

## Long-Term Effect of Radical Gastrectomy on Nutrition and Immunity

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**Abstract:** The long-term effects of gastrectomy on the nutritional and immunologic status were prospectively studied in 79 gastric cancer patients who underwent curative gastrectomy and were followed by us after operation for an average of 5 years and 3 months. The percent of actual weight to pre-illness normal weight was lower than 95% in 80% of all study patients. Retinol binding protein, prealbumin, and albumin were lower than normal in 17%, 26%, and 26% of the patients, respectively. The mean values of the percent normal weight, retinol binding protein, and prealbumin were significantly lower in the totally gastrectomized patients than in the subtotally gastrectomized ones ( $P < 0.01$ ). The procedures of reconstruction did not affect the nutritional status except for the prealbumin level which was significantly decreased in Roux-en-Y cases than in interposed cases of totally gastrectomized patients. Cell-mediated immunological alterations after gastrectomy were observed in 31%, 37%, and 71% of all patients for OKT3 subpopulation, OKT4/OKT8 ratio, and blastogenesis by phytohemagglutinin, respectively. A multivariate analysis revealed that the long-term immunity of the gastrectomized patients after operation was not affected by the levels of albumin and rapid turnover proteins but by the splenectomy and weight loss they underwent.

**Key Words:** gastric cancer, radical gastrectomy, nutritional assessment, immunity

### Introduction

The state of nutrition and immunity plays an important role on the quality of life in the patients who undergo radical gastrectomy. The malnutrition observed in cancer patients can sometimes not be reversed after surgery and the resection of such diseased organs might

thus worsen the patient's overall condition.<sup>1–4</sup> Immunosuppression in the preoperative patients with protein-caloric malnutrition has been reported.<sup>5</sup> The immunity of patients who undergo radical gastrectomy is depressed temporarily by surgical stress,<sup>6</sup> splenectomy,<sup>7–9</sup> and lymphadenectomy. However, the long term effects of radical gastrectomy, splenectomy, and subsequent malnutrition have not yet been clarified.

This study was conducted to elucidate the long-term effects of radical gastrectomy on the nutritional state of the patients, and to clarify the lasting effects of splenectomy and malnutrition after surgery on the immunity of those patients.

### Patients and Methods

Seventy-nine patients who had undergone radical gastrectomy for gastric carcinoma from 1968 to 1990 and were followed at the First Department of Surgery of Yokohama City University, School of Medicine were prospectively studied from October 1989 until September 1990. Patients with liver dysfunction, heart failure, subileus, or any sign of recurrence were excluded. The patients were categorized into four groups based on the types of operation they underwent. The background of the patients is summarized in Table 1. A total gastrectomy was generally accompanied by pancreatic-splenectomy (PS), while in a subtotal gastrectomy the spleen was preserved. The mean age of the whole study population, 55 males and 24 females, was 59.9 years old. The time elapsed from the operation to this study ranged from 3 months to 10 years, while the mean interval was 5 years and 3 months.

Body weight was examined on admission, postoperatively, and at the time of examination. The weight change was expressed as the percent normal weight (% NWT) by dividing the body weight at the time of examination by the pre-illness normal weight.<sup>10</sup>

**Table 1.** Patients' background

Resection	Reconstruction	Age (years; mean $\pm$ S.D.)	Sex (M/F)	Time lapse (n) <sup>a</sup>		
				3–9 months	10–16 months	17– months
Subtotal	B-I	60.0 $\pm$ 11	28/16	3	7	34
Gastrectomy	B-II	67.1 $\pm$ 13	6/2		2	6
Total-PS	Interposition	55.0 $\pm$ 11	3/2	1	2	2
	Roux-en-Y	57.4 $\pm$ 13	18/4	6		16

<sup>a</sup> Months elapsed from surgery to examination

Total-PS, total gastrectomy with pancreatico-splenectomy; B-I, Billroth I; B-II, Billroth II

**Table 2.** Frequency (%) of low values<sup>a</sup> for each index in the whole study population and in each subgroup

Methods for reconstruction	Nutrition				Immunity				
	%NWT	RBP	PA	ALB	TLC	OKT3	OKT4/8	NK	PHA
All cases	80	17	26	26	17	31	37	8	71
B-I	71	11	21	25	21	18	30	7	68
B-II	67	13	13	25	13	50	38	13	63
Interposition	100	0	0	20	0	20	60	0	100
Roux-en-Y	100	33	48	29	14	52	48	10	71

<sup>a</sup> < the lower limit of 95% for %NWT, or < mean  $-2$ SD of our standard laboratory values for the other indices

%NWT, % usual weight; RBP, retinol binding protein; PA, prealbumin; ALB, albumin; TLC, total lymphocyte count; OKT4/8, OKT4/OKT8; NK, natural killer cell; PHA, phytohemagglutinin

Blood was taken to measure the plasma levels of albumin, prealbumin (PA), and retinol binding protein (RBP) for nutritional indices, and the total lymphocyte count (TLC), lymphocyte subpopulations (OKT3, B1, OKT4, OKT8), natural killer cell (NK cell) activity, and phytohemagglutinin (PHA)-induced blastogenesis in the peripheral blood for immunologic indices. The methods for each measurement were as follows: Albumin was measured by the bromocresol binding method in a Nihon-denki RX20 analyzer (Nihon-denki, Tokyo, Japan). PA was measured by a Beckman PAB in an Array Protein System (Beckman, Tokyo, Japan), and RBP by the anti-RBP antibody (Hoechst Japan, Tokyo, Japan).<sup>11</sup> The total lymphocyte count was calculated by multiplying the total leukocyte count in a Nikkaki STK-S counter (Nikkaki, Tokyo, Japan). Lymphocyte subsets were analyzed by the following fluorescein-isothiocyanate-labelled monoclonal antibodies: OKT3, OKT4, OKT8 (Ortho Diagnostic Systems, Tokyo, Japan), and B1 (Nikkaki, Tokyo, Japan), in a Cytron analyzer (Ortho Diagnostic Systems, Tokyo, Japan). PHA stimulation index (S.I.) was calculated by dividing the DNA contents of PHA-stimulated lymphocytes of patients by those of control lymphocytes. The DNA contents were measured utilizing ethidium bromide as a fluorescent probe which combined to DNA. NK cell activity was measured by the <sup>51</sup>Cr releasing method utilizing K-562 cells as effector cells.<sup>12</sup>

All data were statistically analyzed by both the Student's *t*-test and the multiple regression test.

## Results

The percentages of patients with low values for each index are shown in Table 2. Values below 95% for the %NWT, and values below the mean-2SD in our laboratory for other indices were defined as low levels. Weight loss occurred in 80% of the patients. Low levels of RBP, PA, and albumin were observed in 17%, 26%, and 26% of the patients, respectively. OKT3 subpopulation, OKT4/OKT8 ratio, and PHA blastogenesis were low in 31%, 37%, and 71% of the patients, respectively.

Values of nutritional indices depending on the extent of gastrectomy and the reconstruction are shown in Tables 3 and 4. In Table 3, the %NWT and rapid

**Table 3.** Nutritional indices<sup>a</sup> depending on the extent of gastrectomy

Operation	%NWT <sup>b</sup> (%)	RBP (mg/dl)	PA (mg/dl)	Albumin (g/dl)
Subtotal (n = 52)	90.6 $\pm$ 6.4	4.3 $\pm$ 1.3	23.9 $\pm$ 4.4	4.2 $\pm$ 0.2
Total-PS (n = 27)	80.6 $\pm$ 9.5*	3.3 $\pm$ 1.1*	19.1 $\pm$ 4.9*	4.2 $\pm$ 0.3

<sup>a</sup> Mean  $\pm$  standard deviation (S.D.)

<sup>b</sup> The %NWT was calculated in 40 of the cases with subtotal gastrectomy and 21 of those with total gastrectomy

\* Significant at the level of *P* < 0.01 compared to subtotal gastrectomy

Subtotal, subtotal gastrectomy; Total-PS, total gastrectomy with pancreatico-splenectomy

**Table 4.** Nutritional status and methods of reconstruction

Reconstructive method	Nutrition indices <sup>a</sup>			
	%NWT <sup>b</sup> (%)	RBP (mg/dl)	PA (mg/dl)	ALB (g/dl)
B-I ( <i>n</i> = 44)	91.3 ± 5.4	4.3 ± 1.3	23.4 ± 4.1	4.2 ± 0.2
B-II ( <i>n</i> = 8)	86.0 ± 10.3	4.8 ± 1.0	26.5 ± 5.6	4.2 ± 0.2
Interposition ( <i>n</i> = 5)	79.8 ± 12.2	3.9 ± 0.5	22.1 ± 0.4	4.2 ± 0.2
Roux-en-Y ( <i>n</i> = 22)	80.8 ± 9.1	3.1 ± 1.1	18.6 ± 5.2*	4.2 ± 0.2

<sup>a</sup> Mean ± S.D.<sup>b</sup> %NWT was calculated in 34 of BI, 6 of BII, 5 of interposition, and 16 of Roux-en-Y cases\* *P* < 0.01 compared to interposition**Table 5.** Immunological indices<sup>a</sup> and the extent of resection

Extent of resection	OKT3 (%)	B1 (%)	OKT4/8 (ratio)	NK (%)	PHA (S.I.)	TLC (/mm <sup>3</sup> )
Subtotal ( <i>n</i> = 52)	66.2 ± 10	14.4 ± 6.4	1.7 ± 0.9	44.0 ± 15	269 ± 132	1,945 ± 864
Total + PS ( <i>n</i> = 27)	61.0 ± 13	15.9 ± 8.3	1.3 ± 0.6*	44.5 ± 19	222 ± 90	2,742 ± 1,010

<sup>a</sup> Mean ± S.D.\* *P* < 0.05, compared to the group of patients who underwent subtotal gastrectomy

OKT4/8, OKT4/OKT8; S.I., stimulation index

**Table 6.** Immunological indices<sup>a</sup> and methods of reconstruction

Reconstruction	OKT3 (%)	B1 (%)	OKT4/8 (ratio)	NK (%)	PHA (S.I.)+	TLC (/mm <sup>3</sup> )
B-I ( <i>n</i> = 44)	67.9 ± 8	14.2 ± 5.6	1.7 ± 0.9	43.6 ± 15	262 ± 114	1,935 ± 852
B-II ( <i>n</i> = 8)	57.0 ± 11	15.8 ± 10	1.8 ± 0.7	45.8 ± 19	300 ± 207	1,995 ± 982
Interposition ( <i>n</i> = 5)	61.3 ± 12	16.1 ± 14	1.2 ± 0.4	45.0 ± 17	190 ± 37	2,910 ± 1,254
Roux-en-Y ( <i>n</i> = 22)	60.9 ± 14	15.9 ± 6.8	1.3 ± 0.7	44.3 ± 20	231 ± 99	2,696 ± 970

<sup>a</sup> Mean ± S.D.

OKT4/8, OKT4/OKT8; S.I., stimulation index

turnover proteins (PA, RBP) were significantly lower in the totally gastrectomized patients than in the subtotally gastrectomized patients (*P* < 0.01). The serum albumin levels were not different for both groups. Table 4 shows the nutritional indices depending on gastrectomy and the procedures of reconstruction. In the totally gastrectomized patients, the PA level was significantly lower in the Roux-en-Y group than in the interposition group (*P* < 0.01). However, no other statistically significant difference according to reconstruction procedure was observed for nutrition.

Immunological indices depending on the operation were demonstrated in Table 5 and in Table 6. Table 5 shows that the ratio of OKT4 positive lymphocyte to the OKT8 positive one was significantly lower in patients who underwent a total gastrectomy (*P* < 0.05). No statistical difference was observed among both groups with regard to OKT3, the B1 positive lymphocyte subpopulation, NK cell activity, PHA blastogenesis, and total lymphocyte count. Table 6 shows the immunologic indices depending on the reconstruction

procedures. Both in the subtotal group and in the total group, no differences in the immunologic indices according to the reconstruction procedures were observed.

The effects of the operative procedure, nutrition, aging, and postoperative interval on the immunologic state of the patients were analyzed by the multiple regression test and the results are shown in Table 7. The rapid turnover protein, PA, was substituted by RBP, because those two indices were very closely correlated (*r* = 0.76, *P* = 0.0001). Raw data were used for the total lymphocyte count, OKT3 subset, OKT4/OKT8 ratio, NK cell activity, and age. Logarithmical transformed data were used for PHA blastogenesis and the time elapsed after operation. Operative procedures were translated into ordinal scale data according to the gastrectomy and reconstructive procedure, i.e., subtotal BI-1, subtotal BII-2, total interposition-3, total Roux-en-Y-4. The total lymphocyte count was closely correlated with operative procedure (*P* = 0.0024). OKT3 subset was correlated with %NWT (*P* = 0.0033)

**Table 7.** Effect of nutritional status and types of operation on the immune status: multivariate analysis

Criterion variables <sup>b</sup>	Coefficients( <i>r</i> ) and significance levels ( <i>P</i> ) <sup>a</sup> for predictor variables <sup>b</sup>		
	%NWT	Operation	Age
TLC	<i>r</i> :	0.41	
	<i>p</i> :	0.0024	
OKT3	<i>r</i> :	0.39	-0.24
	<i>p</i> :	0.0033	0.048
OKT4/8	<i>r</i> :	-0.23	
	<i>p</i> :	0.071	
B1	<i>r</i> :	-0.30	
	<i>p</i> :	0.029	

<sup>a</sup> Only values below 0.1 are given

<sup>b</sup> Rapid turnover proteins, albumin, and time lapse for predictor variables had no correlation with the criterion variables. Natural killer cell activity and blastogenesis by phytohemagglutinin for criterion variables had no correlation with the predictor variables. Those variables with no correlation with the other ones were excluded from the table.

OKT4/8, OKT4/OKT8

and age ( $P = 0.048$ ), OKT4/OKT8 ratio had a tendency to correlate with operative procedure ( $P = 0.071$ ), B1 subset was correlated with %NWT ( $P = 0.029$ ). Those immunological indices were not affected by either the level of rapid turnover protein or by that of albumin.

## Discussion

Food stuff is digested in the stomach mechanically by mixing and emulsion formation, and chemically by secretion of pepsin and intrinsic factors. In coordination with the stomach's action, the duodenum secretes cholecystokinin-pancreozymin, mixes chyme with bile and pancreatic enzyme, and absorbs some minerals. Those digestive functions of the stomach and duodenum are impaired by gastrectomy. Food intake is also reduced by the symptoms of rapid passage, stasis, or reflux of the food stuff after gastrectomy.<sup>3,13</sup> Taylor reported impaired gastric functions or dumping syndrome in 20% of partially gastrectomized patients.<sup>1</sup> The majority of all gastrectomized patients we studied were nutritionally impaired. In our study, low values for %NWT or weight loss were observed in 80% of all patients. Low values for RBP, PA, and albumin were also observed in 17%, 26%, and 26% of the patients, respectively. Most of the gastrectomized patients did not fully return to the pre-illness state of nutrition for a long period after operation.

In the surgical patients, the %NWT represented combined results of preoperative effect of tumor, surgical stress, and postoperative malnutrition,<sup>14</sup> and was a sensitive indicator of those overall results in our

study. The plasma level of albumin, one of essential visceral proteins, is a common nutritional index. However, serum albumin levels are maintained at normal levels in the early stages of protein energy malnutrition (PEM),<sup>10</sup> and can not be considered as a sensitive indicator of early malnutrition.<sup>15</sup> The plasma albumin level decreases after significant protein depletion occurs because of its long half-life of 3 weeks. In addition, low protein intake is compensated for by a lowered breakdown of albumin, lowered catabolic rate, and redistribution of albumin into intravascular pools from extravascular pools.<sup>15</sup> On the contrary, rapid turnover proteins undergo quick metabolism; for instance the half-life of RBP and PA are 14h and 3 days, respectively. These proteins are generally used for dynamic nutritional assessment.<sup>16,17</sup> However, it has also been reported that they may be extremely sensitive indicators of nutrition in the static phase, when a subtle change is observed in the level of serum albumin.<sup>18</sup> In 26 out of the 79 gastrectomized patients in a stable condition, rapid turnover proteins were measured twice at intervals of 2–11 months (mean 6.6 months), and demonstrated no difference chronologically. PA levels at each measurement were  $20.0 \pm 6.8$  mg/dl and  $20.2 \pm 6.8$  mg/dl, respectively. RBP levels were  $3.6 \pm 1.3$  mg/dl and  $3.1 \pm 1.4$  mg/dl, respectively. The rapid turnover proteins were significantly lower in the totally gastrectomized patients than in subtotaly gastrectomized patients ( $P < 0.01$ ), although both parameters did not differ with regard to the reconstruction procedure, except for the PA levels between the Roux-en-Y cases and the interposition cases. Therefore, a detailed study including the quality and quantity of the food intake is needed to evaluate these bypassing effects. In the gastrectomized patients, mild PEM depending on the extent of resection existed as indicated by the decreased levels of rapid turnover proteins. The rapid turnover proteins were more sensitive than the albumin in detecting the subtle impairment in nutrition.

Immunologic alteration is commonly observed in advanced gastric cancer patients. The number of lymphocytes positive to OKT3, OKT4, or OKT8 antibody were reported to be lower in patients with advanced cancer than in patients with early cancer.<sup>19</sup> NK cell activity is also low in advanced cases.<sup>20</sup> There is a further transient fall of NK cell activity after the operation, although it recovers within a month even in cases who undergo splenectomy.<sup>21</sup> These transient alterations in immunity may be caused by the stress of operation. Splenectomy accompanied by radical total gastrectomy has biphasic effects on the immunity depending on the stage of the stomach cancer.<sup>7,8</sup> Reticuloendothelial dysfunction after splenectomy was also studied.<sup>9</sup> The chronic effects of gastrectomy and splenectomy on the immunologic status have still not been thoroughly dis-

cussed. In our study, the operation did not affect NK cell activity in the long term. Immunologic parameters associated with cell mediated immunity, OKT3, OKT4/OKT8, and PHA blastogenesis, were low in 31%–71% of the cases. The OKT4/OKT8 ratio in the totally gastrectomized patients was lower than that in the subtotaly gastrectomized patients.

In the univariate analysis, splenectomy, gastrectomy, and consequent malnutrition were involved in the factor of operation. In the multivariate analysis, the effect of nutrition could be omitted from the operation, which consequently chiefly represented the splenectomy. In this study, the operation was related positively with the total lymphocyte count and negatively with the OKT4/OKT8 ratio. Rapid turnover proteins and albumin did not correlate with any immunologic index. The %NWT correlated with T cell and B cell subpopulations. These results suggested that the immunity of gastrectomized patients was modified by splenectomy and weight loss.

Impaired humoral and cell mediated immunity has been reported in protein and caloric malnutrition.<sup>22</sup> The patients examined in this study demonstrated either mild or subclinical PEM. The immunity of these patients had been modified, not only by splenectomy but also by impaired nutrition. A specific nutrient of zinc, which is a component of various key enzymes of metabolism, is associated with impaired protein synthesis including RBP<sup>23</sup> and impaired cell mediated immunity.<sup>24,25</sup> Reconstruction procedures that bypass the duodenum may decrease the absorption of zinc in the duodenum.<sup>26</sup> In this study, the PA level was lower in the interposition cases than in the Roux-en-Y cases, although no other significant bypassing effects were observed in the nutrients studied. Further studies including zinc and other nutrients are still needed to evaluate the correlation of the nutrition and immunity in gastrectomized patients.

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