World J. Surg. 19, 570–574, 1995

WORLD
Journal of
SURGERY

Review of Adjuvant Chemotherapy for Gastric Cancer

Toshifusa Nakajima, M.D.

Division of Gastrointestinal Tract Surgery, Cancer Institute Hospital, Tokyo, Japan

Abstract. Controlled randomized studies that compared surgery alone to adjuvant chemotherapy for gastric cancer were reviewed. The amount of residual tumor after surgery, selection of drug regimens, compliance with drug administration, and trial design seem to be responsible for the success of adjuvant chemotherapy. Though there are few beneficial regimens of adjuvant chemotherapy with statistical significance, single drug therapy with mitomycin C (MMC) and combination therapy with 5-fluorouracil (5FU) and methyl-CCNU, MMC/5FU/cytosine arabinoside (MFC), and 5FU/Adriamycin/MMC (FAM) seem to have potential survival benefit for patients with curative surgery. Incorporation of new drugs into adjuvant or neoadjuvant chemotherapy might open a new aspect of multimodality therapy for gastric cancer.

Few reports from Western countries support the survival benefit of adjuvant chemotherapy for gastric cancer, although Japanese papers report favorable results in the limited subsets of patients [1–3]. This favorable circumstance has led us to incorporate adjuvant chemotherapy into routine multimodality therapy of locally advanced gastric cancer in Japan. Recent Japanese trials have employed surgery and chemotherapy as the standard therapy for locally advanced cancer. Responding to the Western criticism about the survival benefit of adjuvant chemotherapy, the Japanese Oncology Study Group has initiated a new trial on the clinical significance of adjuvant chemotherapy. Comparison of reports from Western countries and Japan has revealed some differences in the clinical stages of patients subjected to chemotherapy as well as differences in the selection of regimens. Herein we offer a brief review of adjuvant chemotherapy for gastric cancer and some discussion about future trials.

Methods and Materials

A review was conducted of randomized controlled studies employing surgery alone to control gastric cancer reported over the last 20 years from Western countries and Japan. Regimens were classified into four groups according to the main drugs in the regimen: (1) triethylenethiophosphoramide (thio-TEPA)-containing regimens; (2) 5-fluorouracil (5-FU) with or without methyl-CCNU regimens; (3) mitomycin (MMC) with or without 5-FU regimens; and (4) Adriamycin-based regimens (5FU/Adriamycin/MMC, or FAM). Survival benefit by employed regimens was evaluated by the diagram with spotting five year survival rates of treated and control groups (surgery alone) on the vertical and horizontal axes.

Treatment Results with Adjuvant Chemotherapy

Tables 1 through 4 summarize the results of trials with the main adjuvant chemotherapy regimens [4–24] for gastric cancer. Since the late 1950s, clinical trials of adjuvant chemotherapy have started in the form of a phase III study (controlled randomized study). During the early days, thio-TEPA [4, 5], 5-fluoro-2-deoxyuridine (FUDR) [6], 5FU [7], or MMC [8–11] was employed as a single-drug regimen in the adjuvant setting. The former two drugs did not produce survival benefit in large-scale clinical trials in the United States [4–6] (Table 1).

Although 5FU has proved to be active in the treatment of advanced gastrointestinal cancers, single 5FU did not have any survival benefit in cases of curative resection, except for a temporary benefit in a small subset of patients [7] (Table 2). Conflicting results have been reported for combination chemotherapy with 5FU/methyl-CCNU in the United States. The Gastrointestinal Tumor Study Group (GITSG) [12] reported clinical benefit with combination of 5FU/methyl-CCNU, though two other concurrent studies—by the Veterans Administration Surgical Oncology Group (VASOG) and the Eastern Cooperative Oncology Group (ECOG) [13, 14]—reported no benefit compared with surgery alone. The regimens employed by these three groups were identical, although there was a difference in the selection of patients. The GITSG selected curative cases as the subject of chemotherapy, and the other two groups had no such limitation. Combinations of 5FU/vinblastine (VBL)/cyclophosphamide (CPM) or 5FU/1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) also showed no benefit [15, 16].

Adjuvant MMC has been reported to have the potential to prolong life in patients with moderate locally advanced disease in Japan (Table 3). MMC alone was used in two ways: In one, a regimen of moderate dose delivery over the long term, in which MMC 0.08 mg/kg IV was administered twice a week for 5 weeks [8, 9]. In the other, a large dose was administered over the short term, with 20 and 10 mg of MMC per body given for two consecutive days immediately after surgery [10]. These regimens produced no statistically significant overall survival benefit, although the former regimen yielded a 10% to 20% increase in 5-year survival rates for stage II or III disease between treated (curative surgery + adjuvant chemotherapy) and control (surgery alone) groups ($p < 0.05$). The latter regimen produced a survival benefit exclusively for stage III disease. Another large-dose

Table 1. Surgical adjuvant chemotherapy containing thio-TEPA for gastric cancer.

Study	Regimen	No. of pts.	5-year survival (%)
Longmire et al. [4]	TSPA high dose	82	24
	Control	89	19
Dixon et al. [5][a]	TSPA low dose	177	24
	Control	182	24
Serlin et al. [6]	TSPA high dose	43	16
	Control	112	16
	TSPA low dose	152	18
	Control	138	24
	FUDR	217	17
	Control	241	15

[a]University group (1968, 1971).

Table 2. Surgical adjuvant chemotherapy containing 5-fluorouracil.

Study	Regimen	No. of pts.	5-year survival (%)
Blokhina et al. [7]	5FU	375	40[a]
	Control	402	37
GITSG [12]	5FU/MeCCNU	71	45
	Control	71	32
VASOG [13]	5FU/MeCCNU	66	38[a]
	Control	68	39
ECOG [14]	5FU/MeCCNU	91	27
	Control	89	34
Hugier et al. [15]	5FU/VBL/CPA	27	18
	Control	26	19
Schreml et al. [16]	5FU/BCNU	42	58
	Control	53	42

[a]3-year survival rate.

Table 3. Surgical adjuvant chemotherapy containing MMC.

Study	Regimen	No. of pts.	5-year survival (%)
Imanaga & Nakazato [8]	MMC, moderate dose	242	68
	Control	283	54
Nakajima et al. [9]	MMC, moderate dose	207	52
	Control	223	44
Hattori et al. [10]	MMC, large dose	146	37
	Control	278	50
Alcobendas et al. [11]	MMC, large dose	33	79
	Control	37	38
Nakajima et al. [18]	MMC/5FU/CA	42	67
	Control	38	50
Nakajima et al. [19]	MMC/5FU/CA/5FU	81	68
	MMC/FT/CA/FT	83	63
	Control	79	51

Table 4. Surgical adjuvant chemotherapy containing 5-FU, MMC, or ADM.

Study	Regimen	No. of pts.	5-year survival (%)
Fielding et al. [20]	5FU/VCR/CPA/MTX then 5FU/MMC	140	60[a]
	5FU/MMC	141	66
	Control	130	57
Schein et al. [22]	5FU/ADM/MMC	156	76[b]
	Control		72
Allum et al. [23]	5FU/ADM/MMC	145	27
	Radiotherapy	153	20
	Control	145	24
Coombes et al. [24]	5FU/ADM/MMC	133	46
	Control	148	36
Krook et al. [25]	5FU/ADM	61	32
	Control	64	33

[a]1-year survival rate
[b]2.5-year survival rate

regimen produced a similar result [11]. Three-drug combination chemotherapy [17] of MMC/5FU/cytosine arabinoside (MFC), one of the beneficial regimens for advanced gastric cancer, produced a favorable result in the adjuvant setting [18]. Although a survival difference did not reach statistical significance for the total cases, it was significant in the subset of stage II and III lesions. MFC therapy seemed to be superior to single MMC in terms of survival benefit. Encouraged by this result, our next study was designed to compare the combination of intravenous MFC and oral 5FU (MFC+F) with that where 5FU was replaced by futraful (F'), a derivative drug of 5FU (MF'C+F') in patients undergoing curative surgery [19]. Though there was no statistical difference in the survival of all cases ($p < 0.09$), there was a 17% difference in the 5-year survival rates between MFC+F and control groups, which is encouraging for clinicians. The MFC+F regimen was superior to surgery alone in the subsets of stage I to III disease ($p < 0.05$). These early studies selected all stages of curative surgery for adjuvant chemotherapy. Positive results were obtained only in the moderately advanced diseases (stages II and III) by subset analysis, which leads to no definite conclusions from the statistical point of view.

A British study group failed to prove the advantage of adjuvant chemotherapy with 5FU, MMC and other drugs [20]. FAM therapy [21], a combination of 5FU/Adriamycin (ADM)/MMC, was the most common chemotherapy regimen for advanced gastric cancer. Many clinical trials of FAM therapy have been carried out in the adjuvant setting (Table 4). Recent reports [22–25] seem unfavorable to adjuvant FAM therapy, though a benefit potential was reported in the T3 and T4 subset [24]. The combination of 5FU/ADM also failed to produce a survival benefit [25]. Modification of FAM therapy, FAM 2 [26] or FAMTX [27], is under investigation by the EORTC, but a clinical significance has not yet been reported.

Figure 1 shows the correlation of the 5-year survival rates for treated and control groups. Five-year survival rates of treated groups were plotted on the vertical axis, and those of control groups on the horizontal axis. No studies suggested survival benefit when the 5-year survival rates of control groups were less

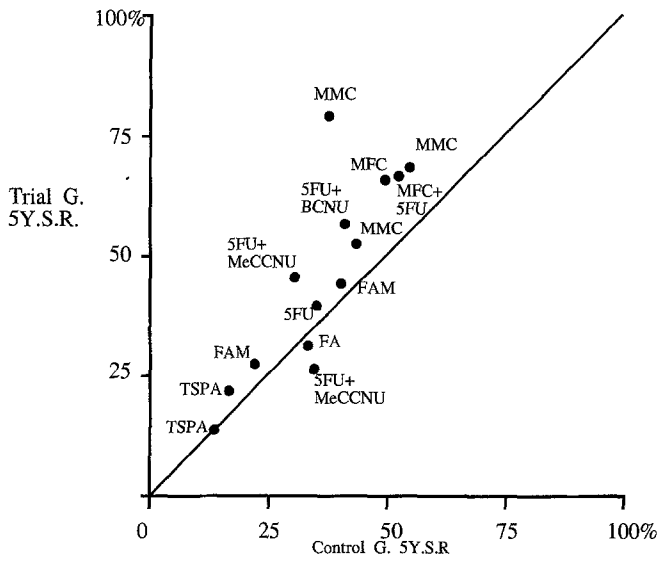

Fig. 1. Treatment results of adjuvant chemotherapy for gastric cancer: 5-year survival rates.

Table 5. Reasons for failure of adjuvant chemotherapy.

1. Inadequate regimen
a. Selection of drugs: low response rate
b. Dose intensity: toxicity
2. Inadequate trial design
a. Excessive estimation of survival difference: small sample size
b. Treatment schedule: complicated, easily confounding
3. Inadequate subjects
a. Too early stage
b. Too advanced stage
4. Inadequate practice
a. Poor surgery, postoperative complication
b. Low compliance: withdrawal
c. Violence of entry criteria: exclusion
5. Inadequate interpretation of data
a. Subset analysis
b. Bias in the comparability between trial and control groups

than 30%. The 5-year survival rates of the control group were around 50% in the favorable reports.

Discussion

Treatment results of adjuvant chemotherapy may substantially depend on the interaction of residual tumor and anticancer drugs. The amount of residual tumor after surgery, sensitivity of tumor to the drugs, and dose intensity are the most fundamental factors that influence the survival data. As shown in Table 5, these factors could be extrapolated to practical levels. Preclinical trials suggest an inverse relation between the response to chemotherapy and the tumor burden. Tumor burden should be reduced to as little as possible by surgery to obtain a survival benefit of adjuvant chemotherapy. Treatment failure in Western countries could be attributed to the excessive residual tumor left behind during surgery and inadequate selection of drugs. The low long-term survival rate (< 30–40% five-year survival rate) of control groups in Western studies suggest that there is large amount of tumor remaining after surgery. In contrast, the 5-year survival rate of surgically treated patients in the Japanese study was around 50%, much better than in the Western countries. The high survival rate, a reflection of the small amount of residual tumor, in the Japanese study might have resulted from the selection of relatively early-stage patients and the extensive gastrectomy, including systematic lymph node dissection. Low mortality and morbidity after surgery may contribute to keeping patients in good performance status and good compliance with the drug administration. Poor performance status of postoperative patients is reflected in their inability to tolerate intensive chemotherapy. Western trails should be evaluated again with patients bearing less tumor burden and having good performance status.

Selection of active regimens of adjuvant chemotherapy is another important issue. Thio-TEPA in early studies might have been a poor selection of drug for adjuvant chemotherapy for gastric cancer. Japanese trials always employed MMC or a combination of MMC/5-FU. The FAM regimen, though once standard therapy for advanced gastric cancer, produced a negative result in the adjuvant setting in Western countries. A recent meta-analysis of adjuvant chemotherapy for gastric cancer suggested that whatever regimens were employed for relatively advanced cancer produced negative results [28]. On the other hand, recent intensive chemotherapy succeeded in the down-staging of advanced disease and allowed us to perform curative resection. These results led to another possible approach, neo-adjuvant chemotherapy, to improve the treatment of rather advanced-stage cancer. EAP therapy [29] gained attention because of its response rate was higher than 70%, with high resectability. Preoperative combination chemotherapy of 5FU/MTX [30], which is supposed to be active owing to the mechanism of biochemical modulation, or preoperative FAMTX (5FU/ADM/MTX), also contributed to an increase in resectability [31]. A combination of CDDP/MMC/UFT/etoposide (PMUE) [32] achieved partial response in seven of eight advanced cases, among which five patients were subjected to gastrectomy. Based on excellent results with biochemical modulation using 5FU/leucovorin (LCV) and the synergism between CDDP and etoposide, I initiated systemic delivery of the combination 5FU/LCV and intraaortic delivery of CDDP/etoposide through a catheter, the tip of which was placed at the level of ninth vertebra. The preliminary report (Nakajima et al., unpublished data) revealed that the response rate was 55.0% (11/20) in patients with unresectable gastric cancers (solitary or multiple M1 lesions), and all responders were subjected to gastrectomy. Seven patients were treated with radical surgery (no macroscopic remaining tumor), and their survival rate was still above 50% level at 3 years after surgery. Other regimens that seem to have a potential for treating gastric cancer include the combination chemotherapy etoposide/5FU/leucovorin (ELF) [33] and FAMTX therapy under investigation in a phase III study by the EORTC (protocol 40902). Moderate-dose MTX/5FU therapy [34] has been reported to be effective for controlling diffuse-type gastric cancer. Immunochemotherapy, including interferon α a2 and 5FU, is reported to be active in esophageal and colon cancers [35, 36]. This regimen deserves a clinical trial for gastric cancer.

Intraperitoneal administration has attracted attention of oncologists because of its potential of controlling intraoperative peritoneal dissemination [37–39]. Intraperitoneal administration may allow high dose intensity in the peritoneal cavity and systemic distribution through the portal vein. The effects of intraperitoneal

administration should be evaluated by a randomized controlled study. The combination of hyperthermia with intraperitoneal chemotherapy was reported to have a survival benefit because it controlled peritoneal dissemination [40–42]. This combined modality may be worthy of a controlled study.

Although these regimens are not yet evaluated in the postoperative adjuvant setting, excellent results with neoadjuvant chemotherapy provide a rationale for combining surgery and combined regional and systemic chemotherapy for treating rather advanced-stage cancer. It is too early to draw final conclusions about the effectiveness of adjuvant chemotherapy for gastric cancer.

Issues concerning Japanese adjuvant chemotherapy are attributed to the trial design. Early Japanese trials enrolled patients with all stages of disease and employed inadequate samples. Early-stage cancer could be cured by surgery alone and did not need adjuvant therapy. In contrast, surgery for late-stage cancer results in excessive residual tumor, which might negate control with adjuvant chemotherapy. Recent trials have employed moderately locally advanced-stage cancer (stages II and III), a practice derived from the results of subset analysis of past trials. An inadequate sample size is responsible for statistically nonsignificant differences in the survival rate. Rapid patients accrual is mandatory for clinical trials of adjuvant chemotherapy. For achieving this purpose, multiinstitutional studies should be conducted. Referring to the experiences in the United States and Europe, the organization of a well equipped data center is essential for controlling the quality of data derived from various institutions.

Résumé

Ont été analysées iei les seules études contrôlées, randomisées, comparant la chirurgie seule et la chimiothérapie adjuvante dans le traitement du cancer gastrique. La masse de tissu résiduel restant après la chirurgie, la sélection de traitements chimiothérapeutiques, la compliance aux traitements et les structures des essais sont peut-être pour quelque chose dans le succés de la chimiothérapie adjuvante. Bien qu'il y ait peu d'études montrant des différences statistiquement significatives, les thérapies comportant seulement du MMC, celles combinant le 5 FU et le Méthyl CCNU, la MFC, et le FAM semblent pouvoir entraîner une survie supérieure dans les groupes comportant une chirurgie à visée curatrice. Incorporer de nouvelles drogues dans les prescriptions de chimiothérapie adjuvante ou néoadjuvante peut ouvrir de nouvelles perspectives dans le traitement du cancer gastrique à modalités multiples.

Resumen

Los estudios controlados y randomizados que emplean la cirugía sola como método de control de la quimioterapia adyuvante en el cáncer gástrico han sido revisados en forma exclusiva. La cantidad de tumor residual luego de la cirugía, la selección de los regímenes de droga antineoplásica, el cumplimiento en la administración de la droga y el diseño del ensayo clínico, parecen ser los factores responsables del éxito de la quimioterapia adyuvante. Aunque sólo existen pocos regímenes que hayan demostrado beneficio con significación estadística, el MMC único, la combinación de 5-FU y Metil-CCNU, el MFC y el FAM, parecen poseer un beneficio potencial de sobrevida en los grupos de pacientes sometidos a cirugía curativa. La incorporación de nuevas drogas a la quimioterapia adyuvante o neoadyuvante podría abrir un nuevo aspecto en la terapia multimodal en el cáncer gástrico.

References

1. Nakajima, T., Nishi, M.: Adjuvant chemotherapy, immunochemotherapy, and neoadjuvant therapy for gastric cancer in Japan. Contemp. Issues Clin. Oncol. *8*:125, 1988
2. Nakajima, T.: Adjuvant chemotherapy for gastric cancer in Japan: present status and suggestions for rational clinical trials. Jpn. J. Clin. Oncol. *20*:30, 1990
3. Nakajima, T., Fukami, A., Ohashi, I., Kajitani, T.: Long-term follow-up study of gastric cancer patients treated with surgery and adjuvant chemotherapy with mitomycin C. Int. J. Clin. Pharmacol. *16*:209, 1978
4. Longmire, W.P., Jr., Dixon, W.J.: The use of triethylenethiophosphoramide as an adjuvant to the surgical treatment of gastric carcinoma. Ann. Surg. *167*:293, 1968
5. Dixon, W.J., Longmire, W.P., Jr., Holden, W.D.: Use of triethylenethiophosphoramide as an adjuvant to the surgical treatment of gastric and colorectal carcinoma: ten year follow-up. Ann. Surg. *173*:26, 1971
6. Serlin, O., Wolkoff, J., Amadeo, J.M., Keehn, R.J.: Use of 5-fluorodeoxyuridine(FUDR) as an adjuvant to the surgical management of carcinoma of the stomach. Cancer *24*:223, 1969
7. Blokhina, N.G., Garin, A.M., Moros, L.V., et al.: Treatment with 5-fluorouracil in prophylaxis of relapse and metastasis of stomach cancer. Neoplasma *19*:351, 1972
8. Imanaga, H., and Nakazato, H.: Results of surgery for gastric cancer and effect of adjuvant mitomycin C on cancer recurrence. World J. Surg. *1*:213, 1977
9. Nakajima, T., Fukami, A., Ohashi, I., Kajitani, T.: Long-term follow-up study of gastric cancer patients treated with surgery and adjuvant chemotherapy with mitomycin C. Int. J. Clin. Pharmacol. *16*:209, 1978
10. Hattori, T., Mori, A., Hirata, K., Ito, I.: Five year survival rate of gastric cancer patients treated by gastrectomy, large dose mitomycin C, and/or allogeneic bone marrow transplantation. Gann *63*:517, 1972
11. Alcobendas, F., Milla, A., Estape, J., Curto, J., Pera, C.: Mitomycin-C as adjuvant in resected gastric cancer. Ann. Surg. *198*:13, 1983
12. Gastrointestinal Tumor Study Group: Controlled trial of adjuvant chemotherapy following curative resection for gastric cancer. Cancer *49*:1116, 1982
13. Higgins, G.A., Amadeo, J.H., Smith, D.E., Humphrey, E.W., Keehn, R.J.: Efficacy of prolonged intermittent therapy with combined 5-FU and methyl-CCNU following resection for gastric carcinoma: a Veterans Administration Surgical Oncology Group report. Cancer *52*: 1105, 1983
14. Engstrom, P.F., Lavin, P.T., Douglass, H.O., Jr., Brunner, K.W.: Postoperative adjuvant 5-fluorouracil plus methyl-CCNU therapy for gastric cancer patients. Cancer *55*:1868, 1985
15. Hugier, M., Destroyes, J-P., Baschet, C.: Gastric carcinoma treated by chemotherapy after resection: a controlled study. Am. J. Surg. *139*: 197, 1980
16. Schreml, W., Schlag, P., Herfarth, C., et al.: Adjuvant 5-FU/BCNU in gastric carcinoma. In Adjuvant Therapy of Cancer IV, S.E. Jones, S.E. Salmon, editors. Grune & Stratton, Orlando, FL, 1984, pp. 441–448
17. Ota, K., Kurita, S., Nishimura, M., et al.: Combination therapy with mitomycin C (NSC-26980), 5-fluorouracil (NSC-19893), and cytosine arabinoside (NSC-63878) for advanced cancer in man. Cancer Chemother. Rep. *56*:373, 1972
18. Nakajima, T., Fukami, A., Takagi, K., Kajitani, T.: Adjuvant chemotherapy with mitomycin C, and with a multi-drug combination of mitomycin C, 5-fluorouracil and cytosine arabinoside after curative resection of gastric cancer. Jpn J. Clin. Oncol. *10*:187, 1980
19. Nakajima, T., Takahashi, T., Takagi, K., Kuno, K., Kajitani, T.: Comparison of 5-fluorouracil with Ftorafur in adjuvant chemotherapy with combined inductive and maintenance therapies for gastric cancer. J. Clin. Oncol. *2*:1366, 1984
20. Fielding, J.W.L., Jagg, S.L., Jones, B.G., et al.: An interim report of a prospective, randomized, controlled study of adjuvant chemotherapy in operable gastric cancer: British Stomach Cancer Group. World J. Surg. *7*:390, 1983

21. Macdonald, J.S., Woolley, P.V., Smythe, T., Ueno, W., Hoth, D., Schein, P.S.A.: 5-Fluorouracil, Adriamycin, and mitomycin C(FAM) combination chemotherapy in the treatment of advanced gastric cancer. Cancer *44*:42, 1979
22. Schein, P.S., Coombes, R.C., Chilvers, C., et al.: A controlled trial of FAM (5-FU, doxorubicin, and mitomycin-C) chemotherapy as adjuvant treatment for resected gastric carcinoma: an interim report. Proc. Am. Soc. Clin. Oncol. *5*:79, 1985
23. Allum, W.H., Halliscey, M.T., Ward, L.C., Hockey, M.S.: A controlled prospective randomized trial of adjuvant chemotherapy or radiotherapy in resectable gastric cancer: interim report. Br. J. Cancer *60*:739, 1989
24. Coombes, R.C., Schein, P.S., Chilvers, C.E.D., et al.: A randomized trial comparing adjuvant fluorouracil, doxorubicin, and mitomycin with no treatment in operable gastric cancer. J. Clin. Oncol. *8*:1362, 1990
25. Krook, J.E., O'Connell, M.J., Wieand, H.R., et al.: A prospective, randomized evaluation of intensive course 5-fluorouracil plus doxorubicin as surgical adjuvant chemotherapy for resected gastric cancer. Cancer *67*:2454, 1991
26. Lise, M., Nitti, D., Buyse, M., et al.: Adjuvant FAM2 in resectable gastric cancer. Anticancer Res. *9*:1017, 1989
27. Klein, H.O., Wickrammanayake, P.D., Farrokh, G.R.: 5-Fluorouracil, adriamycin and methotrexate—a combination protocol (FAMtx) for treatment of metastasized stomach cancer. Proc. Am. Soc. Clin. Oncol. *5*:84, 1986
28. Hermans, J., Bonenkamp, J.J., Boon, M.C., et al.: Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. J. Clin. Oncol. *11*:1441, 1993
29. Preusser, P., Wilke, H., Achterrath, W., et al.: Phase II study with the combination etoposide, doxorubicin, and cisplatin in advanced measurable gastric cancer. J. Clin. Oncol. *7*:1310, 1989
30. Plukker, J.T., Mulder, N.H., Sleijfer, D.T., Grond, J., Verscheuren, R.C.J.: Chemotherapy and surgery for locally advanced cancer of the cardia and fundus: phase II study with methotrexate and 5-fluorouracil. Br. J. Surg. *78*:955, 1991
31. Kremer, B., Henne-Bruns, D., Weh, H.J., Effenberger, T.: Advanced gastric cancer: a new combined surgical and oncological approach. Hepatogastroenterology *36*:23, 1989
32. Kato, S., Kinoshita, K., Sawa, T., et al.: Neoadjuvant chemotherapy in far advanced gastric carcinoma: effect of preoperative chemotherapy with PMUE (CDDP, MMC, UFT, etoposide). Gan to Kagakuryoho *17*:391, 1990 (in Japanese)
33. Stahl, M., Wilke, H., Preusser, P.: Etoposide (E), leucovorin (L), 5-FU (ELF) in advanced gastric carcinoma(GC)—final results of a phase II study. In Abstracts of the European Conference on Clinical Oncology, 1989, p. 0695
34. Akazawa, S., Yoshida, S.: The role of thymidylate synthetase in sequential dose of MTX and 5-FU for the advanced scirrhous type gastric cancer. Gan to Kagakuryouhou *15*:1273, 1988 (in Japanese)
35. Kelsen, D., Lovett, D., Wong, J., et al.: Interferon alfa-2a and fluorouracil in the treatment of patients with advanced esophageal cancer. J. Clin. Oncol. *10*:269, 1992
36. Wadler, S., Lembersky, B., Atkins, M., Kirkwood, J., Petrelli, N.: Phase II trial of fluorouracil and recombinant interferon alfa-2a in patients with advanced colorectal carcinoma: an Eastern Cooperative Oncology Group study. J. Clin. Oncol. *9*:1806, 1991
37. Surbone, A., Myers, C.E.: Regional therapies. In New Directions in Cancer Treatment, I. Magrath, editor. Springer-Verlag, Berlin, 1989, pp. 166–190
38. Speyer, J.L.: The rational behind intraperitoneal chemotherapy in gastrointestinal malignancies. Semin. Oncol. 12(Suppl. 4):23, 1985
39. Sugarbaker, P.H., Cunliffe, W.J., Belliveau, J., et al.: Rationale for integrating early postoperative intraperitoneal chemotherapy into the surgical treatment of gastrointestinal cancer. Semin Oncol. *16*:83, 1989
40. Koga, S., Hamazoe, R., Maeta, M., Shimizu, N., Murakami, A., Wakatsuki, T.: Prophylactic therapy for peritoneal recurrence of gastric cancer by continuous hyperthermic peritoneal perfusion with mitomycin C. Cancer *61*:232, 1988
41. Kaibara, N., Hamazoe, R., Iitsuka, Y., Maeta, M.: Hyperthermic peritoneal perfusion combined with anticancer chemotherapy as prophylactic treatment of peritoneal recurrence of gastric cancer. Hepatogastroenterology *36*:75, 1989
42. Fujimura, T., Yonemura, Y., Fuchida, S., et al.: Continuous hyperthermic peritoneal perfusion for the treatment of peritoneal dissemination in gastric cancers and subsequent second-look operation. Cancer *65*:65, 1990