Beneficial Effects of 5-Fluorouracil and Heparin-Based Portal Infusion Chemotherapy Combined with Mitomycin C and Cisplatin after Curative Resection of Pancreatic Cancer

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Key Words

Cisplatin  Curative resection, pancreatic cancer  5-Fluorouracil  Heparin-based portal infusion chemotherapy  Mitomycin C  Adjuvant therapy

Abstract

Aims: We retrospectively assessed the benefits of 5-fluorouracil (5-FU)- and heparin-based portal infusion chemotherapy combined with systemic administration of mitomycin C (MMC) and cisplatin (CDDP) for 4 weeks following surgery (PI4W). The goal was to determine if this treatment prevented liver metastasis and improved survival for patients with potentially curative resection of pancreatic cancer. Methods: 68 patients who underwent pancreatectomy from January 1995 to August 2007 were treated. Of these cases, 22 patients received portal infusion with 5-FU (250 mg/day) for 2 weeks (PI2W) following surgery, while 25 patients received PI4W therapy (250 mg/day of 5-FU with 2,000 IU/day of heparin everyday for 4 weeks, 4 mg MMC on days 6, 13, 20, 27, and 10 mg CDDP on days 7, 14, 21, 28). The remaining 21 patients were treated without adjuvant therapy during the perioperative period. Results: All patients except one completed the portal infusion chemotherapy without toxicity. The cumulative liver metastasis-free survival rate in the PI4W group was significantly higher than those in the other two groups. Furthermore, in the PI4W group, 3-year survival was 91.6% and 5-year survival was 70.5%, rates which were significantly better than those observed in the other two groups. Conclusion: PI4W therapy after surgery is feasible and could become a promising adjuvant therapy in patients with potentially curative resection of pancreatic cancer.

Introduction

Despite progress in diagnostic technology, most patients with pancreatic cancer have already reached an advanced stage at the time of diagnosis. While the most important curative treatment is considered surgical resection, only 10–20% of patients are candidates for potentially curative resection \cite{1}. Even when radical surgery is carried out, it is difficult for the patients to achieve long-term survival because of early relapse (liver metastasis) and local recurrence after surgery. Its prognosis remains extremely poor. The 5-year overall survival rate after surgical resection is generally less than 15%, unless adjuvant treatments are given \cite{2, 3}. To improve survival after resection, effective adjuvant therapy for prevention of early recurrence is very important. At present, multimodality treatment combining a variety of therapeutic methods...
has been introduced for use as an adjuvant therapy. However, optimal adjuvant therapy for resectable pancreatic cancer remains extremely controversial. Recently, the ESPAC-1 trial has shown a survival benefit for adjuvant chemotherapy with 5-fluorouracil (5-FU) + folic acid for 6 months after R0/R1 resection [2]. The analysis indicated 3- and 5-year survival rates of 38 and 11%, respectively, for chemotherapy and 18 and 7%, respectively, for the non-chemotherapy group. Moreover, the CONKO-001 trial has also indicated a significant increase of disease-free survival in patients who received adjuvant chemotherapy with gemcitabine (GEM) after R0/R1 resection compared with observation alone [3]. The results indicated the 3- and 5-year survival rates were 36 and 14%, respectively, in the GEM arm versus 25 and 8%, respectively, in the observation arm. Since 1986, postoperative adjuvant therapy using portal infusion of 5-FU for 2 weeks (PI2W) has been performed for patients with pancreatic cancer in our institution [4]. Although PI2W therapy significantly decreased the incidence of liver metastasis compared to patients without chemotherapy, the overall survival in the PI2W group was not significantly improved compared to that in the control group. A Kaplan-Meier analysis showed that the 3- and 5-year survival rates were 37.7 and 18.9%, respectively, in the PI2W group versus 11 and 5.5%, respectively, in the surgery only group. These results, as well as the results of recent randomized phase III trials described above, were not satisfactory, and we felt the necessity to improve the regimen and duration of the PI2W therapy.

In past decades, anticoagulant therapy has been proposed to increase overall survival of patients with malignancies. The potential anticancer activity of heparin that is independent of its antithrombotic effect is supported by data from many in vitro and in vivo studies [5–11]. The hypothesis that heparin has the potential to improve the course of human pancreatic cancer after surgery is both appealing and rational.

The purpose of this study was to evaluate the potential benefits of 5-FU + heparin-based portal infusion chemotherapy combined with systemic administration of sequential MMC followed by CDDP for 4 weeks (PI4W). We asked whether this regimen prevented liver metastasis and improved survival and whether it constituted an effective adjuvant strategy for patients with pancreatic cancer after potentially curative resection. The present report suggests that PI4W therapy is important and useful as an adjuvant treatment of postoperative pancreatic cancer.

Materials and Methods

Patient Selection

We retrospectively analyzed patients at Keio University Hospital who underwent curative resection of pancreatic cancer performed between January 1995 and August 2007 to determine the effects of adjuvant portal infusion chemotherapy on reducing the recurrence of liver metastasis. Portal infusion chemotherapy was selectively administered among a limited number of patients with pancreatic cancer just after surgical resection of the tumor. Between January 1995 and June 2001, portal infusion with 5-FU was performed in 22 patients for 2 weeks following surgery (the PI2W group), while after September 2001, we performed 5-FU and heparin-based portal infusion concurrently administered with MMC and CDDP in 25 patients for 4 weeks (the PI4W group). To evaluate the effects of portal infusion on long-term outcome, we also examined a control group consisting of 21 patients with curative resection of pancreatic cancer who were treated without adjuvant therapy during the perioperative period between 1995 and 2007. Then we compared the three groups in terms of the incidence of liver metastasis and the duration of survival.

All patients had staging investigations prior to surgery to exclude evidence of distant metastasis by radiographic imaging including ultrasonography, contrast-enhanced computed tomography (CT), magnetic resonance imaging, endoscopic retrograde cholangiopancreatography, endoscopic ultrasonography, and selective angiography. Patients with infiltration of the portal vein and the superior mesenteric vein were not considered to have unresectable cancer except with complete occlusion or circumferential stenosis of the vein. On the other hand, locally advanced tumors involving the superior mesenteric artery and/or the celiac trunk were judged to be unresectable and were excluded from this study. Final judgment on the resectability was done by explorative laparotomy before resection. In all patients, the diagnosis of pancreatic tubular adenocarcinoma was confirmed by histologic examination of the resection specimen. This study was approved by the institutional review board. All patients received a full explanation of the purpose, procedures, and risks of portal infusion chemotherapy and gave written informed consent.

Treatment Protocol

The catheter for portal infusion chemotherapy (6 Fr; Toray Medical Co., Ltd, Tokyo, Japan) was inserted via the recanalized umbilical vein in the round ligament after radical resection of the tumor with lymphadenectomy before reconstruction of the gastrointestinal tract during the operation. The tip of the catheter was placed at the trunk of the portal vein according to the method of Taylor et al. [12]. For the 22 patients in the PI2W group, we continuously infused 250 mg/day of 5-FU through the portal catheter for 2 weeks starting immediately after the operation. The 25 patients in the PI4W group received 250 mg/day of 5-FU with 2,000 IU/day heparin through the portal vein (days 1–7/week, ×4 weeks) starting just after the operation in combination with MMC (4 mg/day, days 6, 13, 20, 27), and CDDP (10 mg/day, days 7, 14, 21, 28) by systemic administration, although heparin was not administered until 24 h after surgery to prevent bleeding. After portal infusion chemotherapy, the patients in the PI4W group received systemic administration of 500 mg/m2 of 5-FU and 4 mg MMC every 2 weeks for ten cycles at an outpatient clinic, if possible. The patients in the control group did not receive adjuvant...
therapy during the perioperative period because of the failure of recanalization of the round ligament during the operation, or the physician’s clinical decision, or the patient’s refusal to receive anticancer agents.

Postoperative Follow-Up

The recurrence of liver metastasis in the three groups after surgical resection was analyzed by follow-up CT, which was repeated at 3- to 4-month intervals. Serum levels of tumor markers (carcinoembryonic antigen and carbohydrate antigen 19-9) were measured every month. When those data suggested recurrence, additional CT examinations were carried out.

Statistical Analysis

Continuous variables were expressed as a mean ± SD and were examined using analysis of variance (ANOVA). Categorical variables were compared by means of the χ² test. The cumulative liver metastasis-free survival and overall survival were analyzed using the Kaplan-Meier method. Survival time was calculated from the date of surgery to the date of death or the date of the final confirmation of survival as the period of observation. The log-rank test was used to compare the outcome of the cumulative liver metastasis-free survival or the overall survival between two different groups. A p value <0.05 was considered statistically significant.

Results

Patient Demographics and Clinical Characteristics

The patients’ characteristics are shown in Table 1. There were no statistically significant differences among the three groups for the parameters shown. Patients consisted of 14 males and 7 females with a mean age of 69.7 years (range 58–81) in the control group, 15 males and 7 females with a mean age of 66.2 years (range 49–83) in the PI2W group, and 16 males and 9 females with a mean age of 67.1 years (range 55–80) in the PI4W group. Of 21 patients in the control group, 12 were treated by pancreatoduodenectomy (PD) or pylorus-preserving pancreatoduodenectomy (PPPD), 8 by distal pancreatectomy (DP), and 1 by total pancreatectomy (TP). In the PI2W group, 13 of 22 patients were treated by PD or PPPD, 5 by DP, and 5 by TP. In the PI4W group, 15 patients had PD or PPPD, 9 had DP, and 1 had TP.

According to the tumor node metastasis (TNM) classification (UICC TNM classification of malignant tumors, ed. 6, 2001), the majority of patients in each group were in stage IIA or IIB. That is, the proportion of stage IIA and IIB patients was 66.7% (14/21) in the control group, 68.2% (15/21) in the PI2W group, and 84% (21/25) in the PI4W group. Most stage IV patients were first found to have had metastasis of the lymph nodes around the abdominal aorta on microscopic examination of the resected specimens. One patient in the PI4W group was found to have had localized peritoneal carcinomatosis on microscopic examination of the resected specimens after surgery. The pN1 status of lymph node metastasis was observed in 16 patients of the control group, 14 of the PI2W group, and 11 of the PI4W group. Accordingly, the number of M1 patients was 4 in the control group, 4 in the PI2W group, and 1 in the PI4W group. Positive resection margins were seen in 6 of 21 patients in the control group, in 6 of 22 patients in the PI2W group, and in 4 of 25 patients in the PI4W group. Circular resection of the portal vein involved by cancer was performed in 2 patients of the control group, 4 of the PI2W group, and 2 of

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<th>Table 1. Demographics and clinical characteristics</th>
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PD = Pancreatoduodenectomy; PPPD = pylorus-preserving pancreatoduodenectomy; DP = distal pancreatectomy; TP = total pancreatectomy.

¹ The ANOVA test was used to analyze the age of the three groups.

² The χ² test was used to test among the three groups for categorical variables.
Reconstruction of the portal vein was performed in an end-to-end fashion in all the patients. Pathological characteristics of the primary tumors are shown in Table 2. There were no differences in lymphatic infiltration, venous infiltration, or pathological differentiation among the three groups.

Seventeen of 21 patients in the control group with a mean observation period of 20.8 months (range 4–74, median 9) died during the study period because of recurrence of cancer. In the PI2W group, with a mean observation period of 40.2 months (range 5–154, median 16), 18 of 22 patients died during the study period because of cancer recurrence. In contrast, 4 of 25 patients in the PI4W group with a mean observation period of 37.8 months (range 6–85, median 24) died of cancer, and 2 died of other disease not related to pancreatic cancer (table 3).

The patients of the control group did not receive adjuvant therapy during the perioperative period, while additional adjuvant therapy was given to some patients of both the PI2W and PI4W groups. Intraoperative radiotherapy (IORT) using electron-beam energies from 6 to 9 MeV to deliver 20–25 Gy to the pancreatic bed after tumor resection before gastrointestinal reconstruction for control of local recurrence was administered to 17 patients in the PI2W group and 4 in the PI4W group. In addition, another 7 patients of the PI4W group received 5-FU-based chemoradiation at a total dose of 40 Gy before surgery for the same purpose as IORT (table 4).

Treatment-Related Toxicities

There were no local side effects at the site of the portal infusion except for 1 patient. In that patient, the tip of the catheter penetrated a wall of the portal vein during the postoperative period, and solution including 5-FU and heparin leaked into the abdominal cavity. However, the patient recovered without any life-threatening trouble related to the catheter in accordance with conservative observation and had the catheter removed 35 days after surgery. No patients needed to stop the portal infusion chemotherapy due to side effects attributable to anticancer drugs such as bone marrow suppression, liver dysfunction, and anorexia. Therefore, all patients but one successfully completed the treatment schedule.

Liver Metastasis following Surgery

At the time of publication, liver metastasis had been found in 13 of 21 patients (61.9%) in the control group (mean 20.8 months, median 9 months) and 10 of 22 patients (45.4%) in the PI2W group (mean 40.2 months, median 16 months), whereas only 4 of 25 patients (16.0%) in the PI4W group developed liver metastasis after surgery (mean 37.8 months, median 24 months). The incidence of
Liver metastasis in the PI2W group was lower than that in the control group, but the difference was not statistically significant. However, significant decreases in the recurrence incidence of liver metastasis were observed in the PI4W group when compared with the control and the PI2W groups (p < 0.01 and p < 0.01, respectively) (table 5). Furthermore, we analyzed the cumulative liver metastasis-free survival in the three groups by Kaplan-Meier analysis (fig. 1). The 1-, 2-, and 3-year liver metastasis-free survival rates were 54.1, 40.6, and 32.4%, respectively, in the control group, 56.7, 51.5, and 51.5%, respectively, in the PI2W group, and 87.7, 87.7, and 87.7, respectively, in the PI4W group. The cumulative liver metastasis-free survival rates in the PI4W group were significantly better than those in the control patients (p < 0.01). In addition, when the 25 patients in the PI4W group were classified into two subgroups according to the presence or absence of additional adjuvant therapy (see Materials and Methods), the 1-, 2-, and 3-year liver metastasis-free survival rates in the patients in the PI4W subgroup without additional adjuvant therapy were still high (92.3, 92.3, and 92.3%, respectively), suggesting that the advantage of additional adjuvant therapy other than portal infusion chemotherapy was not substantial for prevention of liver metastasis (fig. 2).

**Overall Survival**

The overall survival rates of the patients with portal infusion chemotherapy were compared with those of the control patients (fig. 3). As a result of Kaplan-Meier regression analysis, the overall 1-, 3-, and 5-year survival rates in the control group were 42.9, 32.1, and 16.1%, respectively, and their median survival period was 9

**Table 5. Final number of the patients with liver metastasis during the study period**

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<th>Control</th>
<th>PI2W</th>
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<td>Liver metastasis</td>
<td>13 (61.9%)</td>
<td>10 (45.4%)</td>
<td>4 (16.0%)</td>
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Significant (p = 0.0037) difference between control and PI4W groups.
months. In the PI2W group, the overall 1-, 3-, and 5-year survival rates were 54.5, 36.4, and 27.3%, respectively, and their median survival period was 16 months. There was no significant difference in cumulative survival between the control group and the PI2W group. In contrast, the 1-, 3-, and 5-year survival rates in the PI4W group reached 96.0, 91.6, and 70.5%, respectively, and their median survival period was 24 months. Significant differences were noted between the control and PI4W groups, and between the PI2W and PI4W groups (p < 0.01, and p < 0.01, respectively). Moreover, overall survival was analyzed for patients in cancer stages IIA and IIB (fig. 4). The 5-year survival rate for patients with stage IIA and IIB in the PI4W group was 64.8%, whereas the rates for the patients with the same stages in the control and PI2W group were 23.8, and 27.3%, respectively. There were also statistically significant differences for overall survival of stage IIA and IIB patients between the control and PI4W groups, and between the PI2W and PI4W groups (p < 0.01 and p < 0.01, respectively).

Discussion

In patients with pancreatic cancer, we found significant reductions in liver metastasis and increases in overall survival after surgery when they received 5-FU and heparin-based portal infusion concurrently administered with MMC and cisplatin for 4 weeks.

In 1986, we started 2 weeks of portal infusion chemotherapy with 5-FU to prevent implantation of cancer cells during intraoperative manipulation. The rate of liver metastasis in the patients receiving portal infusion chemotherapy (43%) was significantly lower than in the patients receiving surgery alone (69%) [4]. However, the postoperative survival period in patients treated with 5-FU through the portal vein for 2 weeks was still limited, and thus, these results were unsatisfactory. In a strategy similar to ours, Nakayama et al. [13] continuously infused 250 mg/day of 5-FU via the portal vein for 3 weeks immediately after radical surgery in pancreatic cancer patients. As a result, patients who received 5-FU liver perfusion chemotherapy, especially those with negative expression of dihydropyrimidine dehydrogenase in the tumors, showed a significantly higher survival rate than those without the therapy. However, even if dihydropyrimidine dehydrogenase-negative patients received 5-FU-based portal chemotherapy for 3 weeks, most of them had hepatic metastasis or local recurrences within 3 years of radical resection. The 3-year survival rate was less than 20%. In contrast, Ishikawa et al. [14] reported that the incidence of liver metastasis was significantly decreased by continuous liver perfusion chemotherapy using 125 mg/day of 5-FU via both the portal vein and the hepatic artery for 4–5 weeks after pancreaticoduodenectomy. Thus, the 3-year survival rate reached 54%. Although the perfusion routes included both the portal vein and the hepatic artery, the longer period of liver perfusion with 5-FU seemed to yield a better outcome than periods less than 3 weeks. These findings moved us to extend the infusion period of 5-FU from 2 to 4 weeks.

Furthermore, we administered heparin continuously through the portal vein in combination with 5-FU for 4 weeks. The beneficial effects of heparin on cancer progression have been reported since the 1980s. In experimental studies, heparins have shown a wide variety of biological activities other than anticoagulant effects such as interfering with P- and L-selectin-mediated cell-cell binding [5, 6], anti-angiogenesis [7], and inhibition of heparanase [8, 9]. Borsig et al. [5] revealed that heparin treatment attenuates tumor metastasis in mice by inhibiting P-selectin-mediated interactions of platelets with carcinoma cell-surface mucin ligands, suggesting the potential usefulness of heparin therapy for prevention of metastasis in human malignancy. In clinical settings, several randomized trials are investigating the potential benefits of unfractionated heparin or low-molecular-weight heparin to improve survival in patients with cancer. The FAMOUS study was a prospective, randomized, placebo-controlled trial to examine the possible effects of low-molecular-weight heparin on survival in patients with advanced can-
cancer of different types [15]. The trial failed to show a significant difference in survival. However, two other randomized clinical trials (the MALT study [10] and CLOT study [11]) revealed significant survival benefits among cancer patients treated with low-molecular-weight heparin compared with those who were not. Furthermore, these studies indicated that low-molecular-weight heparin may provide a survival benefit especially in patients with a better life expectancy. Akl et al. [16] conducted a systematic review of randomized controlled trials in cancer patients without clinical evidence of venous thromboembolism comparing unfractionated heparin or low-molecular-weight heparin with placebo or no intervention. This systematic review supports a survival benefit from heparin therapy in cancer patients in general, especially in patients with limited small cell lung cancer. Recently, two retrospective, non-randomized studies have shown a survival benefit of the addition of low-molecular-weight heparin to anticancer chemotherapy in patients with advanced pancreatic cancer [17, 18]. Icli et al. [17] stated that the median survival time for patients receiving low-molecular-weight heparin and GEM + CDDP was significantly higher than the patients treated with chemotherapy alone (13.0 vs. 5.5 months, p = 0.0001). This survival advantage provided by heparin was significant in both metastatic and locally advanced patients. Moreover, von Delius et al. [18] also found a survival advantage for patients with metastatic pancreatic cancer receiving heparin in addition to conventional chemotherapy. These findings support the contention that addition of heparin to adjuvant chemotherapy after surgery could benefit patients with pancreatic cancer.

In addition to infusing 5-FU and heparin, we systematically administered MMC and CDDP. CDDP plays an important role as a modulator of 5-FU in cellular methionine metabolism [19]. Likewise, it has been reported that the intracellular concentration of platinum was significantly increased by preincubation with MMC, suggesting MMC modulates cellular permeability to CDDP or the ability of CDDP to intercalate DNA [20, 21]. Synergistic antitumor activities of MMC and CDDP against human gastric and pancreatic cancer cells were shown in in vivo experiments, especially when MMC was followed by CDDP. Recently, GEM has been considered the most active single agent for non-resectable progressive pancreatic cancer in spite of low efficacy rates ranging from 5 to 18% [22, 23]. Moreover, recent results of the CONKO-001 phase III trial have shown significantly delayed development of recurrent disease after complete resection of pancreatic cancer, compared with surgery alone [3]. However, it is still suggested that combined treatment with 5-FU, MMC, and CDDP in proper sequence could produce as efficient an outcome as GEM for low-sensitivity pancreatic cancer, although the effect of using a single agent such as 5-FU, MMC, and CDDP is restricted and less effective than GEM.

Although the patients in the control group did not receive additional adjuvant treatment during the perioperative period, 17 of 22 patients (77.3%) in the PI2W group and 4 of 25 patients (16%) in the PI4W group received IORT and 7 of 25 patients (28%) in the PI4W group received 5-FU-based neoadjuvant chemoradiation. Therefore, we analyzed liver metastasis-free survival among the patients without additional adjuvant therapy other than PI2W or PI4W in the three groups to remove the effects of IORT or NCR. As a result, we confirmed the substantial advantage of PI4W for prevention of liver metastasis. Moreover, PI4W obviously contributed to improved survival in the patients with pancreatic cancer after potentially curative resection. In this series, the 1-, 3-, and 5-year survival rates were 42.9, 32.1, and 16.1%, respectively, in the control group, and 54.5, 36.4, and 27.3%, respectively, in the PI2W group. In contrast, 1-, 3-, and 5-year survival rates in the PI4W group were 96.0, 91.6, and 70.5%, respectively. Even in the subgroup analysis of patients limited to stages IIA and IIB, the overall survival in the PI4W group was significantly better than those in the other two groups. Although the overall survival rate in the PI4W group was much higher than those reported previously, the overall survival rate in the control group was similar to results previously reported in the literature [2–4].

Caution is required in the interpretation of these results. All of the patients in the PI4W group were treated after 2001, while more than half of the patients (13/21) in the control group underwent surgery before 2001. It is also possible that the patients treated in more recent years were diagnosed by use of more sensitive hepatic imaging modalities such as a magnetic resonance imaging and dynamic multi-row detector CT, leading to preferential selection of patients in the PI4W group without hepatic metastasis compared to the control group. Although the observation periods among the three groups were not significantly different, the number of patients who died of diseases related to pancreatic cancer was obviously smaller in the PI4W group than in the control group. The follow-up periods in 10 of 25 (40%) patients in the PI4W group were less than 3 years. However, all of the 10 patients are still alive and 9 currently lack liver metastasis after more than 1 year.
Local recurrence and liver metastasis are the major causes of treatment failure after attempted curative resection of pancreatic cancer [4, 24, 25]. Chemoradiotherapy is considered useful for local control of the pancreatic bed after pancreatectomy. The GITSG phase III trial was the first randomized trial designed to evaluate the role of postoperative adjuvant therapy and demonstrated a statistically significant survival advantage for the patients with resection [26]. However, two other randomized trials, EORTC [27] and ESPAC-1 [2], have failed to demonstrate the benefit of postoperative chemoradiation on survival of cancer patients following resection of the pancreas. The relationship between pattern of recurrence (and its inhibition) and patient survival remains unclear. Valentini et al. [28] could not show that the improved local control was associated with the prolonged overall survival in patients with resection of pancreatic cancer, although the combination of external radiotherapy + IORT improved the incidence of local recurrence. Based on autopsy findings of 20 patients who died of recurrence after curative resection of pancreatic cancer, Hishinuma et al. [25] concluded that local recurrence was the direct cause of death of only 4 patients. They concluded that treatment focusing on local control could not improve the survival of patients with resectable pancreatic cancer and that effective treatment strategies against systemic metastasis were needed. Furthermore, Shibata et al. [29] analyzed uni- and multivariate clinicopathologic factors associated with postoperative recurrence patterns and concluded that undifferentiated adenocarcinoma was a predictor of poor outcome and that postoperative liver metastasis was the worst form of recurrence in terms of survival of patients with pancreatic cancer. Therefore, they suggested that prevention of postoperative liver metastasis was an important step for improving survival. In our study, improved survival is likely due to a decrease (from 61.9 to 16.0%) in hepatic metastases. There were no side effects or morbidities related to the PI4W therapy except 1 patient in whom complications were not life-threatening. We conclude that PI4W therapy is beneficial in patients with pancreatic cancer when performed immediately after surgical resection.

Our study was not a randomized controlled trial. Furthermore, the patient population was small and the period of follow-up was not long. Thus, the results should be viewed with caution. Nonetheless, our findings support the use of portal liver perfusion with 5-FU + heparin in combination with sequential systemic administration of MMC followed by CDDP for 4 weeks starting immediately after potentially curative resection. This regimen appears to reduce postoperative liver metastasis and improve overall survival in patients with pancreatic cancer. It is possible that PI4W therapy could replace adjuvant treatment by systemic administration of GEM alone. The efficacy of the PI4W therapy needs to be determined by a phase III trial with a large number of patients.

References


