa-negative gastric cancer after curative resection, and there were no remarkable differences in modes of cancer recurrence between the arms, the investigators concluded that adjuvant chemotherapy with this regimen is not recommended for this patient population in clinical practice.

Nakajima et al[10] conducted a randomized, phase III trial (JCOG-8801) in patients with T1 and T2 gastric tumors, who were either observed or received chemotherapy following resection to assess the survival benefit of adjuvant chemotherapy after curative gastrectomy for macroscopically serosa-negative gastric cancer. Patients who were randomly assigned to the chemotherapy group received MMC 1.4 mg/m^2 and 5-FU 166.7 mg/m^2 twice weekly for 3 weeks and oral uracil-tegafur (UFT) 300 mg daily for 18 months following surgery. At the median follow-up time of 72 months, 5-year survival was 82.9% for the observation group versus 85.8% for patients receiving chemotherapy. This difference in survival was not significant (log-rank test, $P = .17$; hazard ratio, 0.738; 95% confidence interval, 0.498–1.093). Toxic effects were generally mild. For patients with T1 (mucosal or submucosal) gastric tumors, 5-year survival was 94.9% in the observation group and 92.0% in the chemotherapy-treated group. Survival for T2 (muscularis propria or subserosa) was 76.9% and 83.0% for the observation and chemotherapy treated groups, respectively; the differences observed between the two groups were not statistically significant. The respective cancer recurrence rate was 13.7% versus 10.1% of the observation and chemotherapy-treated groups. Death from cancer occurred in 0.4% versus 1.0% of the observation and chemotherapy groups, respectively. The investigators concluded that there was no survival benefit with this adjuvant chemotherapy regimen for patients with macroscopically serosa-negative gastric cancer (T1 and T2) after surgery. They also recommended that T1 cancer patients be excluded

Table 2 Japanese Studies of Adjuvant Chemotherapy Versus Surgery Alone in Patients With Resected Gastric Cancer

Study/Trial	Target Patients	Treatment	No. of Patients	5-Year Survival (%)	*P* Value
Nashimoto et al/JCOG-9206-1[9]	T1-T2	5-FU plus MMC plus cytarabine followed by oral 5-FU	127	91.2	.13
	T1-T2	Observation	123	86.1	
Nakajima et al/JCOG-8801[10]	T1-T2	5-FU plus MMC followed by UFT	288	85.8	.17
	T1-T2	Observation	285	82.9	
JCOG 9206-2	T3-T4	5-FU plus cisplatin followed by UFT	135	*	*
	T3-T4	Observation	133	*	

Abbreviations: 5-FU, 5-fluorouracil; JCOG, Japan Clinical Oncology Group; MMC, mitomycin-C; UFT, uracil-tegafur.
*Not yet available: data will be available in 2005.

from future trials because surgery alone resulted in a good survival rate.

Results of a randomized phase III clinical trial evaluating patients with T3 and T4 gastric tumors in Japan will be available in 2005. This ongoing study has enrolled 133 patients who are being observed post-surgery and 135 patients who are receiving 5-FU plus cisplatin followed by UFT.

Another phase III study of adjuvant chemotherapy for gastric cancer in Japan (Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer [ACTS-GC])[11] began accruing patients with stage II, IIIA, or IIIB gastric cancer in October 2001. Anticipated accrual is 1,000 patients (500 patients per arm), and the primary objective is to assess OS. Expected 5-year survival of the control arm compared with the test arm is 70% versus 78%, respectively. There are 108 institutions involved in the study, 825 patients have been accrued, and the expected final accrual was completed in the third quarter of 2004. Table 2 summarizes the results of these studies.

Adjuvant Therapy for Resected Gastric Cancer in the United States

The development of adjuvant chemotherapy for gastric cancer in the West was not based on combinations with MMC, but rather 5-FU. While sometimes showing a survival benefit compared with surgery alone, these 5-FU–containing regimens have been criticized for lack of regimen standardization as adjuvant chemotherapy.

Macdonald et al[12] conducted the randomized, multicenter, phase III intergroup INT-0116 study that evaluated survival at 3 and 5 years following adjuvant chemoradiotherapy (chemoRT) in patients with adenocarcinoma of the stomach or gastroesophageal junction after curative resection. A total of 556 patients were enrolled in the trial; 275 patients were randomly assigned to receive surgery only, and 281 patients received surgery plus chemoRT. Patient tumor stage was 1 (n = 14), 2 (n = 74), 3 (n = 175), and 4 (n = 18). Of the 552 patients whose surgical records were reviewed, 10% had undergone a formal D2 lymph node dissection, 36% a D1 dissection, and most patients (54%) a D0 dissection. Adjuvant chemotherapy consisted of 5-FU 425 mg/m^2 plus leucovorin 20 mg/m^2 per day, for 5 days, followed by 4,500 cGy of radiation therapy (RT) (180 cGy/day), given 5 days per week for 5 weeks. Modified doses of 5-FU and leucovorin were given on the first 4 and the last 3 days of RT. One month after the completion of RT, two 5-day cycles of 5-FU (at 425 mg/m^2/day) plus leucovorin (20 mg/m^2/day) were given 1 month apart. The median 5-year survival was 36 months in patients who received chemoRT plus surgery versus 27 months in patients who received surgery alone. The 3-year survival rates were 50% versus 41% in the chemoRT plus surgery groups and surgery-only groups, respectively. The median duration of relapse-free survival was significantly longer in patients who received chemoRT plus surgery versus those receiving surgery only (30 v 19 months; $P < .001$, log-rank test). Relapses were reported in 64% of patients who received surgery only versus 43% of patients who received surgery plus chemoRT. The investigators concluded that local-regional RT plus fluoropyrimidine-based chemotherapy as adjuvant treatment significantly improves OS and relapse-free survival in patients with gastric cancer. This study also showed that the most frequently performed lymph node dissection in the United States was a D0 lymphadenectomy.

Table 3 Comparison of Results of INT-0116 and JCOG-9501[16]

	INT-0116	JCOG-9501
Surgery (%)	D0: 54 D1: 36 D2: 10	D2: 50 D3: 50
Adjuvant therapy	CT: 5-FU and LV RT: 45 Gy	None
No. of patients	281 (CT arm)	523
Tumor location (%)	Antrum: 53 Gastric body: 24 Cardia: 21 Multiple lesions: 2	Lower-third: 41 Middle-third: 39 Upper-third: 19
pT stage (1:2:3:4)	1: 14 pts 2: 74 pts 3: 175 pts 4: 18 pts	1: 23 pts 2: 257 pts 3: 230 pts 4: 13 pts
Survival (%)	3-yr: 50 5-yr: 42	5-yr: 71.4

Abbreviations: CT, chemotherapy; 5-FU, 5-fluorouracil; LV, leucovorin; pT, pathologic tumor stage; RT, radiation therapy; pts, patients.

Future Directions

Individualizing chemotherapy in various types of cancers has recently received much focused interest. In gastric cancer, individualized chemotherapy is based on subgroups of patients who are evaluated through molecular targeting that includes the use of the epidermal growth factor and vascular endothelial growth factor receptors. Recent studies have confirmed that: (1) the use of cDNA microarray analysis to detect expression files of cancer tissues improves the understanding of molecular changes during the development of gastric cancers, and (2) the expression of the S100A11 gene was useful to distinguish lymph node metastases of gastric cancers.[13–15] The evaluation of individual genetic information may prompt the future development of more personalized adjuvant chemotherapy regimens.

Discussion

In the United States, adjuvant chemoRT is considered a standard treatment and is based largely on the results of INT-0116, whereas in Japan the use of adjuvant therapy is the standard. Sasako[16] compared the results of INT-0116 with those of JCOG-9501 (Table 3).[16] INT-0116 showed a survival advantage with chemoRT plus surgery in patients with gastric cancer following curative resection; however, the 3-year survival rate in INT-0116 was only 50% which, when compared with Japanese studies, is lower than the 3-year

survival rate in patients who received surgery alone. The JCOG-9501 trial was designed to compare survival in patients with D2 versus D3 lymph node dissection without adjuvant chemotherapy or RT, while in INT-0116 the majority of patients had a D0 or D1 lymph node dissection and also received chemoRT. In the Japanese trial JCOG-9501 there was a higher proportion of patients with T2 disease than in the INT-0116 trial (49% v 26%) and also a lower proportion of patients with T3 disease (44% v 62%), respectively. Five-year survival rates were considerably higher (71%) in patients who received surgery only in the Japanese trial versus 42% in patients who received surgery plus chemoRT in the US trial. The Japanese interpretation of these results are that D0 or D1 lymph node dissection plus chemoRT is better than D0 or D1 lymph node dissection alone, but may be worse than D2 surgery alone. Determining whether a D0 or D1 lymph node dissection can replace a D2 lymph node dissection should be evaluated in a randomized, controlled clinical trial; however, D2 lymph node dissection in the United States appears difficult to achieve. Also, whether chemoRT after D2 surgery can improve the results of surgery alone is another unresolved issue.

Several factors should be considered when interpreting the differences in the results of these trials. Because the incidence of gastric cancer is several times higher in Japan than in the United States there are more stringent screening programs in place that may affect the baseline condition of patients accrued onto clinical trials. Moreover, the standard curative resection in the United States is gastrectomy plus D0 or D1 lymphadenectomy, whereas in Japan gastrectomy plus D2 lymphadenectomy with en bloc dissection of the lymph nodes around the common hepatic artery and the splenic artery is used. Japanese surgeons believe that these differences may be because of the additional experience they have acquired due to the higher incidence of gastric cancer in Japan.

The Japanese viewpoint on the use of adjuvant therapy in patients with gastric cancer following curative resection is that the quality of surgery, including diagnostic procedures or pathologic procedures, will be a more important prognostic factor than adjuvant chemotherapy because no survival advantages have been shown in patients with gastrectomy and D2 lymph node dissection in clinical trials. However, standard adjuvant chemotherapy after good local control by surgery (D2 or more) has yet to be established and remains an urgent issue. Also, data from clinical trials indicate that patients with stage 1–2 tumors should be excluded from the target populations of randomized, controlled clinical trials. In the United States and Europe there had been either no or only marginal improvement in OS or disease-free survival for patients receiving adjuvant chemotherapy following gastric cancer resection, until the results of INT-0116 became available, at which time the issue of postoperative chemoRT became the standard treatment for patients with gastric carcinoma. The question as to whether or not chemoRT can improve the results of D2 surgery alone remains unsolved.

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特集 臨床腫瘍学の現状と展望

V．がん薬物療法の実際
4．消化器癌
2）胃　癌
b）進行胃癌のアジュバント療法

Saka Makoto 阪　眞　Sasako Mitsuru 笹子三津留*
*国立がんセンター中央病院外科

はじめに

明らかな遺残腫瘍のない手術，すなわち治癒切除後の再発予防を期待して行われるのが補助療法である．胃癌治療におけるその歴史は長く，1950年代から，様々な臨床試験が行われてきた．しかし，統計学的にその有用性を実証した研究は少なく，欧米では長い間，その有効性に対し否定的な風潮であった[1,2]．2001年に日本胃癌学会から出された『胃癌治療ガイドライン』でも，補助化学療法について，「現在まで確実な延命効果を証明したevidenceは乏しい．しかし複数の無作為化比較対照試験のmeta-analysisでは延命効果を示唆する結果が報告され，延命効果を指標とした臨床試験を引き続き施行すべきである」と記載されている．しかし近年になり，良くデザインされた質の高い無作為化比較対照試験(randomized controlled trial：RCT)のいくつかが，補助療法の延命効果を肯定する結果を報告するようになり，状況は大きく変化してきた．

本稿では，欧米と日本で行われた過去のRCTのレヴューと，最近の臨床試験について概説する．

欧米における胃癌補助化学療法

補助療法の有効性を評価するためには，手術単独群を対照としたRCTが必要である．日本に比べ，手術単独の成績が悪い欧米では，真に有効な補助療法が求められ，行われたRCTはほぼ一貫して手術単独群を対照としている．欧米における胃癌補助化学療法は1960年代にThio-TEPAを用いた研究から始まり[3]，その後は5-FUを中心として5-FU＋MeCCNU，MFC，FAMなどの多剤併用療法が研究された[4-20]．しかし，多くの研究はその有用性を示すことができなかった．その中で，1983年にAlcobendasら[6]がMMC(mitomycin C)の，1996年にNeriら[17]がEPI＋LV＋5-FU(epirubicin＋leucovorin＋5-fluorouracil)の，1999年にCireraら[20]がMMC＋tegafurの，手術単独に対する有意な効果を報告している(表1)．しかし，いずれの研究も，サンプルサイズが小さく，明らかなevidenceにはなり得ていない．

2001年，Macdonaldら[21]は，手術単独群を対照にした大規模RCTで初めてのpositive dataを報告した．これは術後化学放射線療法のRCT(SWOG 9008/INT 0116)で，手術単独群を対照とし，治療群は，術後5-FU＋LV療法に総量45 Gyの体外照射を組み合わせた治療を受けた．手術単独群275例，治療群281例と十分なサンプルサイズをもつこの研究で，overall survival ($p=0.005$)，relapse-free survival ($p<0.001$)ともに有意差をもって治療群の成績が対照を上回り，胃癌に対する術後補助化学放射線療法として，初めて生存期間延長効果を示した．この研究が欧米の臨床腫瘍医に与えた影響は大きく，米国のNational Cancer Institute (NCI)が提供する癌治療ガイドラインであるPhysician Data Query(PDQ)において，胃癌の術後補助化学放射線療法はstandard treatment optionとして採用

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表1　手術単独群を対照に有意差がみられた欧米の補助化学療法RCT

筆頭著者	掲載誌(掲載年)	症例数	レジメン	有効性の評価
Alcobendas	Ann. Surg.(1983)	70	MMC	$p<0.001$
Neri	Br. J. Cancer(1996)	103	EPI+LV+5-FU	$p<0.001$
Cirera	J. Clin. Oncol.(1999)	148	MMC+tegafur	$p=0.04$

MMC：mitomycin C, EPI：epirubicin, LV：leucovorin, 5-FU：5-fluorouracil.

されている．

しかし，わが国にも導入できるかどうかは疑問である．なぜなら，この研究では90%の症例がD0，D1のリンパ節郭清しか受けておらず，わが国で標準的であるD2郭清が行われた症例は10%にすぎない．局所コントロールが不十分なD0，D1手術を局所治療である放射線治療で補いつつ，化学療法の効果を示したともとれる．実際，Hundahlら[22]はこの臨床試験の登録症例を用いて，個々の症例で大きさ，組織型，肉眼型，占拠部位などから各リンパ節の部位別の転移の可能性を評価し，実際の手術で郭清を受けていない場合を理論的遺残と計算して，遺残腫瘍指数を算出した結果，この指数が5を超えると予後が有意に不良となることを発表している．この指数は，D2郭清を行った症例ではほぼ0となる．図らずも，局所コントロールの重要性，ひいてはD2郭清の必要性を示唆する結果となっている．わが国では，D2郭清の安全性は高く，むしろ放射線治療を導入することでmorbidityが高くなる危険性がある．D2郭清に不向きな肥満症例(BMI>30)が30%を占める欧米諸国においてこそ，意味がある結果であると思われる．

日本の胃癌補助化学療法に関するRCT

わが国における胃癌術後補助化学療法の臨床試験の歴史は，1959年の国立病院癌化学療法共同研究班(小山班)[23]より始まる．このRCTは，MMC群，Thio-TEPA群およびMMC+5-FU群など，2～3年ごとに化学療法のレジメンを変え，1978年の第7次研究まで手術単独群を対照として行われたが，化学療法群の優位性を示すことはできなかった．

小山班に少し遅れ，1965年に厚生省今永班の多施設共同RCT[24]がスタートする．今永班は，1973年に終了した第4次研究まで，すべて手術単独群を対照とし，MMC中心のレジメンとの比較を行った．割り付け症例全体で化学療法群の優位性を示す研究はなかったが，後層別解析を行い，StageⅡあるいはStageⅢにおいて，化学療法群が対照に比し良好な生存率であったと報告した．しかし，この当時の臨床試験は大半が封筒法で行われ，除外脱落率が極めて高く，試験の信頼性は低い．1980年に報告されたNakajimaら[25]の研究で，初めて化学療法群(MFC：MMC+5-FU+cytarabine)が手術単独群を上回ったが，サンプルサイズが小さく，さらに同一レジメンで，より大規模に行われた今永班第4次研究で差が出なかったために，evidenceとはなり得なかった．しかし，当時は医師が統計学に関して無知で，臨床試験に対する理解が不足していたために，初期RCTのsuggestive dataをもって，補助化学療法は標準治療として広く普及してしまった．経口フッ化ピリミジン剤や様々な免疫賦活剤の開発も相まって，1970年代後半以降，わが国のRCTは補助(免疫)化学療法同士の比較となる[26-39]．1980年代は，MMC単独あるいは多剤併用療法をactive controlとし，tegafur，免疫療法剤の付加効果を検討した報告が数多く行われたが，当然のごとく補助療法の真の有効性を証明することはできなかった．また，多くの研究が一流誌に投稿されることなく終わり，「薬剤販売のための試験」という痛烈な批判を浴びた．

わが国の癌治療専門施設で構成される日本臨床腫瘍研究グループ(Japan Clinical Oncology Group：JCOG)の胃癌外科グループは，1980年代初めからESAC(Exploratory Study Group of Adjuvant Chemotherapy)として共同研究を展開していた．当初から胃癌術後補助化学療法のRCTでは，対照に手術単独群を置くことが重要であると認識し，1988年から漿膜浸潤陰性胃癌でT2またはリンパ節転移陽性の症例を対象に，手術単独群を対照とするRCTを施行した(JCOG 8801)[40]．補助化学療法としてMMC+5-FU+UFTを採用したが，手術単独群との間に有意な生存率の差を見出すことはできなかった．後層別解析で，pT1はリンパ節転移の有無にかかわらず手術単独でも予後良好であり，補助化学療法が予後を改善する余地がないことが示された．しかし，pT2，pN+では5年生存率で10%以上の差(78%対67%)が認められ，この結果は後述するN・

表2　最近の日本の手術単独群を対照にした補助化学療法RCT

	対　象	症例数	レジメン	有効性の評価
JCOG 8801	漿膜浸潤陰性pT2 or pN＋	573	MMC＋5-FU＋UFT	NS
JCOG 9206-1	漿膜浸潤陰性	252	MFC＋oral FU	NS
JCOG 9206-2	漿膜浸潤陽性	268	CDDP ip＋CDDP iv ＋5-FU iv＋oral FU	NS
N・SAS-GC	pT2，pN1～2	188	UFT	p＝0.0176
ACTS-GC	StageⅡ，Ⅲ	1,000	TS-1	?

MMC：mitomycin C, 5-FU：5-fluorouracil, UFT：tegafur-uracil, MFC：MMC＋5-FU＋cytarabine, CDDP：cisplatin, TS-1：tegafur-gimeracil-oteracil potassium.

SAS-GC(1997年～)の対象絞り込みの根拠となった．

1992年より始まったJCOG 9206では，漿膜浸潤陽性胃癌と陰性胃癌の再発様式のリスクの違いを考慮して，全く別個のプロトコールが用意された．漿膜浸潤陰性例を対象としたJCOG 9206-1[41]はMFC＋oral FUを，漿膜浸潤陽性例を対象としたJCOG 9206-2[42]はCDDP (cisplatin) ip＋CDDP iv＋5-FU iv＋oral FUを治療レジメンとして行われたが，いずれの試験でも全体としての有意差はみられなかった．しかしJCOG 9206-1では，pT2，pN＋で5年生存率90%対81%という差を認め，JCOG 8801と同様に，このサブグループに対する補助化学療法の有用性を示唆した．反対に，pN－では92%対91%と差を認めず，前述のJCOG 8801の結果と併せて，pT1症例とpT2，pN0症例は手術単独でも十分に予後良好であり，今後，補助療法の臨床試験の対象にしないことが確認された．

フッ化ピリミジンの経口剤は，単独投与の延命効果の報告がないのにもかかわらず，その使いやすさを理由に，あたかも胃癌術後の標準治療のごとくわが国で広く施行されてきた．N・SAS-GCは最も繁用されているtegafur-uracil (UFT®)を取り上げ，単独投与の有用性について手術単独群を対照に比較したRCTである．前述したJCOG 8801のsubset analysisの結果をもとに，対象はpT2, pN1～2とされた．予定症例数を500例として1997年に始まったが，症例の集積スピードが遅く，1999年にS-1 (TS-1®)が発売されると，これを用いたRCTを優先させるために，N・SAS-GCは2001年3月に190例の時点で症例登録を中止した．その結果が，2005年のASCO (American Society of Clinical Oncology)総会でKinoshitaらによって報告された[43]．Overall survival (p＝0.0176)，relapse-free survival (p＝0.0040)ともに有意差をもって，治療群が対照群を上回っていた．しかし，予定症例数の半数にも満たない症例数で試験が終わっていること，手術単独群の成績がJCOG 9206-1での同サブグループに比較して5年生存率で約10%も下回ることなどの問題がある．とてもpivotal studyといえない試験であり，この結果をもって補助化学療法の有効性が証明されたとは解釈されていない．JCOGでは早急に大規模な追試のRCTを行う予定である．

一方，第Ⅱ相試験で45%という経口抗がん剤としては驚異的な奏効率をたたき出したTS-1を用いたRCT (ACTS-GC)が，2001年10月に始まり，2004年12月に1,000例の予定症例数を達成して登録を終了している．対象はStageⅡ (ただしpT1は除く)，ⅢとN・SAS-GCよりも広く設定されているが，これほど大規模な試験は過去になく，pivotal studyとしてその結果が待たれるところである(表2)．

術前補助化学療法

術前補助化学療法には2つの目的がある．1つは本来治癒切除可能な進行癌に対して術前化学療法を行い，再発率を低下させようとするもの，2つ目は治癒切除不能と思われる高度局所進行癌に対して術前化学療法を行い，腫瘍の縮小を図って治癒切除に持ち込もうとするものである．いずれについても過去に多くの第Ⅱ相試験が行われてきたが，その評価は定まっていない．

標準治療の確立には，治癒切除可能症例を対象とする場合は，術前化学療法対手術単独，あるいは術後化学療法を含めた3アームによる第Ⅲ相試験が必須である．一方，高度進行胃癌症例では，ほかに良い治療もなく，比較的症例数の多い第Ⅱ相試験でも十分なevidenceたり得ると考えられる．JCOGでは，過去の第Ⅱ相試験の結果から，十分な奏効率と有害反応の少なさから，TS-1＋CDDPをレジメンとして選択し，高度リンパ節転移を伴う進行胃癌に対する術前化学療法の第Ⅱ相試験(JCOG 0405)を2005年3月より開始してい

る．さらに，同じくTS-1＋CDDPを治療レジメンとした大型3型および4型胃癌に対する術前化学療法の手術単独群を対照とした第Ⅲ相試験(JCOG 0501)を計画中である．

英国で行われたMAGIC trialは，ECF(EPI＋CDDP＋5-FU)を術前術後に3クールずつ行う術前術後化学療法のRCTである．1994年に始まったこの試験は，8年をかけて予定の500例を集積し，2005年のASCO総会でその結果が報告された[44]．Overall survival(p＝0.009)，progression-free survival(p＝0.0001)ともに，有意差をもって治療群が手術単独群を上回り，周術期化学療法の有効性を肯定している．しかし，治療対象に1/3の非治癒切除症例が含まれること，25%が食道浸潤胃癌あるいは食道腺癌であること，手術内容が不明であることなど，わが国に当てはめられる内容かどうかはかなり疑問がある．

Meta-analysis

Meta-analysisは，論文として報告され，質の保証された複数のRCTにおける登録症例のオリジナルデータを統計学的に処理して，全体としての傾向を引き出すことを目的とした手法である[45]．

1993年，Hermansら[46]は，手術単独群を対照とした13研究についてmeta-analysisを行い，odds ratio 0.82 (95% CI：0.68～0.98)と，補助化学療法の有用性を示唆する結果を報告した．その後も，1999年にEarleら[47]が(odds ratio 0.80，95% CI：0.66～0.97)，2000年にMariら[48]が(odds ratio 0.82，95% CI：0.75～0.89)同様の報告を行っている．

Meta-analysisは，一定の治療法に関するいくつかの臨床試験を合同して，意義のある結論を導く方法論であるが，胃癌に関するこれらの結果は多種多様な治療法を集計したもので，全体として胃癌術後補助化学療法の有用性を示唆はするが，臨床現場で必要な実際の治療選択には直結しない．この示唆を受けてわれわれが行うべきことは，第Ⅱ相試験や進行胃癌での有用性が示されている治療レジメンを用いて，あくまで手術単独群を対照に置いたpivotal studyといえる大規模RCTを実施することである．

おわりに

胃癌補助化学療法の研究が始まってから半世紀が過ぎようとしている．過去のRCTには，①対象群の設定，②レジメンの選択根拠，③サンプルサイズの算定，④適格性と除外脱落，⑤サブセット解析とその解釈，といった基本的な方法論に問題があったため，補助化学療法の有効性に関するevidenceが未だに得られていないという現状を作り出した．

RCTに関する正しい理解がようやく普及の兆しをみせ，大規模で質の良いRCTが徐々に増えてきた．そのうちのいくつかは肯定的な結果を報告しており，補助療法の有効性は証明されつつある．

しかし，外国で行われたRCTの結果を無批判にわが国に導入することはできない．国により，早期癌と進行癌の比率や，リンパ節郭清などの治療法が大きく異なるからである．D2郭清が標準的に行われ，手術単独群の治療成績が優秀なわが国の胃癌患者に適用できるような，わが国独自のevidenceを確立する必要がある．

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Adjuvant Therapy for Advanced Gastric Cancer

Makoto Saka and Mitsuru Sasako*

*Department of Surgical Oncology, National Cancer Center Hospital, Tokyo

Although many randomized control trials (RCT) as to adjuvant therapy for advanced gastric cancer have been run since 1950s, an efficacy of this therapy has not been proven yet. Because most of doctors had little understanding of RCT or biological statistics, good study had not been carried out especially in Japan. Recently well designed RCTs have been run and some of them have reported positive result. Meta-analyses also have suggested positive effect of adjuvant chemotherapy. However, the introduction of positive data in foreign studies to our country faces many problems because of differences in operative procedure, such as an extent of lymphadenectomy, body type of patients, and so on. Japanese surgeons and medical oncologists have to continue our efforts to establish evidence which is applicable for Japanese gastric cancer patients.

特集 腹膜転移の治療

腹膜転移を有する初発胃癌の治療戦略

吉川 貴己　円谷 彰　小林 理*

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Treatment Strategy for Primary Gastric Cancer with Peritoneal Dissemination: Takaki Yoshikawa, Akira Tsuburaya and Osamu Kobayashi (*Dept. of Gastrointestinal Surgery, Kanagawa Cancer Center*)

Summary

Curative resection is considered to be a standard therapy for gastric cancer with localized peritoneal metastases. For tumors with diffuse dissemination, chemotherapy may play a major role, however, the benefits of reduction surgery and standard chemotherapy have not yet been clarified. Median survival time after reduction surgery was reported to be 4-13 months for patients diagnosed by surgery and/or CT and 5-6 months for chemotherapy for those diagnosed by CT alone. Reduction surgery has a high risk, with a morbidity of 12-44% and a mortality of 3-14%. Palliative surgery should be indicated for stenosis or bleeding due to primary tumors. 5-FU, MTX-5-FU, TS-1, paclitaxel, and their combination are candidates for practice and clinical trials. It is important to evaluate the severity of peritoneal dissemination by diagnostic laparoscopy or laparotomy for decision making. **Key words**: Gastric cancer, Peritoneal metastasis, Treatment strategy, **Corresponding author**: Dr. Takaki Yoshikawa, Department of Gastrointestinal Surgery, Kanagawa Cancer Center, 1-1-2 Nakao, Asahi-ku, Yokohama 241-0815, Japan

要旨　限局した腹膜転移症例では，根治切除術が標準的治療と考えられている。一方，根治切除できない腹膜転移に対しては化学療法が主体となるが，減量手術を先行すべきか，化学療法の標準 regimen は何か，いまだ解明されていない。減量手術の MST は 4～13 か月，化学療法では 5～6 か月と報告されているが，対象が異なっている。自験例 P2P3 症例の MST は CT 所見あり 5 か月，なし 7.7 か月と，化学療法の対象となるような CT 所見を有する場合の予後は短い。一方，減量手術の morbidity と mortality は高く，それぞれ 12～44%，3～14%と報告されている。原発巣に伴う出血や狭窄がある場合には，緩和手術の適応となる。化学療法の regimen としては 5-FU, MTX/5-FU, 低分化型腺癌に有効で腹腔内移行も良好な TS-1 や paclitaxel，これらの combination などが候補と考えられるが，今後適切な臨床試験が必要である。治療方針決定のためには，腹腔鏡または試験開腹により腹膜転移の重症度を評価することが重要である。

緒　言

胃癌が治癒するためには，肉眼的に遺残なく癌を取りきること（根治切除）が必要不可欠である[1]。一方，根治切除できない腹膜転移を伴う胃癌に対しては，化学療法が主体となる場合が多いが，化学療法の標準 regimen は何か，減量手術を先行するべきか否か，いまだ解明されていない。本論文では，現時点で得られる evidence を基に，腹膜転移を有する初発胃癌に対する治療戦略について考察した。

I. 手　術

1. 根治切除術

本邦では，過去の膨大な手術病理所見の詳細な解析と解剖学的見地から，2 群リンパ節郭清と大網盲嚢切除を伴う D2 定型手術が確立された[2]。胃癌がこの局所治療範囲内に肉眼的にとどまっている場合，D2 手術は根治切除の標準とされている。腹膜転移においても例外ではなく，転移が横行結腸より頭側にのみ存在し，通常の D2＋大網盲嚢切除で取り切れる範囲に存在する場合，局所治療である D2 定型根治切除が行われてきた[3]。その結果治癒する症例が少なからず存在することが明らかと

連絡先: 〒241-0815 横浜市旭区中尾 1-1-2　* 神奈川県立がんセンター：消化器外科
吉川　貴己

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表1 減量手術のmedian survival time (MST) と合併症，手術死亡

転移部位	MST (M)	合併症 (%)	手術死亡 (%)	在院死 (%)	文献
P2, P3	8.6	24.1	3.4	13.8	5
P2, P3	12.2	—	2.5*	—	7
P2, P3	7	—	—	1.6**	8
Any	8.1	38	12	—	9
Any	8.4	37	10	—	10
Any	5.5〜10.0	—	13	—	11
Any	8.0	—	11.5	—	12
Any	9.5***	42	7	—	13
Any	4〜6	44	11	—	14
Any	9	37.5	11.3	—	15
Any	10.6	49.0	7.0	—	16
Any	12.7	11.7	2.8	—	17

*: バイパス術，試験開腹術を含む
**: P以外の原因による減量切除術を含む
***: mean survival time

なっている[3]。現時点では化学療法のみで治癒することがほとんどないのに対して，これらの群の5年生存率が10%程度存在する[3]，median survival time (MST) が1〜2年程度[4]と明らかに良好であることから，このような症例に対して根治切除を行うことは標準的治療と考えられる。

D2定型手術の範囲を超えて，腹膜転移が広汎に広がっている場合には，通常，根治切除の適応とはならない。当院におけるMSTは旧P2症例で8.8か月，旧P3症例で5.6か月と予後不良である[5]。D2定型切除範囲外に数個しか腹膜播種結節が存在せず，過大侵襲なく完全切除が可能な場合に根治切除すべきかどうかについてのevidenceはない。しかしながら，まれに治癒することがあるため，根治切除が選択されることもある。JCOG胃癌外科グループでのアンケートによると，腹膜転移巣が肉眼的に取りきれる場合には根治切除を重視すると考える施設が多かった[6]。

2. 原発巣の減量手術

広汎な腹膜転移を有する症例で，通常のD2で根治切除が不可能と判断される場合に原発巣を切除すべきかどうかについてのevidenceはない。腹膜転移や肝転移を含めた非治癒因子を有する初発胃癌症例のretrospective studyでは，非切除群に対して減量手術群で，予後の延長がみられたとする報告が多い[7-15]。特に非治癒因子が一つに限定される場合に減量手術が有効であるとする報告が多い。減量手術によるMSTは，減量手術後の多様な抗癌剤治療を含めて4〜13か月と報告されている（表1）。腹膜転移単独の非治癒因子群を対象とした解析では，減量手術が有効とする報告[7]，有効でないとする報告[5,10]がある。しかしながら，これらの報告はすべてretrospectiveに解析しているため，減量手術群と非切除群との間に明らかな背景因子の偏りがある。われわれの検討では，背景因子を可能なかぎり分析して組み入れた多変量解析を行った場合，非緩和目的の減量切除は予後因子とはならなかった[5]。

減量手術は化学療法の効果を前提にするものであり，そのcomplianceは生存期間に重大な影響を及ぼす。合併症を起こした場合，化学療法を開始することができず，在院死に直結する。これまでの報告では，減量手術のmorbidityは12〜44%，mortalityは3〜14%と報告されている（表1）。D2 vs D4 phase III試験（JCOG 9501）におけるD2群のmorbidityは20.9%，mortalityは0.8%であった[18]ことを考慮すると，減量手術の危険性ははるかに高いために十分なICが必要である。

3. 緩和手術

原発巣による出血や狭窄症状が存在する場合，化学療法が困難なことが多いため，根治切除可能か否かにかかわらず積極的な緩和手術の適応となる[5]。しかしながら，緩和目的の減量手術の場合でもmorbidityとmortalityが高いことを十分に考慮し，バイパス手術，stentやIVRなどの手段で緩和可能か否か，best supportive careとすべき症例かどうか，適切に判断する必要がある。われわれの過去の症例の解析では，初発P2/P3症例における切除は，緩和目的の手術に限られる，という結果であった[5]。

II. 化学療法

これまでに，腹膜転移症例のみを対象として化学療法を行った前向き臨床試験の報告はない。切除不能進行再発胃癌に対する化学療法のphase IIIでは，MSTは7〜9か月である[19-22]。一方，前向き臨床試験の腹膜転移症例に限ったsubset解析では，tegafur+MMC vs UFT+

MMC の randomized phase II試験において5か月[23]，MTX＋5-FU 時間差療法（MF）の phase II試験において6か月であった[24]。化学療法の臨床試験では，適格基準に CT もしくは消化管造影検査で明らかに腹膜転移と診断できることが含まれている。当院で開腹術または腹腔鏡検査を行い P 2 P 3 と診断した群における MST は，CT 所見あり5か月，CT 所見なし7.7か月と，CT 所見を有する症例の予後は有意に不良であった[25]。このように，化学療法の対象（CT で腹膜転移所見を有する症例）と減量切除の対象（CT 所見はなく開腹または腹腔鏡検査で腹膜転移と診断した症例）では腹膜転移の重症度が異なっており，単純に MST を比較することはできない。

腹膜転移では，腸管狭窄によるイレウス，尿管狭窄による水腎症，腹水貯留などにより，容易に PS が低下する。CT で明らかに腹膜転移と診断できる病態では，臨床試験の適格基準を満たす症例においても5～6か月[23,24]と，切除不能進行再発胃癌症例を対象とした best supportive care（BSC）症例の3～4か月[26-28]よりわずかに良好といえる程度である。これらの BSC は TPN などの積極的な緩和医療を行っているわけではなく，画像上明らかな腹膜転移に対する化学療法の意義は適切な臨床試験で検証する必要があろう。

上述のように化学療法の対象となった腹膜転移症例の MST は，リンパ節転移や肝転移などの他の転移形式のそれに比べて短いが，その理由は腹膜転移が重症化しないと CT で確認できないことによる部分が大きいと推測される。CT 所見が明らかでない P 2 P 3 症例の MST は7.7か月[25]と，他の転移形式の MST と大差ない。他の要因としては，腹膜転移の多くがこれまでの抗癌剤では奏効しにくい低分化型腺癌である，腹膜血管バリアーにより抗癌剤が腹腔内に到達しない，ことなどが考えられる。一方，以下の新規抗癌剤は低分化腺癌に有効性が高く，腹腔内への drug delivery が良好であることより，腹膜転移に対する治療薬として期待されている。

1．TS-1

血中 5-FU を高濃度に維持し，かつ 5-FU の用量制限毒性である消化器毒性の軽減を図るために開発された経口抗癌剤が TS-1 である。phase II試験において，低分化型腺癌に対して52.5％と高い有効性を示し[29,30]，原発巣 C 病変に対して20.8％と画期的な奏効率を示した[29,30]ことから，低分化型腺癌に対する有効性が示された。腹膜転移に対して有効であったとする治療成績[31-34]や症例報告[35]も数多くみられる。腹膜播種転移が完全に消失した，とする報告も散見される[36,37]。腹膜播種転移モデルを用いた動物実験では，腹水中に高濃度に 5-FU が維持されるとともに，有意な生存期間の延長がみられている[38,39]。最近，ヒト胃癌患者においても腹膜移行性が良好であることが証明された[40]。

2．Paclitaxel

本邦で行われた phase II試験で，低分化型腺癌に対して29.0％と高い奏効率を示し注目された[41]。paclitaxel は 5-FU，CPT-11，CDDP に交差耐性を示さず，前化学療法歴を有する症例に対しても，奏効率27％と高い有効性を認めることが特徴的である[41]。上記の報告はすべて3週間毎投与法による効果であるが，最近，薬剤投与の間隔を短くして腫瘍細胞に再増殖の時間を与えない dose-density の概念が提唱され[42]，乳癌や肺癌では weekly 投与による優れた抗腫瘍効果と毒性の軽減が報告された[43,44]。胃癌に対しても weekly 投与の有効性が報告されている[45,46]。腹水を有する腹膜転移症例に対して paclitaxel 少量分割療法が有効であったとする報告も相次いでいる[47]。また，paclitaxel は，全身投与をしても速やかに腹水中に移行し有効濃度が長期間維持されることも報告された[45]。

III．病態に応じた治療方針（図1）

肉眼的に根治切除可能な腹膜転移に対しては，2群リンパ節郭清を含めた原発巣の根治切除と播種結節の完全（R 0）切除により，治癒も期待できる。R 0 切除後に，日常診療では術後補助化学療法を行う場合もあるが，現在のところ有用性を示唆する evidence は乏しい。腹水細胞診陽性または腹腔洗浄細胞診陽性（CY 1）で R 1 切除となった症例に対しても，化学療法の有用性を示唆する evidence は乏しいが，予後が極めて不良であることより，日常診療では化学療法が行われている。JCOG では，以前に CY 1 根治切除症例と P 1 P 2 根治切除症例を対象とした手術単独群と手術＋術後化学療法群を比較する phase III試験を施行したが，症例登録が進まず試験中止となった。一方，R 0 または R 1 切除可能な初発腹膜転移症例に対して，術前に化学療法を行うべきか否か，明らかな evidence は乏しい。なお2005年の ASCO meeting で，英国 MRC 主導で行われた根治切除単独と術前化学療法＋根治切除＋術後化学療法を比較する Phase III試験の結果が報告された（MAGIC trial）[48]。術前化学療法により T，N ともに down staging が得られ，全生存期間，無病生存期間ともに試験治療群で有意な延長がみられた[48]。根治切除可能な高度進行胃癌に対して術前化学療法の有用性を示唆する evidence として注目される。

根治切除は不可能だが，原発巣の減量手術が可能である場合，前述のごとく減量手術を先行して行うべきかどうかについての evidence はない。現時点では，減量手術後に化学療法または化学療法のみを行う治療，どちらも

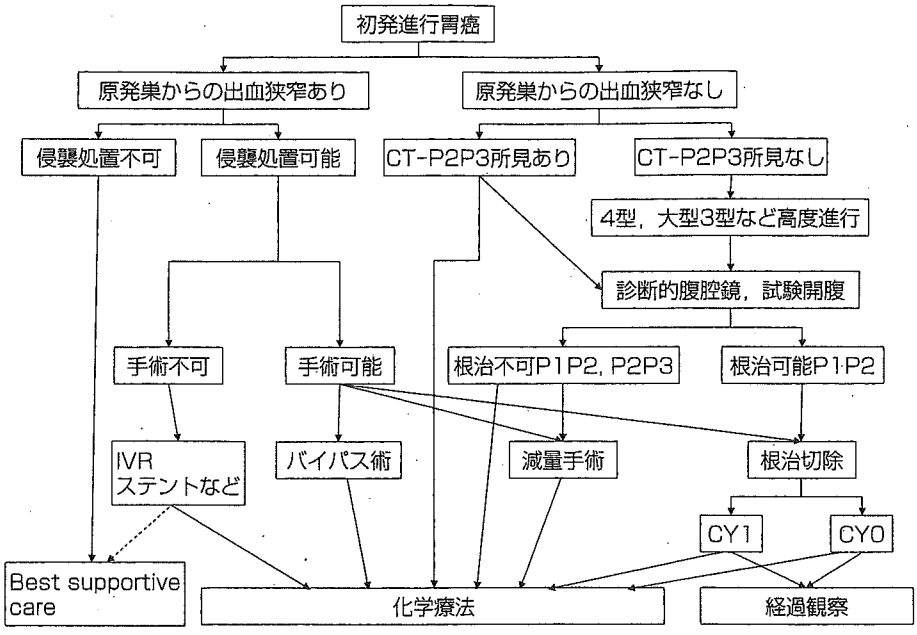

図 1 腹膜転移を有する初発胃癌の治療戦略

日常診療で行われている。しかしながら，減量手術のmortalityとmorbidityは高く食道や十二指腸への著しい浸潤を示す症例や他臓器浸潤症例で安全な減量手術が行えないと判断される場合，化学療法を選択すべきであると思われる。

原発巣に伴う出血や狭窄などが存在する場合には，出血や狭窄をコントロールするための原発巣切除やバイパス手術，stentやIVRなどが適応となる。これらの緩和的手段に伴うリスクを十分に考慮した上で，ICをとる必要がある。緩和的手段により全身状態が改善した場合は，化学療法の適応となる。

根治切除ができない場合，化学療法または緩和治療が中心となる。化学療法を行う場合どのようなregimenを用いるべきかについてはいまだ解明されていない。JCOG臨床試験のcontrol armである5-FU，試験治療群であるMTX-5-FU，低分化型腺癌に有効で腹腔内移行も良好なTS-1やpaclitaxel，あるいはこれらの薬剤を基本にしたcombinationなどが候補と考えられる。

Ⅳ．治療方針を決定するために

胃癌の腹膜播種転移ではbulky massを形成することはまれであり，CTで腫瘍所見をとらえることは困難である。腹膜転移が進行すると腹水，腸管狭窄によるイレウス，尿管狭窄による水腎症などが出現する。ある程度多量の腹水が存在する場合には，腹水細胞診によって癌細胞の有無を確認することが可能でありCY 1, Stage IVと診断できるが，腹膜播種結節が存在しているかどうかはわからない。CT所見での腹水貯留のみで“腹膜転移あり，非切除”と診断することは危険である。

腹腔鏡検査または開腹手術を行った自験例の解析では，CTで検出できる所見として腹水，腸間膜肥厚，腹膜脂肪組織のdensity上昇，結節，水腎症などがあった[25]。CTで明らかにP2あるいはP3と診断できる場合もあるが，根治切除可能かどうかを診断することは難しい。CT所見からみた腹膜転移程度診断の正確性は明らかではない。

一方，近年の化学療法の進歩により，腹膜転移が完全消失することも経験されるようになった[36,37]。遠隔転移が完全消失した場合には，根治切除術を行うchanceである。初発未治療の段階で，腹腔鏡や開腹手術により腹膜転移の程度を正確に評価しておくことは，効果判定と治療方針決定において重要と考えられる。

Ⅴ．現在，進行中または企画中の臨床試験

JCOG消化器内科グループでは，CTで明らかな腹膜転移を有する進行胃癌を対象として，5-FU単独をcontrol armとし，MTX+5-FU療法の有用性を検証するphase Ⅲ試験を実施中である。また，一次治療でfailureした腹膜転移症例を対象として，best available 5-FU (bolusとinfusionを交差させる)とpaclitaxelを比較するphase Ⅲ試験を企画している。一方，JCOG胃癌外科グループでは，腹膜転移を含めた遠隔転移陽性症例を対象として，減量手術＋化学療法と化学療法単独を比較するphase Ⅲ試験を企画中である。

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原 著

大型3型/4型/Bulky N 2進行胃癌に対するTS-1+CDDPを用いた術前化学療法の経験

種村 廣巳*1 大下 裕夫*1 菅野 昭宏*1 日下部光彦*1 波頭 経明*1
山田 誠*1 足立 尊仁*1 西尾 公利*1 齋藤 史朗*1 冨田 栄一*2
杉山 昭彦*2 山田 鉄也*3

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Neoadjuvant Chemotherapy Using TS-1 and CDDP against Large Type 3/Type 4/Bulky N 2 Advanced Gastric Cancer:

Hiromi Tanemura*1, Hiroo Oshita*1, Akihiro Kanno*1, Mitsuhiko Kusakabe*1, Tsuneaki Hatoh*1, Makoto Yamada*1, Takahito Adachi*1, Kimitoshi Nishio*1, Shiro Saito*1, Eiichi Tomita*2, Akihiko Sugiyama*2, and Tetsuya Yamada*3
(*1*Dept. of Surgery,* *2*Dept. of Gastrointestinal Medicine and* *3*Dept. of Clinical Laboratory, Gifu Municipal Hospital*)

Summary

This study was conducted to assess therapeutic results following neoadjuvant chemotherapy (NAC) for large type 3/type 4/Bulky N 2 advanced gastric cancer having a poor prognosis following resection. The subjects consisted of cases (≦75 y. o.) having large type 3 (diameter≧8 cm), type 4 or Bulky N 2 gastric cancer curable by resection based on preoperative imaging diagnostics. The NAC regimen consisted of TS-1 at 80-120 mg/body on days 1-21 p. o. and CDDP at 60 mg/m² on day 8 divided. Upon completion of two courses of 4 weeks per course, gastrectomy with≧D_2 lymphnode dissection was carried out on days 21-34. The average age of the subjects was 60.7 years, and the therapy completion rate was 80% (8/10 cases). Five of ten cases were responders diagnosed as grade 2 by histopathological examination of excised specimens (response rate 50%). Two of five responders were histopathologically evaluated as down-staging as a result of NAC (Stage IIIA → f Stage I A, Stage IV→ f Stage I A). Three of the five non-responders have relapsed, and the relapse-free interval was an average 238 days. In the five responders, one has relapsed at 331 days, while the other 4 responders have shown no relapse yet. Although NAC consisting of TS-1 and CDDP is considered to be effective against advanced gastric cancer, a phase III study with surgical treatment only will be necessary to confirm its true value. Key words: Advanced gastric cancer, Neoadjuvant chemotherapy, Down-staging (*Received Apr. 4, 2005/Accepted Jun. 21, 2005*)

要旨 【目的】大型3型(径≧8 cm) 4型胃癌，あるいはBulky N 2を有する進行胃癌に対する術前化学療法(neoadjuvant chemotherapy: NAC)の治療成績を検討した。【対象】年齢75歳以下で，術前画像診断にて根治切除可能と判断された症例を対象とした。NACのregimenはTS-1 80～120 mg/bodyを1～21日経口投与し，CDDP 60 mg/m²を8日目に点滴投与し，1コース4週×2コース終了後21～34日に胃切除＋D 2以上リンパ節郭清を行った。治療完遂率，手術摘出標本の病理組織学的効果判定について検討した。【結果】検討対象となった症例数は10例で，その平均年齢60.7歳，治療完遂率8/10例(80%)であり，切除標本の病理組織学的診断にてGrade 2の診断が得られたresponderは5例であり，response rateは50%であった。responder 5例のうちの2症例はNACによるdown stagingが病理組織学的に評価できた症例であり，1例はStage IIIAからStage I Aへ，別の1例はStage IVからStage I Aにdown stagingされたと推察される。non-responderの5例中3例が再発しており，そのrelapse free interval (RFI)の平均値は238日であった。一方，responderの5例中では1例が術後331日で再発を認めたが，他の4例はいまだ再発を認めていない。【結語】大型3型/4型/Bulky N 2進行胃癌に対するTS-1+CDDPのNACは有効と考えられるが，その真価を確認するために手術単独療法とのphase III studyの必要性がある。

*2 岐阜市民病院・消化器内科
*3 同 ・中央検査部

連絡先: 〒500-8513 岐阜市鹿島町7-1 *1 岐阜市民病院・外科
種村 廣巳

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