Prognostic Markers for Immunochemotherapy Using Tegafur-Uracil (UFT) and Protein-Bound Polysaccharide K (PSK)

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Prognostic Markers for Immunochemotherapy Using Tegafur -Uracil (UFT) and Protein-Bound Polysaccharide K (PSK)

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Abstract

Aim/Background : We previously reported that PSK-induced lymphocyte blastogenesis reaction (PSK-stimulation index ; PSK-SI) may be a prognostic marker for immunochemotherapy using PSK in gastrointestinal cancer patients. In this study we evaluated the usefulness of PSK-SI as a prognostic marker for PSK therapy at higher and lower serum immunosuppressive acidic protein (IAP) levels.

Patients and Methods : 98 gastric and 135 colorectal cancer patients were analyzed. PSK-SI and serum IAP levels were measured preoperatively. After operation, patients received UFT and PSK for two years.

Results : There were no differences between patients with higher and those with lower PSK-SI with respect to the clinicopathological factors. In patients with higher serum IAP levels (≥ 500 μg/ml), recurrence-free survival (RFS) and overall survival (OS) were apparently more favorable in the higher PSK-SI group (gastric cancer ; ≥ 1.75, colorectal cancer ; ≥ 2.1)than in lower PSK-SI group, although the differences were not significant.

Conclusion : Serum IAP levels and PSK-SI may be useful markers for prediction of response to immunochemotherapy using PSK, although further studies are necessary.

Key words : Gastric cancer・Colorectal cancer・Biomarker

Introduction

PSK is an anti-cancer agent and is composed of protein-bound polysaccharide extracted and purified from the cultured mycelia of a basidiomycete, *Coriolus versicolor* strain CM-101[1]. For gastric and colorectal cancers, PSK has been shown to prolong the survival period when used in combination with chemotherapeutic agents[2)~4)]. Moreover, the efficacy of PSK has been verified in multiple meta-analyses[5)6)]. PSK has been reported to reverse or attenuate tumor-induced immunosuppression[7)]. PSK plays important roles in the induction of dendritic cell (DC) maturation[8)], correction of Th1/Th2 imbalance[9)] and other immunological processes. PSK has also been reported to exhibit direct actions against tumor cells, such as apoptosis induction, anti-metastatic effect and chemotherapy potentiating effect[10)11)]. Although various mechanisms of action of PSK have been reported, it is undeniable that the major mechanism of action is unclear. The diversity of mechanisms of action of PSK suggests that PSK probably does not exert the same effects on all

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patients. Previous reports have indicated that the prognosis of cancer patients with higher serum immunosuppressive acidic protein (IAP) levels is poorer compared to cancer patients with lower serum IAP levels[12)13)]. Serum IAP level has been reported to be lower in PSK-treated cancer patients[13)14)]. Therefore improved immunological capability of patients through lowering of serum IAP level by PSK treatment may have markedly affected the prognosis in patients with higher serum IAP levels than in patients with lower serum IAP levels[14)15)]. Identifying the biomarker that indicates clinical response to PSK is necessary. Several reports have already suggested that patients' immune functions, as indicated by purified protein derivative of tuberculin (PPD) skin test, serum IAP level, peripheral granulocyte/lymphocyte ratio, DC infiltration of tumor tissue, NK cell population in peripheral blood, Th1/Th2 ratio, as well as HLA type, are potential prognostic markers for adjuvant immunochemotherapy using PSK[12)14)~16)]. However, these markers are not yet ready for clinical use to predict prognosis. In a previous study, we isolated peripheral blood lymphocytes from patients with gastric or colorectal cancer, cultured the lymphocytes *in vitro* with PSK and measured blastogenesis reaction to obtain the PSK stimulation index (PSK-SI). We found that PSK-SI was lower in patients with gastric or colorectal cancer compared with normal subjects, and that the magnitude of PSK-SI was not associated with factors involved in tumor progression, such as tumor invasion and lymph node metastasis[17)]. We also reported that gastric and colorectal cancer patients with high PSK-SI had better survival outcome[18)]. However, the survival outcome did not improve to a satisfactory level.

Cancer patients have elevated levels of humoral factors with immunosuppressive functions, such as IAP[19)]. It is possible that these factors suppress lymphocyte blastogenesis reaction *in vivo*. In the present study, we evaluated the possibility of using PSK-SI as a prognostic marker at higher and lower IAP levels. The usefulness of PSK-SI as a prognostic marker for PSK immunotherapy remains to be fully elucidated. The aim of this study was to confirm the potential of PSK-SI as a prognostic marker by conducting a long-term observational study, not by randomized controlled study.

Patients and Methods

Patients : This study was conducted in 52 hospitals in the Kyushu region of Japan. A total of 118 patients who underwent curative resection (Cur A or Cur B) for stages Ib to IIIb primary gastric cancer, and 158 patients who underwent curative resection (Cur A) for stages I to IIIb primary colorectal cancer between January 1995 and December 1996 were entered into this study. Other eligibility criteria were as follows : no prior chemotherapy and immunotherapy ; up to 80 years of age ; no multiple cancers ; and adequate organ functions with no severe complications, defined as leukocyte count $\geq 3,000/\mu l$, platelet count $\geq 70,000/\mu l$, serum glutamate oxaloacetate transaminase (GOT) $\leq$ 100 U/l, and serum glutamate pyruvate transaminase (GPT) $\leq$ 100 U/l. All patients provided informed consent.

Study Design : In all analyzed patients, blood samples were collected before operation for measurements of PSK-SI and serum IAP level. Mitomycin C (10 mg/body) was administrated on the day of operation. Oral PSK (3 g/day) and tegafur-uracil (300 mg/day) were started from day 15 after operation and continued for two years. Patients were followed for 10 years for cancer recurrence and survival.

Measurement of PSK-SI : PSK-SI was measured by the method described previously[17)]. Briefly, peripheral blood lymphocytes were isolated from each subject and adjusted to 1×10^6 cells/ml in RPMI medium (Gibco Laboratories, Chagrin Falls, Ohio, USA) containing 10% human serum blood type AB. Lymphocytes (1×10^5 cells) were exposed to 20 U/ml of IL-2 (Shionogi & Co., Osaka, Japan) with or without 100 μg/ml of PSK

(Kureha Corporation, Tokyo, Japan) for 96 h. ^{3}H-Thymidine (18.5 kBq) was added and the mixture was incubated for another 24 h. After cell harvesting, the radioactivity was measured using a liquid scintillation counter. The PSK-SI was determined as the ratio of radioactivity of PSK-treated lymphocytes to that of PSK-nontreated cells. The assays of individual patients were performed in triplicate.

Measurement of serum IAP levels : Serum IAP levels were determined by a turbidimetric immunoassay using San test IAP-N kits (Sanko Junyaku Co., Tokyo, Japan), according to the manufacturer's instructions. All serum samples were assayed in triplicate.

Statistical analysis : Data are presented as mean ± SD or number of patients. All statistical analyses were performed with SAS software (version 9.1.3, SAS Institute Inc., Cary, NC, USA). The clinicopathological data of cancer patients with higher PSK-SI and those with PSK-SI were compared by Student's t-test, chi-square test or Mann-Whitney U test. RFS and OS curves were generated by Kaplan-Meier method, and log-rank test was used to compare the curves of two groups. A p value less than 0. 05 was considered to be statistically significant.

Results

Patients analyzed : Twenty gastric cancer patients were excluded from analysis : 10 were disqualified because of protocol violation, 2 were lost to follow-up, and 8 had no PSK-SI data (Figure 1a). Twenty-three colorectal cancer patients were excluded from analysis : 5 were disqualified because of protocol violation, 3 were lost to follow-up, 11 failed to achieve curative resection, and 4 had no PSK-SI data (Figure 1b). Finally, 98 gastric cancer patients and 135 colorectal cancer patients were analyzed.

Gastric cancer patients : The distribution of PSK-SI in 98 gastric cancer patients is shown in Figure 2. We previously defined a cutoff value of 1.75 to stratify patients into higher and lower PSK-SI groups, because the most pronounced difference in prognosis was observed at this cutoff[18]. The numbers of patients in higher and lower PSK-SI groups were 36 and 62, respectively. The clinicopathological data and serum IAP levels in higher and lower PSK-SI groups are shown in Table 1. There was no association between PSK-SI level and each clinicopathological factor.

According to the report of Ikuta et al.[20], we divided the subjects into higher and lower serum IAP groups using the cutoff value of 400 μg /ml. Then we analyzed RFS (Figure 3a and b) and OS (Figure 3c and d) in higher and lower IAP groups. In patients with higher serum IAP, the 10-year RFS was 63.9% in higher PSK-SI (n = 18) and 44.9 % in lower PSK-SI (n = 42) group, and 10-year OS was 65.8% in higher PSK-SI and 50.6% in lower PSK-SI group. The prognosis was apparently more favorable in higher PSK-SI group, although the differences were not statistically significant. On the other hand, in patients with lower serum IAP, the 10-year RFS was 61.3% in higher PSK-SI (n = 17) and 70.7% in lower PSK-SI (n = 20) group, and 10-year OS was 65.7% in higher PSK-SI and 70.9 % in lower PSK-SI group, showing no difference between lower and higher PSK-SI groups.

Colorectal cancer patients : The distribution of PSK-SI in 135 colorectal cancer patients is shown in Figure 2. We previously defined a cutoff value of 2.1 to stratify colorectal cancer patients into higher and lower PSK-SI groups, because the most pronounced difference in prognosis was observed at this cutoff[18]. The numbers of patients in higher and lower PSK-SI groups were 26 and 109 respectively. The clinicopathological data and serum IAP levels in higher and lower PSK-SI groups are shown in Table 2. There was no association between PSK-SI and each clinicopathological factor.

According to the report of Ohwada et al.[12], we divided the subjects into higher and lower serum IAP groups using a cutoff value of 500 μg/ml.

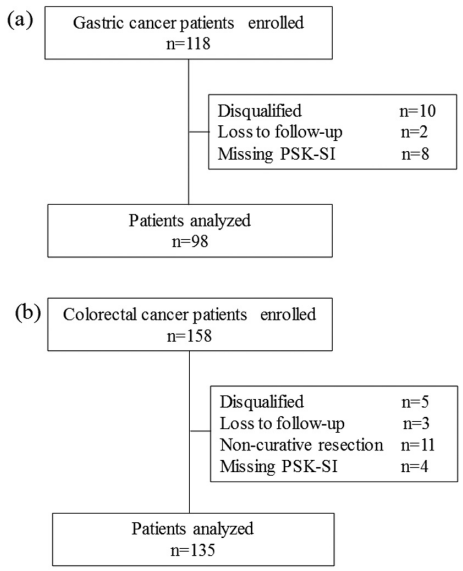


Fig. 1 Patient disposition flow chart : (a) gastric cancer, (b) colorectal cancer.

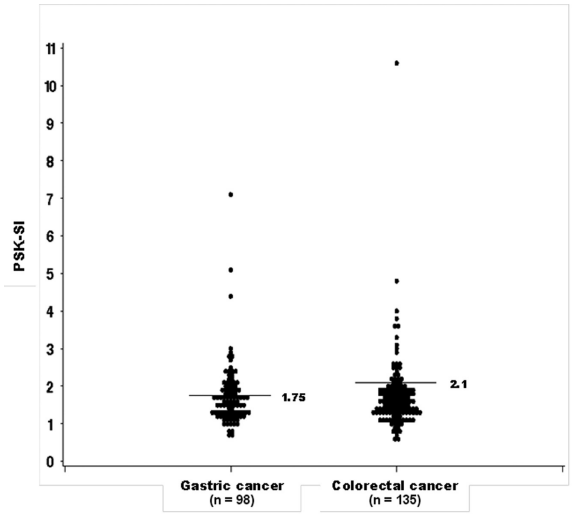
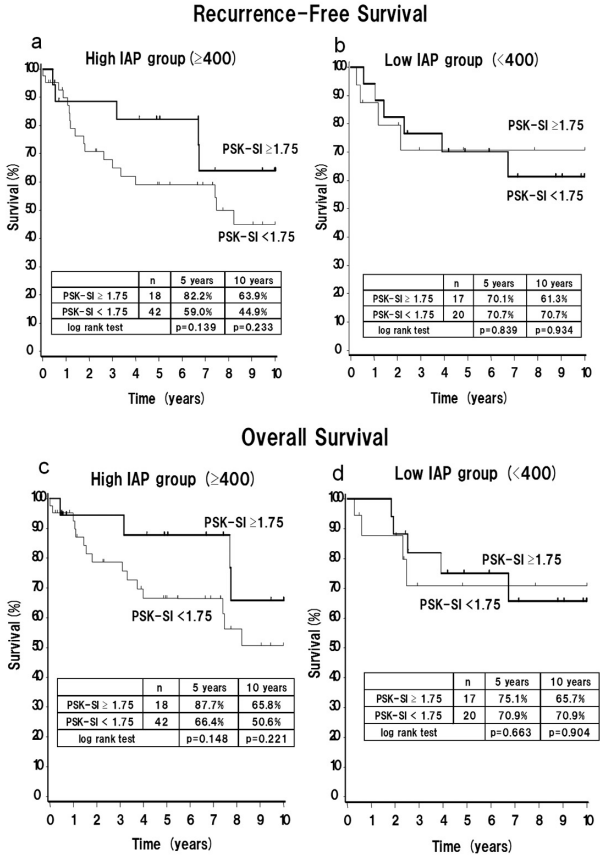


Fig. 2 The distribution of PSK-SI in gastric and colorectal cancer patients.
The bar on the graph represents cutoff value.

Table 1 Clinicopathological data of gastric cancer patients divided into higher PSK-SI (≥ 1.75) and lower PSK-SI (< 1.75) groups.

		PSK-SI ≥ 1.75	PSK-SI < 1.75	*p* -Value
Sex	male	28 (77.8%)	38 (61.3%)	0.146
	female	8 (22.2%)	24 (38.7%)	
Age (years, mean ± SD)		63.6 ± 9.6 (n=36)	64.3 ± 10.5 (n=62)	0.744
Size (cm, mean ± SD)		4.5 ± 3.1 (n=25)	5.0 ± 3.3 (n=50)	0.479
Primary tumor	m	5 (14.7%)	3 (4.8%)	0.121
	sm	8 (23.5%)	10 (16.1%)	
	mp	6 (17.6%)	17 (27.4%)	
	ss	9 (26.5%)	15 (24.2%)	
	se	6 (17.6%)	16 (25.8%)	
	si	0 (0.0%)	1 (1.6%)	
	missing	2	0	
Regional lymph nodes	n0	14 (41.2%)	30 (48.4%)	0.716
	n1	13 (38.2%)	18 (29.0%)	
	n2	7 (20.6%)	13 (21.0%)	
	n3	0 (0.0%)	1 (1.6%)	
	missing	2	0	
Lymphatic vessel invation	ly0	9 (26.5%)	15 (25.0%)	0.819
	ly1	7 (20.6%)	20 (33.3%)	
	ly2	14 (41.2%)	14 (23.3%)	
	ly3	4 (11.8%)	11 (18.3%)	
	missing	2	2	
Venous invation	v0	18 (54.5%)	35 (58.3%)	0.436
	v1	6 (18.2%)	16 (26.7%)	
	v2	8 (24.2%)	9 (15.0%)	
	v3	1 (3.0%)	0 (0.0%)	
	missing	3	2	
PSK-SI		2.5 ± 1.0 (n=36)	1.3 ± 0.3 (n=62)	<0.001
IAP		437.5 ± 197.7 (n=35)	472.0 ± 163.7 (n=62)	0.359

PSK-SI : PSK-Stimulation Index. IAP : immunosuppressive acidic protein.



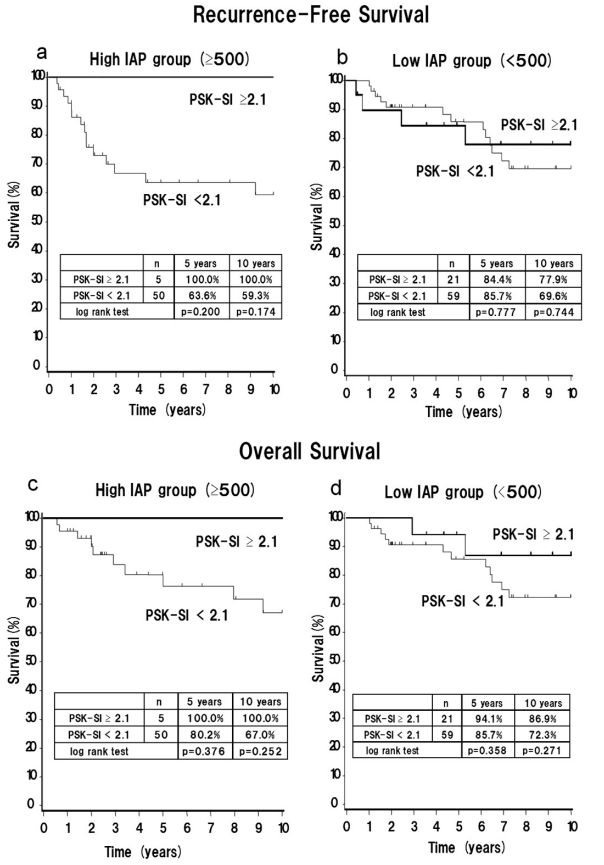
	n	5 years	10 years
PSK-SI ≥ 1.75	18	82.2%	63.9%
PSK-SI < 1.75	42	59.0%	44.9%
log rank test		p=0.139	p=0.233

	n	5 years	10 years
PSK-SI ≥ 1.75	17	70.1%	61.3%
PSK-SI < 1.75	20	70.7%	70.7%
log rank test		p=0.839	p=0.934

	n	5 years	10 years
PSK-SI ≥ 1.75	18	87.7%	65.8%
PSK-SI < 1.75	42	66.4%	50.6%
log rank test		p=0.148	p=0.221

	n	5 years	10 years
PSK-SI ≥ 1.75	17	75.1%	65.7%
PSK-SI < 1.75	20	70.9%	70.9%
log rank test		p=0.663	p=0.904

Fig. 3 Comparisons of recurrence-free survival (a and b) and overall survival (c and d) in gastric cancer patients divided into higher serum IAP (a and c) and lower serum IAP (b and d) groups. The bold line represents higher PSK-SI group and the fine line represents lower PSK-SI group.



	n	5 years	10 years
PSK-SI ≥ 2.1	5	100.0%	100.0%
PSK-SI < 2.1	50	63.6%	59.3%
log rank test		p=0.200	p=0.174

	n	5 years	10 years
PSK-SI ≥ 2.1	21	84.4%	77.9%
PSK-SI < 2.1	59	85.7%	69.6%
log rank test		p=0.777	p=0.744

	n	5 years	10 years
PSK-SI ≥ 2.1	5	100.0%	100.0%
PSK-SI < 2.1	50	80.2%	67.0%
log rank test		p=0.376	p=0.252

	n	5 years	10 years
PSK-SI ≥ 2.1	21	94.1%	86.9%
PSK-SI < 2.1	59	85.7%	72.3%
log rank test		p=0.358	p=0.271

Fig. 4 Comparisons of recurrence-free survival (a and b) and overall survival (c and d) in colorectal cancer patients divided into higher serum IAP (a and c) and lower serum IAP (b and d) groups. The bold line represents higher PSK-SI group and the fine-line represents lower PSK-SI group.

Then we analyzed RFS (Figure 4a and b) and OS (Figure 4c and d) in higher and lower IAP groups. In patients with higher serum IAP, the 10-year RFS was 100% in higher PSK-SI (n = 5) and 59.3% in lower PSK-SI (n = 50) group, and the 10-year OS was 100% in higher PSK-SI and 67.0% in lower PSK-SI group. Prognosis was apparently more favorable in higher PSK-SI group, although the differences were not statistically significant. On the other hand, in patients with lower serum IAP, the 10-year RFS was 77.9% in higher PSK-SI (n = 21) and 69.6% in lower PSK-SI (n = 59), and the 10-year OS was 86.9% in higher PSK-SI and 72.3 % in lower PSK-SI group, showing no differences between lower and higher PSK-SI groups.

Discussion

In the present study, we focused on whether PSK-induced lymphocyte blastogenesis reaction and serum IAP level are associated with the prognosis of gastrointestinal cancer patients on immunochemotherapy with PSK.

Our data showed favorable prognosis in higher PSK-SI group compared to lower PSK-SI group in patients with higher serum IAP, although the differences were not significant. The small number of cases in each group probably precludes detection of a significant difference. On the other hand, there was no difference in prognosis between higher and lower PSK-SI groups in patients with lower serum IAP. This result showed that PSK-SI was not a prognostic marker

Table 2 Clinicopathological data of colorectal cancer patients divided into higher PSK-SI (≥ 2.1) and lower PSK-SI (< 2.1) groups.

		PSK-SI ≥ 2.1	PSK-SI < 2.1	*p* -Value
Sex	male	19 (73.1%)	57 (52.3%)	0.089
	female	7 (26.9%)	52 (47.7%)	
Age (years, mean ± SD)		60.9 ± 10.1 (n=26)	62.3 ± 10.0 (n=109)	0.524
Size (cm, mean ± SD)		4.6 ± 2.1 (n=19)	4.4 ± 1.9 (n=93)	0.710
Primary tumor	T1	4 (15.4%)	10 (9.2%)	0.380
	T2	17 (65.4%)	73 (67.0%)	
	T3	5 (19.2%)	24 (22.0%)	
	T4	0 (0.0%)	2 (1.8%)	
Regional lymph nodes	N0	17 (65.4%)	74 (68.5%)	0.967
	N1	8 (30.8%)	22 (20.4%)	
	N2	1 (3.8%)	11 (10.2%)	
	N3	0 (0.0%)	1 (0.9%)	
	missing	0	1	
Dukes stage	A	4 (15.4%)	28 (25.9%)	0.420
	B	13 (50.0%)	46 (42.6%)	
	C	9 (34.6%)	34 (31.5%)	
	missing	0	1	
Lymphatic vessel invasion	ly0	7 (26.9%)	25 (24.0%)	0.225
	ly1	13 (50.0%)	37 (35.6%)	
	ly2	5 (19.2%)	36 (34.6%)	
	ly3	1 (3.8%)	6 (5.8%)	
	missing	0	5	
Venous invasion	v0	10 (38.5%)	40 (38.5%)	0.884
	v1	10 (38.5%)	38 (36.5%)	
	v2	5 (19.2%)	19 (18.3%)	
	v3	1 (3.8%)	7 (6.7%)	
	missing	0	5	
PSK-SI		3.1 ± 1.7 (n=26)	1.5 ± 0.3 (n=109)	<0.001
IAP		460.5 ± 168.5 (n=26)	532.5 ± 199.7 (n=109)	0.092

PSK-SI : PSK-Stimulation Index. IAP : immunosuppressive acidic protein.

in patients with lower serum IAP.

Previous reports have indicated that the prognosis of cancer patients with higher serum IAP level is poorer compared to cancer patients with lower serum IAP level[12)13)]. Our study suggests that PSK-SI may be a candidate prognostic marker for patients whose prognosis is poor due to higher serum IAP levels.

The reason why PSK-SI is a prognostic marker for PSK therapy in patients with higher serum IAP has not been elucidated. Initially, we hypothesized that since higher serum IAP level may affect the prognosis, the significance of PSK-SI may manifest more clearly at lower serum IAP levels. However, our results were contrary to our hypothesis. PSK has been reported to lower serum IAP level in cancer patients[13)14)]. Therefore improved immunological capability of the patients through lowering of serum IAP level by PSK treatment may have markedly affected the prognosis in patients with higher serum IAP levels than in patients with lower serum IAP levels.

In the study of Sakamoto et al.[15)] on postoperative adjuvant immunochemotherapy for gastric cancer, PSK exhibited beneficial effect when preoperative serum IAP level was lower than 580 μg/ml. Ohwada et al.[12)] studied postoperative adjuvant immunochemotherapy for colorectal cancer, and reported that PSK exhibited beneficial effect when preoperative serum IAP level was 500 μg/ml or below. In our present study, for gastric cancer patients, the serum IAP levels in higher IAP group were 400 μg/ml and above, and

our result did not contradict with that of Sakamoto et al. For patients with colorectal cancer, the serum IAP levels in the higher IAP group were 500 μg/ml and above, and our result was not consistent with that of Ohwada et al. While the reason for the discrepancy is unknown, the study of Ohwada et al. had more advanced cases than our study, and it is also possible that the even though serum IAP was higher, the prognosis was good as long as PSK-SI was high in our patients.

Tamada et al.[14] investigated postoperative adjuvant immunochemotherapy for gastric cancer, and reported high efficacy of PSK combined therapy in patients who were PPD-positive before operation. Takahashi et al.[21] reported that in postoperative adjuvant immunochemotherapy for colon cancer, the efficacy of PSK combination therapy was higher in patients with preoperative PPD reaction less than 19 mm. Toge et al.[16] showed that in postoperative adjuvant immunochemotherapy for gastric cancer, PSK combination therapy was highly effective in patients whose preoperative peripheral granulocyte/lymphocyte ratio was high. Tsujitani et al.[22] reported that in postoperative adjuvant immunochemotherapy for gastric cancer, PSK combination therapy was effective in patients showing slight DC infiltration in the resected tumor tissue. Ohwada et al.[12] reported that in postoperative adjuvant immunochemotherapy for colorectal cancer, the efficacy of PSK combination therapy was higher when the NK cell population in peripheral blood was 8% or above at three months after surgery. Yoshino et al.[23] reported that in colorectal cancer patients, the prognosis was good when PSK was administered before surgery and Th2 dominance was improved after administration.

The above findings probably imply that response to PSK is not observed when the immunological capability of the patient is almost normal or, conversely, when the immunological competence of the patient is seriously impaired. The immunological capability in a cancer-bearing state differs from that in a normal state, and PSK normalizes these abnormalities ; in other words, PSK acts by maintaining the homeostasis. This may explain the favorable prognosis in higher PSK-SI group among patients with higher serum IAP levels.

Further studies are needed to explore the prognostic markers (including whether or not such markers exist) for immunochemotherapy with PSK in patients with lower serum IAP levels. In addition, research has to be continued to identify more sensitive prognostic markers in patients with higher IAP levels. Recent studies have detected the presence of regulatory T cells (Treg), which possess immunosuppressive actions, among peripheral blood lymphocytes[24]. Treg have been reported to suppress the proliferation of lymphocytes[24]. Also, low CD8 + T to Treg ratio in colorectal cancer tissue has been associated with poor prognosis[25], suggesting the importance of the balance between effectors cells and Treg. Although the effect of PSK on Treg has not been completely clarified, Lu et al.[26] reported that PSK administration reduced the proportion of Treg among lymphocytes infiltrating tumors in cancer-bearing mice. Analysis of the proportion of Treg in patients' peripheral blood together with PSK-SI and serum IAP level may refine the prognostic marker for postoperative adjuvant immunochemotherapy using PSK.

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（和文抄録）

胃癌・大腸癌症例に対するクレスチン（PSK）療法のレスポンダー探索

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【背景】われわれはこれまでに健常人，胃・大腸癌患者リンパ球の PSK 添加による幼若化反応（以下 PSK-SI）の検討を行い，胃・大腸癌患者の PSK-SI は健常人に比し低値であること，胃・大腸癌患者の PSK-SI 高値は PSK による免疫療法のレスポンダー指標になる可能性があることを報告してきた．今回 PSK によるリンパ球活性化が胃癌・大腸癌の PSK 治療効果予測因子となるか否かを検討した．
【対象と方法】解析対象は胃癌 98 症例，大腸癌術後 135 症例であった．患者の末梢血単核球を分離し，PSK 添加，非添加下での PSK-SI を ^{3}H-thymidine 取り込みで評価した．胃癌では PSK-SI 1.75 倍以上を高値群，未満を低値群とし，大腸癌では PSK-SI 2.1 倍以上を高値群，未満を低値群とした．血中免疫抑制酸性蛋白（IAP）は TIA 法で評価した．術後補助化学療法は UFT, PSK を術後 15 日より 2 年間連日投与した．各群の予後を PSK-SI と IAP の高値群，低値群間で解析した．
【結果】胃癌・大腸癌症例の PSK-SI 高値群，低値群で両群間患者背景に有意な差はなかった．また術前 IAP（胃癌；≧ 400μg/ml，大腸癌；≧ 500μg/ml）と PSK-SI（胃癌；≧ 1.75，大腸癌；≧ 2.1）が高い患者群において，PSK を用いた術後補助免疫療法の有効性が高かった．
【結語】今後のさらなる臨床試験がなされることが必要であるが，PSK によるリンパ球活性化が治療効果予測に有用な因子となる可能性が示唆された．