Results of Surgery on 6589 Gastric Cancer Patients and Immunochemosurgery as the Best Treatment of Advanced Gastric Cancer

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Results of 6589 gastric cancer operations at the Department of Surgery, Seoul National University Hospital, from 1970 to 1990 were reported. About two thirds (76.6%) were advanced gastric cancer (stages III and IV). The 5-year survival rate of operated stage III gastric cancer was only 30.6%, with frequent recurrence. Conversely, cell-mediated immunities of advanced gastric cancer patients were significantly decreased. Therefore, to improve the cure rate and to prevent or delay recurrence, curative surgery with confirmation of free resection margins and systematic lymph node dissection of perigastric vessels were performed and followed by early postoperative immunotherapy and chemotherapy (immunochemosurgery) in stage III patients. To evaluate the effect of immunochemosurgery, two randomized trials were studied in 1976 and 1981. In first trial, 5-fluorouracil, mitomycin C, and cytosine arabinoside for chemotherapy and OK 432 for immunotherapy were used. The 5-year survival rates for surgery alone (n = 64) and immunochemosurgery (n = 73) were 23.4% and 44.6%, respectively, a significant difference. In the second trial, there were three groups: group I, immunochemosurgery (n = 159); group II, surgery and chemotherapy (n = 77); and group III, surgery alone (n = 94). 5-Fluorouracil and mitomycin C for chemotherapy and OK-432 for immunotherapy were administered for 2 years. The 5-year survival rate of group I was 45.3%, significantly higher than the 29.8% of group II and than the 24.4% of group III. The postoperative 1-chloro-2.4-dinitrobenzene test, T-lymphocyte percentage, phytohemagglutinin- and con-A–stimulated lymphoblastogenesis and the antibody-dependent cell-mediated cytotoxicity test showed more favorable values in the immunochemosurgery group. Therefore, immunochemosurgery is the best multimodality treatment for advanced gastric cancer.

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GASTRIC CANCER IS the most frequently seen malignancy and the first cause of cancer death in Korea.[1-3] One of four patients with malignant tumor has gastric cancer. During the period from July 1, 1989 to June 30, 1990, a total of 10,511 newly diagnosed cases of gastric cancer were registered,[1] and 663 new gastric cancer patient were treated at Seoul National University Hospital in 1991.

Despite the fact that endoscopic diagnostic technique has been developed and popularized, more than 70% of patients in Korea suffer from advanced cancer (Table 1).

Even thorough and extensive radical operations have been performed for patients with stage III gastric cancer, recurrent disease is found in many patients within 2 to 3 years after their operations, and the reported 5-year survival rate varies from only 6% to 33.2%.[4-9] Survival curves of 957 patients who underwent surgery for gastric cancer at the Seoul National University Hospital during a 7-year period are shown in Figure 1.

The more effective radical curative surgical treatments, such as (1) radical resection of primary tumor with adequate resection margin, (2) complete systematic lymph node dissection, and (3) the consideration of reasonable anastomotic techniques to increase the surgical cure rate in advanced gastric cancer patients.

Materials and Methods

A Total of 6589 gastric cancer patients were treated at the Department of Surgery, Seoul National University Hospital, for 21 years, from 1970 to 1990.

Clinical Stage

The International Union Against Cancer tumor, nodes, metastases classification of these 6589 cases were stage I: 11.1% (16.6% in 1990), stage II: 12.3% (15.0% in 1990), stage III: 48.7% (47.7% in 1990) and stage IV: 27.9% (20.8% in 1990) (Table 1). The incidence of early gastric cancer in 1990 was 23% among resected gastric cancer patients.

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TABLE 1. *TNM Stages of 6589 Gastric Cancer Patients at Seoul National University Hospital (1970–1990)*

Period	No. of Cases	Stage I No. (%)	II No. (%)	III No. (%)	IV No. (%)
1970–1979	1209	42 (3.5)	140 (11.6)	547 (45.2)	480 (39.7)
1980–1984	1858	158 (8.5)	175 (9.4)	957 (51.5)	568 (30.6)
1985–1987	1512	224 (14.8)	212 (14.0)	728 (48.1)	348 (23.0)
1988	710	94 (13.2)	91 (12.8)	364 (51.3)	161 (22.7)
1989	660	106 (16.1)	99 (15.0)	304 (46.1)	151 (22.9)
1990	640	106 (16.6)	96 (15.0)	305 (47.7)	133 (20.8)
Total	6589	730 (11.1)	813 (12.3)	3205 (48.7)	1841 (27.9)

Male to Female ratio was 2:1, and peak age incidence was the 6th decade, with an average age of 54 years.

Frequency of Pathologic Characteristics of 6589 Cases of Gastric Cancer

Location: Antrum-pylorus 61.6%
Depth: m 9.0, sm 7.4, s 36.6, ss 27.4%
Borrmann: III 57.2%; II, 28.0%; I, 3.2%
Differentiation: Poor 43.3, Mod. 25.2, Well 14.1%
Lauren type: Int. 52.3, Diff. 42.0, Mix. 5.7%
LN Meta: N 38.1, P 61.9 (1–3, 19.3, ≧4, 42.6)%

Prognostic Factors

To detect the most significant prognostic factors affecting gastric cancer, firstly, univariate analysis of prognostic factors was done, which showed some significance except for age and sex. Then multivariate analysis by multiple regression method with SAS software/life regression procedure showed two significant factors: lymph node metastasis ($p = 0.001$) and depth of invasion ($p = 0.004$) (Table 2). Epidermal growth factor receptors, oncogenes, suppressive oncogenes, and other prognostic factors are currently being carefully investigated.

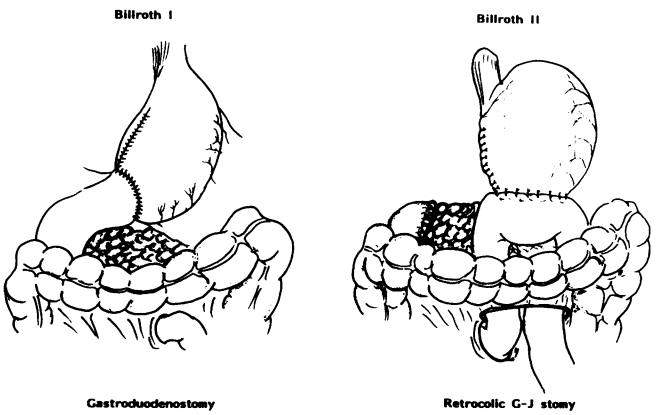

FIG. 1. Gastroduodenostomy (Billroth I) and retrocolic gastrojejunostomy (Billroth II) after subtotal gastrectomy.

TABLE 2. *Multivariate Analysis of 1488 Resected Gastric Carcinomas (1981–1986, SNUH by Multiple Regression With SAS Software/Life-Regression Procedure)*

Variable	Category 1	2	3	4	5	6	Statistics Chi-square	P
Sex	M	F					0.30	0.580
Age (yr)	<30	30	40	50	60	>69	10.93	0.054
Location	A	M	C				4.07	0.130
Gross type	I	II	III	IV	EGC		9.41	0.051
Histology	W	M	P	SIG	MUC	PAP	8.11	0.229
Depth	MM	SM	PM	SS	S	Organ	16.81	0.004*
Lymph node	N0	N1	N2	N3			73.59	0.001*
Resection	ST	T	ET				3.86	0.144

A, antrum; M, body; C, cardia and fundus; I–IV: Borrmann type; EGC, early gastric cancer; W, well differentiated; M, moderately differentiated; P, poorly differentiated; SIG, signet ring cell; MUC, mucinous; PAP, papillary; MM, mucosa; SM, submucosa; PM, proper muscle; SS, subserosa; S, serosa; N, lymph node group; ST, subtotal; T, total; ET, extended total.

Operability and Resectability

In 6589 cases of gastric cancer, average operability (Table 3) was 94%; an improvement from 87% in the early 1970s to 96% in 1990. Resectability was 79%, improved from 70% in the early 1970s to 82% in 1990. Fifty-eight per cent of operated gastric cancer patients received subtotal gastrectomy, and 24% received total or extended total gastrectomy in 1990. Total gastrectomy is a more popular procedure for Borrmann type IV, cardia, or fundus cancer and for signet ring cell or poorly differentiated cancers.

Curative Surgery

Three Essential Surgical Techniques in Curative Surgery

(1) The resection margin should be more than 6 cm from the cancer margin in advanced stomach cancer and at least 2 cm in early gastric cancer on the proximal site, 2 to 3 cm from the pylorus on the distal site.

(2) Complete systematic lymph node (LN) dissection, including LNs around the celiac axis LN (7, 9) common hepatic LN(8), and proper hepatic artery and portal vein LN (12); retropancreatic LN (13) and splenic artery LN (11) must be dissected out (so called skeletonization of vessels). Modified R_3 ($R_2 + \alpha$) resections of LN (8, 9, 11, 12, and 13) are highly recommended because there was a high incidence of LN metastasis in the N3 node. We adopted the Japanese gastric cancer study group's classification of 18 regional LNs (LN 1, right cardia; LN 2, left cardia; LN 3, lesser curvature; LN 4, greater curvature; LN 5, suprapyloric; LN 6, subpyloric; LN 7, left gastric artery; LN 8, common hepatic artery; LN 9, celiac artery; LN 10, splenic hilum; LN 11, splenic artery; LN 12, hepatoduodenal; LN 13, retropancreatic; LN 14, mesenteric

TABLE 3. *Procedures Performed in 6589 Patients With Adenocarcinoma of Stomach (SNUH, 1970–1990)*

Period	No. of Cases	Operation (% Operation/Total)	Resection (% Resection/Operation)	ST (% ST/Operation)	T and ET (%/Operation)
1970–1979	1209	1105 (91)	790 (71)	663 (60)	127 (11)
1980–1984	1858	1768 (95)	1364 (77)	1094 (62)	273 (15)
1985–1987	1512	1408 (93)	1166 (83)	910 (65)	256 (17)
1988	710	646 (91)	514 (80)	388 (60)	126 (20)
1989	660	624 (95)	520 (83)	381 (61)	139 (22)
1990	640	617 (96)	507 (82)	359 (58)	148 (24)
Total	6589	6168 (94)	4861 (79)	3795 (62)	1069 (17)

ST, subtotal; T, total; ET, extended total.

artery; LN 15, midcolic artery; LN 16, aortic artery; LN 110, lower thoracic paraesophageal; LN 111, diaphragmatic) in our surgery.

(3) Reasonable anastomosis after subtotal or total gastrectomy (Fig. 1)
   (a) Billroth I or II?: Billroth I anastomosis is usually done after subtotal gastrectomy in the distal gastric cancer, especially in early gastric cancer, and Billroth II anastomosis is done in most cases of advanced cancer located in the body of stomach.
   (b) Retrocolic or antecolic anastomosis? Whenever it was feasible, retrocolic gastrojejunostomy was performed because
      (1) There are no cancer cells in the mesocolon.
      (2) It creates a short afferent (blind) loop.
      (3) It results in more absorbtion of nutrients and more iron absorption in the duodenum and proximal jejunum.
      (4) There is less postoperative retrostomal herniation.

      However, if the mesocolon is congenitally short or abscent, antecolic anastomosis is necessary.
   (c) Esophagojejunostomy with EEA stapling

      Loop, end-to-side esophagojejunostomy was commonly used in the past. Reflux esophagitis, however, after loop esophagojejunostomy was one annoying postoperative complication. Therefore, many reconstruction methods including Roux-en-Y, reverse 6, β or ρ anastomosis, and jejunal interposition were tested for many years, and the long-term results were similar among various anastomosis techniques (Fig. 2). The authors used loop end-to-side esophagojejunostomy with an afferent loop obstruction method because it is easy, safe, requires a shorter operation time (209 *versus* 254 minutes), and results in less postoperative leakage (1.9% *versus* 2.9%) (Table 4, Fig. 3). Recently we have been using the disposable premium type EEA stapler anastomosis, which provides us with a markedly shorter operation time and fewer leakage problems.
   (d) Comparison study of esophageal reflux between the afferent loop ligated and unligated groups showed a significant preventive effect in the afferent loop ligated group.
   (e) A quality of life study, including reservoir function (number of meals, weight), symptoms (appetite, dysphagia, vomiting, dumping regurgitation), tests and Spitzer's quality of life index (activity, daily living, health, support, and outlook), on 100 consecutive patients gave acceptable results, showing improvement in the patient with total gastrectomy and loop esophagojejunostomy and afferent loop occlusion.

Therefore, loop esophagojejunostomy with the afferent loop obstruction method is a good enough anastomosis after total gastrectomy.

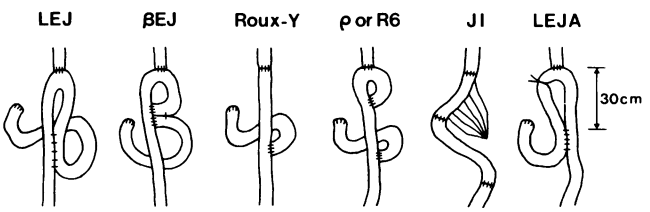

FIG. 2. Various methods of reconstruction after total gastrectomy.

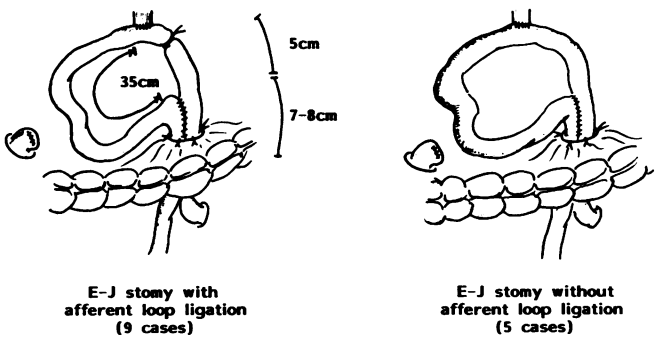

FIG. 3. Esophageal reflux study on the patients receiving loop esophagojejunostomy with or without afferent loop obstruction after total gastrectomy.

TABLE 4. *Comparison of Roux-en-Y and Loop Esophagojejunostomy*

	Roux-en-Y (n = 68)	Loop Esophagojejunostomy (n = 122)
Operating time (min)	254 ± 37	209 ± 53 ($p < 0.001$)
Postoperative leakage (%)	2.9 (2 patients)	1.8 (2 patients)

Postoperative Complications and Mortality Rate

Major postgastrectomy complications were fistula from the esophagojejunostomy site and pancreatic fistula, bleeding, and intestinal obstruction.

The postoperative complication rates after subtotal, total, and extended total gastrectomy were 3%, 9%, and 18%, respectively, and the overall complication rate was 5%.

The overall operative mortality rate was 0.34% (0.3% for subtotal gastrectomy and 0.4% for total or extended total gastrectomy).

Results

The overall 5-year survival rate of resectable gastric cancer was 46.6%, which was well correlated with primary tumor location, number of LN metastases, depth of invasion. The International Union Against Cancer tumor, nodes, metastases (TNM) clinical staging correlated especially well with number of LN metastases and depth of invasion, but not with age and sex.

The 5-year survival rate according to TNM clinical staging was 97.8% for stage I and 72.3% for stage II, but only 30.6% for stage III gastric cancer patients, which is still very dismal (Fig. 4).

Because most of our gastric cancer patients are gastric cancers advanced beyond stage III, we have to consider to developing more effective treatment modalities for advanced gastric cancer patients.

Immunochemosurgery (Postoperative Immunochemotherapy)

Why is immunochemosurgery necessary? Most gastric cancer patients are still in stage III or IV when they are first diagnosed. And the 5-year survival rate for stage III gastric cancer was only 30.6%, which is disappointing. Therefore, the question is raised, "Can surgery alone cure gastric cancer patients?" Yes, but only in stage I and II patients. Surgery alone, however radical it is, can not cure patients with gastric cancer in advanced stages. Stomach cancer in stage III is already systemic disease. To improve the prognosis of advanced stomach cancer, we need systemic treatment such as immunotherapy or chemotherapy in the early postoperative period to kill the micrometastatic or remaining cancer cells even after curative resection (Fig. 5).

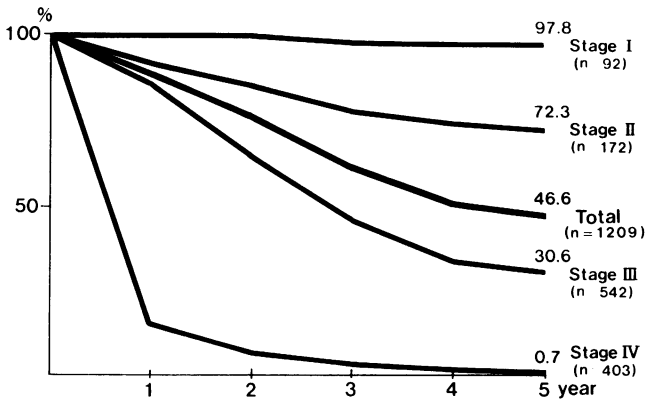

FIG. 4. Survival curves of patients with gastric cancer according to TNM stage (SNBUH, 1975–1981). Number of follow-up cases/total: 1209/1387 (87.1%).

There have been some encouraging reports of prolonged survival and disease-free interval. Taguchi et al.[10] reported improved survival in patients with stage III gastric carcinoma who received mitomycin C and 5-fluorouracil (5-FU) after surgery. Livstone and Stablein[11] reported a prolonged disease-free interval and survival after curative resection for gastric carcinoma using 5-FU and methyl-CCNU (lomustine). Although the results of primary chemotherapy in advanced cases are generally poor, combined administration of mitomycin C, 5-FU, cytosine arabinoside (MFC), or 5-FU and methyl-CCNU (FME) was documented to be efficacious.[12,13]

In the late 1960s, Mathè[14] reported an immunotherapeutic effect of bacillus Calmette-Guérin and allogenic tumor cell vaccine, with an increase in remission duration and survival in a child with leukemia, and Morton et al.[15] reported an immunotherapeutic efficacy of intradermal bacillus Calmette-Guérin inoculation on metastatic cutaneous malignant melanoma. Since then the interest in immunotherapy has greatly increased. Rosenberg[16] and many others[17–25] have shown that immunotherapy can be effective against certain malignancies, including gastric cancer. Immunotherapy alone is rarely effective against clinically measurable cancer. It would be an important therapy, however, to attack cancer cells and to improve

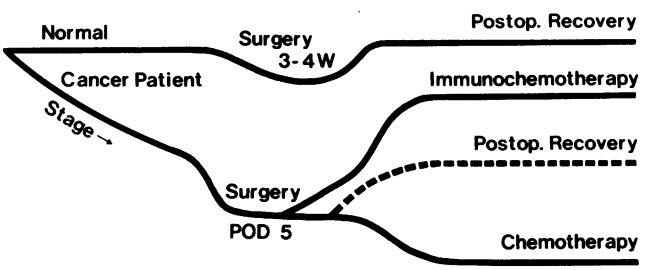

FIG. 5. Change of cell-mediated immunity (CMI) of gastric cancer patients. CMI is decreased according to clinical stage and further decreased by surgery and postoperative chemotherapy. Simultaneous immunochemotherapy may revive immunity to a near normal level.

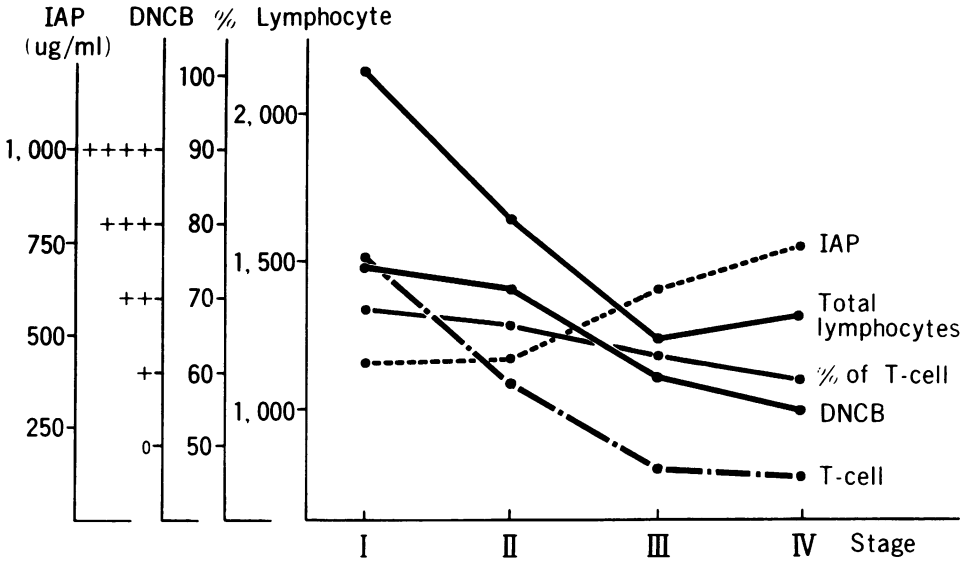

FIG. 6. Levels of various immune parameters in each clinical stage of gastric adenocarcinoma. T cell percentage and DNCB positivities were decreased, whereas immunosuppressive acidic proteins were increased according to the advancement of clinical stage.

host immune status in the case of conjunction with other treatment modalities.

Kim and others[26-28] have shown that both cell-mediated immunity, measured by T-lymphocyte quantitations, and the positivity of 1-chloro-2.4-dinitrobenzene (DNCB) delayed cutaneous hypersensitivity in patients with malignancy are decreased significantly, and the level of immunosuppressive acid protein (IAP) is significantly higher than that of normal individual. The further the clinical stage of gastric cancer progresses, the more depressed is the cell-mediated immunity of the host (Fig. 6).[29,30] In view of this finding, enhancement of the depressed immune status of the host is thought to be an important aspect in the treatment of cancer patients.

The purpose of this study is to evaluate the therapeutic effectiveness of postoperative immunochemotherapy in advanced, but resectable, adenocarcinoma of the stomach. Survival rate and immune status of patients with stage III gastric carcinoma who received postoperative immunochemotherapy were compared with those of patients who received surgery with no adjuvant therapy.

Materials and Methods

First Trial

One hundred thirty-eight patients who had received radical subtotal gastrectomy for stage III gastric cancer were enrolled in this study from 1976 to 1978 at the Department of Surgery, Seoul National University Hospital (Table 5). Before surgery, all patients with stomach cancer underwent a complete history and physical examination with measurements of disease, immune parameters as mentioned below, performance status, routine laboratory tests, and liver scan, and two groups were found comparable. After curative surgery as mentioned in curative surgery section, patients, specifically chosen with histologically confirmed LN-positive stage III adenocarcinoma of the stomach, were randomized as to receiving postoperative immunochemotherapy or not after the routine examination including hemogram, liver function test, and renal function test showed normal values. Patients were ineligible for study if they had previous history of chemotherapy or radiation therapy or if their age was older than 70 years. Initial performance status was within the range of the Eastern Cooperative Oncology Group (ECOG): 0 to 2 in all patients.

Immunologic studies. The following immunologic tests were performed before operation and in the third to fourth postoperative month.

DNCB cutaneous hypersensitivity test. Doses of 0.1 mL 2% DNCB (J.T. Baker Chemical Co., Phillipsburg, NJ) solution in acetone (sensitizing dose) and 0.05% DNCB solution in acetone (challenge dose) were smeared over a 2-cm area of the inner surface of the arm, respectively. The flare-up reaction was measured between 7 and 14 days after application, and it was evaluated as follows: (1) erythema on both sides of sensitizing dose area and challenge dose area, ++++; (2) erythema on sensitizing dose area only, +++ (if there was no reaction until 14 days, 0.1 mL 0.05% DNCB solution was smeared again and the reaction was evaluated 48 hours later); (3) extent of erythema and induration exceeding that of challenge

TABLE 5. *Method (Immunochemosurgery)*

138 Patients With Stomach Cancer, Stage III by TNM Classification	
Group A	Group B
64 patients	74 patients
Radical subtotal gastrectomy alone	Radical subtotal gastrectomy followed by immunochemotherapy

dose area smeared, ++; (4) erythema and induration not exceeding half of challenge dose area smeared, +; and (5) no response, 0.

T lymphocytes (percent and count). Lymphocytes were isolated by Ficoll-Hypaque method from the heparinized peripheral blood of patients. Isolated lymphocytes were washed with saline and Hanks' solution and then mixed with washed sheep erythrocytes and incubated for 18 hours at 37 C. After incubation, the number of rosette-forming cells with at least three sheep erythrocytes was counted among 200 lymphocytes, and it was represented as the percentage of T lymphocytes.

Lymphoblastogenesis by phytohemagglutinin and concanavalin-A stimulation. Lymphocytes were prepared by the Ficoll-Hypaque method from peripheral blood of patients. The prepared lymphocytes were adjusted to 1.5×10^6/0.2 mL with Tissue Culture-199 media. Phytohemagglutinin (PHA) (0.1 mL) and 50 μg Concanavalin-A (con-A) were added to the mixture of 0.2 mL cell suspension and 3 mL media, respectively, and incubated for 72 hours in the presence of 5% CO_2. Four hours before harvest, 0.5 μCi tritiated thymidine was added to each culture tube. After culture, tubes were centrifuged at 4 C and washed with cold saline. Five milliliters 5% trichloroacetic acid solution was added to the precipitates and centrifuged at 4 C, and 0.5 mL 90% formic acid solution was added and kept overnight. Radioactivity was determined using a scintillation counter.

Antibody-dependent cellular cytotoxicity. Lymphomononuclear cells were isolated from the peripheral blood of patients. ^{51}Cr-labeled chicken red blood cells, anti-chicken red blood cell antibody from rabbit, and 10% fetal calf serum-RPMI (Roswell Park Memorial Institute, NY) media were mixed together and incubated for 18 hours at 37 C. After culture, radioactivity of the supernatant was determined. The lymphomononuclear cells (effector cell) to ^{51}Cr-labeled chicken red blood cells (target cell) ratio was 10:1. Cytotoxicity was calculated as follows:

$$^{51}\text{Cr release (\%)} = \frac{\text{experimental release} - \text{spontaneous release}}{\text{maximum release} - \text{spontaneous release}} \times 100$$

Survival rate. Survival rates were calculated from the day of operation, and immune status were compared between the two groups. Statistical comparison of patient characteristics and immune parameters was performed using the chi square test or Student's t test. The differences were considered significant at $p < 0.05$. The difference in survival rate between the two groups was determined using the Cox-Mantel test.

Postoperative immunochemotherapy. Patients in the immunochemosurgery group received the following therapy:

Immunotherapy. OK-432 (*Streptococcus pyogenes* preparation) was given intramuscularly with a dosage of 1.0 Klinische Einheit every week from the fourth or fifth postoperative day.

Chemotherapy. The MFC (mitomycin C, 5-FU, and cytosine arabinoside) regimen was selected at random for the patients and started at the eighth to tenth postoperative days. The dosage administration schedule was as follows: MFC-mitomycin C, 4 mg/50 kg; 5-FU, 500 mg/50 kg; cytosine arabinoside, 40 mg/50 kg, given intravenously twice a week for the first 2 weeks and then every week for the next 6 weeks. Then oral 5-FU was given daily with the dosage of 600 mg/50 kg for 18 months after surgery, if the patients tolerated it. Just before each chemotherapy cycle, white blood cell and platelet counts were obtained and liver function tests were checked if indicated. Drug dosage was controlled based on the parameters of hematologic toxicity and other adverse reactions.

Second Trial

Postoperative immunochemotherapy. Three hundred seventy histologically proven stage III gastric cancer patients, ranging in age from 30 to 70 years and with performance status between 0 and 2, without systemic disease, were randomly assigned to three groups after curative subtotal gastrectomy as mentioned in curative surgery section from 1981 to 1983: 170 for immunochemosurgery, 100 for postoperative chemotherapy, and 100 for surgery alone (Table 6). Forty patients were excluded because they altered or discontinued treatment.

Before surgery, all patients with stomach cancer underwent a complete physical examination with staging of the disease, immune parameters as mentioned above, performance status, routine laboratory test, and liver scan. Patients were ineligible for the study if they had a previous history of chemotherapy or radiation therapy, or if their age was older than 70. The initial performance status was within the range of the Eastern Cooperative Oncology Group (ECOG): 0 to 2 in all patients.

Postoperative immunotherapy was started from the 4th or 5th postoperative day with OK-432, and chemotherapy

TABLE 6. *Randomization of Gastric Cancer Patients**

Treatment/Patient	No. Entered	No. Evaluated
Immunochemosurgery	170	159†
Postoperative chemotherapy	100	77†
Surgery only	100	94†
Total	370	330 (89%)

* Criteria: age > 30 yr, <70 yr; stage III; performance status 0–2; subtotal gastrectomy with lymph node dissection; Billroth II GJS.

† Discontinued or altered treatment cases were excluded from evaluation.

was started from the 8th to the 10th postoperative day with mitomycin and 5-FU. Immunotherapy and chemotherapy was continued for 2 years. Three groups were comparable in terms of age, sex, performance status, preoperative immune parameter data, number of LN metastases, and Lauren's classification. The protocol of immunochemotherapy in the second trial was essentially the same as the that of the first trial, except for the omission of cytosine arabinoside in chemotherapy because of toxicity, and the treatment duration is 24 months (Table 7).

Survival rate and immunoparameter studies. Survival rates, calculated from the day of operation, and immune statuses were compared among the three groups. A statistical comparison of patient characteristics and immune parameters was performed, using the chi square test or Student's t test. Differences were considered significant at $p < 0.05$. Differences in survival rates among the three groups were determined using the Cox-Mantel test.

Results

Results of the First Trial

One hundred thirty-eight patients were randomly divided into two groups and followed at least 5 years. Of 138 patients, 74 received postoperative immunochemotherapy, and 64 patients received no further anticancer therapy after surgery. Patient characteristics, preoperative values of immune parameters, and the proportion of histologic type and extent of LN involvement of the two groups of patients were similar.

Curative surgery for gastric cancer performed in this center includes subtotal gastric resection, complete dissection, so-called skeletonization of regional LNs along the celiac axis, hepatic artery, splenic artery, portal vein, and retropancreatic LN, as well as perigastric LNs and removal of omentum with adjacent tissues. All the tissues were removed in an *en bloc* fashion. Frozen biopsy of both resection margins was done in all cases.

Survival rates. Survival curves of the two groups of patients are shown in Figure 7. The 5-year survival rate of the postoperative immunochemotherapy group is 44.6%, and that of the surgery-alone group is 23.4%. The difference in survival rate determined by the Cox-Mantel test is statistically significant ($Z = 2.09$, $p < 0.05$).

Immunoparameter studies. In the DNCB cutaneous hypersensitivity test, preoperative DNCB positivity is 47.4% in the surgery-alone group and 54.8% in the postoperative immunochemotherapy group. 1-Chloro-2.4-dinitrobenzene positivity at the fourth postoperative month is 73% in the surgery-alone group and 92.9% in the immunochemotherapy group. More patients were converted from negative to positive after postoperative immunochemotherpay.

TABLE 7. *Postoperative Immunochemotherapy Programs*

Immunotherapy starts at the 4th or 5th postoperative day, Picibanil (*Streptococcus pyogenes* preparation); 1.0 KE, IM weekly		
Chemotherapy starts at the 8th to 10th postoperative day		
MF	Mitomycin-C; 4 mg/50 kg 5-Fluorouracil; 500 mg/50 kg	IV × 2/week for 2 weeks, then weekly 6 times
Duration, 24 months (PMF/2M, PF/22M)		

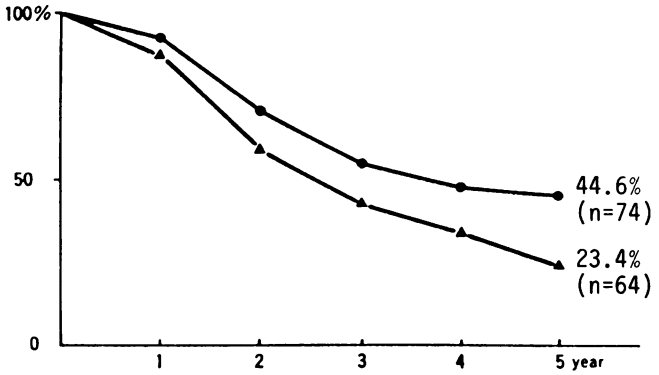

FIG. 7. Survival curve of the immunochemosurgery group and the surgery-alone group in stage II stomach cancer. (●—●) Immunochemosurgery; (▲—▲) surgery alone.

The T lymphocyte percentage and count in the surgery-alone group were decreased from 58.8 ± 7.8% and 1142 ± 344/mm^3 to 56.4 ± 6.9% and 985 ± 495/mm^3, respectively, after surgery. In the postoperative immunochemotherapy group, preoperative T cell percentage and count, 55.2 ± 5.6% and 1133 ± 509/mm^3, were increased to 58.4 ± 5.9% and 1179 ± 537/mm^3, respectively, after therapy.

Postoperative degrees of lymphoblastogenesis by PHA and con-A stimulation are 3653 ± 403 cpm and 4304 ± 463 cpm, respectively, in the surgery-alone group, and 4779 ± 559 cpm and 5412 ± 476 cpm in the immunochemotherapy group. They were much less decreased in the postoperative immunochemotherapy group.

Antibody-dependent cellular cytotoxicity activity at the third postoperative month was 37.7 ± 12.9% in the surgery-alone group and 39.6 ± 11.4% (not significant) in the immunochemotherapy group. Preoperative and postoperative values of immune parameters are shown in Table 8.

Results of the Second Trial

Follow-up study of the second trial was performed on 330 of 370 (89%) patients for at least 5 years. Of these, 159 patients received postoperative immunochemotherapy; 77, conventional adjuvant chemotherapy after operation; and 94, no further therapy. Patient characteristics, preoperative values of immune parameters, histologic type, and extent of LN involvement of the three groups of patients were similar (Table 9).

TABLE 8. *Values of Immune Parameters Before and After Surgery*

Immune Parameter	Control		Immunochemotherapy	
	Before Surgery	After Surgery	Before Surgery	After Surgery
DNCB positivity (%)	47.4 (9/18)	73.0 (14/19)	54.8 (24/42)	92.9 (40/42)
T-cell (%)	58.8 ± 7.8	56.4 ± 6.9	55.2 ± 5.6	58.4 ± 5.9
T-cell (count/mm^3)	1142 ± 344	985 ± 495	1133 ± 509	1179 ± 537
Blastogenesis (cpm)				
PHA-stimulated	5535 ± 1315	3653 ± 403	5183 ± 852	4779 ± 559
Con A-stimulated	8547 ± 1301	4304 ± 463	8882 ± 1336	5412 ± 476
ADCC activity (%)	36.9 ± 11.6	37.7 ± 12.9	37.2 ± 12.1	39.6 ± 11.4

DNCB, 1-chloro-2.4-dinitrobenzene; ADCC, antibody-dependent cellular cytotoxicity.

Survival rate. Survival curves of the three groups of patients are shown in Figure 8. The 5-year survival rate of the immunochemosurgery group was 45.3%; of the chemotherapy group, 29.8%; and the surgery-alone group, 24.4%. The difference between the immunochemosurgery group and the other two groups is statistically significant.

Immunoparameter studies. The postoperative T-cell percentage was increased in the immunochemosurgery group after immunochemotherapy, but was decreased in both the postoperative chemotherapy and surgery-alone groups. The positive conversion rate of DNCB-negative patients after treatment was 85.9% in the immunochemosurgery group compared with 72.5% in the postoperative chemotherapy group and 75% in the surgery-alone group. Lymphoblastogenesis and antibody-dependent cellular cytotoxicity activity also was favorable in immunochemosurgery (Table 8).

Discussion

The result of gastric cancer surgery is dependent primarily on clinical stage, the radicality of surgery, and also on patient immunity and other biologic characteristics. Certainly depth of invasion, presence of LN metastases, especially multiple involvement in more than four LNs, and distant metastases are the most important prognostic factors in gastric carcinoma.[29] The authors[30] analyzed 448 cases of stomach cancer recently to evaluate the prognostic value of Lauren's histologic classification. The 5-year survival rate of the intestinal type (43.7%, $n = 190$) is higher than that of diffuse type (30.4%, $n = 138$) ($p < 0.05$). The distribution of these histologic types are similar among the three groups in this study. Further, the extent of LN metastases as well as presence or absence of metastatic LNs are significant prognostic indicators. It was demonstrated in the author's previous study that 5-year survival rate of patients with one to three metastatic LNs is significantly higher than that of patients with more than four metastatic LN.[29]

Although adjuvant therapy after radical gastric resection has been expected to be the most promising treatment for stomach cancer, there is no long-term follow-up report to demonstrate improvement of survival with use of adjuvant therapy. Several regimens for adjuvant chemotherapy have been suggested and evaluated clinically. The MFC[10,12]; 5-fluorouracil, adriamycin, and mitomycin-C (FAM)[11]; and FME[13] regimens were reported to have good response rate in advanced gastric cancer. The Gastrointestinal Tumor Study Group[6] reported long-term follow-up results of adjuvant chemotherapy with 5-FU and methyl-CCNU after curative resection of gastric cancer. Nissen-Meyer et al.[31] reported decreasing recurrence and death rates when adjuvant chemotherapy was started in the early postoperative period for breast cancer, and no improvement when started 3 weeks after mastectomy. A survival advantage was associated with adjuvant treatment

TABLE 9. *Values of Immune Parameters Before and After Surgery*

Immune Parameter	Immunochemosurgery		Postoperative Chemotherapy		Surgery Alone	
	Before Surgery	After Surgery	Before Surgery	After Surgery	Before Surgery	After Surgery
DNCB positivity (%)	52.5 (41/78)	85.9 (67/78)	48.9 (14/29)	72.5 (21/29)	46.8 (15/32)	75.0 (24/32)
T cell (%)	56.4 ± 6.1	59.7 ± 5.8	59.2 ± 7.4	57.3 ± 6.8	58.7 ± 7.9	56.1 ± 6.8
T cell (count/mm^3)	1135 ± 507	1182 ± 541	1146 ± 352	974 ± 496	1154 ± 440	1152 ± 364
Blastogenesis (cpm)						
PHA-stimulated	5279 ± 759	4638 ± 602	5567 ± 1872	2302 ± 290	5536 ± 1321	3654 ± 411
Con A-stimulated	8879 ± 1301	5327 ± 494	8624 ± 1312	2872 ± 340	8502 ± 1321	4409 ± 472
ADCC activity (%)	37.8 ± 11.9	40.2 ± 11.2	36.7 ± 11.0	37.8 ± 11.3	36.8 ± 11.4	37.9 ± 12.8

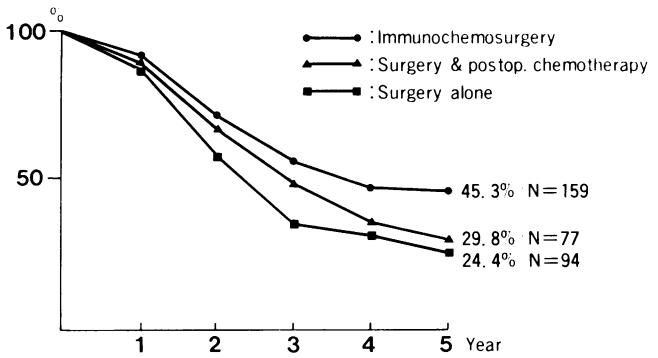

FIG. 8. Survival curve of immunochemosurgery group, surgery and postoperative chemotherapy group and surgery-alone group in stage III stomach cancer (330 cases, 1981–1985). (●) Immunochemosurgery, 45.3% (n = 159). (▲) Surgery and postoperative chemotherapy, 29.8% (n = 77). (■) Surgery alone, 24.4% (n = 94).

and lasted up to 24 months after surgery. The survival difference between the control and adjuvant therapy groups was nearly 20% after 4 years of follow-up. The survival benefit of the present study is similar to that of the Gastrointestinal Tumor Study Group.[6]

There have been many reports on the effectiveness of immunotherapy for certain malignancies such as acute myeloblastic leukemia, lymphoma, breast cancer, malignant melanoma, ovarian cancer, childhood neuroblastoma, head and neck cancer, esophageal cancer, and stomach cancer.[14–25] Theoretically, specific immunotherapy should be more beneficial than nonspecific immunotherapy, but is not yet available for clinical use. Nonspecific immunotherapy such as various immune potentiators or biologic response modifiers are now commonly in use.

Advantages of postoperative immunochemotherapy have been described in terms of prolonged remission and survival, improved bone marrow tolerance, delayed recurrence, and possible prevention of recurrence. Suga et al.[32] reported prolonged survival for patients treated with MFC and OK-432 (picibanil) compared with those treated with MFC alone for advanced gastric cancer. In these studies, the treatment procedure consisted of two components. Firstly, radical gastrectomy was performed as thoroughly as possible, and regional LNs including adjacent tissues were removed *en bloc*. Then early postoperative immunochemotherapy as a second treatment modality was performed to achieve a destruction of residual tumor cells, including micrometastases, with the body burden of tumor cells minimal.

According to the data presented in this study, it is evident that the 5-year survival rate of patients receiving surgery with early postoperative immunochemotherapy is better than that of the chemotherapy or control group. Immune status data also show improved reactivity in the immunochemotherapy group.

Surgery, as a complete removal of visible tumor mass, is of primary importance for multimodality therapy. Both types of therapy, however, should be practiced almost simultaneously to prolong the survival of gastric cancer patients.

Gastric carcinoma probably can be cured with active immunochemosurgery in the near future. To reach this goal, further prospective randomized controlled clinical studies on immunochemosurgery should be initiated. Additionally, measures for local control, such as intraoperative radiation therapy and intraperitoneal chemotherapy, should be considered.

Conclusion

Real radical curative resection of gastric cancer together with complete systematic LN dissection is the most important primary treatment.

Retrocolic gastrojejunostomy after subtotal gastrectomy is highly recommended. And after total gastrectomy, ligation of afferent limb is an effective modification of loop esophagojejunostomy with Braun anastomosis to prevent alkaline reflux.

Immunochemosurgery, radical surgery, and early postoperative immunochemotherapy is the best multimodality treatment for advanced gastric cancer. To kill the micrometastatic and remaining few cancer cells, postoperative immunochemotherapy should be started in the early postoperative period. It is hoped that immunotherapy would be started from 4th or 5th postoperative day and chemotherapy from 8th to 10th postoperative day. Postoperative immunotherapy also may revive the depressed immunity of the advanced cancer patient and may alleviate the adverse effect of postoperative chemotherapy.

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Discussion

DR. ISIDORE COHN, JR. (New Orleans, Louisiana): Dr. Organ, members and guests: It is not often that one gets one's first name immortalized in someone else's presidential address. And even though Jim Thompson's address had nothing to do with me, it was fun to see my name up there along with the people he really admires.

[Slide] When we analyzed our experience at Charity Hospital a number of years ago, we thought we had a big series, having collected 1,710 patients over a period of 35 years. When you compare that with the experience Professor Kim has presented today, it gives you some idea of the tremendous experience that he and his group have had with this disease. By looking at our survival curves with various types of operative procedures, each of these taking all comers and not dividing them just into stage 3, you can once again see the difference between our survival rate and his and see what a superb job he has done with the use of chemotherapy.

The World Health Organization statistics now indicate that Korea has the world's highest incidence of carcinoma of the stomach, so we have a great deal to learn from individuals who look at their experiences as carefully as Professor Kim has.

Our overall 5-year survival for the entire series was 7.9%, which is very different from that which he is reporting. So we have much to learn from the experience of those who see more cases of this disastrous disease than we do, and we hope that we can follow some of the leads they have projected.

DR. HAROLD J. WANEBO (Providence, Rhode Island): Dr. Kim is to be complimented on amassing not only a large number of cases at his institution, but also on capitalizing on information that he had, putting together a random trial to look at chemotherapy and chemoimmunotherapy.

It is interesting, in comparing his data with the American College of Surgeons' database of almost 19,000 patients collected from around the United States, that the percentage of high-stage patients is about the same, (approximately two thirds of the patients were high stage); however, his survival results were much better according to each stage category, approximately 15 to 20%.

An exciting aspect of your presentation is your adjuvant use of OK 432, an immune stimulant that contains *Streptococcus pyogenes* and is very similar to what was used by William Bradley Coley to treat cancer patients some 100 years ago.

You have dissected out very nicely that the addition of this immunotherapy to chemotherapy is actually what produced the survival differences: in your second study, you showed that the chemotherapy itself did not add any survival benefit.

I have a couple of questions. One of these is a little bit of a housekeeping question. That is, I noticed in your second trial you had about 170 patients in one arm and about 80 or so in the other arms, and I wondered if this is a two-to-one randomization scheme?

The second regards your intriguing use of OK 432, and you might want to comment how you happened to use this agent. I know the Japanese have used this agent in a variety of studies. In the United States,