PSK added to standard anti-cancer therapy extends survival:

Randomised trials and meta-analysis

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Abstract

Polysaccharide-K(PSK) is a unique immunotherapeutic agent extracted from the mycelia of the *Coriolus versicolor* strain, an edible mushroom belonging to the Basidiomycete family. PSK is a proteoglycan of approximately 100kDa with a major β-1-4-glucan portion bound to the protein. PSK is a potent immuno-stimulator of various components of the immune system both *in vitro* and *in vivo.* This has been documented as the basis for its antitumour activity through its capacity to regulate the host immune response and so to inhibit immune suppression caused by cancer treatment. Outlined in this presentation are summaries of several randomised clinical trials and their meta-analysis which have demonstrated that PSK has surprisingly marked potential as an adjunctive immunotherapeutic agent, with impressive results seen in adjuvant chemotherapeutic and radiation treatment of colorectal, gastric, breast, oesophageal, nasopharyngeal and lung cancers. Five-year overall survival (OS) and disease-free survival (DFS) endpoints in most cancers were clinically significant for chemotherapy or/+ radiotherapy plus PSK compared with those for standard treatments. In colorectal cancer, patients with Stage II/III disease benefited from chemotherapy plus PSK after surgery (Stage II disease OS p=0.056; DFS p=0.016, Stage III disease OS p=0.002; DFS p=0.003). A meta-analysis of data from three clinical trials (n=1094) was highly significant (OS, p<0.006; DFS p <0.003). In other cancers, PSK can improve survival or disease-free survival or both when used in cancer treatment regimens (gastric cancer OS p=0.044; DFS p=0.047, HLA-B40+ breast cancer DFS p=0.05, non-small cell lung carcinoma p =0.0001). These studies have documented the efficacy and tolerability of PSK with the proven benefits to extend survival and quality of life. The findings make PSK ideally suited for cancer treatment regimens as a combination therapy with either surgery, chemotherapy and/or radiotherapy.

Introduction

The healing properties of mushrooms have been known since human recorded history. In Japan, China and Korea, mushroom-derived preparations are still used in modern clinical practice. Recent scientific and clinical studies have shown that the healing properties are due to the immunological effects of beta-D-glucans isolated from the cell walls of mushrooms. Beta-D-glucans exist as long-chain biopolymers of monopolysaccharides with glycodic linkages to form a triple helical structure or they are bound to a protein core to form a proteoglycan. These molecules have been shown to have anti-tumour properties through their capacity to activate key humoral and cellular components of the host immune system. In particular, beta-D-glucan induces cellular cytotoxicity against tumour cells by binding to complement receptor type 3 (CR3) on immune effector cells such as neutrophils, macrophages and natural killer cells (Kidd, 2000). Among the mushroom substances, the proteoglycan PSK from *Coriolus (or Trametes) versicolor*, an edible mushroom belonging to the Basidiomycete family, has proceeded to clinical trials conducted mostly in Japan and China. It has a molecular weight of 100 kDa and is highly soluble in water. Taken orally, PSK has been proven to be effective as an adjunctive with chemotherapy and/or radiotherapy in patients with cancers of the colon, rectum, stomach, oesophageal, lung and breast. Increase in overall survival and disease-free survival rates have been reported in patients given PSK and no significant side effects due to PSK have been reported. A recent study on the effects of PSK on immune parameters has reported that the omission of PSK from standard cancer treatment regimen was a significant risk factor for recurrence of metastasis in patients with colorectal cancer (Ohwada et al. 2006). Natural killer cells and high serum immunosuppressive acidic protein values were possible PSK response predictors. Taken together, these studies seemed to suggest that PSK is an effective immuno-modulator which could be used as an adjunctive immunotherapeutic agent in standard cancer treatment using chemotherapy and/or radiation therapy to improve survival rate and quality of life. However, many studies reporting treatment efficacy have a number of deficiencies including study design, not randomised-controlled or insufficiently powered. The purpose of this study was to review in a systematic manner the efficacy and safety of PSK as an adjunctive in clinical trials of conventional therapies for cancer.

Methods

The MEDLINE (1970-2006) was searched using medical subject heading terms for cancer therapies along with free-text terms such as "*Coriolus (Trametes) versicolor*", or "protein-bound polysaccharide PSK" The results were linked to cancer terms ('tumour' or carcinoma'). The search was designed to maximise precision.

The criteria for including studies are as follows:

We included reports of conventional cancer treatments that involved administration of PSK with chemotherapy or/and radiotherapy in patients diagnosed with cancer. The aim of the treatment must have been to extend survival rather than to control symptoms. Trials that studied cancer patients at any stage were included.

Trials were included if they explicitly described them phase I or II/III or phase III and the end-point was survival. Study regimens that included both conventional treatments and PSK were included if they compared two groups of patients receiving similar treatment other than the addition of PSK in one group.

We excluded trials from China or Japan on the grounds that such trials translated into English could lead to loss of information on the design and the methodologies. For this reason, we included only trials that were published in full text in the West.

Efficacy end-points were categorised as: disease-free and overall survival. We document the rationale for the dose on the basis that it is used in clinical practice or public use.

Results

Almost exclusively, the trials have been carried out in Japan. There were 15 eligible articles with trials that met the criteria of a phase III. Two articles were reported on more than one occasion when the data were re-analysed for tumour markers and HLA-B40 antigen. There was one meta-analysis of colorectal cancer. There were 11 randomised controlled, 2 prospective and 2 retrospective studies which assessed both overall survival and disease-free survival in a majority of cases. The following tables summarise the methodological parameters and the results of the trials for various cancers treated with conventional therapies and combined with PSK.

PSK and colorectal cancer

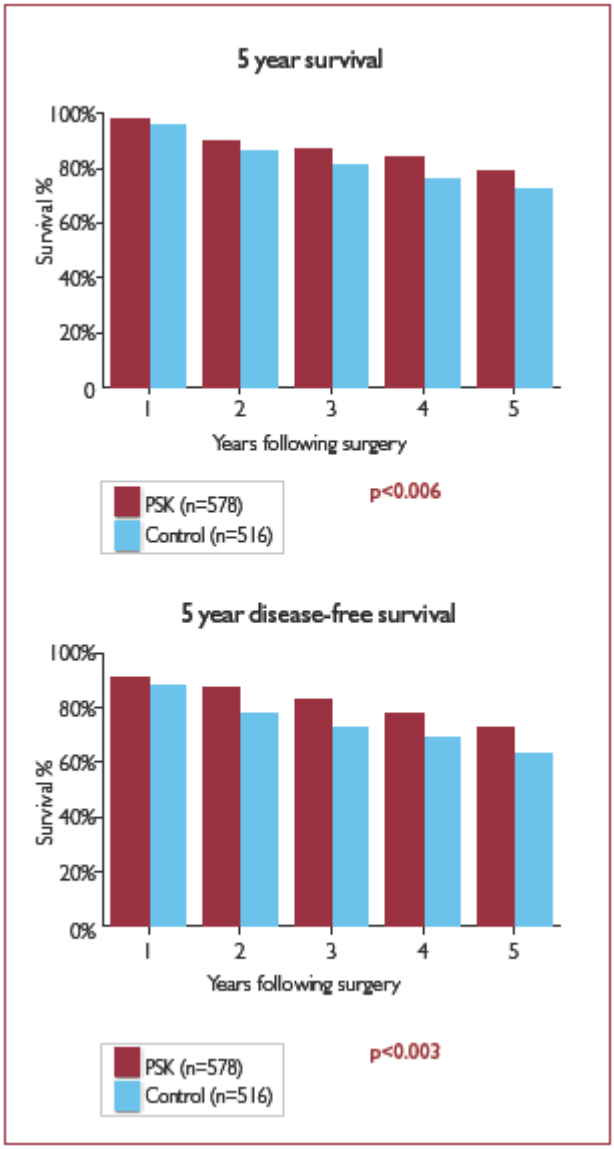


Fig. 1 Bar Plot - Meta-analysis of three randomized controlled trials for survival in 1094 colorectal cancer patients (Sakamoto et al. Cancer Immunol Immonother 2006; 55:404-411).

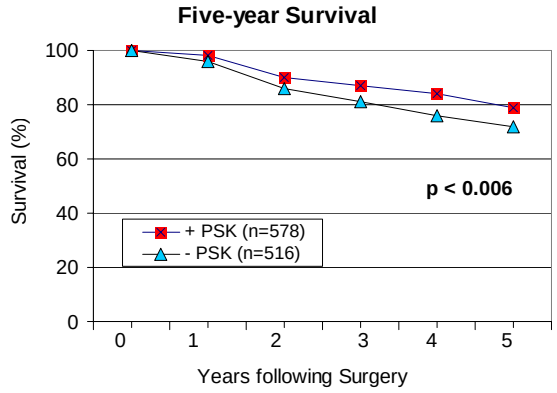
PSK and colorectal cancer

PSK was assessed for its potential activity in patients with advanced colorectal cancer. Table 1 (on next page) shows the trials in which patients were randomised into two groups and then put through surgery and chemotherapy (oral pyrimidines) plus or minus PSK given orally at 3 grams/day for the duration of the trial in most cases or in one case a step-wise decreasing dosage of 3 grams/day for 2 months, 2 grams/day for 24 months then 1 gram/day thereafter.

The overall combination regimen consistently and significantly improved survival and the disease-free at five- to eight-year period compared with chemotherapy alone.

A recent meta-analysis combining data from three randomised trials with a total of 1094 colorectal patients indicated a significant improvement in survival as a result of chemotherapy with PSK (*P*=0.006 for survival and 0.003 for disease-free survival) (Fig. 1). A reduction of the death rate by 29% (OR=0.71, 95% CI: 0.55-0.90) and of recurrence by 28% (OR=0.72, 95% CI: 0.58-90) were significant. The results suggest that chemotherapy with PSK offers a significant advantage over chemotherapy alone.

Fig. 1 – Survival Curve - Meta-analysis of three randomized controlled trials for survival in 1094 colorectal cancer patients (Sakamoto et al. Cancer Immunol Immonother 2006; 55:404-411).



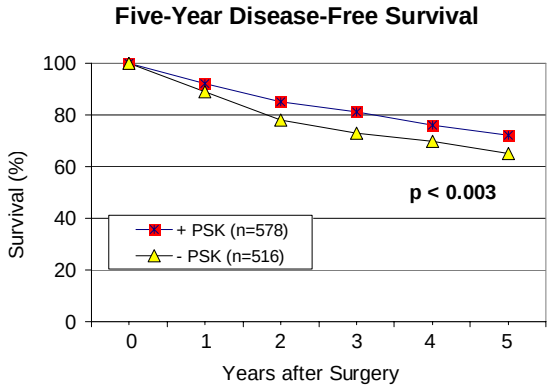


Table I. Randomised Controlled Trials for Colorectal Cancer

Ref.	Patients	Stage	Treatment	Results
Torisu (1990)	56 cases 55 controls	Advance (II/III)	1. Surgery + placebo 2. Surgery + PSK (3gm/day for 2 months; 2g/day for 24 months; 1 gm/day thereafter)	8-yrs overall survival rate significant in the PSK group 25% (14/56) *vs.* 8%(4/55), p<0.05) and in the disease-free group, 39.2%(22/56) *vs.* 25%(13/55), (p<0.05) versus the control group.
Mitomi (1992)	Multicentre 221 cases 227 controls	Various	1.Surgery + Chemo 2.Surgery + Chemo+ PSK (3g/day for 3 years)	Disease-free interval and overall survival significantly better in the PSK group (p<0.05 for both)
Ohwada (2003)	Total 207 134 cases 67 controls 6 withdrew	Primary (II/III)	1. Chemo 2.Chemo+ PSK (3g per day for >2 yrs)	Overall survival rate higher in the PSK group but not significant (p=0.21). Three-year disease-free survival significantly higher in the PSK group 80.6%(108/134) *vs.* 68.7%(46/67) than in the control group, (p=0.02). Stage III carcinoma: three-year overall survival in the PSK group significantly higher 83%(44/53) *vs.* 59.3%(16/27), p=0.02) than in the control group.
Ohwada (2004)	Total 205 137 cases 68 controls	Primary (II/III)	All patients received Mitomycin-C post-surgery. 1. Chemo 2. Chemo + PSK (3g/ day) Both treatments for 2 yrs	Five-year overall survival and disease-free survival significantly higher in the PSK group 81.8%(112/137) *vs.* 72.1%(49/68), p= 0.056 and 73%(100/137) *vs.* 56.6%(40/68), p = 0.016 than the control group, respectively Stage III carcinoma: Overall five-year survival and disease-free survival significantly higher in PSK group 74.6%(41/55) *vs.* 46.4%(13/28), p <0.003 and 60%(33/55) *vs.* 32.1%(9/28), p<0.002) in the control group, respectively.
Ito (2004)	Colon cancer with lymph node metastasis Total 441 220 cases 221 controls	Dukes A:7% B:45.5% C:47.3%	All patients received chemo after surgery for 3-4 weeks, then 10 courses of treatment. 1. PSK 4 weeks then 4 weeks chemo. 2. 4 weeks rest then 4 weeks chemo.	Seven- year survival rate until death significantly higher in the PSK group (p=0.019). Overall seven-year survival or disease-free rates were not significant.
Kudo (2002)	Colorectal 58 total 48 PSK 10 controls	II/III	After curative surgery 1. PSK + Chemo 2. Control: chemo Limitation: low control numbers	3-year survival significantly higher *vs.* control (74.3% *vs.* 40%, p=0.0467). Serum type IV collagen levels lower in the treatment group than in the control group, p = 0.0072, indicating basement membrane destruction.

PSK and breast cancer

PSK also showed to have efficacy in the adjuvant treatment of cancer (Table II). One trial involving 227 patients were randomised to receive chemotherapy with or without PSK following curative resection of breast cancer with a vascular invasion in the primary tumour and/or in the metastatic lymph node. A trend towards improvement in 10-year overall survival in the PSK group which has a better prognosis than the control group with chemotherapy alone but the difference was short of statistical significance. There was also a trend toward disease-free survival being the best prognosis in the PSK treatment arm but again the difference was not significant. However, subset analysis based on HLA-B40 antigen showed that patients who had taken PSK and were positive for HLA-B40 had almost a double overall survival of HLA-B40 negative patients at 10-years. Taken together, this study concluded that chemotherapy with PSK improves the prognosis of operable breast cancer patients with vascular invasion and that patients who are positive for HLA-B40 might benefit more from chemotherapy with PSK.

Table. II Randomised controlled trials for breast cancer

Refs	Patients	Stage	Treatment	Results
Toi (1992)	914 cases Standard or Radical mastectomy	IIA, IIB, III	1.Patients(ER+ tumours) chemo+/- tamoxifen 2.Patients(ER^{-} tumour) Chemo +/- PSK	Longer overall survival for patients in Stage IIA T2N1 cancer ER^{-} and node-negative treated with chemo + PSK compared with other ER^{-} subgroups without PSK.
Lino (1995)	227 cases operable breast cancer with v+ and/or n+ involvement		Chemo (n=77) Chemo + Levamisole (n=76) Chemo + PSK (n=74)	Risk ratio lower in the chemo+ PSK group. However, overall and disease- free survival rates were not significant versus controls. 81.1%(60/74) *vs*. 64.6%(49/77); p=0.0739 and 74.1%(55/74) *vs*. 64.6%(49/77), p=0.16, respectively. ****See re-analysis of results based on HLA-status of these patients below**
Yokoe (1997)	134 cases typed as HLA-A, HLA-B and HLA-C Total six subtypes	Operable with v+ and/or nv+	Previously randomised into two groups: 1. Chemo 2. Chemo +PSK Each group stratified by HLA type B40+ or B40-.	Disease-free survival at 5 and 10 Years for chemo + PSK group: HLA-B40+: 100% (9/9) and 100% (9/9), respectively. HLA-B40- : 76%(10/13) and 55%(7/13), respectively. Significant difference at p =0.05.

v+, vascular invasion; n+, lymph node involvement; 5-fluorouracil, cyclophosphamide, mitomycin;, prednisolone; LMS; levamisole, ER, estrogen receptor

PSK and gastric cancer

PSK has also been used with conventional therapies for the treatment of other cancers (Table III and Table IV).

A landmark trial comparing the use of PSK combined with chemotherapy to chemotherapy alone in patients who had undergone curative resection of primary tumour stage I-IV gastric carcinoma was published in the Lancet. Patients were given orally a standard dose of 3 grams of PSK per day for 4 weeks alternating with 5-fluoruracil for 10 cycles. Five-year follow-up time showed that PSK improved significantly both overall survival and disease-free survival rates in the PSK treatment arm. Interestingly, a review of 872 gastric cancer cases showed that patients with raised serum levels of carcinoembryonic antigen (CEA) as well as other acute phase reactants such as immunosuppressive acidic protein (IAP), acid-soluble glycoprotein, α_1-antichymotrypsin and sialic acid benefited most from chemotherapy with PSK.

Table III. Randomised controlled trials for gastric cancer

Ref	Site	Patients	Stage	Treatment	Results
Nakazato (1994) Randomised controlled trial	Stomach	124 cases 129 controls	I-IV	Surgery + chemo Surgery + chemo + PSK	PSK significantly improved in both five-year overall survival 73%(90/124) *vs.* 60%(77/129); p=0.044) and disease-free survival (70.7%(87/124) *vs.* 59.4%(77/129); p=0.047) compared with the placebo group.
Ogoshi(1998) Retrospective study	Stomach	Review of 872 cases based on acute phase reactants (CEA, sialic acid, acid-soluble glycoproteins, immunosuppressive proteins, α1-antichymotrypsin)	I-IV	Surgery + Chemo with or without PSK	Patients with elevated levels of acute phase reactant benefited most from chemotherapy with PSK

PSK and oesophageal cancer

A multi-center randomised study of 158 oesophageal cancer patients who underwent radical oesophageal resection followed by radiotherapy had 4 treatment arms consisting chemotherapy with or without PSK, or no chemotherapy with or without PSK. Five-year survival rates were significantly better in the PSK group plus radiation and/or chemotherapy compared with the control group.

Stratification according to acute phase reactants, patients with elevated serum levels of IAP, sialic acid and $\alpha -1$ anti-chymotrypsin had better 5-year survival. This study concluded that chemotherapy with PSK achieved better survival in oesophageal cancer, especially those with elevated levels of one or both of these tumour markers.

Table IV Clinical trials for oesophageal cancer

Ref	Site	Patients	Stage	Treatment	Results
Ogoshi (1995) Randomised controlled trial	Oesophagus	85 cases 73 controls		Radiation and/or Chemo +/- PSK	Overall five-year survival significantly better in the PSK group with radiation, 42.2%(36/85) *vs.* 35.7%(26/73) in the control group, p =0.025. Five-year survival significantly better in the PSK group with chemo plus radiation, 39.4%(19/49) *vs.* 31.5%(13/41) in the control group, p = 0.0404).
Ogoshi (1995) Retrospective analysis	Oesophagus	158 completed treatment Stratified according to pre-surgery acute phase reactant (APT) levels of sialic acid (SA) and α–1-chymotrypsin.		Surgery plus: 1. Radiation with or without PSK 2. Radiation + chemo with or without PSK	5-year survival: 1. Normal APT-no difference 2. Abnormal APT – PSK better (55% *vs.* 26%, p =0.008) 3. Abnormal SA-PSK better (58.3% *vs.* 33%, p =0.07)

PSK and other cancers

Patients (n=185) with stage I-III non-small cell lung cancer selected to receive chemotherapy with PSK (3 g/day) 2 weeks on and 2 weeks off in repeated cycles following radiotherapy had better five-year survival rates for stage II (39%), stage III (22%) than those in the control group (5%). However, this may not be clinically useful since the study was not randomised and contained a patient selection bias which compared the PSK group with a group already not doing well at the start of the study.

No statistically significant benefit in duration of remission or survival was demonstrated for leukemia using PSK plus chemotherapy. However, there was an indication that PSK prolonged the 50% remission period compared with treatment without PSK but this was short of significance.

Table V. Clinical trials with PSK for other cancers

Ref.	Sites	Patients	Stage	Treatment	Results
Hayakawa (1993) Prospective controlled trial	Lung	62 cases 123 controls	I-III	Radiation With/without PSK 3g/dya for two weeks followed by 2 weeks rest	Five-year survival rates (cases *vs.* placebo) 27%(17/62) *vs.* 7%(8/123) p=0.0001; Stage I/II carcinoma: 39% (8/22) *vs.* 16% (6/42), p=0.005; Stage III carcinoma: 32%(7/32) *vs.* 5%(2/46), P=0.004.
Ohno (1984) Prospective randomised	Myelogenous leukemia	36 cases 31 controls	Acute	Chemo +/- PSK	No significant difference in duration of remission or survival at 12, 18 and 24 months (p=0.105). PSK prolonged the 50% remission period by 418 days (885 days vs. 467 days)

PSK side effects

No death, toxic symptoms or obvious pathological and haematological changes were observed after long period of dosing with PSK in all trials. Treatment arms with PSK were clinically well-tolerated and compliance was good.

Conclusion

An evaluation of the clinical usefulness of PSK, a protein-bound polysaccharide immunomodulator isolated from *Coriolus (Trametes) versicolor* mushrooms was conducted. A large number of phase III clinical trials of conventional cancer therapies with PSK were identified.

When administered orally with conventional treatments, PSK is beneficial for preventing recurrences of cancer and in prolonging survival for patients who have undergone curative resection.

PSK has no toxic effects and is clinically well-tolerated.

The benefits of a combination of conventional cancer therapies with PSK may be due to the restorative effect of PSK in patients whose immunity has been suppressed by surgery and subsequent chemotherapy and/or radiotherapy.

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