
原 著

Studies on Early Enteral Nutrition for Patients with Gastric Cancer from the View of Immunity

HIROSHI TANABE

Department of Surgery, Kizawa Memorial Hospital, 590 Kobi-cho, Minokamo-shi, Gifu 505, Japan

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Summary

The enteral nutrition after operation for gastric cancer patients with special reference to its immunological improving effect was examined. The subjects were 25 patients who underwent an operation and they were classified into 2 groups by the postoperative nutritional control method.

E group: patients who recieved enteral nutrition after operation ($n=12$) and T group those who reviewed TPN postoperatively ($n=13$). In the 25 subjects the serum proteins, nitrogen balance and 3-methylhistidine (3-Mehis) were measured before and after the operation. The total lymphocyte counts were measured before and after operation. The total lymphocyte subsets and NK cell activity were determined with monoclonal antibodies. Nutritioaly, there was no significant difference in the serum proteins and nitrogen balance and 3-Mehis/Cr ratio also showed no significant difference. Immunologically, an improving effect was observed in E group postoperatively with $CD4^+CD45R^-Leu8^-$ (helper T) cell subpopulation, $CD8^+CD11b^-$ (cytotoxic T) cell subpopulation and $CD3^-CD16^+CD56^+$ (NK-LAK) cell subpopulation.

Introduction

The postoperative nutritional control method has made remarkable progress recently and total parenteral nutrition (TPN) has been mainly used. However, TPN is originally to be performed restricted to cases in wich the intestinal function does not work, and usefulness of the enteral nutrition has been accepted recentrly from various viewpoints. This time we examined the immunological improving effect of the enteral nutrition using lymphocyte subsets obtained with monoclonal antibodies.

Material and Methods

The subjects were 25 patients in whom a diagnosis of advanced gastric cancer was made based

Key words: Gastric cancer, Enteral nutrition, Immune activity, Lymphocyte subsets, Three color flow cytometry

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Present address: Department of Surgery, Kizawa Memorial Hospital, 590 Kobi-cho, Minokamo-shi, Gifu 505, Japan

on a postoperative histological examination among those with gastric cancer who underwent operation at Department of surgery of our hospital during a period from 1990 to 1991. They were classified into 2 groups by the postoperative nutritional control method, E group: patients whose nutrition was controlled by the enteral nutrition after the operation ($n=12$) and T group: those who received TPN postoperatively ($n=13$). The background factors of the subjects are shown in Table 1, but there were no significant differences between the 2 groups.

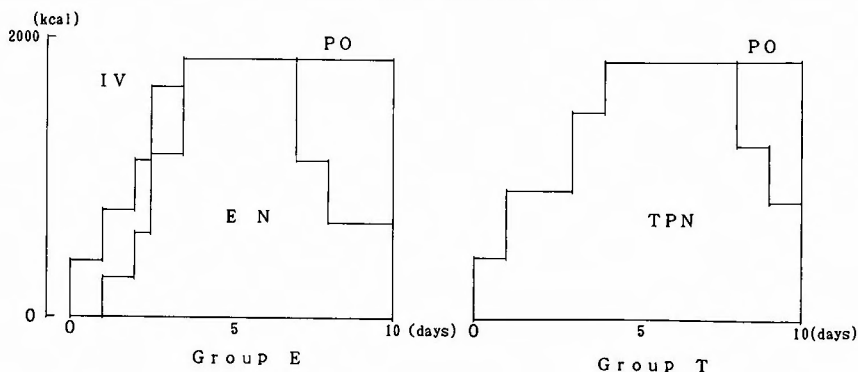
Furthermore, the nutritional control method of E and T groups are illustrated in Table 2. In the E group, enteral nutrition with ED-AC was started on the 2nd hospital day and the full strength 1800 kcal/1200 ml was reached on the 5th hospital day. In the T group, intravenous hyperalimentation

Table 1 Subjects

		E group (n = 12)	T group (n = 13)	Significance
Age mean $\pm$ SD		48~77 48.9 $\pm$ 9.2	53~75 66.9 $\pm$ 11.4	NS
Sex (♂ : ♀)		7 : 5	7 : 6	NS
stage	I	0	0	NS
	II	1	1	
	III	5	5	
	IV	7	7	
Operative procedure	Total gastrectomy	4	5	NS
	Subtotal gastrectomy	8	7	
Blood transfusion	+	1	1	NS
	-	11	12	

NS : not significant

Table 2 Nutritional control method



was started on the 1st hospital day and the 3rd hospital day on.

We measured total protein (TP), albumin (Alb) and transferrin (Tf), prealbumin (PA) and retinol binding protein (RBP) as rapid turn over protein (RTP) in the 25 subjects before the operation and on the 1st, 3rd, 5th, 7th, 10th day after operation. We determined the nitrogen balance from the amount of nitrogen administered. Furthermore, 3-methylhistidine (3-Mehis) in urine and creatinine clearance were measured. As immunological factors the total lymphocyte counts were obtained from the peripheral blood before operation and on the 1st, 5th, 10th, 20th and 30th day after operation, lymphocyte subsets were determined with monoclonal antibodies; CD3, CD4, CD8, CD11b, CD16, CD45R, CD56 and Leu8, and further NK cell activity was measured.

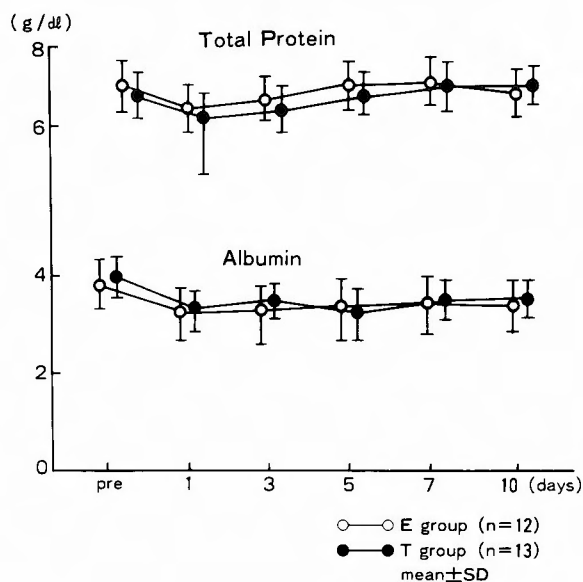


Fig. 1 Daily changes of serum protein

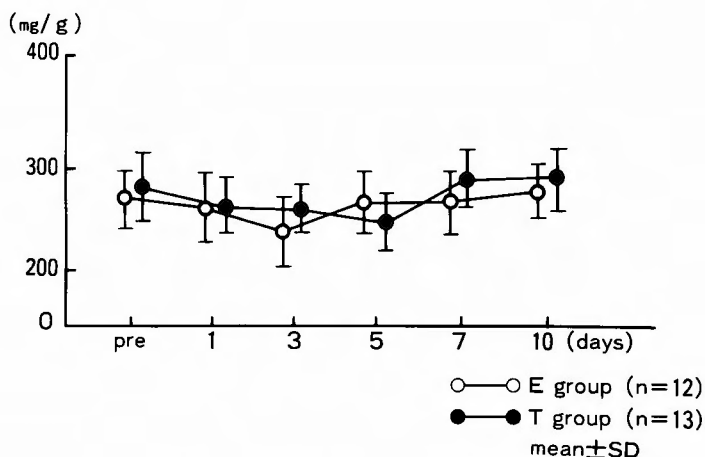


Fig. 2 Daily changes of Transferrin

The nutritional and immunological parameters obtained at examinations were studied comparatively between the 2 groups. The measured values were expressed in the mean $\pm$ standard deviation and the statistical significance was examined by Students' *t* test.

Results

1) Changes of serum proteins

The TP and Alb showed a fall after operation and then a recovery, but there were no significant difference between the 2 groups (Fig. 1).

With changes of RTP, any of Tf, PA and RTP showed a transient fall after operation, but there

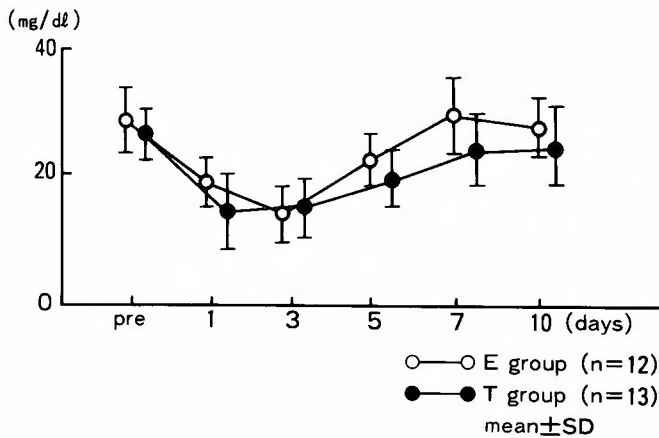


Fig. 3 Daily changes of Prealbumin

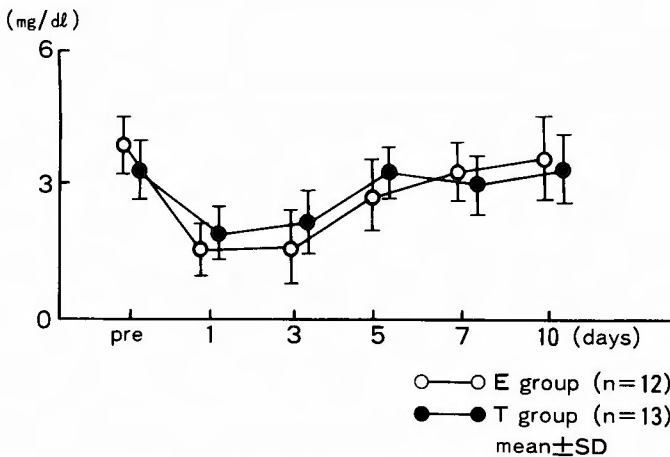


Fig. 4 Daily changes of Retinal Binding Protein

were no significant difference between the 2 groups (Fig. 2, 3, 4).

2) Changes of nitrogen balance

Changes of the nitrogen balance returned to normal on the 3rd day in T group and the 5th day in E group, but there was no significant difference between the 2 groups (Fig. 5).

3) Changes of 3-Mehis/Cr ratio

With changes of the 3-Mehis/Cr ratio, a transient rise was found after operation, but there was no significant difference between the 2 groups (Fig. 6).

4) Changes of total lymphocyte counts

With changes of the total lymphocyte counts in the peripheral blood, both the 2 groups indicated a transient fall after operation, but showed no significant difference between the 2 groups.

5) Changes of lymphocyte subsets

With the changes of the $CD3^+$ (pan T) cell population, there was no significant difference between the 2 groups before and after operation.

With the changes of the $CD8^+CD11b^+$ (suppressor T) cell subpopulation, both the 2 groups

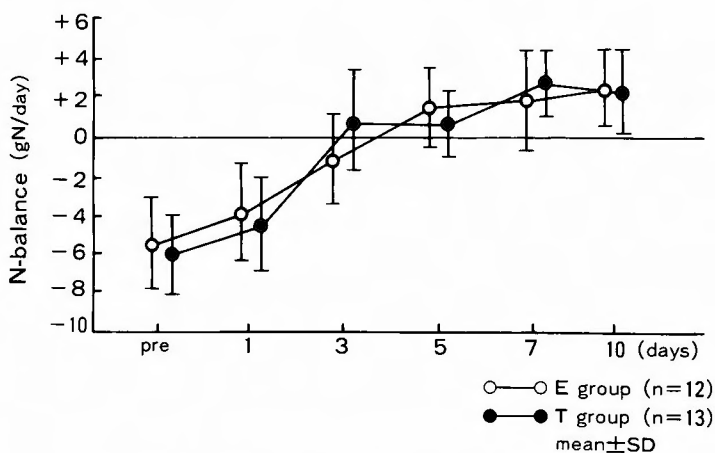


Fig. 5 Daily and cumulative nitrogen balance

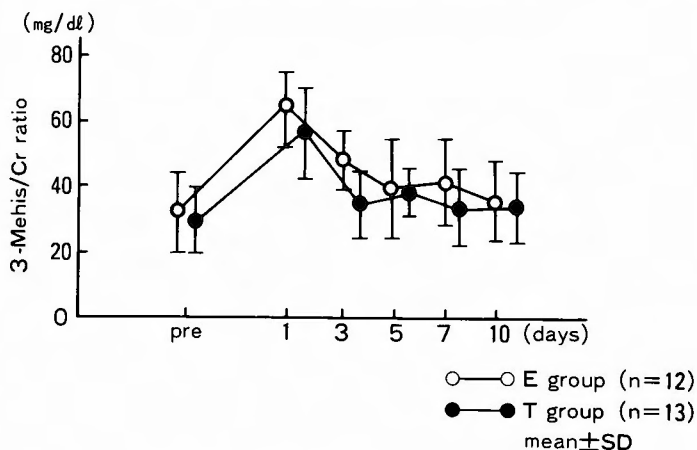


Fig. 6 Daily changes of 3-Mehis/Cr ratio

showed a fall after operation and showed a rising tendency after the 10 day, but no significant difference was found between the 2 groups (Fig. 7).

With the changes of the $CD8^+CD11b^+$ (cytotoxic T) cell subpopulation, whereas T group showed a fall after operation, E group indicated a slight fall and a significant difference was found on the 10th day ($p<0.05$) (Fig. 8).

With the changes of the $CD4^+CD45R^-Leu8^-$ (helper T) cell subpopulation, whereas T group showed a fall after operation, E group showed a recovery and a recovery and a significant difference was found on the 30th hospital day ($p<0.05$) (Fig. 9).

With the changes of the $CD4^+CD45R^-Leu8^+$ (helper inducer T) cell subpopulation, a falling tendency was found on the 10th hospital day after the operation, but no significant difference was seen.

With the changes of the $CD4^+CD45R^+Leu8^+$ (suppressor inducer T) cell subpopulation, the

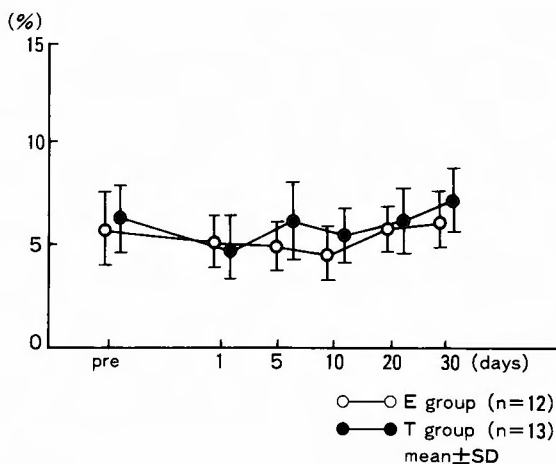


Fig. 7 Daily changes of $CD8^+CD11b^+$ (suppressor T) cell subpopulation

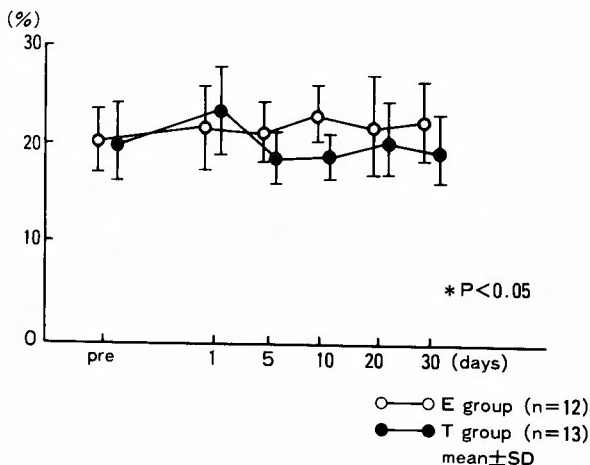


Fig. 8 Daily changes of $CD8^+CD11b^-$ (cytotoxic T) cell subpopulation

ratio rose after the operation and then showed a fall, but there was no significant difference between the 2 groups.

With the changes of the $CD3^+CD16^-CD56^+$ (T-LAK) cell subpopulation, both the groups showed a rising tendency after operation, but there was no significant difference between the 2 groups.

With the changes of the $CD3^-CD16^+CD56^+$ (NK-LAK) cell subpopulation, whereas T group showed a fall after operation, E group indicated a rise and significant difference was found on the 10th day ($p < 0.05$) (Fig. 10).

6) Changes of NK cell activity

The NK cell activity showed a remarkable fall after operation and then a rise, but no significant difference was found between the 2 groups (Fig. 11).

Discussion

The prognosis in the postoperative nutrition control has been remarkable in the field of

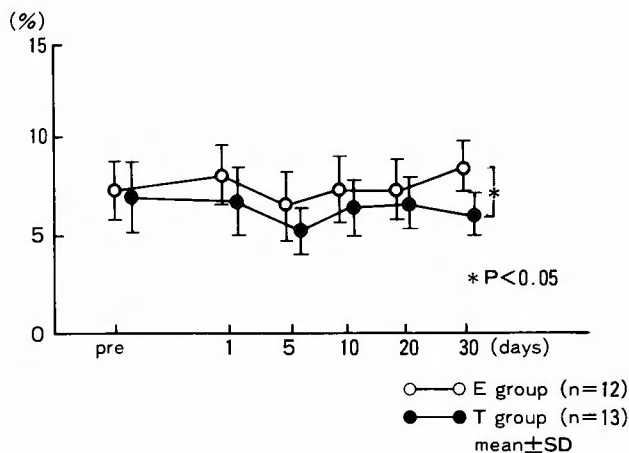


Fig. 9 Daily changes of $CD4^+CD45R^+Leu8^-$ (helper T) cell subpopulation

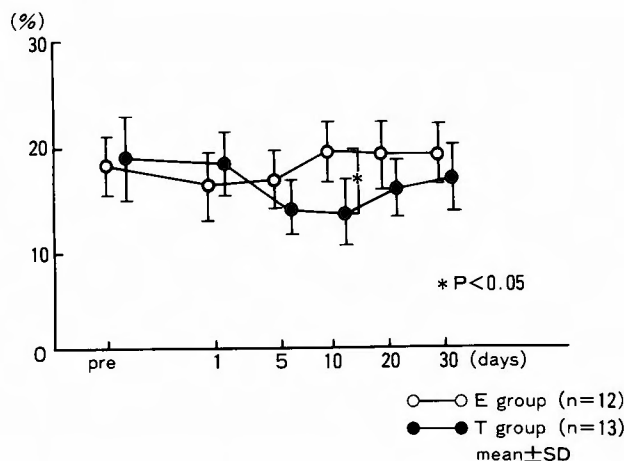


Fig. 10 Daily changes of $CD3^-CD16^+CD56^+$ (NK-LAK) cell subpopulation

gastroenterological surgery and contributed greatly to the improvement of operative results. In operations for gastric cancer patients, nutrition which used the digestive tract in an early stage has been recognized again recently and its usefulness has been valued from various viewpoints^{1,2)}.

The tract that the digestive tract works not only as an organ for digestive and absorption, but as a central organ of the living body has been accepted³⁾ and postoperative enteral nutrition is presumed to cause improvement of the immunomechanism of the intestinal tract lies in the background of such evaluation. This time we examined the nutritional effect of the enteral nutrition in an early stage after operation for gastric cancer patients and also immunologically improving effect using lymphocyte subsets.

In nutritional examination no significant difference was observed in changes of the serum proteins. We have seen a report¹⁾ stating that rapid turnover protein (RTP) with a short half-life is useful as a parameter for changes in proteins for a relatively short period like a postoperative one, but we could not observe differences even in such RTP in this study.

On the other hand, the nitrogen balance returned to normal in a relatively early stage in the 2 groups, but there was no significant difference. There is a view that the administration course of nutrition does not always associate with the nitrogen balance⁵⁾. This seems to be attributable to the fact that the time of administration and severity of invasion differ considerably depending on reports. With the invasion at an operation for gastric cancer patients the nitrogen balance is considered not affected by the administration course of nutrition.

When surgical stress is added to living bodies, destruction of muscle proteins occurs.

3-Methylhistidine in urine which does not undergo resorption is said useful as its parameter⁶⁾ and early improvement of nourishment are considered to suppress such destruction of muscle proteins. This time we examined the 3-Metyl/Cr ratio which reflects it well in the 2 groups, but could observe no significant difference. Thus we presumed that the difference in the administration course, but could observe no significant difference. Thus we presumed that the difference in the administration course, or problem of intravenous alimentation or enteral nutrition, does not cause a significant difference in nutrition at operation for gastric cancer patients.

In contrast, improvement of immune function of the intestinal tract as utility of enteral nutrition

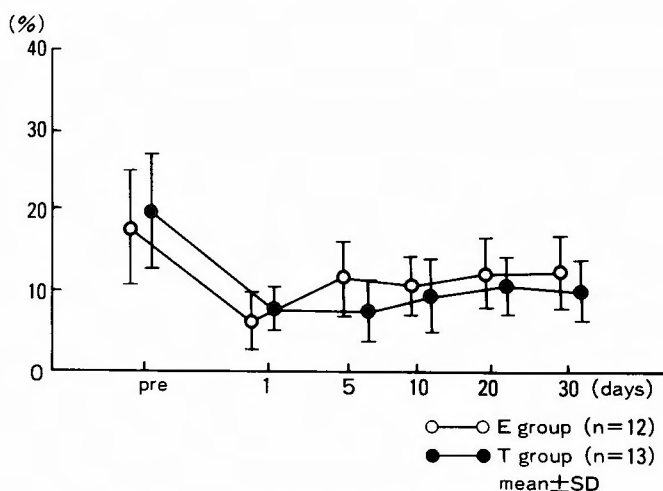


Fig. 11 Daily changes of NK cell activity

has been watched. It has been proved in particular that the method increases the Ig A in the intestinal mucosa⁷⁾ and hence infection mechanism such as translocation is presumed to be suppressed⁸⁾. Contractly to such local immunity improving effect of the enteral nutrition, its systemic effect has been reported still scantily.

In the present studies on lymphocyte subsets derived from the peripheral blood, an improving effect of specific immunologically-competent cells, such as helper cells and cytotoxic cells was observed after operation because of enteral nutrition produces an improving effect on the systemic immune system, we consider that the operation cause antigen stimulation as food and active the systemic immune system⁹⁾.

It is known that nonspecific immunologically-competent cells, such as NK cells and LAK cells are involved greatly in metastasis and proliferation of tumors^{10,11)} contrary to such specific immunologically-competent cells. In thsi study it was observed that the NK-LAK cells derived from NK cells were improved significantly after the operation in E group and the enteral nutrition in an early stage was proved to produce an improving effect also on such nonspecific immuolly-competent cells.

From the above studies it was observed that the enteral nutrition in an early stage after operation for gastric cancer patients produced an early system immunity improving effect though nutritional improving was not obtained compared with TPN; postoperative prevention of metastasis and proliferation of tumor can be anticipated from such facts, and these interesting results are reported here.

References

- 1) Wilmore DW, Smith RJ, O'Dwyer ST, et al: The gut: A centrl organ after surgical stress. *Surg* **104**: 917-923, 1988.
- 2) Hiramatu T: Benefical effects of postoperative enteral nutrition on protein metabolism, immunocompetence and catabolic hormones. *Jpn J Gastroenterol Surg*: 1207-1219, 1990.
- 3) Carrico CJ, Meakins JL, Marshal JC, et al: Multiple-Organ-Failure Syndrome. *Arch Surg* **121**: 196-208, 1986.
- 4) Malana G: Serum prealbumin, retinol binding protein, transferrin and an albumin levels in patients with large bowel cancer. *J Natl Cancer Inst* **61**: 687-691, 1978.
- 5) Mcardle AH, Palmason C, Morency I, et al: A rationale for hyperalimentation. *Surg* **90**: 616-623, 1981.
- 6) Iapichino G, Radrizzani D, Solca M, et al: Influence of total parenteral nutrition on protein metabolism following acute injury: assessment by urinary 3-Methylhistidine excretion and nitrogen balance. *JPEN* **9**: 42-46, 1985.
- 7) Alverdy J, Chi HS, Sheldon GF, et al: The effect of parenteral nutrition on gastrointestinal immunity, the importance of enteral stimulation. *Ann Surg* **202**: 681-684, 1985.
- 8) Maddaus MA, Wells CL, Platt JL, et al: Effect of T cell modulation on the translocation of bacteria from the gut and mesenteric lymphnode. *Ann Surg* **207**: 387-398, 1988.
- 9) Kudsk KA, Stone JM, Carpenter G, et al: Enteral and parenteral and feeding influences mortality after hemoglobin-E. coli peritonitis in rats. *J Trauma* **23**: 605-609, 1983.
- 10) Tuji K, Abo S, Kudoo T, et al: A clinical study on natural killer activity in the patients with esophageal cancer. *Jpn J Gastroenterol Surg* **18**: 8-14, 1985.
- 11) Dross HF, Baines MG: Spontaneous human lymphocyte mediated cytotoxicity against tumor targets. I. The effect of malignant disease. *Int J Cancer* **18**: 593-598, 1976.

和文抄録

免疫能からみた胃癌術後早期における
経腸栄養法の検討

木沢記念病院外科

田辺 博

胃癌術後早期における経腸栄養法について免疫能の改善効果の面から検討を加えた。進行胃癌症例25例を対象とし、術後の栄養管理法により以下の2群に分類した。E群：術後経腸栄養を行った群 (n=12), T群：術後中心静脈栄養を行った群 (n=13)。両群において術前、術後にわたり栄養学的パラメータとして TP, Alb, RTP, 窒素平衡, 3-MeHis/Cr 比を測定した。また免疫学的パラメータとして末梢血から総タンパク、モノクローナル抗体によるリンパ球サブセット、さらに NK 細胞活性を測定した。

栄養学的な検討では血漿タンパクの推移に差を認めず、窒素平衡, 3MeHis/Cr 比の変化においても両群間に有意差を認めなかった。一方免疫学的な検討では $CD8^+CD11b^-$ (cytotoxic T), $CD4^+CD45R^-Leu8^-$ (helper T) 細胞比率がE群で術後高値を示し、非特異的免疫細胞として $CD3^-CD16^+CD56^+$ (NK-LAK) 細胞比率が術後E群において高値を示した。以上より胃癌術後早期の経腸栄養法により免疫能の改善効果が示唆された。