

Coriolus versicolor Detailed Scientific Review

Overview

Background

Mushrooms have been used for at least 5000 years for nutritional and medicinal purposes^{1,2}. Anti-viral and anti-cancer effects have been demonstrated in more than 50 species through animal and *in vitro* studies. Six components of these mushrooms have been investigated for their activity in human cancers: the lentinan component of shiitake, schizophyllan, active hexose correlated compound (AHCC), maitake D-fraction and two components of *Coriolus versicolor*. According to the review by Kidd, lentinan and schizophyllan have limited oral bioavailability, and the AHCC and maitake D-fractions are still in the early stages of investigation, but the two *Coriolus versicolor* components have been extensively investigated and show promise².

Coriolus versicolor was first recorded during the Ming Dynasty of China³, and subsequently in a 1965 Japanese report of a patient with stomach cancer who benefited from drinking a tea, *Saru-no-koshikake*, that contained this mushroom. Subsequent laboratory and animal research identified the source of the tea's anti-tumor effects to be two polysaccharides^{1,4-6}.

In 1989, two investigators at the U. S. National Cancer Institute (Jong and Donovick⁷) published a review of antitumor and antiviral substances from fungi including *Coriolus versicolor*. This review noted seven studies and two U. S. patents issued for polysaccharides extracted from *Coriolus versicolor*. One extract was a polysaccharide-protein (proteoglycan) known as polysaccharide Kurcha (PSK or Krestin), and it had been found to be effective in the treatment of Ehrlich carcinoma and sarcoma 180 tumors in mice. Furthermore, PSK had not exhibited any of the cytotoxicity or other side effects commonly seen with conventional anticancer treatment⁷.

Subsequent laboratory and animal studies have further defined the antitumor, antimicrobial, antiviral and immune enhancing properties in both PSK and another protein-bound polysaccharide known as polysaccharide-protein complex (PSPC or PSP). Both substances are extracted by hot water from the mushroom's cultured mycelium (thread-like extensions)^{2,3,8,9}.

Mechanisms of Action: Polysaccharide Kurcha (PSK or Krestin)

Prevention and cancer control properties of PSK have been associated with its antioxidant and free radical scavenging properties *in vitro* and *in vivo*^{9,10}. PSK has demonstrated prevention of chemically induced DNA damage (sister chromatid exchanges)⁵ and subsequent tumors due to chemicals, radiation or other causes^{4,5}.

PSK also seems to work in multiple steps of the malignant process by inhibiting adhesion, invasion, motility, and metastatic growth of tumor cells in animal models of cancer^{5,9}. Adhesion and invasion are inhibited by suppression of cell matrix-degrading enzyme production by malignant cells. Motility of malignant cells and subsequent attachment to blood vessels are inhibited by suppression of tumor-cell induced platelet aggregation and anti-angiogenic factors^{4,10}. PSK has also induced apoptosis (programmed cell death) in lymphoma, leukemia and pancreatic cells^{11,13}.

Immune responsiveness of the host does not appear to be affected by PSK under normal conditions, but immune systems depressed by tumor-burden or chemotherapy, have reportedly been restored to normal levels by PSK in animal studies^{1,9,14}. Immune restoration has included antibody and cytokine production and improvement of impaired antitumor activity of natural killer cells, T cells, macrophages and peripheral blood lymphocytes *in vivo* and *in vitro*^{4,9,15,18}. PSK has also been demonstrated to inhibit the decline of immunocompetence during the perioperative period¹⁹ and inhibit the growth of residual tumors following cryoablation²⁰.

A variety of other mechanisms have been observed in laboratory studies of PSK. It was found to alter the expression of the p53 gene²¹, inhibit Epstein-Barr virus induced B-cell proliferation²² and suppress heat shock proteins that are thought to be involved in the progression of fibrosis¹⁰. PSK has also been observed to stimulate differentiation (orderliness) of human myeloblastic leukemic cells⁸.

When injected directly into a tumor, PSK produces local inflammatory responses that result in the non-specific killing of tumor cells⁹. One study on vaccine therapy against cancer found that PSK promotes the maturation of dendritic cells to produce IL-12 and Th1 type cytokines²³; however, another study concluded that PSK was not as effective as OK432, a preparation of the bacteria *Streptococcus pyogenes*²⁴.

Mechanisms of Action: Polysaccharide-Peptide (PSP)

Multiple and complex mechanisms of action of PSP have been demonstrated through *in vitro* and animal studies. PSP has suppressed the growth of human cancer cell lines in mice (sarcoma 180, lung adenocarcinoma and Lewis lung cancer)^{3,7,9}. It has also inhibited incorporation of two structural units of DNA (uridine and thymidine) in Ehrlich ascites tumor cells, inhibited the growth of P388 leukemia cells, and demonstrated anti-proliferative activity against cell lines of human gastric cancer, lung cancer, lymphoma, and mononuclear leukemia³.

PSP has reversed tumor-induced immunodeficiencies in sarcoma-bearing mice by increasing immunoglobulin G and C3 complement levels⁹. It has also been associated with increases in white blood cell count, serum IgG, CD4, CD8, B-lymphocytes, and neutrophils, along with a higher survival rate of tumor bearing mice³. Many of these effects have been attributed to PSP being a strong scavenger of superoxide and hydroxyl radicals^{9,10}. PSP has also been found to restrict the cell cycle of HL-60 leukemic cells through apoptosis²⁶.

These and other immune effects of PSK and PSP are described in reviews by Fisher and Yang¹⁰, Ooi and Liu⁹ and Chu, Ho and Chow¹⁴.

Possible Toxicities of PSK and PSP

PSK has been associated with side effects of gastrointestinal upset⁵ and darkening of the fingernails, but these effects have been limited and general safety has been demonstrated with

daily oral doses for extended periods of time². It does not seem to interact with hepatic drug-metabolizing enzymes involved in the chemical processing of most chemotherapy agents¹⁰, and no genetic damage has been detected by the Ames test⁵.

At doses that produced necrotic changes in tumor cells, PSP produced no lesions in the vital organs of tumor-bearing mice after treatment for two months. It has not been associated teratogenic effects in mice or rats³.

Human Trials of PSK and PSP

All trials of PSK have been in combination or supplemental to chemotherapy and/or radiation. These trials have included numerous randomized, but non-blinded, clinical trials in Japan where it has been approved as an adjuvant (supplementary) treatment for digestive system, lung and nasopharyngeal cancers¹⁰. PSP has had fewer trials, all of them in China³. Designs and results of these human trials are reviewed in the Summary of Research.

*Polysaccharide

Polysaccharides are composed of groups of interconnected monosaccharides (single sugars) and are a structurally diverse group that occurs widely in nature. Unlike the nucleotides in nucleic acids and amino acids in proteins that can only be interconnected in one way, polysaccharides can be interconnected at several points to form a wide variety of branched or linear structures. The number of possible permutations for four different monosaccharides can be up to 35,560 unique arrangements, while four amino acids can only form 24 different permutations. (Hodgson, J. Biotechnology, 1991, 9, 609-613, cited below.)

Reference

Ooi VE, Liu F. Immunomodulation and anti-cancer activity of polysaccharide-protein complexes. [Review] [179 refs]. Current Medicinal Chemistry. 2000 Jul;7(7):715-29.

Summary of Research

Amount and Type of Research

Based on our review of the literature and other sources between September 1, 2002, and February 28, 2005, we have identified 41 references to "Coriolus versicolor", "PSK", "Krestin" or "PSP", of which 32 (78%) were applicable to these terms and the treatment of cancer. A previous review between October 1, 1997 and August 31, 2002, identified 59 references, of which 50 (85%) were applicable to cancer. Another previous review of the literature ending in October of 1997 had identified 136 articles, of which 97 (71%) were applicable to cancer.

Combining the results of these three reviews yields 236 articles, of which 179 (75%) are applicable to cancer. Of these, we have retrieved 163 articles as complete articles (reviews and human studies) or abstracts (animal and in vitro studies). We have classified these references into the following types of information:

Human	Animal	In vitro	Reviews	Other
43*	55	37	11	17

*Four articles referenced one study.

Of the human related articles, we coded the studies (40) by the following study designs:

Study Design	No. of Studies
Randomized Controlled and Blinded Clinical Trial	(1)
Randomized Controlled Clinical Trial (RCT)	19 (16)
Non-Randomized Controlled Trial /Prospective Cohort with controls	10 (6)
Controlled trial/Prospective Cohort with historical (Literature) Controls	(1)
Prospective Cohort/Clinical Series/ Trial with No Controls	4 (1)
Case-Control Study	0
Re-analysis of a Previous RCT with New Criteria	3 (3)
Retrospective Review	2 (1)
Best Cases	0
Case Report	0
Total Human Studies	40 (29)

Note: Numbers in parentheses indicate trials designed to evaluate the specific effects of PSK or PSP.

Summary of Research

Only one of the 40 studies identified in the literature used polysaccharide P (PSP)²⁷; the rest used polysaccharide K. The PSP study was a double-blinded RCT that compared the effects of PSP versus placebo on non-small cell lung cancer. Those treated with PSP had significant increases in IgG, IgM, leukocyte count, neutrophil count and percent body fat (p<.05 for all), and significantly fewer subjects in the PSP group withdraw from the study due to disease progression.

A review by T. B. Ng notes nine human trials of PSP that reportedly demonstrated protective effects upon the immune systems of patients treated with chemotherapy or radiotherapy³; however, these are not described here because complete articles are either not published outside of oral presentations at symposiums or not available in English.

The 39 studies of PSK included 11 studies in which the effects of PSK could not be evaluated, as they were combined with other treatments and not compared with similar groups without the PSK²⁸⁻³⁸. The 28 remaining studies include 14 studies that evaluated effects of PSK upon disease and survival^{6,39-44,45-51} and eight studies that evaluated survival without disease response⁵²⁻⁵⁹. The remaining six studies evaluated immune effects⁶⁰⁻⁶³, anti-oxidation⁶⁴ and interaction with chemotherapy⁶⁵.

Survival with Disease Response

Of the 14 studies assessing survival and disease response, 11 were RCTs^{6,39-44,46,48,49,51}, one was a retrospective stratified analysis of a previous RCT⁴⁴ utilizing new criteria⁴⁷ and two were non-randomized prospective controlled studies^{45,50}.

One of the 11 RCTs compared chemotherapy plus PSK with chemotherapy plus placebo for patients with colorectal cancer and reported that the group receiving PSK had significantly longer disease-free intervals and survival (both $p < 0.05$)⁴⁶. Four other RCTs compared patients treated with chemotherapy with or without PSK and each reported significantly longer disease-free and overall survival with PSK ($p < 0.05$)^{6,39,40,43}. Another RCT compared patients treated with chemotherapy with or without PSK and reported significantly longer disease free survival ($p = .016$), but not overall survival ($p = .056$)⁴⁸. The remaining five RCTs reported non-significant trends toward longer remission and survival (all $p < 0.1$)^{41,42,44,49,51}. One of these RCTs⁴⁴ was subsequently reanalyzed after stratifying treatment groups by HLA status. Patients in the chemotherapy plus PSK group who were HLA positive had five- and 10-year disease free survival rates of 100% compared with survival rates of 76% and 55% for those in the chemotherapy plus PSK group who were HLA negative ($p < 0.05$)⁴⁷.

One of two non-randomized prospective controlled trials reported significantly longer disease-free intervals and survival for lung cancer patients treated with PSK + chemotherapy compared with the chemotherapy alone group⁴⁵. The other trial compared patients receiving chemotherapy plus PSK to those receiving chemotherapy alone, and reported a significantly higher three-year disease free survival rate for the PSK group ($p = .0467$)⁵⁰.

Table 1 summarizes disease response and survival.

Survival without Disease Response

Of the eight studies that assessed survival without assessing disease response, two were RCTs^{52,54}, one was a non-randomized prospective cohort study⁵⁹, three were re-analyses of previous RCTs^{6,43,54} using new criteria^{53,56,57}, one was a prospective cohort with historical (literature) controls⁵⁵, and one was a retrospective review⁵⁸.

One of the two RCTs reported significantly better survival times for patients with esophageal cancer⁵². Although the other RCT did not report significant differences, the authors stated their belief that PSK was the most important factor contributing to longer survival for *some patients*⁵⁴.

The non-randomized prospective controlled study was a large multi-institutional of patients with gastric cancer. Treatment groups were gastrectomy alone, chemotherapy, chemotherapy plus PSK, or PSK alone. They were stratified by serum levels HLA-A2, an antigen previously correlated with a low risk of lymph node metastasis. Survival was found to be significantly shorter with chemotherapy without PSK for patients who were HLA-A2 positive (RR without PSK=1.8, $p = 0.0405$), while there were no significant differences in survival with or without PSK for patients in the HLA-A2 negative group (RR without PSK=1.0037, $p = .99$)⁵⁹.

The three re-analyses of previous RCTs^{6,43,54} utilizing new criteria^{53,56,57} reported longer survival associated with PSK among sub-groups with abnormally high a1-antichymotrypsin and sialic acid levels⁵³, high granulocyte/lymphocyte ratios⁵⁶, and low immunosuppressive acidic protein levels in patients with gastric cancer who did not have splenectomies⁵⁷ (All $p < 0.05$).

The prospective for patients with nasopharyngeal cancer reported longer survival with chemotherapy plus PSK compared with historical controls ($p < 0.05$)⁵⁵.

One retrospective study evaluated the survival of 872 gastric cancer patients with resections and chemotherapy with or without PSK. Treatment groups were stratified according to preoperative serum levels of carcinoembryonic antigen (CEA) and acute-phase reactants (APR) including immunosuppressive acidic protein, acid-soluble glycoproteins, a1-antichymotrypsin, and sialic acid. Patients with abnormal levels of CEA and one or more abnormal APR levels had significantly shorter survival if they were not treated with PSK (RR 1.9, 95% C.I. 1.1, 3.3)⁵⁸.

[Table 2](#) summarizes survival outcomes without disease response.

Immune Effects

Effects upon the immune system were evaluated by one double-blinded RCT²⁷, three non-blinded RCTs^{46,51,62} and three prospective controlled studies^{60,61,63}. The blinded RCT evaluated four weeks of treatment with PSP for patients with lung cancer and found significant increases in IgG, IgM, leucocytes and neutrophils compared with placebo²⁷. One unblinded RCT for colon and gastric patients⁶² found positive effects on immune function influenced by the duration but not the frequency of PSP administration⁶². A second unblinded RCT reported decreased ratios of T4 (CD4 or T helper) to T8 (CD8 or T cytotoxic) lymphocytes in peripheral blood of patients with hepatocellular carcinoma⁵¹. The third unblinded RCT found increased locomotion and enhanced phagocytic activity in leucocytes from patients treated with PSK⁴⁶.

The first of three prospective studies for head and neck cancer had mixed results: PSK reduced the immune inhibition by radiation (as measured by PHA skin reaction and absolute number of T-lymphocytes in peripheral blood), but had no effect on the transformation of lymphocytes⁶⁰. The second study of gastric cancer patients and healthy volunteers found that tumor necrosis factor alpha and interleukin-8 gene expression were significantly induced in five of 12 volunteers and four of nine cancer patients⁶¹. The third prospective controlled trial reported that PSK reduced the decline in leukocytes and platelets associated with chemotherapy, but not as much as another immune stimulator, Granulocyte Colony Stimulating Factor (G-CSF). PSK and G-CSF combined were associated with actual recovery of these blood counts; however, measures of statistical significance were not reported⁶³.

[Table 3](#) summarizes immune system outcomes.

Other Effects

The previously described double blinded RCT for patients with lung cancer also found significantly increased percent of body fat content associated with PSK²⁷. A non-randomized prospective controlled study for patients with colorectal cancers found significantly higher levels of collagen IV after 12 months of treatment with PSK plus chemotherapy compared with chemotherapy alone. (Type IV collagen is an indicator of breakdown of collagen due to tumor invasion of the basement membrane)⁵⁰. Two studies of uncontrolled clinic series examined other potential effects of PSK in patients with gastric cancer. In one series PSK was associated with antioxidant activity in serum and serum-free systems⁶⁴ and in the other series, PSK did not interfere with the metabolism of 5-FU chemotherapy⁶⁵.

[Table 4](#) summarizes other outcomes, and [Table 5](#) summarizes studies not designed to evaluate the specific contribution of PSK.

Conclusions

PSP may have positive effects upon immune parameters, percent body fat and disease progression in patients with non-small cell lung cancer based upon one randomized and blinded controlled clinical trial.

PSK may have positive effects upon disease and survival outcomes based upon the preponderance of findings from randomized controlled studies; however, the lack of blinding in these trials is a cause of concern.

Reviews by Others

Three other reviews of human studies with PSK have had positive conclusions: The 1998 review by T. B. Ng concluded that extracts from *Coriolus versicolor* helped alleviate symptoms and prevented the decline in immune status of patients with esophageal, gastric and lung cancers treated with radiotherapy or chemotherapy³. A review in 2000 by Parris Kidd cited high tolerability, benefits to survival, quality of life and compatibility with chemotherapy and radiation therapy². The review in 2002 by Fisher and Yang concluded that the greatest amount of clinical evidence for the use of PSK was in the treatment of gastric cancer after curative resection¹⁰.

The potential of *Coriolus versicolor* and other mushrooms for the prevention and treatment of cancer are discussed in a book by Smith, Rowan and Sullivan, [Medicinal Mushrooms and Cancer](#)⁶⁶. Note: Page will open in a new browser window.

Study descriptions and sources for these data are provided in the Annotated Bibliography.

Annotated Bibliography

Human Studies Only Survival And Disease Response

Blinded Randomized Controlled Trial

²⁷Tsang KW, Lam CL, Yan C, Mak JC, Ooi GC, Ho JC, *et al.* Coriolus versicolor polysaccharide peptide slows progression of advanced non-small cell lung cancer. *Respir Med* 2003 Jun;97(6):618-24.

Purpose: Survival and disease response; immune system outcomes

Type of Study: Randomized controlled trial, double blinded

Methods: (Lung) Sixty-eight patients (out of an unknown eligible number) with advanced and inoperable non-small cell lung cancer (NSCLC) who had a Karnofsky performance scale 60, life expectancy of 12 weeks or greater and TNM stage III or IV with at least one measurable lesion were recruited into the study. Previous radiotherapy and chemotherapy was permitted if it was completed at least four weeks prior to the study. Patients were randomly assigned to receive either polysaccharide peptides (PSP) (n=34) or placebo (n=34) three times daily for four weeks. Clinical and laboratory evaluations were performed on patients at baseline and four weeks to evaluate the effect of PSP on NSCLC-specific morbidity and the safety profile of this preparation. Both the patients and evaluators were blinded to the treatment. Patients were required to have a minimum of two weeks treatment to be evaluable for response.

Results: The two groups did not differ at baseline with respect to previous treatment, performance scale or TNM staging, although PSP patients were significantly older than control patients. All patients had 100% compliance with treatment. There was a significant increase in the level of IgG and IgM after four-week treatment with PSP (p=.002 and .01), but not with placebo (p=.57 and .31). Total leukocyte and neutrophil counts increased significantly after PSP (p=.003 and .005), but decreased significantly after placebo treatment (p=.006 and .01). Body mass index was not found to be significantly different between treatment groups. A significant increase in percent body fat content after PSP (p=.02) was found, but not after placebo (p>.05); however, the PSP group had a lower percent body fat at the beginning of treatment. Hemoglobin levels rose after the four-week treatment with PSP, but this was not statistically significant. Tumor response was evaluated on 58 patients who attended reassessment at four weeks and none of the patients in either group were found to have complete or partial clinical response. Significantly less PSP patients were withdrawn from the study, compared with the placebo group, due to disease progression (5.9% and 23.5% respectively; p=.04). No patients reported any adverse reactions to either placebo or PSP.

Randomized Controlled Trials (RCTs)

⁴⁸Ohwada S, Ikeya T, Yokomori T, Kusaba T, Roppongi T, Takahashi T, *et al.* Adjuvant immunochemotherapy with oral Tegafur/Uracyl plus PSK in patients with stage II or III colorectal cancer: a randomised controlled study. *Br J Cancer* 2004 Mar;90(5):1003-10. (Study also published in ⁶⁷)

Purpose: Survival and disease response

Type of Study: Randomized controlled trial

Methods: (Colorectal) A total of 207 patients were enrolled in the study (out of an unknown eligible number) from 19 affiliate hospitals in Japan. All had confirmed colorectal cancer, were less than 75 years old, had measurable serum immunosuppressive acidic protein levels, had a primary tumor at stage II or III and underwent curative resection. Two patients were later deemed ineligible, leaving 205 patients to be analyzed. Immediately after their colon resection, patients were randomly assigned to two groups, PSK and control, in the ratio of 2:1 (137 PSK and 68 controls). All patients received bolus injections of mitomycin C (MMC) on postoperative days 1 and 2. The PSK group (n=137) received oral protein-bound polysaccharide K (PSK) and tegafur/uracil (UFT) daily, starting two weeks after surgery and continuing for two years or until tumor recurrence. The control group (n=68) followed the same timeline, receiving only UFT. Patients were followed until five years after surgery. The primary endpoints of the study were disease-free and overall survival rates, and causes of death and recurrence were also assessed.

Results: At baseline, the only significant difference between the two groups, was that the histopathologic grade was higher in the PSK group (p=.009). Compliance with the treatment regimen was 87.6% in the PSK group and 91.2% in the control group. The PSK group had less recurrences than the control group (23.3% vs. 36.5%, p=.06), although this difference was not significant. Although the median time to recurrence was not significantly different between the two groups (2.14 years for PSK vs 1.61 years for controls), the six-month hazard rate for recurrence in the control group was higher in the first two years after surgery whereas it was consistently low in the PSK group for the entire five years of follow-up. The five-year disease free survival was significantly higher for the PSK group than for the control group (73% vs. 58.8%, p=.016). Analysis of the proportional hazard rates for recurrence adjusted for nine different characteristics identified the presence of metastases (RR 2.973; 95% CI 1.712 – 5.165), omission of PSK (RR 2.109; 95% CI 1.712 – 5.165; P<.001), and higher pathologic grade of primary tumor (RR 4.398; 95% CI 1.1017 – 19.014) as significant indicators for recurrence. In sub-group analysis of pathologic stage III patients, the five-year disease free survival benefit from PSK was also significantly greater (p=.002) as was the overall survival (74.6% vs. 46.4% p=.003). The five-year overall survival rate difference for all patients was almost significant between patients in the PSK and the control groups (81.8% vs. 72.1%, p=.056). Haematological or gastrointestinal toxicity was observed in 31 patients (15.1%) and was induced by the MMC and subsequent UFT treatments.

Note: In a commentary⁶⁸, Alliot criticized the choice of tegafur/uracil (UFT) for chemotherapy in both groups since 5-FU and leucovorin had become the standard treatment. He also noted that 50% of patients in the control arm had rectal cancer and that they had not been treated with pre-operative radiotherapy, again the standard treatment. In addition, he noted variation in the timing and administration of chemotherapy that would have introduced other confusing variation. In response⁶⁹, Ohwada and Morishita said that 5-FU and Levamisole had not been approved of in Japan until after their study had concluded. They also cited clinical trials in which UFT alone had improved survival. Because of concern about the proportion of patients with rectal cancer, they had reanalyzed the disease-free survival rate adjusted for histology and tumor location and found that the survival remained significantly better for the PSK group. For more details see the commentary by Alliot⁶⁸ and the

response by Ohwada and Morishita⁶⁹.

⁴⁹Ito K, Nakazato H, Koike A, Takagi H, Saji S, Baba S, *et al.* Long-term effect of 5-fluorouracil enhanced by intermittent administration of polysaccharide K after curative resection of colon cancer. A randomized controlled trial for 7-year follow-up. *Int J Colorectal Dis* 2004 Mar;19(2):157-64.

Purpose: Survival and disease response

Type of Study: Randomized controlled trial

Methods: (Colon) Subjects (N=441) from 93 cooperating institutions in Japan with primary colon cancer who had undergone resection with curative intent and had developed lymph node metastasis participated in the study. Detailed eligibility requirements are described in the article. The article is unclear on the number of patients initially and subsequently judged to be eligible. All patients received a 48-hour constant intravenous infusion of 5-fluorouracil (5-FU) weekly for three to four weeks as pretreatment. At the point when the 5-FU infusion courses were completed, patients were randomly stratified by degree of lymph node metastasis (N0, N1, N2, N3), preoperative serum CEA level, PPD skin test reaction (positive or negative) and institution. Patients were assigned to either the PSK or control group. The PSK group (n=220) was given oral PSK daily for four weeks followed by four weeks of oral 5-FU as one course. The control group (n=221) received four weeks of rest followed by four weeks of oral 5-FU as one course. Both groups received a total of 10 courses, lasting approximately 80 weeks, and then were followed for seven years. Detailed follow-up procedures are described in the article. The primary endpoints of the study were overall survival, disease-free survival and survival until cancer related death. (*Note:* Criteria for cancer related deaths are not described.)

Results: At baseline, the clinical characteristics of the two groups were similar; however, there was an imbalance in the distribution of the patients' performance status. The sample size of 224 in each group that was needed to ensure 80% power was not met. The drug compliance levels and discontinuation of therapy in both groups were essentially the same, suggesting no difference between the two groups. The seven-year overall survival rates showed non-significant differences between groups (79.6% vs. 75.6%). The seven-year disease free survival rates of both groups were also statistically similar (74.1% vs. 71%). The seven-year survival rate until cancer death for the PSK group, however, was statistically significantly higher than the control group (83% vs. 78.5%, adjusted P = .019). Subgroup analysis suggested interactive effects of performance status on these survival rates in that those with a poor performance status apparently experienced less effectiveness from the combination of 5-FU and PSK. No characteristic toxic effect was identified for PSK.

⁵¹Suto T, Fukuda S, Moriya N, Watanabe Y, Sasaki D, Yoshida Y, *et al.* clinical study of biological response modifiers as maintenance therapy for hepatocellular carcinoma. *Cancer Chemotherapy and Pharmacology* 1994;33:S145-S148.

Purpose: Survival and disease response

Type of Study: Randomized controlled trial

Methods: (Hepatocellular carcinoma (HCC)) Patients with HCC who had been treated with percutaneous ethanol injection (PEI), transcatheter arterial embolization (TAE) or arterial infusion (AI) were eligible for the study. All subjects (n=58) received 5-fluorouracil (5-FU) daily and were randomized into four groups to receive either PSK daily, lenitin weekly, OK-432 weekly or 5-FU alone. The duration of treatment and follow-up are not provided in the article. The mean survival time, mortality rate, time to progression and T4/T8 ratio of lymphocytes in the peripheral blood were evaluated.

Results: The only difference between groups at baseline was a tendency for the PSK group to include more cases with deteriorated reserve liver function. No significant differences between groups were found in survival time, mortality rate or time to progression. The mean survival rate compared as a function of the previous therapy found PEI to be significantly higher than TAE or AI (p<.05). The T4/T8 ratio significantly decreased in the PSK group after three months of therapy (p<.05).

³⁹Toi M, Hattori T, Akagi M, Inokuchi K, Orita K, Sugimachi K, *et al.* Randomized adjuvant trial to evaluate the addition of Tamoxifen and PSK to chemotherapy in patients with primary breast cancer. 5-year results from the Nishi-Nippon Group of the Adjuvant Chemoendocrine Therapy for Breast Cancer Organization. *Cancer* 1992;70(10):2475-83.

Purpose: Disease response and survival

Type of Study: RCT

Methods: (Breast) (n=967, 914 evaluable) Women younger than 76 years of age with Stage IIA, IIB and IIIA primary breast cancer who received extended, standard or modified radical mastectomy were entered in the study. Patients were stratified and randomized to receive one of four treatments:

Patients with ER-positive tumors received

- A. Mitomycin-C (MMC) + fluorouracil (FU) + tamoxifen (TMX)
- B. MMC + FU only

Patients with ER-negative tumors received

- C. MMC + FU with PSK
- D. MMC + FU only

Results: For patients with ER-negative tumors, no significant difference in relapse free or overall survival for MMC + FU with PSK was observed. However, subset analyses demonstrated a longer overall survival with MMC + FU with PSK for patients who were node negative stage IIA TxN1 (95.7% versus 80.8% at five years; p< 0.0017 by log-rank test). (Disease free and overall survival advantage was also observed for postmenopausal patients with TMX and ER-positive, Stage IIIA T2N0 cancer (p<.0098).)

⁴⁰Go P, Chung C-H. Adjuvant PSK immunotherapy in patients with carcinoma of the nasopharynx. *The Journal of International Medical Research* 1989;17:141-9.

Purpose: Disease response and survival

Type of Study: RCT

Methods: (Nasopharynx) (n=38, 34 evaluable) A total of 17 patients in the PSK group and 17 in the control group were evaluated. Immunotherapy with PSK was initiated within one month after completion of primary treatment (radiotherapy plus chemotherapy). Monthly blood chemistry and counts were analyzed to detect PSK toxicity.

Results: In the PSK group, eight developed local recurrences and three died due to distant metastasis, whereas in the control group, three developed local recurrence and six patients died due to distant metastasis. Estimated median survival time was significantly (p<0.04) longer for the PSK group (35 mos) versus controls (25 mos). The five-year survival was significantly (p<.04) higher for the PSK (28%) versus control (15%) also.

⁴¹Ohno R, Yamada K, Masaoka T, Ohshima T, Amaki I, Hirota Y, *et al.* A randomized trial of chemoimmunotherapy of acute nonlymphocytic leukemia in adults using a protein-bound polysaccharide preparation. *Cancer Immunology, Immunotherapy* 1984;18:149-54.

Purpose: Disease response and survival.

Type of Study: RCT

Methods: (Leukemia) (n=73) Patients with ANLL who achieved complete remission were randomized to maintenance chemotherapy only (n=38, 36 evaluable) or chemotherapy plus immunotherapy plus PSK (n=35, 31 evaluable). No significant differences between the two groups were observed by age, sex or type of ANLL. All patients were followed by outpatient clinics at one- to two-week intervals until relapse. After chemotherapy was terminated two years later, patients were assessed at two- to four-week intervals. PSK was continued as long as the patients were in remission.

Results: Treatment with PSK for six months tended to extend remission (p<0.09) and survival (p<0.06) time; however, at 12, 18 and 24 months, no significant

differences improvement was found for remission and survival. A subset analysis by length of remission before starting the PSK and chemo showed that patients who had achieved a remission of more than 270 days tended (not significant) to have longer survival with PSK ($p<0.11$).

⁶Mitomi T, Tsuchiya S, Iijima N, Aso K, Suzuki K, Nishiyama K, *et al.* Randomized, controlled study on adjuvant immunochemotherapy with PSK in curatively resected colorectal cancer. *Diseases of the Colon and Rectum* 1992;35(2):123-30.

Purpose: To study the effect of immunochemotherapy with PSK on prolonged survival

Type of Study: RCT

Methods: (Colorectal) (n=462, 448 evaluable) The control group (n=227) received mitomycin C on the day of and the day after surgery, followed by oral 5-fluorouracil (5-FU) for over six months. The PSK group (n=221) received PSK orally for over three years, in addition to mitomycin C and 5-FU. Median follow-up time was four years (range three to five years).

Results: The disease-free overall survival curves of the PSK group were better than those of the control group; these differences were statistically significant for disease-free survival ($p<0.01$) and survival ($p<0.01$).

⁴²Nagao T, Komatsuda M, Yamauchi K, Nozaki H, Watanabe K, Arimori S. Chemoimmunotherapy with Krestin in acute leukemia. *Tokai Journal of Experimental and Clinical Medicine* 1981;6(2):141-6.

Purpose: Disease response and survival

Type of Study: RCT

Methods: (Leukemia) (n=28) Patients were placed at random in the chemotherapy and chemo-immunotherapy groups with 14 patients each. Remission had been induced by combination therapy (neocarzinostatin, cytosine arabinoside, prednisolone or vincristine, daunorubicin, prednisolone). After complete remission, two to three courses of consolidation therapy consisting of mercaptopurine chemotherapy with or without Krestin (PSK) daily until relapse.

Results: The median duration for complete remission and survival were longer in the chemoimmunotherapy (PSK) than the chemotherapy group. The complete remission rate was higher in the chemoimmunotherapy group (36 weeks; range 17 – 128) than the chemotherapy group (25 weeks; range 9 to 66+). The average survival time of the PSK group was 21 months (range 8 to 37+) while that of the control group was 12 months (range four to 26). The cell-mediated immunity was somewhat enhanced in the chemoimmunotherapy group, while it was not enhanced in the chemotherapy group. No subjective or objective side effects due to PSK were observed for over one year.

⁴³Nakazato H, Koike A, Saji S, Ogawa N, Sakamoto J. Efficacy of immunochemotherapy as adjuvant treatment after curative resection of gastric cancer. *The Lancet* 1994;343:1122-6.

Purpose: Disease response and survival

Type of Study: RCT

Methods: (Gastrointestinal) (n=262, 253 evaluable) Patients who had a gastrectomy were randomly assigned to standard treatment with mitomycin and fluorouracil or standard treatment plus PSK. The minimum follow-up time was five years.

Results: Compared with the standard care group, PSK treatment increased five-year disease-free period (70.7% vs. 59.4%, $p<0.05$) and five-year survival (73.0% vs. 60.0%, $p=0.04$). The two regimens had slight toxic effects, consisting of nausea, leucopenia and liver function impairment, with no significant differences between the two groups. No characteristic toxic effects could be identified for PSK. The treatments were clinically well tolerated and compliance was good.

⁴⁴Iino Y, Yokoe T, Maemura M, Horiguchi J, Takei H, Ohwada S, *et al.* Immunochemotherapies versus chemotherapy as adjuvant treatment after curative resection of operable breast cancer. *Anticancer Research* 1995;15:2907-12.

Purpose: Disease response and survival

Type of Study: RCT

Methods: (Breast) (n=227) Patients with operable breast cancer with vascular invasion in the tumor and/or in the metastatic lymph node were entered in the study. The patients were randomized into three groups:

1. 5-fluorouracil, cyclophosphamide, mitomycin C and prednisolone (FEMP)
2. FEMP+ levamisole (LMS)
3. FEMP+PSK.

Each treatment was carried out at six-month intervals for five years.

Results: Risk ratio lower for the PSK group (1.00) than the FEMP (1.64) and FEMP+LMS (1.19) groups. Disease-free survival rates at 10 years were 64.6% for the FEMP, 70.7% for the FEMP+LMS and 74.1% for the FEMP+PSK (not statistically significant). Overall survival rates were 64.6% FEMP, 76.9% FEMP+LMS and 81.1% FEMP+PSK ($p=0.07$). Side effects of leukopenia and nausea observed in five patients were mild and tolerable.

⁴⁶Torisu M, Hayashi Y, Ishimitsu T, Fujimura T, Iwasaki K, Katano M, *et al.* Significant prolongation of disease-free period gained by oral polysaccharide K (PSK) administration after curative surgical operation of colorectal cancer. *Cancer Immunology, Immunotherapy* 1990;31:261-8.

Purpose: Disease response and survival

Type of Study: RCT

Methods: (Colorectal) (n=120) Patients were randomized to receive PSK (n=56) or placebo (n=55) at 10-15 days post surgery in decreasing doses over three years.

Results: The number of patients in remission and surviving at 10 years were significantly higher ($p<0.05$ for both measures) in the PSK group than in the placebo group. The authors attributed these benefits to their laboratory finding of enhanced locomotion and phagocytic activity of polymorphonuclear leukocytes from PSK treated patients.

Non-Randomized Prospective Controlled Trials

⁵⁰Kudo S, Tanaka J, Kashida H, Tamegai Y, Endo S, Yamano H. Effectiveness of immunochemotherapy with PSK, a protein bound polysaccharide, in colorectal cancer and changes of tumor marker. *Oncology Reports* 2002 May-2002 Jun;9(3):635-8.

Purpose: Survival

Type of Study: Prospective (? - Article not clear) cohort with controls

Methods: (Colorectal) Patients with stages II or III colorectal cancer who had undergone curative resection were eligible for the study, and 58 out of an unknown eligible number were enrolled. Forty-eight subjects received chemotherapy and PSK within one month after surgery and continued for at least 12 months, while 10 subjects following the same schedule received only chemotherapy. Blood was collected before surgery and at one, three, six and 12 months after surgery to measure type IV collagen levels. (Type IV collagen is a marker for the invasiveness of tumors as it is released when collagen is broken down.) Patients were followed for three years after surgery to determine their three-year disease free survival rate.

Results: No significant differences were observed between the two groups at baseline. The PSK group had a mean administration period of 10.9 2.9 months (range 0.5 – 14 months). The chemotherapy group had a mean administration period of 11.3 6.7 months (2.4 – 27 months). Both groups received varying doses of chemotherapy, although the PSK dosage was more consistent (3 g/day). The three-year disease free survival rate was 74.3% in the PSK group compared to 40% in the chemotherapy

group ($p=0.0467$). Serum type IV collagen levels were significantly higher ($p=0.0072$) in the chemotherapy group than the PSK group over the 12-month period following surgery, signifying more destruction of the basement membrane in the chemotherapy group.

Note: The varying lengths of time that PSK was taken and the varying amounts of chemotherapy given limit the reliability of these results.

⁴⁵Hayakawa K, Mitsuhashi N, Saito Y, Takahashi M, Katano S, Shiojima K, *et al.* Effect of Krestin (PSK) as adjuvant treatment on the prognosis after radical radiotherapy in patients with non-small cell lung cancer. *Anticancer Research* 1993;13:1815-20.

Purpose: Disease response and survival

Type of Study: Prospective cohort with external controls

Methods: (Lung) (n=185) Among patients with little residual tumor and considered to be highly curable, PSK was administered after radical radiotherapy.

Results: Five-year survival of PSK patients with stages I or II disease, as well as stage III was 39% and 22% respectively, compared with the control group of 16% and 5%. These differences are statistically significant.

Note: The PSK group was compared with a group that was not doing as well at start of study. Thus, statistical significance, in this situation, is not clinically meaningful.

Re-Analyses of Previous RCTs with New Criteria

⁴⁷Yokoe T, Iino Y, Takei H, Horiguchi J, Koibuchi Y, Maemura M, *et al.* HLA antigen as predictive index for the outcome of breast cancer patients with adjuvant immunochemotherapy with PSK. *Anticancer Research*. 1997 Jul-Aug;17(4A):2815-8.

Purpose: Survival

Type of Study: Re-analysis of previous RCT 44

Methods: (Breast) The previous study randomized patients with vascular invasion (n=134) into two groups:

1. Chemotherapy (5-fluorouracil, cyclophosphamide, mitomycin, prednisolone (FEMP))
2. FEMP plus PSK

Patients received two 28-day courses of this treatment a year for five years. This study stratified each of these groups by HLA type B40 positive or negative.

Results: The disease-free survival rates at five and 10 years for the FEMP plus PSK group with B40 positive was 100%. For those with B40 negative, the five- and ten-year survival was 76% and 55%, respectively. Other disease free survival group differences were not significant.

Survival Studies Without Disease Response

Randomized Controlled Trials

⁵²Niimoto M, Hattori T, Tamada R, Sugimachi K, Inokuchi K, Ogawa N. Postoperative adjuvant immunochemotherapy with mitomycin C, futraful and PSK for gastric cancer. An analysis of data on 579 patients followed for five years. *Japanese Journal of Surgery* 1988;18(6):681-6.

Purpose: Survival

Type of Study: Randomized clinical trial

Methods: (Gastric cancer) (n=579) Patients under 75 years of age with gastric cancer, no previous cancer therapy and successful surgery were entered into the study. MMC 20 mg IV was administered on the day after gastrectomy, followed by an additional 10 mg the next day for patients who were less than 70 years of age, 40 kg or more and no total gastrectomy with combined resection of the colon or pancreas. PSK was administered orally at a daily dose of 3 g for one year, commencing from one to two weeks after the operation in the patients of Group A. FT was administered as a daily dose to the patients in Group B in the same manner, and a combination of PSK plus FT was administered to the patients in Group C.

Results: The MMC+FT+PSK group showed a significant increase in five-year survival compared with the other groups ($p<0.05$) as was survival compared the MMC+FT group ($p<0.01$). According to subset analyses, the MMC+FT+PSK group had significantly improved survival among cases with positive lymph node metastases, positive serosal invasion or both ($p<0.01$) and undifferentiated carcinoma by histological type and in those with a preoperative positive PPD reaction ($p<0.05$).

⁵⁴Ogoshi K, Satou H, Isono K, Mitomi T, Endoh M, Sugita M, *et al.* Immunotherapy for esophageal cancer: A randomized trial in combination with radiotherapy and radiochemotherapy. *American Journal of Clinical Oncology* 1995;18(3):216-22.

Purpose: Survival

Type of Study: Randomized clinical trial

Methods: (Esophagus) (n=174) Among 187 patients, 174 (93.1%) eligible patients with biopsy-proven esophageal squamous cell carcinoma underwent esophagectomy and were randomly assigned to receive radiotherapy (RT) with or without protein-bound polysaccharide (PSK), or RT plus chemotherapy (CT) with or without PSK. The immunotherapy group received oral PSK for three months, commencing as soon as possible after esophagectomy. PSK or Futraful were then given for as long as possible after surgery.

Results: The five-year survival rates for each group are as follows: RT (40.0%), RT+PSK (42.3%), RT+CT (29.1%) and RT+CT+PSK (37.2%). The survival difference between the RT + CT group and the RT + CT+PSK group was significant (log-rank and generalized Wilcoxon tests, $p = 0.1370$, $p = 0.0404$).

⁵³Ogoshi K, Satou H, Isono K, Mitomi T, Endoh M, Sugita M. Possible predictive markers of immunotherapy in esophageal cancer: Retrospective analysis of a randomized study. *Cancer Investigation* 1995;13(4):363-9.

Note: This is a stratified re-analysis of the Ogoshi *et al.* RCT study⁵⁴.

Purpose: Survival

Type of Study: Randomized clinical trial

Methods: (Esophagus) (n=158) Initially, 187 esophageal cancer patients entered in the study, 174 were eligible and 158 actually completed therapy. Pre-treatment blood samples were collected for examination of the levels of two markers with immunosuppressive activity, 1-antichymotrypsin (ACT) and sialic acid (SA).

Results: Stage IV patients had significantly higher serum levels of ACT. In addition to the significant differences in survival between the patients with and without PSK therapy reported in the previous study⁵⁴. For 43 patients with normal levels of ACT, no significant differences occurred in five-year survival rates. However, for the 68 patients with abnormal levels of ACT, higher better survival rates occurred for those who received PSK (54.8% and 25.9%; log-rank and generalized Wilcoxon tests, $p = 0.0077$, $p=0.0057$). Among patients with normal levels of SA, no significant survival differences occurred with or without PSK. However, patients with abnormal levels of SA had significantly better survival with PSK (58.3% and 30.8%; log-rank and generalized Wilcoxon tests, $p = 0.0671$, $p=0.0333$).

⁵⁵Chung C-H, Go P, Chang K-H. PSK immunotherapy in cancer patients - a preliminary report. *Chinese Journal of Microbiology and Immunology* 1987;20:210-6.

Purpose: Survival

Type of Study: Prospective cohort with historical controls

Methods: (Various) (n=67, 43 evaluable) PSK (1 g/daily) was administered for at least a month upon completion of primary treatment for the tumor, with a maximum use of one to

two years. All patients received radiotherapy prior to the start of PSK, and 23 (34.3%) of the patients underwent chemotherapy and surgery in addition to radiotherapy.

Results: Only four sites, nasopharynx, uterine cervix, breast and gastrointestinal carcinoma, had sufficient numbers for analysis. Nasopharyngeal patients with PSK had significantly improved ($p < .05$) survival compared with controls. The cervical carcinoma patients had no significant differences in survival; however, the authors state that "there seems to be an increase in the survival period among patients with carcinoma of the uterine cervix who are maintained on a longer period of PSK immunotherapy".

⁵⁶Toge T, Yamaguchi Y. Protein-bound polysaccharide increases survival in resected gastric cancer cases stratified with a preoperative granulocyte and lymphocyte count. *Oncology Reports*. 2000 Sep-2000 Oct;7(5):1157-61.

Purpose: Survival

Type of Study: Stratified re-analysis of the Mitomi *et al.* RCT study⁶

Methods: (Gastric) The previous study evaluated treatment of 751 patients with gastric cancer by comparing treatment with surgery plus chemotherapy with surgery plus chemotherapy plus PSK. This study re-analyzed the data according to pre-operative granulocyte/lymphocyte (G/L) ratios.

Results: Five-year survival for patients with G/L ratios less than 2.0 differ not differ significantly with or without PSK. However, patients with G/L equal to or above 2.0 had significant differences in five-year survival with and without PSK. For patients with PSK, 68.7% survived five years versus 55.4% for those without (Log rank $p = 0.007$; generalized Wilcoxon $p = 0.006$, Cox regression $p = 0.002$ as adjusted for sex, age, primary tumor and regional lymph nodes.)

⁵⁷Saji S, Sakamoto J, Teramukai S, Kunieda K, Sugiyama Y, Ohashi Y, et al. Impact of splenectomy and immunochemotherapy on survival following gastrectomy for carcinoma: covariate interaction with immunosuppressive acidic protein, a serum marker for the host immune system. *Tumor Marker Committee for the Study Group of Immunochemotherapy with PSK for Gastric Cancer. Surgery Today*. 1999;29(6):504-10.

Purpose: Survival

Type of Study: This is a stratified re-analysis of the Nakazoto *et al.* RCT study²⁴.

Methods: (Gastric) The previous RCT evaluated the impact of splenectomy on the survival of 253 patients gastric cancer patients by comparing immunochemotherapy (PSK) versus standard chemotherapy. This study analyzes these groups according to sub-groups with and without splenectomy and preoperative levels of the immune defense parameter, immunosuppressive acidic protein (IAP) for 228 patients in whom these levels were measured. Note that patients with splenectomies generally had more advanced pathological stage of tumors ($p < 0.001$, Wilcoxon).

Results: (This description is limited to the effect of PSK upon survival in relation to splenectomy and IAP levels.) In the group with low IAP levels, survival was better with PSK with and without splenectomy, but only the low level group without splenectomy was significantly better ($p = 0.024$). Some differences in the hazard ratios also occurred in the high IAP group between those with and without splenectomy, but these differences were not significant.

⁵⁸Ogoshi K, Miyaji M, Nakamura K, Kondoh Y, Makuuchi H, Tajima T. Immunotherapy and combined assay of serum levels of carcinoembryonic antigen and acute-phase reactants. *Cancer Immunology, Immunotherapy*. 1998 Mar;46(1):14-20.

Purpose: Survival

Type of Study: Retrospective review of tumor markers, treatment and other characteristics

Methods: (Gastric) Demographic and disease factors including pre-operative serum levels of tumor/immune markers were analyzed in reference to treatment with PSK for 872 resected gastric cancer patients with histologically confirmed adenocarcinoma. Tumor/immune markers included carcinoembryonic antigen (CEA) and the following acute phase reactants (APR): immunosuppressive acidic protein, acid-soluble glycoproteins, I-antichymotrypsin, sialic acid.

Results:

1. Patients with abnormal levels of CEA had significantly longer survival with PSK (log-rank test, $p = 0.0136$; Breslow test, $p = 0.0125$).
2. Patients with abnormal levels of CEA and one or more APR levels (Group D, $n = 73$) had significantly longer survival with PSK (log-rank test, $P = 0.0015$; Breslow test, $P = 0.0042$).
3. Cox multivariate regression analysis of four factors significantly related to survival in Group D (PSK, pathological stage, age and differentiated type) indicated that "PSK was the most significant factor", but *this statistic was not reported*.
4. PSK was not significantly related to survival in Group A (normal CEA & APR) or Group B (abnormal CEA, normal APR) or Group C (normal CEA, abnormal APR).

⁵⁹Ogoshi K, Tajima T, Mitomi T, Makuuchi H, Tsuji K. HLA-A2 antigen status predicts metastasis and response to immunotherapy in gastric cancer. *Cancer Immunology, Immunotherapy*. 1997 Oct;45(1):53-9.

Purpose: Survival (related to PSK & HLA-A2 status)

Type of Study: Prospective controlled study with internal controls for PSK

Methods: (Gastric) Among 847 patients with gastric cancer, 739 patients were followed from two to twenty years to investigate the outcome of gastrectomy with or without adjuvant treatment consisting of chemotherapy with or without PSK. Chemotherapy and PSK were continued for at least three months or until tumor progression. Survival interval was defined as from operation until death. Risk of metastasis and survival was analyzed by multiple variable logistic regression.

Results: For the entire group of 847 patients, multiple logistic regression analysis showed that HLA-A2 and HLA-B52 antigens were significantly related to low and high risk of lymph node metastasis ($p = 0.0372$ and 0.0271). For the 739 patients followed for at least two years, PSK was significantly related to better survival in HLA-A2 positive patients (RR for no PSK = 1.8081 , $P = 0.0405$). No significant differences in survival occurred within the HLA-A2 negative patients treated with or without PSK (RR = 1.0037 for no PSK, $P = 0.9880$).

Immune Effects

²⁷Tsang KW, Lam CL, Yan C, Mak JC, Ooi GC, Ho JC, et al. Coriolus versicolor polysaccharide peptide slows progression of advanced non-small cell lung cancer. *Respir Med* 2003 Jun;97(6):618-24.

Type of Study: Blinded randomized controlled trial

Methods: See Survival with Disease Response above.

Results: Significant increases in the levels of IgG and IgM after four-week treatment with PSP ($p = .002$ and $.01$), but not with placebo ($p = .57$ and $.31$). Significant increases in total leukocyte and neutrophil counts after PSP ($p = .003$ and $.005$), but significant decreases after placebo ($p = .006$ and $.01$).

⁶²Nio Y, Tsubono M, Tseng C-C, Morimoto H, Kawabata K, Masai Y, et al. Immunomodulation by orally administered protein-bound polysaccharide PSK in patients with gastrointestinal cancer. *Biotherapy* 1992;4:117-28.

Purpose: Immune effects

Type of Study: Randomized clinical trial

Methods: (Gastrointestinal) ($n = 47$) A total of 29 gastric and 18 colorectal cancer patients were randomly assigned to either the control or PSK group. All patients had no prior treatment. Patients in the PSK group were given PSK orally before surgery, either daily or every other day, and were later divided into short and long duration groups. Peripheral blood lymphocytes (PBL) were compared before and after administration of PSK, and those of the regional node lymphocytes (RNL) were compared between groups.

Results: The results indicate that the effects of PSK were significantly influenced by the duration, not by frequency of administration. Among patients in the short duration group, the response of the PBL to PSK and Con A was significantly stronger compared to pre-test whereas the cytotoxicity against K562 and KATO-3, and the proportion of CD16+ cells increased significantly among patients in long duration group. In peripheral blood, natural killer cells were activated and increased in number. In the regional node lymphocytes, suppressor cells were suppressed so that helper cells increased in proportion.

⁶⁰Takahashi H, Okamoto M, Saito A, Suzuki T. Clinical experience of PSK to head and neck cancer; with special reference to combination with irradiation. *Gan Kagakuryoho* 1980;7(3):489-95.
(Abstract only)

Purpose: Immune effects

Type of Study: Prospective cohort with internal controls

Methods: (Larynx and hypopharynx) (n=26) PSK and radiation were administered to a 12 cases of laryngeal and two cases of hypopharyngeal cancer. This treatment group was compared with a control group of 12 cases (also with laryngeal and hypopharyngeal cancer) receiving radiation alone.

Results: The inhibition of immune response from radiation (as demonstrated by PHA skin reaction and absolute number of T-lymphocytes in peripheral blood) "tended to be reduced" by PSK. However, there was no difference between the PSK administered group and the control group in the transformation rate of lymphocytes by PHA *in vitro* and PPD skin reaction. According to the authors, "These results suggest that PSK is capable of restoring non-specific immunoactivity in patients with head-and-neck cancer given irradiation therapy."

⁶¹Kato M, Hirose K, Hakozaki M, Ohno M, Saito Y, Izutani R, *et al.* Induction of gene expression for immunomodulating cytokines in peripheral blood mononuclear cells in response to orally administered PSK, an immunomodulating protein-bound polysaccharide. *Cancer Immunology, Immunotherapy* 1995;40:152-6.

Purpose: Gene expression and immune effects - production of inflammatory and host-defensive cytokines, tumor necrosis factor (TNF) and interleukin-8 (IL-8)

Type of Study: Prospective cohort

Methods: (Gastric) (n=21) Healthy volunteers (n=12) and cancer patients with gastrectomy (n=9) were entered into the study; both groups received orally, once, PSK. Samples of whole blood were collected in heparinized tubes from volunteers before, and one, three, six, 12, 24 and 48 hour after PSK administration, and whole blood of patients was collected before and 24 hours after PSK administration in the same way as from the volunteers. The gene expression for cytokines in PBMC of each subject was assessed.

Results: The induction of gene expression for both TNF and IL-8 was detected in PBMC from five of the 12 healthy volunteers (42%) and four of the nine patients (44%). Furthermore, the concentration of serum IL-8 was elevated in five healthy volunteers given PSK who had shown induction of IL-8 gene expression. According to the authors, "These findings indicate that responsiveness of PBMC to PSK, in terms of gene expression and production of cytokines, varies among individuals."

⁶³Kato R, Takenoshita S, Shimizu Y, Tanaka S, Yajima Y, Nagamachi Y. Changes in serum soluble IL-2 receptors (sIL-2R) and immunosuppressive acidic protein (IAP) associated with chemotherapy for lung cancer. *Anticancer Research*. 1997 Sep-1997 Oct;17(5B):3787-92.

Purpose: Detection of changes in immune parameters during chemotherapy with/without PSK

Type of Study: Prospective control

Methods: (Lung) Fifteen patients (11 males and four females) "excluding those in Stage I" were enrolled in this study. Chemotherapy consisting of VP therapy (CBDCA, CDDP, VP-16) was given in combination with Granulocyte Stimulating Colony Factor (G-CSF) or PSK. Surgery and/or radiotherapy was also received by all except two patients. Patients were followed for five to 21 months after two to nine cycles of chemotherapy. Peripheral blood counts of leukocytes, lymphocytes and platelets were serially measured. Serum soluble IL-2 receptor (sIL-2R) and immunosuppressive acidic protein (IAP) levels were quantified by (ELISA) and colorimetric methods respectively.

Results:

1. Leucocyte and platelet counts fell during chemotherapy with all treatments to their lowest levels in week two; however, G-CSF was associated with reduced leukopenia and showed a similar but lesser effect upon platelet count. PSK was also associated with a reduced fall in these counts, but had a weaker effect than G-CSF. The combination of G-CSF and PSK was associated with the actual recovery of leucocyte and platelet counts in weeks two through four and this recovery was greater than that of patients who recovered without either treatment.
2. sIL-2R and IAP levels: In all deaths due to early postoperative relapse, sIL-2R levels rapidly increased while there was no relapse or a slow course after relapse in patients showing gradual changes in sIL-2R and IAP levels. IAP levels remained low however in two patients with relapse who were continuously treated with PSK and this allowed their continual treatment with chemotherapy.

Note: Acceptance of the findings of this study is limited by the lack of explanatory labeling of treatment groups in figures 1 and 2 and lack of assessment of statistical significance.

Other Effects

⁶⁴Kariya K, Nakamura K, Nomoto K, Matama S, Saigenji K. Mimicking of superoxide dismutase activity by protein-bound polysaccharide of *Coriolus versicolor* QUEL, and oxidative stress relief for cancer patients. *Molecular Biotherapy* 1992 Mar;4(1):40-6.

Purpose: Relief of "oxidative stress"

Type of Study: Clinical series

Methods: (Digestive tract) Patients with malignant neoplasms in the digestive tract were entered in the study. Blood superoxide and red blood cell levels were traced before and after the administration of PSK by the authors' method. Heparinized peripheral blood was collected and centrifuged, and 10 l of plasma and RBCs were diluted by saline. Ten liters of each were injected into a vial containing 1 M CLA in 990 l distilled water. Chemiluminescence was read by a chemiluminescent reader and peak values and total counts were recorded.

Results: Superoxide in plasma and then RBC-O₂ decreased suddenly. Patients with digestive tract cancer who suffered from oxidative stress were relieved by a single intraperitoneal administration of PSK or a once per day oral prescription.

⁶⁶Anai H, Sakaguchi Y, Emi Y, Kohnoe S, Maehara Y, Sugimachi K. A protein-bound polysaccharide immunomodulator, PSK, does not suppress the conversion from 1-(2-tetrahydrofuryl)-5-fluorouracil to 5-fluorouracil in patients with gastric cancer. *Anti-Cancer Drugs* 1991 Jun;2(3):275-8.

Purpose: Effects on metabolism of 5-FU chemotherapy

Type of Study: Clinical series

Methods: (Gastric cancer) (n=10) Patients with gastric cancer were given PSK and tegafur for eight to 14 months from post-operative day 14. Blood samples were collected pre-operatively to determine the concentrations of tegafur and 5-FU. The same test was performed after tegafur administration was withdrawn for two weeks to eliminate 5-FU from the bloodstream.

Results: Following administration of PSK, there was no change in the plasma level of 5-FU, in any patient.

Studies Not Designed to Evaluate the Specific Effects of PSK

³⁷Munemoto Y, Iida Y, Ohata K, Saito H, Fujisawa K, Kasahara Y, *et al.* Significance of postoperative adjuvant immunotherapy after curative resection of colorectal cancers:

identification of responders incorporating the age factor. *Oncol Rep* 2004 Mar;11(3):623-35.

Purpose: Identification of responders to PSK

Type of Study: Clinical series with analysis of prognostic factors related to age

Treatment Groups: (Colorectal) Subjects (N=101) were divided into two groups based on age (less than 65 years and 65 years and older), but both groups were treated with mitomycin C, fluoropyrimidine and PSK for two years.

³⁸Koda K, Miyazaki M, Sarashina H, Suwa T, Saito N, Suzuki M, *et al.* A randomized controlled trial of postoperative adjuvant immunochemotherapy for colorectal cancer with oral medicines. *Int J Oncol* 2003 Jul;23(1):165-72.

Purpose: Survival

Type of Study: Randomized controlled study

Treatment Groups: (Colorectal) A total of 558 patients with stage II or III primary colorectal cancer underwent curative resection, and were subsequently randomized to receive either 5-DFUR and PSK or 5-FU and PSK.

²⁸Sugimachi K, Maehara Y, Ogawa M, Kakegawa T, Tomita M. Dose intensity of uracil and tegafur in postoperative chemotherapy for patients with poorly differentiated gastric cancer. *Cancer Chemotherapy and Pharmacology* 1997 Jul;40(3):233-8.

Purpose: Disease response and survival

Type of Study: RCT (not evaluable for specific PSK effects)

Treatment Groups: (Gastric cancer) (n=224) Surgery plus random assignment to either group A with Mitomycin C (MMC) and 5-fluorouracil and uracil (UFT)) plus PSK orally for one year or group B with UFT (higher dose) and MMC plus PSK.

²⁹Maehara Y, Inutsuka S, Takeuchi H, Baba H, Kusumoto H, Sugimachi K. Postoperative PSK and OK-432 immunochemotherapy for patients with gastric cancer. *Cancer Chemotherapy & Pharmacology* 1993;33(2):171-5.

Purpose: Survival

Type of Study: Retrospective review

Methods: (n=963) A total of 627 patients received postoperative chemotherapy and 336 were also given the immunomodulators PSK or OK-432 and this postoperative immunochemotherapy was more often prescribed for patients with advanced disease.

³⁰Kodama Y, Kano T, Tamada R, Kumashiro R, Okamura T, Inokuchi K. Combined effect of prophylactic lymphadenectomy and long term combination chemotherapy for curatively resected carcinoma of the stomach. *Japanese Journal of Surgery* 1982;12(4):244-8.

Purpose: Survival

Type of Study: Prospective cohorts with internal controls

Treatment Groups: (Stomach) (n=487) Of the three patient groups who had curative gastric resection with prophylactic extensive lymph node dissection (PELD), controls received no anticancer drugs, a second group received Mitomycin-C (MMC) and a third received MMC, tegafur and PSK (PLCC).

³¹Kano T, Kumashiro R, Masuda H, Tamada R, Inokuchi K. Late results of postoperative long-term cancer chemotherapy for the gastric cancer patients subjected to curative resection. *Japanese Journal of Surgery* 1983;13(2):112-6.

Purpose: Survival

Type of Study: Randomized clinical trial

Treatment Groups: (Gastrointestinal) (n=528 evaluable) All patients underwent curative gastric resection and had PLCC as a main adjuvant chemotherapy. Mitomycin-C (MMC) injection was prescribed from 1964-1971, and Mitomycin-C, FT-207 and PSK was prescribed from 1971.

³²Kano T, Tamada R, Abe Y, Hiramoto Y, Notsuka T, Shiraishi M, *et al.* Postoperative long-term cancer chemotherapy (PLCC) extends life-span of non-curatively resected patients with stage IV gastric cancer. *Japanese Journal of Surgery* 1982;12(3):201-7.

Purpose: Survival

Type of Study: Prospective cohort with controls.

Treatment Groups: (Gastrointestinal) (n=324) Patients with stage IV gastric cancer underwent a non-curative resection; the 324 eligible patients were treated with:

1. MMC, Tegafur and PSK
2. MMC (Mitomycin-C)
3. No chemotherapy

³³Kano T, Kumashiro R, Tamada R, Kodama Y, Inokuchi K. Late results of postoperative long term cancer chemotherapy for advanced carcinoma of the stomach. *Japanese Journal of Surgery* 1981;11(4):291-6.

Purpose: Survival

Type of Study: Prospective cohort with controls

Treatment Groups: (Stomach) (n=157) A total of 157 Japanese patients with advanced gastric cancer received gastrectomy and combined adjuvant chemotherapy. PLCC included intermittent iv administration of Mitomycin-C (MMC) and oral FT-207 and PSK. Controls were given MMC only during the surgery. All cases were divided into either the PLCC group or the control group.

³⁴Shibata M, Nezu T, Kanou H, Nagata Y, Kimura T, Takekawa M, *et al.* Immunomodulatory effects of low dose *cis*-Diaminedichloroplatinum (cisplatin) combined with UFT and PSK in patients with advanced colorectal cancer. *Cancer Investigation*. 2002;20(2):166-73.

Purpose: Immune effects

Type of Study: Clinic series

Treatment Groups: One group treated with cisplatin and UFT, a form of uracil and tegafur, a prodrug of 5-FU, were administered with PSK to 10 patients.

³⁵Munemoto Y, Iida Y, Abe J, Saito H, Fujisawa K, Kasahara Y, *et al.* Significance of postoperative adjuvant immunochemotherapy after curative resection of colorectal cancers: Association between host or tumor factors and survival. *International Journal of Oncology*. 2002 Feb;20(2):403-11.

Purpose: Survival

Type of Study: Clinical series with analysis of prognostic factors related to survival

Treatment Groups: One group treated with surgery plus mitomycin C, fluoropyrimidine and PSK.

³⁶Kawa K, Konishi S, Tsujiino G, Mabuchi S. Effects of biological response modifiers on childhood ALL being in remission after chemotherapy. *Biomedicine & Pharmacotherapy* 1991;45:113-6.

Purpose: Disease response

Type of Study: Prospective cohort with controls

Treatment Groups: After termination of chemotherapy, patients were treated with biological response modifiers such as *Nocardia rubra* cell wall skeleton, PSK and Bestatin or no therapy. The 20 patients treated with PSK were included in the no therapy group because "no significant difference had been observed in a previous study".

Note: The previous study referred to was not obtained for this review because it was in Japanese. An English abstract of that study reported that six of 20 patients treated with PSK relapsed compared with four of 17 with no treatment and eight out of 54 who received other biological response modifiers (N-CWS or OK-432)⁷⁰.

The complete list of full citations is available in the Reference List.

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