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Alternating immunochemotherapy of advanced gastric carcinoma: A randomized comparison of carbazilquinone and PSK to carbazilquinone in patients with curative gastric resection

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Abstract

A total of 103 patients with advanced gastric carcinoma were randomized after curative surgery to receive an alternate administration of carbazilquinone (CQ) and PSK (Krestin) or carbazilquinone alone. Each course of therapies started 1 week after the surgical operation and therapy schedules consisted of 9 courses. In each course of 6 weeks, CQ (2 mg/m^2/week) was administered on day 0, 8, and 15. In combined immunochemotherapy group, PSK was given orally in 3-divided doses of 2 g/m^2/day from the day of the third CQ administration for consecutive 4 weeks. Estimated survival rate and cumulative survival curve were compared utilizing the data up to 7 years after the operation. There was no overall significant difference in survival rates between the CQ plus PSK group and the CQ alone group, but a group of patients whose disease was classified as $S_1 + S_2(N_{1-2})$ survived significantly longer when treated with the combination of CQ and PSK. Neither in more advanced cases ($>S_3$ or $>N_3$) nor in cancers of early stages, the addition of PSK provided an additive effect. The favorable result obtained in one subgroup treated with PSK, suggests that the use of this agent in treating gastric cancers should be carefully evaluated in terms of serosal infiltration and nodal metastasis.

Abbreviations: CQ: carbazilquinone; PSK: Krestin, BRM: biological response modifier.

Introduction

Gastric cancer is one of the most common cancers among Japanese. Treatment with surgery for small locally confined gastric cancers at early stages has resulted in 5 year survival rates of 90–95%. For patients with advanced, resectable cancers, 5 year survival rates range from 6% to 77% [1]. Despite radical surgical treatment, the control of local tumor and distant metastasis remained to be a significant problem, and only a small percentage of the patients can be salvaged with further surgery or radiation.

Moore started the investigation on the effect of addition of chemotherapy to surgery for those patients at high risk for recurrence nearly 30 years ago [2, 3]. In Japan,

randomized controlled study with mitomycin C was extensively performed from the sixties to the seventies, and those initial studies demonstrated the feasibility of short-term postoperative adjuvant chemotherapy in gastric cancers [4]. With the advent of fluorated pyrimidine derivatives, the long-term supportive therapy for more advanced cases had become available, and this type of treatment was proved successful in several studies [5, 6].

On the other hand, adjuvant maintenance chemotherapy to erradicate regional and distant micrometastasis arose a question about 'adverse effect' that cannot be ignored in the long course of treatment. Kondo reported that the outcome of treatment in advanced cancers depends on the selection of chemotherapeutic agents and administration protocols [7]. In the early seventies, polysaccharides derived from bacteria and plants were presented as immunotherapeutic agents, and the possibility to enhance the host defence mechanism by non-specific immunotherapy with these agents was examined extensively [8, 9]. From 1974 to 1976, controlled randomized study on immunochemotherapy was performed involving 28 institutions, but the result of this trial did not show difference in effects between the chemotherapy and immunochemotherapy [10].

Prior studies in murine systems have suggested that some improvement in the therapeutic index may be obtained by alternating administration of carbazilquinone (CQ) with Krestin (PSK) instead of continuously administering PSK with intermittent injections of CQ [11]. In order to confirm that chemotherapy is more effective when alternated with immunotherapy, new randomized trial for resectable gastric cancers was planned to start in July 1977 according to these preclinical findings. The current report details the results of this prospective, randomized trial of induction and maintenance adjuvant immuno-chemotherapy for operable advanced gastric carcinoma.

Materials and methods

Patients and parameters

Patient under 75 years of age and with informed consent were eligible for treatment. All cases had histologically confirmed adenocarcinoma of the stomach without any clinical evidence of other malignancy. The operations performed were macroscopically judged to be curative resection according to the rule of Japanese Research Society for Gastric Cancer and specialized gastrointestinal surgeons were involved in all operations, to minimize methodological and technical difference between institutions. The treatment was randomly allocated to each institution by the envelope method just after the operation.

Pretreatment and follow-up evaluations included history, physical examination, blood cell counts, serum chemistry and radiographs or scans as necessary. Blood cell count, serum creatinine and liver transaminases were checked prior to chemotherapy treatment, and patients who had WBC $<4000/mm^3$, platelet count >100000, serum GOT >80IU or serum creatinine >1.5 mg/dl were excluded before randomization.

Treatment schedule and patient evaluation

The treatment schedule started 1 week after the surgical operation as shown schematically in Figure 1. CQ was administered at a dose of 2 mg/m^2 on day 0, 8 and 15 in each course. In the immunochemotherapy group, PSK totaling 2 g/m^2/day was administered in three-divided dose a day from day 15 for 4 weeks during each course. In chemotherapy group, no treatment with drugs was performed during this period. Treatment was composed of nine courses of which each lasted for 6 weeks. During the first six-week course, CQ was given intravenously: however, CQ was administered orally in all subsequent courses while considering such side effects as leukopenia, thrombocytopenia, nausea, vomiting,

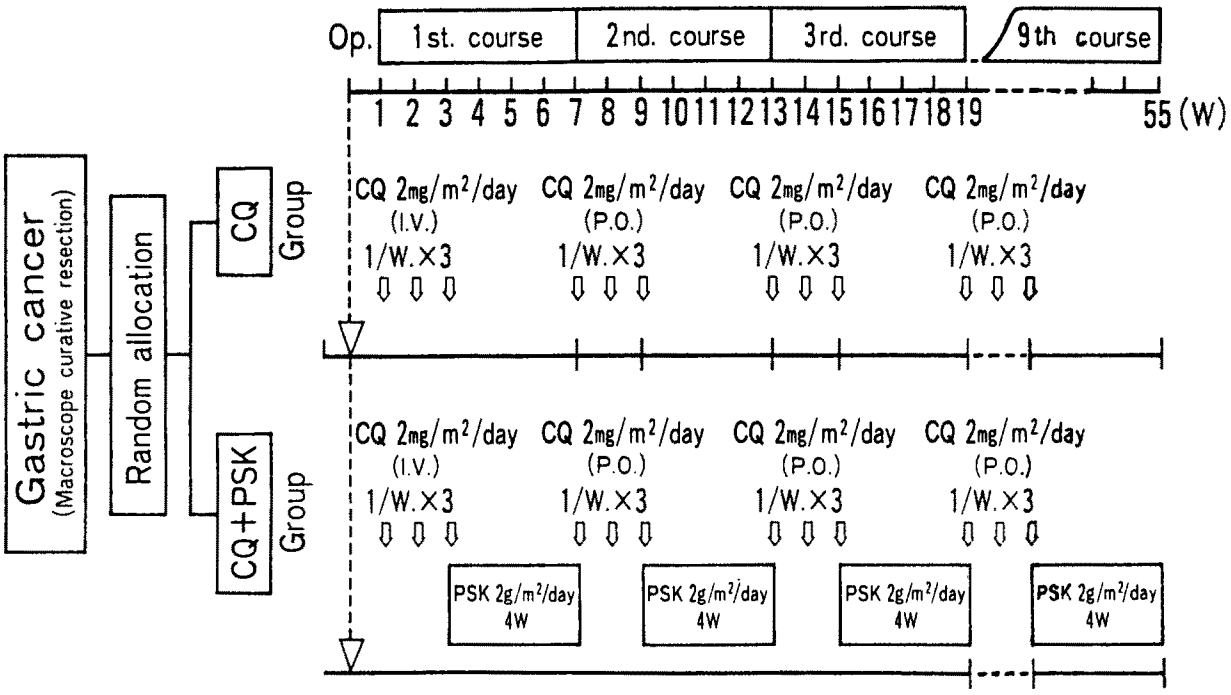


Fig. 1. Regimes and administration method.

liver dysfunction and renal dysfunction. Under such symptoms, treatment was either rescheduled or dosage was reduced.

The median time of observation for the overall series of time from allocation to death, and deaths from other causes were considered as censored cases. Survival arms of the 2 groups were calculated using the method of Kaplan and Meier [12]. The log-rank test and the generalized Wilcoxon test were used to assess the statistical significance of difference between the different subgroups [13, 14].

Data from patients in the study, including copies of surgical pathology and immunochemotherapy reports were reviewed and controlled by one of the authors (H. Nakazato). Questions concerning eligibility, evaluability, and response assessment were resolved by discussion between the controller and the investigators.

Results

Patient characteristics

Of 120 patients registered by 16 institutions between July 1977 and June 1980 in the initial portion of the trial, 17 were considered to be ineligible by the controller and therefore excluded from the trial. The reason for exclusion is listed in Table 1. Non-curative resection, double cancer and non-cancer cases could only be determined after the completion of pathological examination and we considered those cases inappropriate for the comparison of the two treatment regimens. There was neither withdrawal nor dropout case from the trial and all cases were followed up until 7 years after the operation. The follow-up was accomplished with the cooperation of the prefectural and city family registration office covering almost 100% of the

Table 1. Numbers of exclusion and withdrawal.

Treatment	CQ	CQ + PSK	Total
Numbers registered	62	58	120
Numbers excluded	8	9	17
>75 years old	1	0	1
Non-curative resection	5	5	10
Non-cancer disease	1	2	3
Double, multi-centric cancer	1	2	3
Numbers withdrew or dropped out	0	0	0
Numbers of evaluable cases	54	49	103

Table 2. Distribution of patient characteristics.

Characteristic	CQ	CQ + PSK	Total
Number of patients	54	49	103
Age (yrs)			
<50	12	10	22
50–69	37	34	71
>70	5	5	10
Sex			
Male	32	31	63
Female	22	18	40
WBC(count/mm^3)			
<2999	1	0	1
3000–4999	13	8	21
5000–9999	37	38	75
>10000	3	3	6
Liver transaminase(GPT) (unit/ml)			
<39	53	48	101
>40	1	1	2
Subcutaneous tuberculin test			
negative	10	8	18
borderline	8	6	14
positive	10	15	25
not tested	26	20	46
Performance status			
0	3	4	7
1	51	45	96

Table 3. Distribution of prognostic factors by regimen.

Variable	CQ	CQ + PSK	Total
Number of patients	54	49	103
Operation			
1. Gastrectomy			
Total	11	9	20
Partial	43	40	83
2. Curability			
Absolute	32	28	60
Relative	22	21	43
3. Combined resection			
+	10	10	20
−	44	39	83
Tumor factor			
1. Largest tumor diameter (cm)			
<4.9	21	16	37
5.0 − 9.9	28	28	56
>10.0	5	5	10
2. Serosal infiltration (macroscopic)			
S_0	12	9	21
S_1	10	8	18
S_2	28	29	57
S_3	4	3	7
3. Lymph node metastasis (macroscopic)			
N_0	12	6	18
N_1	20	24	44
N_2	20	17	37
N_3	2	2	4
4. Borrman's classification			
1	4	1	5
2	19	22	41
3	26	20	46
4	5	6	11
5. TNM			
1a	7	1	8
1b	7	6	13
2	8	11	19
3a	13	16	29
3b	14	11	25
4	5	4	9
6. Histology			
Intestinal	20	26	46
Diffuse	30	17	47
Unclassified	4	6	10

personal registration in Japan. Thus, 103 patients randomized in a CQ group or CQ and PSK are available for analysis. Table 2 and Table 3 shows the characteristics of these patients and their distribution in terms of the prognostic variables. As is evident, the groups were well balanced with respect of age, stage of the disease at allocation, and stratification level.

Toxicity

Table 4 indicates leukopenia and other side effects experienced by each of the patient

Table 4. Toxicity.

Toxic effects and grades	Chemotherapy CQ (N = 54)	Immunochemotherapy CQ + PSK (N = 49)
Leukopenia		
Nadir WBC count ($\times 10^3$)		
3.0 – 3.9	2	0
2.0 – 2.9	2	2
1.0 – 1.9	1	2
< 1.0		
Total	5(9%)	4(8%)
Other side effects		
Nausea	9 (17%)	5 (10%)
Anorexia	6 (11%)	4 (8%)
Diarrhea	4 (7%)	5 (10%)
Oral mucositis	0 (0%)	2 (4%)
Abdominal pain	1 (2%)	0 (0%)
Abnormal liver transaminase	5 (10%)	10 (21%)

groups during the course of treatment. As is evident from the table, this therapy resulted in predominantly mild to moderate myelosuppression or gastrointestinal symptoms in approximately 10 to 20% of all treated patients. Expression of toxicity were about equally distributed in both patient groups, and consisted largely of nausea, anorexia and diarrhea. Liver transaminase was more than twice as prevalent in the CQ + PSK group.

Overall survival

Overall 7 year survivals were summarized in Figure 2. As shown in the figure, there was no significant difference of overall survival between the two groups [P = 0.827 (logrank test), P = 0.724 (generalized Wilcoxon test)]. From the initiation of the treatment to 35 months after the operation, immunochemotherapy group showed a better survival compared to the group treated only by chemotherapy but the difference disappeared after 36 months to 89 months. The shape of the survival curve was spindle type till 35 months and turn into twister type thereafter. The follow-up after 60 months revealed several cancer deaths in the chemotherapy group, whereas in immunochemotherapy group, no decrease in survival curve was observed.

Survival of patients with $S_1 + S_2$ ($N_{1\text{-}2}$) category

The effects on survival of major prognostic factors were assessed by fitting a Cox's proportional model to the data. Serosal infiltration of carcinoma and the nodal metastasis had considerable effect on prognosis. We excluded categories S_0 and S_3 and N_0 and N_3 and compared the distribution of analysing cases in Table 5. The reason for the analysis of this subset was that the complete curability of the cases in category N_0 or S_0 with surgical therapy alone has increased to 91–94% in recent years [1] and therefore we presumed that the effect of immunochemotherapy on those patients were minimized. On the contrary, in cases of category N_3 or S_3, the presence of remaining tumors were likely even after the macroscopically curative operation. Thus, the analysis we performed was like peeling off the skin of onion which do not seem really necessary for evaluating the effect of immunochemotherapy.

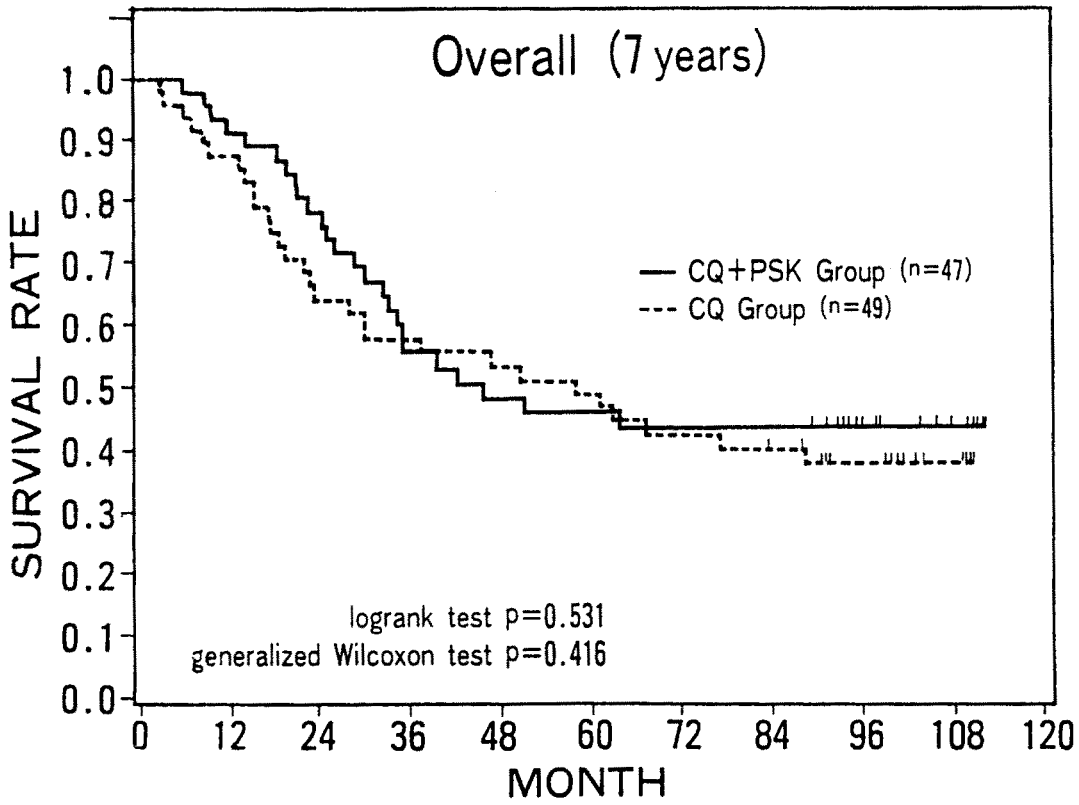


Fig. 2. Cumulative survival curves at the 7 year (April 1987).

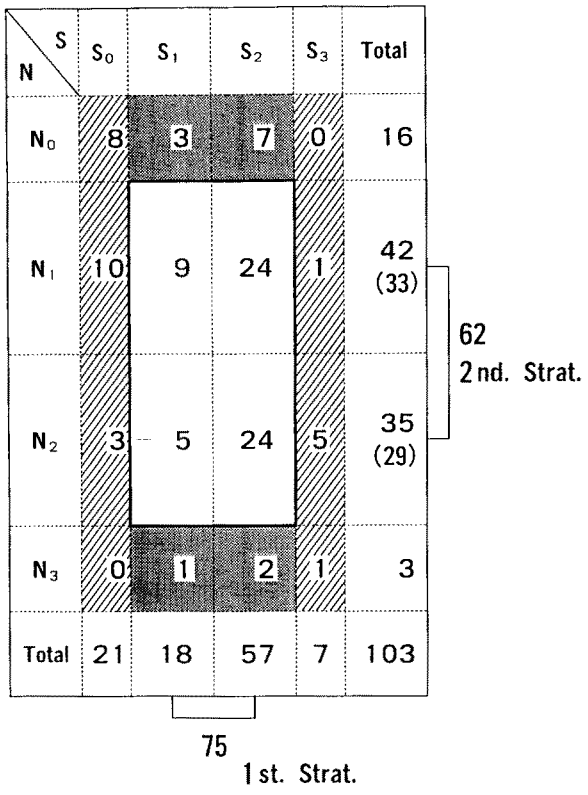
Survival curves from 62 patients who belong to the category $S_1 + S_2(N_{1\text{-}2})$ are presented in Figure 3. Thirty patients received CQ and PSK and 32 patients were given only CQ after the curative resection. As is evident from the figure, 7 year survival of immunochemotherapy group was 43.4% and that of chemotherapy group was 32.3%. The difference of these two groups was calculated. ($P = 0.153$ in logrank test and $P = 0.089$ in generalized Wilcoxon test.) There was no significant deviation of background factors between the CQ and CQ + PSK group in this subset analysis.

Discussion

Numerous reports have described the effect of adjuvant chemotherapy against gastric carcinoma after curative resection and extended lymph node dissection. Chemotherapy using thio-TEPA, triethylenethiophosphamide, 5-fluorodeoxyuridine or 5-fluorouracil + methyl-CCNU were performed in several institutions and by the study groups [15–18]. Since gastric cancer is the primary cause of cancer deaths among Japanese, many studies involving adjuvant chemotherapy for gastric cancers were performed also in Japan [19–21]. The most extensive trial was performed in a prospective randomized and controlled study involving 2064 patients in 297 hospitals from 1975 to 1976 to evaluate the effect of mitomycin C and tegafur as adjuvant chemotherapeutic agents on surgical operations [22] of gastric cancers. Although the cases entered in this study were huge, significant results were not achieved.

With the advent of immunotherapeutic agents, advocated as biological response modifiers (BRM), combination

Table 5. Distribution of analyzing cases by S, N, levels.



immunochemotherapy for gastric cancers have been postulated to be more effective in recent years. The rational for using such agents are based on the concept of enhancing or preserving host defense mechanism affected by tumor or by chemotherapy and the other possibility was the direct antitumor effect of those immunotherapeutic drugs [23, 24].

In our present exploratory trial, we selected carbazilquinone as a chemotherapeutic agent in combination with PSK because of its marked antitumor activity in experimental animals in human cancer cell lines and in clinical trials [25–29]. Based on these studies, the trial was designed to evaluate the effect of PSK, one of BRM extracted from fungi Basidiomycetes [30, 31]. This substance composed mainly of polysaccharides is currently used in many experimental and clinical studies to confirm its effects [32–34]. In designing phase 3 clinical trials, administration schedule should also be carefully determined as well as the dose and the drug combination. We expected from our preclincal study, that the alternating administration of CQ and PSK is the most effective in the treatment [11].

Information with the most immediate clinical relevance obtained from this exploratory study is the fact that the effect of the treatment was substantially affected by factors on the tumor side, mainly serosal invasion and nodal involvement. Although we did not obtain significant difference by the overall analysis of the two groups, longer survival and favorable response were seen in $S_1 + S_2(N_{1\text{-}2})$ subgroup of patients ($P = 0.089$ in generalized Wilcoxon test). One of the points we would like to emphasize in this subset analysis, is that we did not try to select one subgroup or strata which shows significant difference between two treatment modalities. As evident from statistical viewpoint, even in prespecified analysis, the more we increase the number of strata, the more we get a chance of obtaining 'false' positive results by the 'play of chance' [35]. Unlike those subgroup analysis usually employed, we tried to exclude groups of patients to whom this immunochemotherapy seems to have minimal effect like 'peeling off the skin of an onion' and compared the effect of immunochemotherapy in those 'core' group of patients presented in Table 4. In these 62 patients, 7 year survival rates were 32.3% in the CQ group and 43.3% in the CQ + PSK group. To obtain a statistical significance of 0.01 in the trial, the minimal number of entries required was 216.

Our present data suggest that the alternating administration of PSK with CQ seems to offer a benefit for patients with advanced gastric cancers who underwent curative gastrectomy. In this Phase 3 study, we could not substantiate the significant difference in the overall analysis. The favorable results of $S_1 + S_2(N_{1\text{-}2})$ were not confirmative but

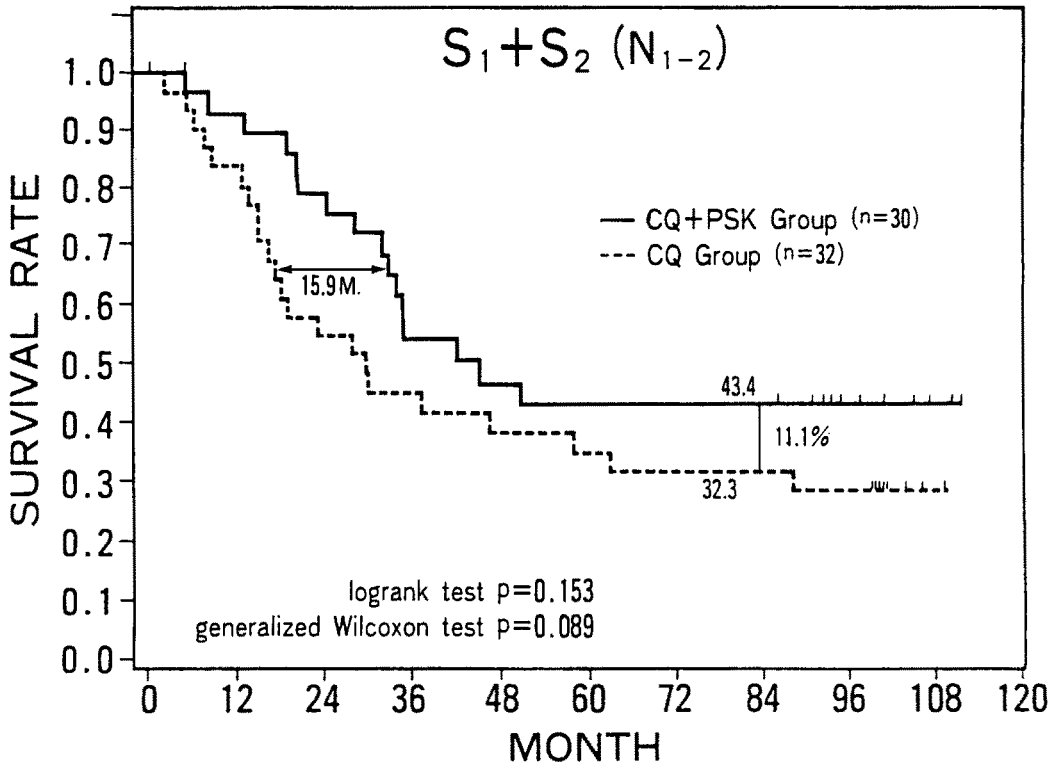


Fig. 3. Cumulative survival curves at $S_1 + S_2$, $(N_{1\text{-}2})$.

suggestive in that the regimen might be beneficial for patients of that category. Based on this study, a new randomized controlled study using mitomycin C, 5-FU and PSK was designed and started from 1985. This combination of schedules will hopefully improve survival of $S_1 + S_2(N_{1\text{-}2})$ gastric cancer patients.

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