Preoperative CEA and PPD Values as Prognostic Factors for Immunochemotherapy Using PSK and 5-FU*

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Abstract. Purpose: Immunochemotherapy using PSK, used as postoperative adjuvant chemotherapy for colorectal cancer in Japan, is a treatment that depends on the immuno-competence of the host. Therefore, we analyzed the data of Hokuriku district conducted by the CIP study group to compare the long-term survival for preoperative CEA level and PPD reaction. Patients and Methods: Between February 1991 and March 1993, 87 patients with primary colon cancer and macroscopic lymph node metastasis (macroscopic Dukes’ C) underwent macroscopic curative resection. The patients were randomly allocated to receive 5-FU/PSK therapy or 5-FU alone. The 7-year disease-free survival (DFS), 7-year overall survival (OS) and 7-year cancer death survival (CDS) were compared using the preoperative CEA levels and PPD values. Results: In cases with preoperative CEA level ≥3.0 ng/mL, the 7-year DFS, 7-year OS and 7-year CDS were significantly better in the PSK group (85.7, 90.5, 90.5%) than in the control group (52.4, 52.4, 57.1%; p=0.019, 0.007, 0.014). In cases with preoperative PPD level <19.0 mm, the 7-year DFS, 7-year OS and 7-year CDS were significantly better in the PSK group (85.7, 85.7, 89.3%) than in the control group (56.7, 60.0, 63.3%; p=0.018, 0.036, 0.028). Recurrence was significantly less in the PSK group. The DFS tended to be superior in the PSK group (87.4%) compared to the control group (69.9%) for hematogenous metastasis. Conclusion: The present study demonstrated that preoperative CEA and PPD, that can be measured easily in the clinical setting, may be effective indicators of postoperative adjuvant immunochemotherapy using PSK.

In the early nineties, the 5-fluorouracil (5-FU)/levamisole combination was considered to be the standard postoperative adjuvant chemotherapy for colon cancer (1). With the subsequent development of leucovorin (LV), 5-FU/LV became globally accepted as the standard therapy. According to the review of postoperative adjuvant therapy for colon cancer reported by Chau et al. at the 38th ASCO Meeting in 2002, the 3- to 5-year disease-free survival (DFS) with 5-FU/LV therapy was 59-74%, and the 3- to 5-year overall survival (OS) was 65-83% (2).

In Japan, immunochemotherapy using PSK in combination with fluoropyrimidines is used widely as postoperative adjuvant chemotherapy for colorectal cancer. PSK is a protein-bound polysaccharide isolated from the mycelium of *Coriolus versicolor* and has a putative mean molecular weight of 100 kD. PSK has been confirmed to be effective for gastric cancer (3, 4), colorectal cancer (5, 6, 7) and small cell lung cancer (8), and is being used widely in Japan as a treatment for these cancer groups.

Recently, Ito et al. reported the final results of a randomized clinical trial on alternate PSK and 5-FU therapy for Dukes’ C colon cancer (the CIP study, upon which the present study is based), with a 7-year cancer death survival (CDS) of 83.4% (7). In addition, Ohwada et al. reported the results of a randomized controlled trial of PSK and...
tегафур/урацил (УФК) комбинационная терапия для стадий II и III
колоректального рака, с 5-летним DFS 73.0% и 5-летним OS
81.8% (5). Эти результаты указывают на то, что 5-ФУ/ПСК или УФК/ПСК
комбинационная терапия обеспечивает выживаемость, сопоставимую с той
5-ФУ/ЛВ. Однако, иммунонуклеотидотерапия является лечением,
что зависит от иммунокомпетентности организма. Индикатор,
что точно идентифицирует пациентов, кто ответит на
ПСК требуется.

В исследовании проводилось случайное контролируемое исследование
группы CIP в Чубо и Хокурiku областях в Японии. Протокол
проведения исследования был независимым в каждой области.

В частности, хотя хирургические техники более однородны
в области Хокурiku, данные из разных областей были
использованы для сравнения 7-летнего DFS, 7-летнего OS и 7-летнего CDS
для предоперационного CEA уровня и ППД в качестве
прогностических маркеров, которые можно измерить в клинических условиях.
Этот подход позволил установить, что предоперационный CEA и ППД
являются эффективными маркерами постоперационной адъювантной
терапии в группах ПСК и фторопirimидинов.

Материалы и Методы

История. Эта работа была проведена под руководством груп
CIP, и все результаты вместе с детальной описанием
студии, которую уже предложили Ito et al. (7).

Пациенты, которые получили не менее трех сессий 5-ФУ
индукционную терапию, были зарегистрированы и случайно
выделены либо в группу ПСК (n=43) или контрольную (n=44).

Постоперационная терапия включала 48-часовую инфузию
5-ФУ (1000 мг/м2/24 ч х 2) ежедневно в течение 3
4 недель. В неделю 4, ПСК (300 мг/сут) была инъекция для 4 недель
в группу ПСК, и эта процедура была продолжена
в течение курсов альтернативной терапии. Тен курсы
диагностических процедур были выполнены за счет
контрольной группы. Группа контроля получила 10 курсов
итервальной проводимой терапии с 5-ФУ, и
не получала лечения во время приема ПСК.

Послеоперационное наблюдение выполнялось ежемесячно в течение
18 месяцев после операции, и затем каждые 3 месяц
до 7 лет. Рекуррентность определялась в ходе наблюдения.

Установка пороговых значений для предоперационного CEA уровня
и предоперационного PPD значения. 
Предоперационные CEA уровни, меняющиеся от 2.0 до 15.0 нг/мл,
были установлены пороговые значения в 1 мг/мл вкrementах. Используя
справедливый лог-ранк тест, были сопоставлены случаи,
были определены пороговые значения при 0.05 уровне статистической значимости.

Предоперационные PPD значения, меняющиеся от 6.0 до 20.0 мм,
были установлены пороговые значения в 1 мм вкrementах. Используя
справедливый лог-ранк тест, 7-летний DFS контрольной
группы и группы ПСК были сопоставлены, чтобы установить пороговые значения
для случаев, при которых пороговые значения
еще меньше, чем пороговые значения
в группах CEA уровни, которые были установлены как
пороговые значения для прогнозирования
анализа.

Предоперационные PPD значения, меняющиеся от 6.0 до 20.0 мм,
были установлены пороговые значения в 1 мм вкrementах. Используя
справедливый лог-ранк тест, 7-летний DFS контрольной
группы и группы ПСК были сопоставлены, чтобы установить пороговые значения
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еще меньше, чем пороговые значения
в группах CEA уровни, которые были установлены как
пороговые значения для прогнозирования
анализа.

В процедуре статистического анализа учитывались все случаи,
которые соответствовали критериям включения,
и не было статистически значимых различий в факторах
включения.

Результаты

История. Всего 87 случаев зарегистрировано в группе CIP
в Хокурiku области в Японии. Четыре случая в группе контрольной
и 43 случая в группе ПСК были необъяснимыми.

Единственный случай в контрольной группе и 2 случая в
группе ПСК имели неоперабельные изъятия. В конце концов, 43 случая в
группе контрольной и 41 случая в группе ПСК были
объектами. Таблица показывает
фон групп. Два группы не
были статистически значимо
му значением факторов.

Восстановление 7-летнего DFS было проведено
используя коэффициентов риска Cox модельные
модели для всех вариантов
гендер, возраст, физическое
состояние, прошлые заболевания,
PPD уровень, CEA уровень,
хистологический тип, глубина
вторичные хирургические
процедуры и управление.

В ходе анализа коэффициентов риска CVS была
выбрана 7-летняя выживаемость
и 7-летнее OS в качестве
прогностических факторов
для развертывания исследования
CEA уровня и фторопirimидинов.

Мультивариантный анализ 7-летнего DFS был выполнен
используя массовую модель риска Cox
для всех вариантов
гендер, возраст, физическое
состояние, прошлые заболевания,
PPD уровень, CEA уровень,
хистологический тип, глубина
вторичные хирургические
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В ходе анализа коэффициентов риска CVS была
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и 7-летнее OS в качестве
прогностических факторов
для развертывания исследования
CEA уровня и фторопirimидинов.

Статистический анализ. Условия для включения пациентов были
представлены в соответствии с принципом
намеренной терапии. Пациенты включались,
предварительно сопоставляются с
многочисленными заболеваниями,
и 2 случая в группе ПСК имели
необъяснимые результате.

В конце концов, 43 случая в
группе контрольной и 41 случая в
группе ПСК были
объектами. Таблица 1
показывает фон группы. Два группы не
были статистически значимо
му значением факторов.

Восстановление 7-летнего DFS было проведено
используя коэффициентов риска Cox модельные
модели для всех вариантов
гендер, возраст, физическое
состояние, прошлые заболевания,
PPD уровень, CEA уровень,
хистологический тип, глубина
вторичные хирургические
процедуры и управление.

В ходе анализа коэффициентов риска CVS была
выбрана 7-летняя выживаемость
и 7-летнее OS в качестве
прогностических факторов
для развертывания исследования
CEA уровня и фторопirimидинов.
Figure 2 shows the 7-year DFS and 7-year OS for cases having CEA levels below (<3.0 ng/mL) and above (≥3.0 ng/mL) the cut-off value. The 7-year DFS was significantly better \((p=0.019)\) in the PSK group (85.7\%) than in the control group (52.4\%) and the hazard ratio of the PSK group was 0.269 in cases with preoperative CEA level ≥3.0 ng/mL (Figure 2b), whereas no significant differences in 7-year DFS (control group: 68.2\%, PSK group: 75.0\%; \(p=0.644\)) were observed between the two groups in cases with preoperative CEA level <3.0 ng/mL (Figure 2a). The 7-year OS was significantly better \((p=0.007)\) in the PSK group (90.5\%) than in the control group (52.4\%) and the hazard ratio of the PSK group was 0.206 in cases with preoperative CEA level ≥3.0 ng/mL (Figure 2d), whereas no significant differences in 7-year OS (control group: 77.3\%, PSK group: 80.0\%; \(p=0.890\)) were observed between the two groups in cases with preoperative CEA level <3.0 ng/mL (Figure 2c). The 7-year CDS was also significantly better

<table>
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<th>Table I. Patients' background of the eligible cases.</th>
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well: well-differentiated adenocarcinoma
mod: moderately-differentiated adenocarcinoma
(p=0.014) in the PSK group (90.5%) than in the control group (57.1%) and the hazard ratio of the PSK group was 0.224 in cases with preoperative CEA level ≥3.0 ng/mL, whereas no significant differences in 7-year CDS (control group: 77.3%, PSK group: 85.0%; p=0.596) were observed between the two groups (data not shown). In both groups with preoperative CEA level <3.0 ng/mL and ≥3.0 ng/mL, no significant differences in the background factors were observed between the control group and the PSK group.

**Prognosis analysis by preoperative PPD value.** Table III shows the results of comparison of the cut-off values of preoperative PPD value for the range of 6.0 to 20.0 mm. At the cut-off value of 19 mm, the p value was smallest for cases below cut-off. Therefore subsequent analysis was performed using the cut-off value of 19 mm.

Figure 3 shows the 7-year DFS and 7-year OS for cases having PPD values below (<19.0 mm) and above (≥19.0 mm) the cut-off value. The 7-year DFS was significantly better (p=0.018) in the PSK group (85.7%) than in the control group (56.7%) and the hazard ratio of the PSK group was 0.317 in cases with preoperative PPD level <19.0 mm (Figure 3a), whereas no significant differences were observed in the 7-year DFS (control group: 69.2%, PSK group: 69.2%; p=0.897) between the two groups in cases with preoperative PPD level ≥19.0 mm (Figure 3b). The 7-year OS was significantly better (p=0.036) in the PSK group (85.7%) than in the control group (60.0%) and the hazard ratio of the PSK group was 0.350 in cases with preoperative PPD level <19.0 mm (Figure 3c), whereas no significant differences were observed in the 7-year OS (control group: 76.9%, PSK group: 84.6%; p=0.573) between the two groups in cases with preoperative PPD level ≥19.0 mm (Figure 3d). The 7-year CDS was also significantly better (p=0.028) in the PSK group (89.3%) than in the control group (63.3%) and the hazard ratio of the PSK group was 0.308 in cases with preoperative PPD level <19.0 mm, whereas no significant differences were observed in 7-year CDS (control group: 76.9%, PSK group: 84.6%; p=0.573) between the two groups (data not shown). In both groups, with preoperative PPD values <19.0 mm and ≥19.0 mm, no significant differences in the background factors were observed between the control group and the PSK group.

No significant differences in 7-year DFS, OS and CDS were observed between the control group and the PSK group in cases with both low CEA levels and high PPD reaction (control group: 71.4%, 85.7%, 85.7%, PSK group: 60.0%, 80.0%, 80.0%; p=0.774, 0.854, 0.854, respectively), although both the patient numbers were small (control group: n=7, PSK group: n=5). On the other hand, the 7-year DFS, OS and CDS were significantly better in the PSK group than in the control group in cases with high
CEA levels and/or low PPD reaction (control group: 58.3%, 61.1%, 63.9%, PSK group: 83.3%, 86.1%, 88.8%; \( p = 0.021, 0.019, 0.015 \), respectively).

Recurrence. Recurrence was found in 15 cases in the control group and 6 cases in the PSK group, being significantly fewer in the PSK group (\( p = 0.04 \)). By site of metastasis, liver metastasis was observed in 6 cases in the control group and 1 case in the PSK group, lung metastasis in 4 cases in the control group and 2 cases in the PSK group, lymph node metastasis in 1 case in each in the control and PSK groups, peritoneum metastasis in 3 cases in the control group and 1 case in the PSK group, and ovary metastasis in 1 case in each in the control and PSK groups; with no significant differences between the two groups for all metastatic sites.

Liver metastasis and lung metastasis were grouped as hematogenous metastasis and others as non-hematogenous metastasis, and the 7-year DFS was compared (Figure 4). For non-hematogenous metastasis, the DFS was not significantly different (\( p = 0.446 \)) between the control group (80.4%) and the PSK group (87.1%) (Figure 4a). For hematogenous metastasis, the DFS tended to be superior (\( p = 0.066 \)) in the PSK group (87.4%) compared to the control group (69.9%), and the recurrence hazard ratio of the PSK group was 0.409 (Figure 4b).

Discussion

In the early nineties, the 5-fluorouracil (5-FU)/levamisole combination was considered to be the standard postoperative adjuvant chemotherapy for colon cancer (1). With the subsequent development of leucovorin (LV), 5-FU/LV became globally accepted as the standard therapy. According to the review of postoperative adjuvant therapy for colon cancer reported by Chau et al. at the 38th ASCO Meeting in 2002, the 3- to 5-year disease-free survival (DFS) with 5-FU/LV therapy was 59-74%, and the 3- to 5-year overall survival (OS) was 65-83% (2).

In Japan, clinical studies have been conducted to examine the usefulness of immunochemotherapy in combination with PSK, a biological response modifier (BRM) developed in Japan, for the treatment of colorectal cancer. In the report of Mitomi et al., who treated stage III colorectal cancer with 5-FU/PSK therapy, the 5-year DFS was 72.3% and 5-year OS was 78.5%, while the 5-year DFS for colon cancer alone was 80.1% (6). Ohwada et al. used UFT/PSK to treat stages II and III colorectal cancer and achieved 5-year DFS of 73.0% and 5-year OS of 81.8% (5). In the final report by the CIP study group on macroscopic Dukes’ C colon cancer, upon which the present study is based, alternate 5-FU/PSK therapy yielded a 7-year DFS of 74.1%, a 7-year OS of 79.6%, and a 7-year CDS of 83.4% (7). Our results were 80.5%, 84.5% and 87.7%, respectively, and also reproduced the efficacy of 5-FU/PSK therapy for colon cancer.

However, PSK is a BRM that exhibits antitumor effects mainly through the immune functions of the cancer-bearing host. This implies that the beneficial effect of the therapy largely depends on the host factors. In the present study, we examined the factors that may potentially predict the prognosis of 5-FU/PSK therapy. The preoperative CEA level and preoperative PPD value were identified as strong candidates as prognostic factors. When the cut-off point of...
preoperative CEA level was set at 3.0 ng/mL, cases in the PSK group with CEA ≥3.0 ng/mL showed significantly more favorable 7-year DFS, OS and CDS than those in the control group. Furthermore, when the cut-off point of preoperative PPD value was set at 19.0 mm, cases in the PSK group with PPD <19.0 mm showed significantly superior 7-year DFS, OS and CDS to those in the control group.

The involvement of preoperative CEA level in immunochemotherapy using PSK has been reported by Munemoto et al. (9). In their study, patients who underwent curative resection for colorectal cancer were treated with fluoropyrimidine/PSK as adjuvant therapy, and the patients were stratified into two groups by the preoperative CEA level of 8.0 ng/mL. The 5-year OS in patients with CEA <8.0 ng/mL was 80.0% and was significantly lower than the rate of 37.5% in patients with CEA ≥8.0 ng/mL. However, these results were obtained by analysis within a single arm. In contrast, our present study was a comparison between two arms; PSK treatment and control treatment without PSK. Our results showed that when the preoperative CEA level is above 3.0 ng/mL, the survival advantage of PSK is promoted. Medoff et al. reported that an immunosuppressive factor existed in malignant ascites was released from human lymphocyte by CEA stimulation (10, 11). PSK has been shown clinically to suppress immunosuppressive substances that increase in the cancer-bearing state, such as immunosuppressive acidic protein (IAP) (12) and immunosuppressive substance (IS) (13). These observations may suggest that in patients with high CEA level, PSK relieves the CEA-induced immunosuppression and contributes to prolong survival. In patients with low CEA level, the contribution of relieving immunosuppression by PSK is relatively small and, therefore, the difference may not be observable in long-term results.

The PPD reaction is delayed-type hypersensitivity and is caused by various cytokines such as migration inhibition factor (MIF) secreted from T-cells activated by PPD (14). The involvement of the PPD reaction has been reported by Tamada et al. in a histological study of curatively resected gastric cancer (15). In their study, a PPD reaction of 10 mm or above was rated as positive and a reaction less than 10 mm as negative. When 4-year OS was compared between chemotherapy (MMC+FT) and immunochemotherapy (MMC+FT+PSK), there was no significant difference between the two groups in PPD-negative cases, but the 4-year OS was significantly higher for immunochemotherapy using PSK (78.6%) compared with chemotherapy alone (70.3%) in PPD-positive cases, showing improvement in long-term results. These results show that the survival advantage of PSK may be expected in patients with preserved immune capacity to an extent that the PPD intradermal reaction can be elicited. Based on these results, we also adopted PPD intradermal reaction as a potential prognostic factor in the present study. Using the evaluation criteria of positivity and negativity based on a 10-mm reaction, we were not able to detect a difference between the control and PSK groups (Table III). No significant differences in 7-year DFS, OS and CDS were observed at the 10 mm PPD reaction within the control group (DFS: 60.0% vs 60.9%; p=0.974, OS: 65.0% vs 65.2%; p=0.994, 15%

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<th>Preoperative PPD (mm)</th>
<th>Control group &lt; cut-off value</th>
<th>PSK group</th>
<th>p-value</th>
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Stratified log-rank test adjusted by Dukes stage

Table III. Comparison of the cut-off values of preoperative PPD value for the range of 6.0 to 20.0 mm.
The present study demonstrated that the preoperative CEA level and preoperative PPD value, which can easily be measured in the clinical setting, may be effective indicators of postoperative adjuvant immunotherapy using PSK in combination with fluoropyrimidines. However, the present study was a sub-analysis of a randomized controlled study and, therefore, was of a small scale. A large-scale controlled clinical study is necessary to validate the usefulness of these factors.

References


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