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Adjuvant chemotherapy for gastric cancer in Japan: global and Japanese perspectives

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Abstract Adjuvant therapy for gastric cancer after surgical resection has been under clinical investigation for decades. However, up until now, consistent and concrete evidence has not been generated either in Japan or other countries in favor of adjuvant therapy in terms of survival compared to surgery alone. Meta-analyses reported from Western countries have shown either no or borderline benefit for chemotherapy after surgical resection of gastric cancer. A recent trial showed significant benefit for chemoradiotherapy. However, Japanese specialists believe that their perspectives are different from those in the West due to the following: (1) gastric cancer incidence is several times higher in Japan; (2) more stringent screening programs are emphasized in Japan, thus baseline conditions of cancer patients are different; (3) specific operative techniques are used; and (4) Japanese surgeons have probably acquired additional experience in gastric cancer resection techniques. From the 1960s to the 1980s first mitomycin (MMC) and, later, a combination of oral fluorinated pyrimidines (o-FP) and MMC showed improved survival benefit in Japan compared to surgery alone. However, in the late 1980s, an expert group re-examined the results of previous trials, questioned them, and suggested fresh trials. Since then, the Japanese Clinical Oncology Group (JCOG) has conducted relevant trials to re-examine the effect of MMC and/or o-FP as adjuvant chemotherapy. The results of trials JCOG 8801 and JCOG 9206 have already been reported, and the accrual of patients for another trial (NSAS-GC trial) has just been completed. A pooled analysis of the two preceding trials showed a borderline survival benefit for o-FP compared to surgery alone. If o-FP treatment shows a 5% difference in survival benefit in the NSAS-GC trial, a meta-analysis of the three trials would probably reveal overall significant results. In conclusion, this therapy could become the standard adjuvant treatment regimen for gastric cancer patients after curative resection in Japan.

Keywords Adjuvant therapy · Gastric cancer · Surgical resection · Chemotherapy · Japan

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Introduction

Gastric cancer is the fifth most common cancer worldwide (8.7% of all new cancers) [20]. In 2000, an estimated 870,000 new cases were diagnosed globally, with 647,000 deaths (second most common after lung cancer), of which almost two-thirds were in developing countries [20]. This cancer has a wide variation in geographical distribution. High-risk areas include Japan, Central and South America and Eastern Asia [20]. To date, however, standard therapy has not been established either for advanced disease or for curatively resected gastric cancers. The objectives of this present review were to summarize Japanese and global perspectives on adjuvant chemotherapy for gastric cancer and outline the prevailing differences in terms of its use and outcome.

Rationale for adjuvant chemotherapy for gastric cancer

Surgical resection remains the mainstay for the curative treatment of gastric cancer. Nevertheless, there is a high relapse rate and survival remains poor following surgical resection, irrespective of the methods used. The

assumption that micrometastases are responsible for recurrence and poor survival led to the investigation of numerous adjuvant chemotherapies. However, the rationale for using adjuvant therapy after curative resection remains controversial as no conclusive evidence has been generated so far based on meta-analyses of previous randomized controlled trials either in Japan or in other countries.

Adjuvant chemotherapy in gastric cancer: global perspectives

Hermans et al. were the first to report the results of a meta-analysis of 11 randomized clinical trials comparing postoperative chemotherapy with surgery alone for gastric cancer. In their preliminary meta-analysis, the effect of chemotherapy did not show a significant benefit over surgery alone [odds ratio (OR) 0.88, 95% confidence interval (CI) 0.72–1.08] [4]. Commenting on this report, Pignon et al. pointed out that the meta-analysis had failed to include two important clinical trials [21], and eventually, reappraisal of the meta-analysis demonstrated a borderline significant effect of chemotherapy on survival (OR 0.82, 95% CI 0.68–0.98; Fig. 1) [3, 22, 23].

Several other meta-analyses have been performed comparing chemotherapy with surgery alone, and they have demonstrated a significant effect of adjuvant chemotherapy for curatively resected gastric cancer (Table 1). A global consensus was established that "certain" adjuvant therapies might be effective. However, consensus on the type, dose, combination and schedules of therapy is yet to be reached [2, 7, 12, 19]. Thus, answers to the questions regarding the individually specific effective regimen remain obscure; i.e. what type of anticancer agent is most effective? Which combination of those agents is the best? And which is the most appropriate administration schedule?

An important clinical trial has shed light on the above questions. Macdonald et al. demonstrated a significant benefit of chemoradiotherapy for curatively resected gastric cancers in a clinical trial conducted in the USA [11]. Since then, it has been regarded as the Western standard as adjuvant therapy for gastric cancer. However, should it be considered universally for patients who have undergone curative resection for gastric cancer? Many questions need to be answered before designating it as a global standard.

Development of standard operative procedures in Japan

In Western countries, the standard "curative operation" signifies gastrectomy plus D0 or D1 lymphadenectomy. In Japan, however, the standard operation for gastric cancer has been established as gastrectomy plus D2 lymphadenectomy, with an *en bloc* dissection of the lymph nodes around the common hepatic artery and the splenic artery. As far as the survival rates of the curative operation for each stage of gastric cancer are concerned, results from Japan and the West are similar for stage Ia and Ib, but a higher survival rate has been observed for Japanese patients with later stage cancer: 72% vs 53% for stage II, 49% vs 32% for stage IIIa, and 30% vs 9% for stage IIIb gastric cancer, respectively [8, 9]. When we simply compare these figures, Japanese-style gastrectomy with D2 lymphadenectomy appears to be superior to the standard Western operative procedures. This difference could be attributable to the increased number of gastrectomies performed for gastric cancer in Japan than in the West. In Western countries, due to a lower incidence and less emphasis on prevention and screening systems, most gastric cancers are detected at a relatively advanced stage, and are not eligible for "curative" operation. In Japan, in contrast, the high incidence of gastric cancer has resulted in improvement in the

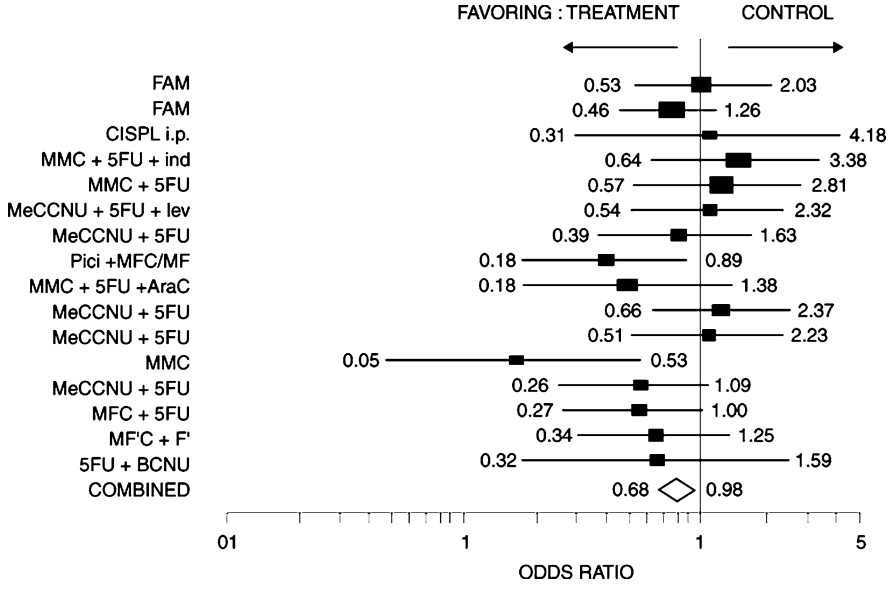

Fig. 1 Final results of the meta-analysis of adjuvant gastric cancer trials by Hermans et al. [4], recalculated by Sakamoto et al. [23]. Reprinted with permission from Sakamoto et al. [23]

Table 1 Meta-analyses of adjuvant chemotherapy

Number of studies	Number of patients	Odds ratio/hazard ratio for death	Reference
11	2414	0.82 (95% CI 0.68–0.98)	4 3 (reappraised)
13	1900	0.80 (95% CI 0.66–0.97)	2
21	3658	0.82 (95% CI 0.75–0.89)	12
20	3962	0.84 (95% CI 0.74–0.96)	7
17	3118	0.72 (95% CI 0.62–0.84)	19

techniques for diagnosis and therapy, and over 90% of patients undergo D2 operation. For example, the incidence of gastric cancer in males per 10^5 population is 124.6 in Japan and 10.1 in the USA [6]. Japanese surgeons, therefore, theoretically have over 12 times the chance to operate on gastric cancer patients than surgeons in the USA. The difference in the number of gastric cancer operations per surgeon may account for the difference in survival rates between Western countries and Japan.

Clinical trials comparing D1 vs D2, and D2 vs D3 lymphadenectomy

In order to obtain a more suitable comparison, a clinical trial comparing Western-style D1 and Japanese-style D2 lymphadenectomy operations for gastric cancer was conducted by Dutch investigators in collaboration with the Japanese National Cancer Center. In this trial, a total of 711 gastric cancer patients were registered, and allocated either to D1 or to D2 lymphadenectomy. However, final results of this trial failed to prove any difference between the two types of lymphadenectomy [1]. Moreover, in this trial, hospital mortality was higher in the D2 group (9.7%) compared to the D1 group (3.9%; $P = 0.004$). Interpretations of this trial by the principal investigator were presented at the American Society of Clinical Oncology Meeting (ASCO 2003) [25] and included the following: (1) superiority of D2 was not proved; (2) although the D2 lymphadenectomy operation is a technically sound surgical method, the Dutch trial was closed before reaching the plateau of the learning curve for most of the participating surgeons; and (3) high postoperative mortality might have offset the effect of the D2 operation in terms of longer duration prognosis.

A similar randomized clinical trial has been conducted in Japan. In this trial, which was started in 1995, D2 lymphadenectomy was compared to the more extensive D3 lymphadenectomy for gastric cancer. A total of 523 patients were enrolled and allocated either to D2 ($n = 263$) or to D3 ($n = 260$) operation. Although the final outcome of the trial will not be available until 2005, preliminary results regarding operative mortality and morbidity have already been presented [24]. Operative mortality in this trial was similar (0.8% in both the D2 and D3 groups), although morbidity was slightly higher in the D3 group (28.1% vs 20.9%). The operative mortality and morbidity in the D2 group was lower compared to the results of any similar Western clinical trial (Table 2). Such a large difference in operative results could be influenced by the specific operative technique, and in this way the outcome of adjuvant therapy can be affected. In particular, high operative mortality and morbidity and the amount of minimal residual disease are presumed to offset the long-term effect of any cancer treatment including extended lymphadenectomy and adjuvant chemotherapy.

The INT-0116 trial, which generated evidence for the effectiveness of adjuvant therapy in the West, included 54% D0, 33% D1, and 10% D2 lymphadenectomies. Meanwhile, in the Japanese trial (JCOG 9501), the patients were split equally between the D2 and D3 categories. Despite the fact that the baseline criteria for both trials were identical (gastric cancer patients eligible for curative resection), total 5-year survival rates were 42% in the INT-0116 trial (half of the patients received chemoradiotherapy) and 71% in the JCOG 9501 (no adjuvant chemotherapy) trial. Comparison of these two trials showed: (1) D0 or D1 plus chemoradiotherapy is better than D0 or D1 alone; (2) D0 or D1 operation proved to be an inadequate procedure in terms of local treatment; (3) chemoradiotherapy treatment could still be inferior to D2 surgery alone; (4) surgical undertreatment clearly undermined survival; and (5) although it is essential to test whether D0 or D1 plus chemoradiotherapy can replace D2 lymphadenectomy by a randomized clinical trial, quality assurance of D2 surgery based on a multi-institutional study appears to be unrealistic in Western countries [25].

In this context, it is necessary to re-examine the results of the previous clinical trials aiming to establish standard adjuvant chemotherapy in Japan, where elaborated D2 lymphadenectomy followed by adjuvant chemotherapy could have been investigated in multicenter studies.

Development of adjuvant chemotherapy for gastric cancer in Japan from the 1960s to the 1980s

Preliminary results of adjuvant chemotherapy for gastric cancer patients in Japan were available in the late

Table 2 Morbidity and mortality after D2 lymphadenectomy for gastric cancer

Trial	Number of patients (D2)	Number of operations/ hospital per year	Mortality (%)	Morbidity (%)
MRC	200	1.5	13	46
Dutch	331	1.0	9.7	43
Japan	263	3.8	0.8	21

1960s [5]. In that trial, which involved 528 gastric cancer patients after curative resection, postoperative treatment with mitomycin (MMC) was shown to result in a better prognosis compared to surgery alone (Fig. 2). These findings, reported more than 25 years ago, were widely accepted. Since then, almost all the clinical trials for gastric cancer in Japan have been designed based on these findings, and used MMC-treated patients as the control group. Soon after, it was reported that a combination of oral fluorinated pyrimidines (o-FP) and MMC resulted in better survival benefit than MMC alone [14]; thereafter, this combination has been considered as the standard adjuvant chemotherapy in Japan (Table 3). Later, the Japanese Cancer Institute examined the pooled effect of the related clinical trials performed between the 1960s and 1980s on adjuvant chemotherapy, and reconfirmed that there was a significant advantage in survival for the combination of MMC and o-FP (pooled odds ratio 0.63, 95% CI 0.51–0.79; Fig. 3) [16].

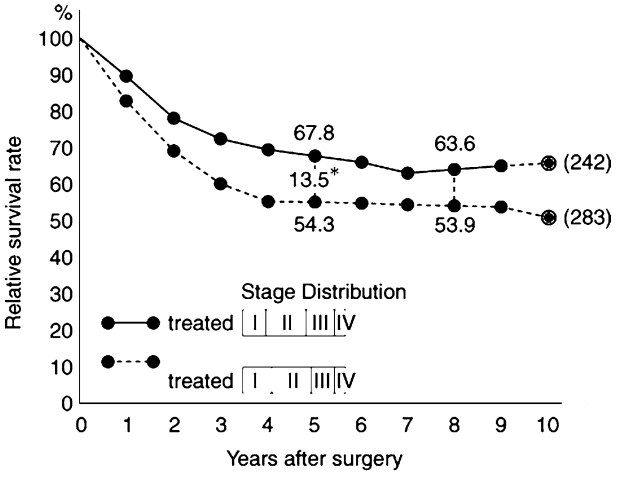

Fig. 2 Survival curves in the first adjuvant chemotherapy for gastric cancer. Reprinted with permission of Springer from Imanaga et al. [5]

Table 3 Randomized clinical trials of adjuvant therapy for gastric cancer in Japan (*MMC* mitomycin C, *TSPA* thio-TEPA, *CPA* cyclophosphamide, *CHRM* chromomycin A3, *CQ* carbazilquinone, *CA* cytosine arabinoside, *FT* ftorafur; *NS* not significant)

Reference	Accrual period	Treatment arms	Number of eligible patients	Conclusions	Suggestive data	
10	1st	1956–61	A: MMC B: TSPA C: control (surgery alone)	209	NS	(−)
	2nd	1962–63	A: MMC B: TSPA C: control (surgery alone)	159	NS	(−)
	3rd	1964–66	A: MMC B: CPA + CHRM C: control (surgery alone)	350	NS	(−)
	4th	1966–69	A: MMC B: control (surgery alone)	313	NS	(−)
	5th	1969–71	A: MMC B: 5-FU C: control (surgery alone)	476	NS	(−)
	6th	1972–75	A: MMC + 5-FU (simultaneous) B: MMC + 5-FU (sequential) C: control (surgery alone)	479	NS	(−)
	7th	1975–78	A: MMC + 5-FU B: 5-FU+ CQ C: control (surgery alone)	812	NS	(−)
5	I	1965–66	A: MMC B: control (surgery alone)	505	NS	Stage II A vs B
	II	1966–68	A: MMC B: control (surgery alone)	517	NS	Stage III A vs B
	III	1969–70	A: MMC + CPA B: MMC C: control (surgery alone)	457	NS	(−)
	IV	1971–73	A: MMC B: MMC + 5-FU + CA C: control (surgery alone)	639	NS	(−)
13		1966–68	A: MMC B: control (surgery alone)	160	NS	Stage III A vs B
15		1974–77	A: MMC + 5-FU + CA B: MMC + FT + CA C: control (surgery alone)	223	NS	Stage II A vs C
27		1977–79	A: MMC + 5-FU B: MMC + 5-FU + OK-432 C: control (surgery alone)	99	NS	(−)

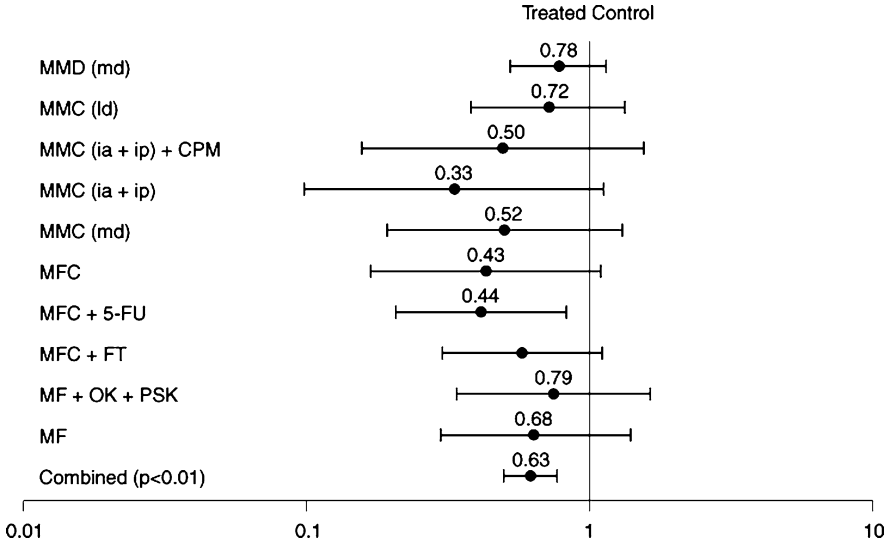

Fig. 3 Meta-analysis of clinical trials conducted in Japan. Reprinted with permission from Nakajima et al. [16]

However, during the late 1980s, the quality of the individual Japanese clinical trials before 1980 was re-examined by the Japanese National Cancer Center. This review revealed the following: (1) in the first adjuvant trial comparing MMC to surgery alone, there were too many exclusions and patients lost to follow-up (nearly 50% of the registered patients), and it did not comply with contemporary standards for clinical trials; (2) the standard lymphadenectomy operation had greatly changed from the time of the first adjuvant chemotherapy trial, and survival rates for patients with each stage of gastric cancer had improved; and (3) no clinical trial was performed comparing adjuvant chemotherapy with surgery alone as controls after 1981 [26]. This review of the Japanese adjuvant MMC plus o-FP treatment for gastric cancer demonstrated that the regimen should not be regarded as standard treatment, irrespective of whether they are clinically or empirically plausible. It was recommended that all future trials on adjuvant chemotherapy in Japan should include surgery alone again as the control.

Relevant adjuvant chemotherapy clinical trials restarted from the end of the 1980s

During the late 1980s, JCOG began to conduct trials on adjuvant chemotherapy in which o-FP and surgery alone were compared. Two relevant trials were performed. JCOG 8801 commenced in 1988 accruing 573 patients, and JCOG 9206 started in 1992 enrolling 252 patients. In both trials, subjects were gastric cancer patients who underwent curative resection. In the JCOG 8801 and JCOG 9206 trials, survival rates were 86.1% and 91.4% in the adjuvant chemotherapy groups, and 82.1% and 86.3% in the control groups, respectively [17, 18]. A meta-analysis of these two trials demonstrated an odds ratio of 0.70 (95% CI 0.48–1.04) for survival, with a *P* value of 0.076 (Fig. 4). Although the meta-analysis did not show a significant benefit for adjuvant chemotherapy compared to surgery alone, a favorable effect of additional postoperative administration of o-FPs to Japanese-style D2 lymphadenectomy appeared to be promising.

From 1997, another new adjuvant therapy trial (NSAS-GC) was started under the instruction of the Ministry of Health and Welfare in Japan. In this trial, adjuvant chemotherapy with UFT was compared to surgery alone for stage II gastric cancers. Accrual of a total of 190 patients (95 for treatment and 95 for the control arm) was completed by 2000. The results will be available in 2005. In this NSAS-GC trial, the expected 5-year survival rate is 70–75%. If the survival advantage of adjuvant chemotherapy turns out to be 5–6%, as it was in the previous JCOG trials, a hypothetical meta-analysis will prove a significant advantage of o-FPs over Japanese-style D2 lymphadenectomy surgery alone (Table 4).

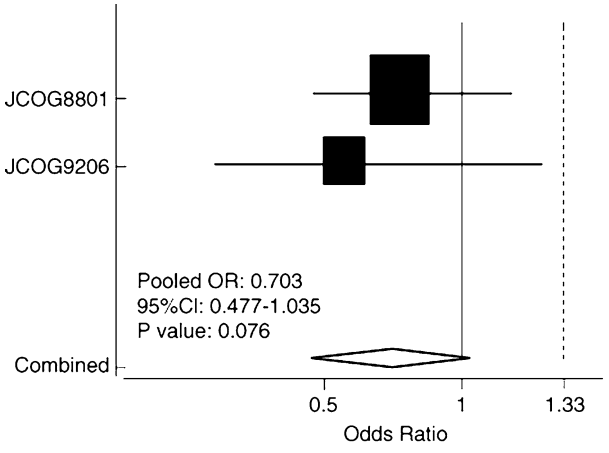

Fig. 4 Meta-analysis of two relevant clinical trials of adjuvant therapy for gastric cancer conducted in Japan

Table 4 Results of JCOG trials and expected results of NSAS-GC trial

	Dead	Alive	Total
JCOG8801			
Surgery + chemo	40	248 (86.1%)	288
Surgery alone	51	234 (82.1%)	285
	91	486	573
JCOG9206			
Surgery + chemo	11	117 (91.4%)	128
Surgery alone	17	107 (86.3%)	124
	28	224	252
NSAS–GC			
Surgery + chemo	20	75 (78.9%)	95
Surgery alone	25	70 (73.7%)	95
	45	145	190

Pooled odds ratio 0.714, 95% CI 0.511–0.998 ($P = 0.0495$)

Table 5 Five-year survival rates of curatively resected gastric cancer patients in Japan and the West [8, 9]

Stage[a]	5-year survival rate (%)	
	West	Japan
Ia	92	96
Ib	84	85
II	53	72
IIIa	32	49
IIIb	9	30

[a]UICC-TNM stage

Difference between global and Japanese perspectives regarding adjuvant chemotherapy for gastric cancer

Differences exist in the incidence (124.6 vs 10.1 per 10^5 among males in Japan and the USA, respectively), baseline patient characteristics, operative procedures, postoperative mortality and 5-year survival of gastric cancer patients between the West and Japan [9]. Gastric cancer patients are diagnosed much earlier in Japan due to an existing well-designed screening system. In addition, operative procedure is typical (D2 with lymphadenectomy), operative mortality is very low (Table 2), and the 5-year survival rate is much higher (Table 5) than in the West [8, 9]. Other plausible reasons for the difference should also be considered. In general, Japanese patients have a lower body mass index and have fewer life-threatening cardiovascular risk factors; thus, Japanese patients are able to tolerate the invasive lymphadenectomy operations better than their Western counterparts. Stage migration associated with more meticulous examination of the lymph nodes was also assumed to be the reason for the difference in survival seen between Western countries and Japan. These features could have a significant beneficial impact on the effectiveness of adjuvant therapy for gastric cancer.

Trial based on a new agent

Since 1999, S-1 (TS-1) has been approved in Japan as therapy for gastric cancer. A new clinical trial comparing adjuvant therapy with S-1 to surgery alone began in 2002. To date, 600 patients have been registered, and accrual of the required patients will be completed by the end of 2004. Results of this trial are expected to be available by 2010.

Future perspectives and conclusions

The results of the adjuvant chemotherapy trials using Japanese-style D2 lymphadenectomy operation as control, have shown o-FPs, which have long been utilized in Japan, to be highly promising. In conclusion, this therapy could become the standard adjuvant treatment regimen for gastric cancers after curative resection in Japan. At the same time, large-scale clinical trials based on existing treatment modalities, new agents with novel mechanisms of action, and molecularly directed therapy should be continued to find more effective adjuvant chemotherapy for this malignancy.

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