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Adjuvant Therapy After Curative Resection for Gastric Cancer: Meta-Analysis of Randomized Trials

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Purpose: An overview is presented of reports published since 1980, in which postoperative adjuvant chemotherapy is compared with surgery alone for patients with gastric cancer. A MEDLINE literature review yielded 123 reports, 14 of which were relevant randomized trials; data from 11 of these trials were (or became) available for analysis of crude mortality odds. These 11 trials included 2,096 patients.

Methods: Odds ratios were calculated by comparing the adjuvant treatment arm with the observation-only arm. Those odds ratios that could be considered homogeneous yielded an estimated common odds ratio of 0.88 (95% confidence interval [CI], 0.78 to 1.08), which was slightly, but far from significantly, in support of adjuvant treatment.

Results: The results confirm the common opinion that the adjuvant chemotherapy regimens prescribed in these trials, although effective in phase II studies, do not improve survival. Furthermore they indicate that postoperative chemotherapy in general offers no additional survival benefit for patients with curatively resected gastric cancer.

Conclusion: In conclusion, at present, postoperative chemotherapy cannot be considered as standard adjuvant treatment. New trials of adjuvant therapy for gastric cancer must include a no-treatment control arm.

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SURGERY IS THE TREATMENT of choice for gastric cancer patients. In the advanced stage (stage IV), resection, if at all possible, is palliative in intent. In early stages, resection can usually be performed with a curative intent, but even for these cases the 5-year survival rate has been disappointing. A number of studies have investigated whether adjuvant therapy after a curative resection leads to an improvement in this survival rate, but individual reports have not been encouraging.

In the cases of breast cancer, colon carcinoma, and multiple myeloma, an overview of results, obtained by meta-analysis, has led to better understanding of the treatment benefits^{1,2} and even to unexpected viewpoints.³

The aim of the present meta-analysis was to summarize the results of randomized trials performed to evaluate the effect of adjuvant therapy for gastric cancer. The analysis was restricted to trials published since 1980, because adjuvant regimens studied earlier failed to produce sufficient response rates in gastric cancer patients. Only after MacDonald et al⁴ reported encouraging results using fluorouracil, doxorubicin, and mitomycin (FAM), was new research in this field initiated.

Combination of evidence arising from several trials is only possible and meaningful if the trials have one treatment in common. Surgical resection without any adjuvant therapy is to be considered standard treatment. Therefore, only adjuvant trials with a no-treatment control arm were taken into consideration in this meta-analysis.

METHODS

Literature Search

In June 1991, a search was performed of the MEDLINE data base for the following items: randomized trial, adjuvant therapy for gastric

cancer, published since 1980, and with an English abstract; 123 abstracts were found. Screening of these abstracts for possible relevant randomized trials yielded 62 reports, which were retrieved. Of the remaining 61 abstracts, six were overviews, seven were not randomized studies, 32 dealt with only palliative treatment for advanced disease, four did not include adjuvant therapy, 11 were not concerned with cancer treatment, and one was written in Russian.

The 62 retrieved reports were summarized independently by two of the investigators, using a standardized summary form. The two forms were compared, and in case of discrepancy, the report was again studied to achieve consensus. The following criteria were used for final acceptance of the trial: (1) Was it a randomized trial? (2) Was adjuvant therapy applied after resection, which was performed in the majority of cases with curative intent? and (3) Was there a control arm that underwent surgery alone? The adjuvant regimens, the number of patients in each arm, the number of deaths in each arm, and the follow-up time were then recorded.

Finally, the references of the 62 retrieved reports were scanned for additional trials.

Statistical Methods

Within a trial, the odds for crude mortality were calculated for each treatment arm, ie, the observed number of deaths divided by the number of patients alive. Within each trial, the odds of death within the treatment group divided by the odds of death within the surgery-alone group resulted in an odds ratio. For trials with three arms (two treatment arms) this procedure led to two odds ratios.

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Criteria other than crude mortality, eg, 3- or 5-year survival ratios, are sometimes applied. However, crude mortality ratios are often easier to obtain. Moreover, in situations in which the crude mortality figures are greater than 50%, but do not reach the extreme of 100%, as in the trials analyzed in this study, the latter are suitable for determination of the odds ratios. In other meta-analyses, they were also given priority.²

An odds ratio of 1.0 indicates no effect of treatment on crude mortality, less than 1.0 means a beneficial effect, and greater than 1.0 means a harmful effect of adjuvant therapy. The odds ratios were tested for homogeneity, ie, whether they might have resulted from merely chance variations around a common odds ratio. The homogeneous odds ratios were combined using the Mantel-Haenszel procedure.³

All calculations of the odds ratios, the 95% confidence intervals (CIs), the testing of homogeneity, and calculation of the combined odds ratio were performed with the EGRET program.⁴

RESULTS

Scanning the Retrieved Reports

Of the 62 retrieved reports, 38 were written in English (or a Western language) and 24 in Japanese. The Japanese reports included one and the Western reports 13 relevant clinical trials. These 14 reports are listed in Appendix A.

Forty-eight reports were excluded from meta-analysis; they are listed in Appendix B (Western reports) and Appendix C (Japanese reports). A large majority (31 reports) were excluded due to the absence of a surgery-only control arm (2B, 3B, 4B, 5B, 6B, 10B, 12B, 13B, 14B, 15B, 16B, 18B, 20B, 21B, 24B, 25B, 3C, 4C, 5C, 6C, 8C, 10C, 11C, 13C, 14C, 16C, 17C, 20C, 21C, 22C, 23C). Other reasons for exclusion were no adjuvant treatment (1B, 23B, 1C), advanced disease (7B), trial not or inadequately randomized (9B, 17B, 19B, 7C, 12C), second report on one trial (11B, 18C, 19C), preliminary report (22B) while final report is included in our meta-analysis (5A), early report on toxicology data (8B) while a final report did not yet appear, and report could not be retrieved (2C, 9C, 15C).

Scanning the references of the retrieved reports did not lead to as yet unknown relevant studies.

Relevant Trials

Seven of 14 relevant reports provided all data needed for calculation of an odds ratio. In the remaining seven reports, the number of deaths was not reported. Contact with the senior author to obtain this extra information was successful in four cases. Ultimately, complete data on three trials were not available (1A, 12A, 14A), so they were not included in the formal meta-analysis. The 11 reports with complete data represented eight trials with two arms and three trials with three arms, resulting in 14 odds ratios. Of the 14 comparisons with a control arm, 13 were chemotherapy (in two cases combined with im-

muno-therapy) and one was radiotherapy alone as adjuvant versus a control arm. The latter was excluded from the combination procedure.

Table 1 lists the 14 relevant trials; 11 were included in the meta-analysis. A total of 2,096 patients were analyzed.

Adjuvant Chemotherapy Trials and Odds Ratios

The odds ratios, together with their 95% CIs, calculated for the 13 comparisons of adjuvant chemotherapy with surgery alone, are depicted in Fig 1. In two cases, a significant odds ratio in support of adjuvant therapy was reported (7A and 11A), while one study (13A) found a nearly significant favorable result.

The test for homogeneity (or a common odds ratio) yielded $P = .01$, ie, rejection of the hypothesis of homogeneity. Evaluation of the individual odds ratios showed that study 11A was different from all others. Combination of the 12 homogeneous comparisons yielded an estimation of their common odds ratio of 0.88, with a 95% CI of 0.72 to 1.08 (Fig 1, last line).

Those reports that provided the median follow-up time reported medians of 1.5 to 8 years. The remaining studies gave survival curves over a period of 3 to 5 years.

DISCUSSION

Our aim was to summarize the published results of adjuvant therapy after resection with a curative intent for gastric cancer. We restricted meta-analysis to reports on randomized clinical trials published since 1980. Publication bias because insignificant results were not published or unsuccessful trials were not completed might be present.

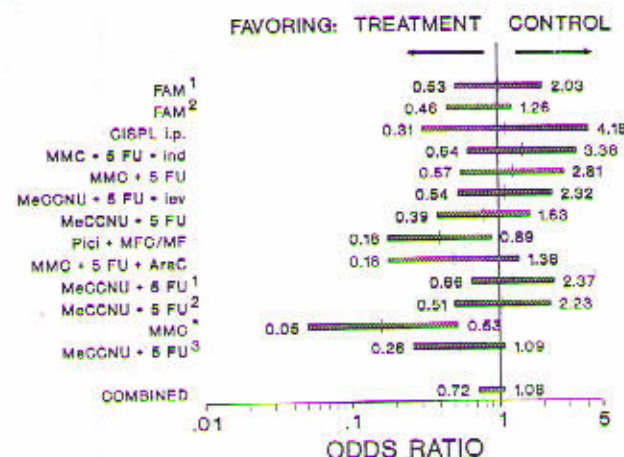


Fig 1. Odds ratios for 13 adjuvant chemotherapy regimens for gastric cancer after curative resection versus surgery alone (see Table 1 for references and abbreviations). The combined odds ratio refers to 12 homogeneous adjuvant chemotherapy studies after exclusion of MMC³.

Table 1. Data From 14 Trials Published Since 1980 on Adjuvant Therapy Versus Surgery Alone After Resection for Gastric Cancer

Reference in Appendix A (first author)	Treatment Arms	Reference in Fig 1	No. of Eligible Patients	No. of Deaths	Odds Ratio	Median FU Time or Maximal Time SURV Curves (years)	Authors' Conclusion
1A (Kraak)	5FU + doxorubicin v Surgery alone	No	61	NA	NA	FU: 7	No substantial benefit for this chemotherapy regimen
2A (Allum)	5FU + Adria + mitomycin v Radiotherapy	FAM ¹	64 119	NA 95	1.04	SURV: 5	No survival advantage
3A (Coombes)	Surgery alone 5FU + Adria + mitomycin v Surgery alone	FAM ²	125 133	99 73	0.76	FU: 5.5	FAM not indicated as routine treatment of operable gastric cancer
4A (Schiessel)	Cisplatin i.p. v Surgery alone	CISPL i.p.	33	26	1.14	FU: 1.5	No significant difference in survival time
5A (Allum)	5FU + mitomycin + induction v 5FU + mitomycin	MMC + 5FU + ind MMC + 5FU	34 140 141	26 127 126	1.47 1.26	FU: 8	No survival advantage for chemotherapy when used as adjuvant to resection
6A (Banfanti)	Surgery alone MeCCNU + 5FU + levamisole v MeCCNU + 5FU	MeCCNU + 5FU + lev MeCCNU + 5FU	130 69 75	113 38 35	1.12 0.80	FU: 7	No effect on survival of either chemotherapy or immunotherapy
7A (Kim)	Surgery alone Picibanil + {MeCCNU} or {5FU + MMC + Ara C} + futrafut* v Surgery alone	Pici + MFC/MF	69 74	36 42	0.40	SURV: 5	Survival was significantly prolonged in the immunochemotherapy group
8A (Jakesz)	Mitomycin + 5FU + Ara C v Surgery alone	MMC + 5FU + AraC	64 53	49 29	0.50	FU: 5	No survival benefit
9A (Engstrom)	MeCCNU + 5FU v Surgery alone	MeCCNU + 5FU ¹	34 91 89	24 57 51	1.25	FU: 5.5	No meaningful disease-free interval or survival advantage for chemotherapy group
10A (Higgins)	MeCCNU + 5FU v Surgery alone	MeCCNU + 5FU ²	66	36	1.07	SURV: 3.5	No improvement in survival or reduction in risks of recurrence
11A (Alcabendas)	Surgery alone Mitomycin v Surgery alone	MMC*	68 33	36 7	0.16	SURV: 4	Adjuvant therapy may be useful
12A (Ochiai)	BCG-CWS + (mitomycin + 5FU + Ara C) v Only MFC v Surgery alone	No No	37 39 35 24	23 NA NA NA	NA	SURV: 5	BCG-CWS is an effective immunotherapeutic agent

Table 1. Data From 14 Trials Published Since 1980 on Adjuvant Therapy Versus Surgery Alone After Resection for Gastric Cancer (Cont'd)

Reference in Appendix A (first author)	Treatment Arms	Reference in Fig 1	No. of Eligible Patients	No. of Deaths	Odds Ratio	Median FU Time or Maximal Time SURV Curves (years)	Authors' Conclusion
13A (Douglass)	MeCCNU + 5 FU v Surgery alone	MeCCNU + 5FU ²	71	29	0.54	FU: 4	Survival advantage for chemotherapy
14A (Yamamura)	OK-432 + mitomycin + 5FU v Mitomycin + 5FU v Surgery alone	No No	71 39 40 43	40 NA NA NA	NA NA	SURV: 4	Chemo-immunotherapy may be effective

Abbreviations: NA, not available; 5FU, fluorouracil; Adria, doxorubicin; i.p., intraperitoneal; MeCCNU, 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea; MMC, mitomycin; Ara C, cytarabine; BCG-CW5, bacillus Calmette-Guérin cell wall skeleton; FU, follow-up; SURV, survival.

*Tegafur.

Moreover, one requirement was a control arm that underwent surgery alone in order to have a common basis for comparison of all therapies, because we felt that a standard adjuvant chemotherapy for gastric cancer did not exist. This requirement excluded a large number of studies in which different adjuvant regimens were compared with each other.

Radiotherapy alone as adjuvant therapy was investigated only once (2A) and was therefore not included in the overall comparison. In this particular trial, radiotherapy did not yield a benefit (odds ratio, 1.62). All other treatment arms represented chemotherapy regimens, two times in combination with immunotherapy. All chemotherapy was administered postoperatively.

Essentially for calculation of the odds on crude mortality, the exact numbers of deaths and patients alive are required. Three reports did not provide these numbers and we were not able to obtain these data later. In one case (1A), no survival benefit was recorded in the original report. In the other two reports, a slight benefit was obtained with immunochemotherapy (12A, 14A). Finally, 13 chemotherapy regimens were available for comparison with the corresponding control arm. Two of the 13 comparisons gave an odds ratio that was significant for adjuvant therapy (7A, 11A). The test on homogeneity of the odds ratios indicated that report 11A was heterogeneous compared with the others. This study showed a clearly positive effect of single-agent therapy with high intermittent infusion of mitomycin; evaluation of 33 patients on mitomycin and 37 controls yielded an odds ratio of 0.16, with a 95% CI of 0.05 to 0.53. The upper limit is still far below the lower limit (0.72) of the CI for the common odds ratio calculated for the remaining 12 odds ratios. This study, with its strong positive effect, stands so apart

that inclusion in a combination of odds ratios is not meaningful. The remaining 12 odds ratios had a combined value of 0.88 in favor of adjuvant chemotherapy; however, this is not significantly different from 1.0.

As far as the numbers of patients are concerned, it should be noted that they are relatively small in the trials analyzed. To detect an increase in survival from 30% to 40% requires 500 patients in each arm, which far exceeds the numbers of patients in the individual trials evaluated in this meta-analysis.

The trials evaluated differ, of course, in many respects other than the difference in treatment regimens. Entry criteria, surgical procedures, the definition of curative intent, pathologic examination of the specimens, follow-up policy, etc, vary widely among trials. However, the intent of this analysis was to evaluate the efficacy of chemotherapy in a treatment arm compared to a control arm, which was the common goal of these trials. Within each trial, factors such as the surgical technique are usually similar in both treatment arms, so they do not affect the odds ratio.

Measuring an effect on survival by calculating the odds ratios proved to be effective in an analysis performed by Buyse et al.² They demonstrated a net positive effect of fluorouracil-containing regimens versus the corresponding control, but did not find such an effect for the other regimens tested. The absence of a significant benefit of adjuvant chemotherapy for gastric adenocarcinoma might be disappointing, but it helps to delimit future research. It appears that the regimens used in the past 10 years, like fluorouracil, doxorubicin, and mitomycin (FAM), were not powerful enough to eradicate (dormant) micrometastasis, although clinical observations yielded response rates of 30%.⁷ A new generation of regimens (etoposide, doxorubicin, and cisplatin [EAP]; fluorouracil, doxoru-

bicin, and methotrexate [FAMTX]) may be more promising as far as response rate is concerned.

A second factor may be even more important. All trials included in our meta-analysis were based on the postoperative administration of chemotherapy and evaluated enhanced survival induced by this chemotherapy. Recently, it has been demonstrated in various phase II studies that preoperative chemotherapy induces not only tumor regression in up to 70% of the treated patients, but in some cases also

complete macroscopic and even microscopic disappearance of all tumor remnants, as substantiated by pathologic examination.⁸ This has led to curative resection procedures for a number of patients who would otherwise have been regarded as incurable. Whether this will influence survival has yet to be demonstrated in randomized trials. However, the symptomatic and psychological benefit to the patient justifies the initiation of new research in the field of adjuvant therapy for gastric adenocarcinoma.

Appendix A. Reports Relevant for Meta-Analysis of Adjuvant Therapy After Curative Resection for Gastric Cancer

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| 1A* | Krook JE, O'Connell MJ, Wieand HS, et al: A prospective, randomized evaluation of intensive-course 5-fluorouracil plus doxorubicin as surgical adjuvant chemotherapy for resected gastric cancer. <i>Cancer</i> 67:2454-2458, 1991 |
| 2A† | Allum WH, Hallissey MT, Ward LC, et al: A controlled, prospective, randomized trial of adjuvant chemotherapy or radiotherapy in resectable gastric cancer. Interim report. British Stomach Cancer Group. <i>Br J Cancer</i> 60:739-744, 1989 |
| 3A | Coombs RC, Schein PS, Chilvers CE, et al: A randomized trial comparing adjuvant fluorouracil, doxorubicin, and mitomycin with no treatment in operable gastric cancer. International Collaborative Cancer Group. <i>J Clin Oncol</i> 8:1362-1369, 1990 |
| 4A | Schiessel R, Funovics J, Schick B, et al: Adjuvant intraperitoneal cisplatin therapy in patients with operated gastric carcinoma results of a randomized trial. <i>Acta Med Aust</i> 16:68-69, 1989 |
| 5A | Allum WH, Hallissey MT, Kelly KA: Adjuvant chemotherapy in operable gastric cancer. 5 year follow-up of first British Stomach Cancer Group trial. <i>Lancet</i> 1:571-574, 1989 |
| 6A | Bonfanti G, Gennari L, Bozzetti F, et al: Adjuvant treatments following curative resection for gastric cancer. The Italian Gastrointestinal Tumor Study Group. <i>Br J Surg</i> 75:1100-1104, 1988 |
| 7A | Kim JP: Immunochemosurgery as a new approach to reasonable treatment of advanced cancer. <i>Ann Acad Med Singapore</i> 17:48-54, 1988 |
| 8A | Jakesz R, Dittich C, Funovics J, et al: The effect of adjuvant chemotherapy in gastric carcinoma is dependent on tumor histology: 5-year results of a prospective randomized trial. <i>Recent Results Cancer Res</i> 110:44-51, 1988 |
| 9A | Engstrom PF, Lavin PT, Douglass HO Jr, et al: Postoperative adjuvant 5-fluorouracil plus methyl-CCNU therapy for gastric cancer patients. Eastern Cooperative Oncology Group study (EST 3275). <i>Cancer</i> 55:1868-1873, 1985 |
| 10A† | Higgins GA, Amadeo JH, Smith DE, et al: Efficacy of prolonged intermittent therapy with combined 5-FU and methyl-CCNU following resection for gastric carcinoma. A Veterans Administration Surgical Oncology Group report. <i>Cancer</i> 52:1105-1112, 1983 |
| 11A | Alcobendas F, Milla A, Estape J, et al: Mitomycin C as an adjuvant in resected gastric cancer. <i>Ann Surg</i> 198:13-17, 1983 |
| 12A* | Ochiai T, Sato H, Hayashi R, et al: Postoperative adjuvant immunotherapy of gastric cancer with BCG-cell wall skeleton. 3- to 6-year follow up of a randomized clinical trial. <i>Cancer Immunol Immunother</i> 14:167-171, 1983 |
| 13A | Douglass HO, Stablein DM, Bruckner HM, et al: Controlled trial of adjuvant chemotherapy following curative resection for gastric cancer. The Gastrointestinal Tumor Study Group. <i>Cancer</i> 49:1116-1122, 1982 |
| 14A* | Yamamura Y, Nishimura M, Sakamoto J, et al: A randomized controlled trial of surgical adjuvant therapy with mitomycin C, 5-fluorouracil and OK-432 in patients with gastric cancer. <i>Gan To Tagaku Ryoho</i> 13:2134-2140, 1986 |

*No number of deaths available.

†Palliative cases excluded.

Appendix B. Reports Retrieved in English (or Western language), but Excluded From Meta-Analysis

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| 1B | Peters KM, Beuth J, Ko HL, et al: Prospective immunostimulation with propionibacterium avidum KP-40 in patients with gastric carcinoma: A prospective randomized study. <i>Onkologie</i> 13:124-127, 1990 |
| 2B | Niimoto M, Saeki T, Toi M, et al: Prospective randomized controlled study on bestatin in resectable gastric cancer—Third report. <i>Jpn J Surg</i> 20:186-191, 1990 |
| 3B | Hattori T, Nakajima T, Nakazato H, et al: Postoperative adjuvant immunochemosurgery with mitomycin C, tegafur, PSK and/or OK-432 for gastric cancer, with special reference to the change in stimulation index after gastrectomy. <i>Jpn J Surg</i> 20:127-136, 1990 |
| 4B | Youn JK, Kim BS, Min JS, et al: Adjuvant treatment of operable stomach cancer with polyadenylic-polyuridylic acid in addition to chemotherapeutic agents: A preliminary report. <i>Int J Immunopharmacol</i> 12:289-295, 1990 |
| 5B | Bleiberg H, Goffin JC, Dalesio O, et al: Adjuvant radiotherapy and chemotherapy in resectable gastric cancer. A randomized trial of the Gastro-intestinal Tract Cancer Cooperative Group of the EORTC. <i>Eur J Surg Oncol</i> 15:535-543, 1989 |
| 6B | Niimoto M, Hattori T, Tamada R, et al: Postoperative adjuvant immunochemosurgery with mitomycin C, flutrafur and PSK for gastric cancer. An analysis of data on 579 patients followed for five years. <i>Jpn J Surg</i> 18:681-686, 1988 |

- 7B Popiela T, Zembala M, Kulig J, et al: Postoperative immunochemotherapy (BCG + 5-FU) in advanced gastric cancer. *Anticancer Res* 8:1423-1427, 1988
- 8B Lise M, Nitri D, Buyse M, et al: Phase-III clinical trial of adjuvant FAM2 (5-FU, Adriamycin and mitomycin C) vs control in resectable gastric cancer: A study of the EORTC Gastrointestinal Tract Cancer Cooperative Group. *Recent Results Cancer Res* 110:36-43, 1988
- 9B Sindelar WF: Intraoperative radiotherapy in carcinoma of the stomach and pancreas. *Recent Results Cancer Res* 110:226-243, 1988
- 10B Villar A, Asensio F, Candel M, et al: Chemotherapy of advanced gastric carcinoma (stage IV): A randomized study of FAM versus 5-FU plus BCNU. *Chemioterapia* 6:57-62, 1987
- 11B Jakesz R, Dittich C, Funovics J, et al: Adjuvante Chemotherapie bei Patienten mit radikal reseziertem Magenkarzinom 5-Jahres-Ergebnisse einer prospektiv randomisierten Studie. (Adjuvant chemotherapy in patients with radical resection of stomach cancer: 5-year results of a prospective randomized study.) *Wein Klin Wochenschr* 98:824-830, 1986
- 12B Papaioannou AN, Kozonis JA, Polychronis AP, et al: Preoperative chemotherapy for gastric cancer: A prospective study with at least 1 year follow-up. *Recent Results Cancer Res* 103:142-147, 1986
- 13B Hattori T, Inokuchi K, Taguchi T, et al: Postoperative adjuvant chemotherapy for gastric cancer, the second report. Analysis of data on 2873 patients followed for five years. *Jpn J Surg* 16:175-180, 1986
- 14B Koyama S, Ozaki A, Iwasaki Y, et al: Randomized controlled study of postoperative adjuvant immunochemotherapy with Nocardia rubra cell wall skeleton (N-CWS) and Tegafur for gastric carcinoma. *Cancer Immunol Immunother* 22:148-154, 1986
- 15B Schnitzler G, Quicsser W, Heim ME, et al: Phase III study of 5-FU and carmustine versus 5-FU, carmustine, and doxorubicin in advanced gastric cancer. *Cancer Treat Rep* 70:477-479, 1986
- 16B Fujimoto S, Furue H, Kimura T, et al: Clinical evaluation of schizophyllan adjuvant immunochemotherapy for patients with resectable gastric cancer—A randomized controlled trial. *Jpn J Surg* 14:286-292, 1984
- 17B Moertel CG, Childs DS, O'Fallon JR, et al: Combined 5-fluorouracil and radiation therapy as a surgical adjuvant for poor prognosis gastric carcinoma. *J Clin Oncol* 2:1249-1254, 1984
- 18B Niimoto M, Hattori T, Ito I, et al: Levamisole in postoperative adjuvant immunochemotherapy for gastric cancer. A randomized controlled study of the MMC + Tegafur regimen with or without levamisole. Report I. *Cancer Immunol Immunother* 18:13-18, 1984
- 19B Matsubara Y, Uragari Y, Yamamoto M, et al: A randomized clinical trial of adjuvant chemotherapy after resection in patients with stomach cancer. *Clin Ther* 6:689-692, 1984
- 20B Fujimoto S, Miyazaki M, Katsukawa Y, et al: Clinical evaluation of prolonged chemotherapy combined with induction of hepatic drug-metabolizing enzymes as an adjuvant for treating patients with gastric cancer. *Jpn J Surg* 13:486-492, 1983
- 21B Hattori T, Niimoto M, Toge T, et al: Effects of levamisole in adjuvant immunochemotherapy for gastric cancer: A prospective randomized controlled study. *Jpn J Surg* 13:480-485, 1983
- 22B Fielding JW, Fagg SL, Jones BG, 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* 7:390-399, 1983
- 23B Schein PS: A comparison of combination chemotherapy and combined modality therapy for locally advanced gastric carcinoma. *Gastrointestinal Tumor Study Group. Cancer* 49:1771-1777, 1982
- 24B Yasue M, Murakami M, Nakazato H, et al: A controlled study of maintenance chemoimmunotherapy vs immunotherapy alone immediately following palliative gastrectomy and induction chemoimmunotherapy for advanced gastric cancer. *Tokai Cooperative Study Group for Adjuvant Chemoimmunotherapy of Stomach Cancer. Cancer Pharmacol* 7:5-10, 1981
- 25B Makowka L, Falk RE, Ambus U, et al: Adjuvant chemoimmunotherapy for gastric carcinoma. *Can J Surg* 23:429-431, 1980

Appendix C. Reports Retrieved in Japanese and Excluded From Meta-Analysis

- 1C Sato H, Wakui A, Hoshi M, et al: Randomized controlled trial of induced hypertension chemotherapy (IHC) using angiotensin II human (TY-10721) in advanced gastric carcinoma (TY-10721 IHC Study Group Report). *Gan to Kagaku Ryoho* 18:451-460, 1991
- 2C Wang ZY: Long-term results of surgery combined with or without chemotherapy in the treatment of stomach cancer—An analysis of 170 cases. *Chung Hua Chung Liu Tsa Chih* 12:132-134, 1990
- 3C Nakazato H, Koike A, Ichihashi H, et al: An effect of adjuvant immunochemotherapy using krestin and 5-FU on gastric cancer patients with radical surgery (first report)—A randomized controlled trial by the Cooperative Study Group. *Study Group of Immunochemotherapy with PSK for Gastric Cancer Gan To Kagaku Ryoho* 16:2563-2576, 1989
- 4C Kuroda Y, Arima S, Ohsato K, et al: Multihospital randomized study on adjuvant chemotherapy with mitomycin C and futraful or UFT in gastric cancer—(part 2). Comparisons between futraful and UFT. *North Kyushu Co-operative Study Group for Cancer Chemotherapy. Gan to Kagaku Ryoho* 16:2235-2240, 1989
- 5C Yamamura Y, Nakazato H, Koike A, et al: A randomized controlled trial comparing short-term MF chemotherapy with MF plus long-term HCFU chemotherapy as an adjuvant to a curative resection of stomach cancer. *Mifuro Study Group for Stomach Cancer. Gan No Rinsho* 34:1936-1942, 1988
- 6C Sugimachi K, Okamura T, Furusawa M, et al: Long-term chemotherapy in patients with stage IV gastric cancer after surgical treatment—A randomized comparative study of FT-207 and UFT. *Gan To Kagaku Ryoho* 15:2953-2957, 1988
- 7C Kan N, Ohgaki K, Okino T, et al: Immunotherapy of gastric cancer. *Gan To Kagaku Ryoho* 15:755-762, 1988