Placement of an Expandable Metallic Stent Improves the Efficacy of Chemoradiotherapy for Pancreatic Cancer with Malignant Portal Vein Stenosis or Obstruction

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Abstract. Background: Advanced or recurrent pancreatic cancer can sometimes cause obstruction or stenosis of the portal vein (PV), resulting in various symptoms of portal hypertension (PH), such as ascites, pancytopenia, hemorrhagic tendencies and liver dysfunction. We placed an expandable metallic stent into the PV to improve PH-associated complications and liver function. The placement of the PV stent was beneficial for administering chemotherapeutic agents and radiotherapy (RT) safely, and resulted in an improved response rate (RR) and survival.

Patients and Methods: In the present study, 14 patients with malignant portal obstruction due to advanced or recurrent pancreatic cancer received PV stent placement to manage their PH-associated symptoms. After a mini-laparotomy at the ileocecal region, the ileocecal vein was cut and an expandable metallic stent (6-8 mm in diameter and 6-8 cm in length) was inserted into the PV under image roentgenography. After placement of the PV stent, the patients received anti-coagulation treatment with heparin and bisapirin for 1-3 months. All patients received chemotherapy with UFT, cyclophosphamide (CPA) and gemcitabine (GEM), and 11 patients also received RT.

Results: The RR was 43% (3 complete (CR), 3 partial (PR), 3 stable disease (SD), and 5 progressive disease (PD)), and the mean survival times (MST) after the initiation of therapy or placement of the PV-stent were 12.6 and 9.5 months, respectively, while the 1-year survival rates were 54.5% and 35.1%, respectively. In the 3 CR patients, 2 died of carcinomatous ascites 13 and 21 months later, and 1 is still disease free. In the PR and SD patients, pain and PH-associated symptoms such as ascites and hyperglycemia were also improved. Conclusion: The placement of a PV stent is beneficial for improving PH-associated symptoms as well as facilitating chemo-RT and the efficacy of therapy.

Pancreatic cancer is the fifth leading cause of cancer death in Japan, and the fourth in the USA, and remains one of the most lethal common malignancies. Only 15-20% of these patients can undergo a curative resection, and the prognosis is very poor: the median survival time (MST) after surgical resection ranges between 11 and 24 months (1). More than 80% of these patients have pancreatic cancer that cannot be cured by surgical resection, and the MST ranges between 8-12 months for locally advanced disease, and 3-6 months for metastatic disease (2). Advanced or recurrent pancreatic cancer that cannot be resected frequently invades the surrounding organs or tissues. In particular, if the pancreatic cancer invades the portal vein (PV) and occludes it, the patient suffers from various portal hypertension (PH)-associated symptoms and liver dysfunction, including jaundice, ascites, and bleeding tendencies. In the case of liver failure, the patients cannot receive the full dose of chemotherapy (CT) or radiotherapy (RT) because these cancer therapies sometimes aggravate the liver dysfunction or its complications.

In the case of intrahepatic or hilar PV stenosis due to malignant disease, a wall stent has typically been used (3); however, for extrahepatic PV stenosis, a wall stent cannot always be used because the splenic vein joins the PV and thus the wall stent may occlude the splenic vein, leading to...
serious complications. In order to improve the blood flow in the PV in patients with extraperitoneal PV obstruction due to the invasion of pancreatic cancer, we placed an expandable metallic stent into the PV via the ileocecal vein following a laparotomy. The present study reports the treatment results of a total of 14 patients with advanced or recurrent pancreatic cancer who received placement of a PV stent and subsequent chemoradiotherapy (CRT).

Patients and Methods

Patients. The present study included 14 patients with recurrent or advanced pancreatic cancers: 10 primary unresectable carcinomas and 4 recurrent. All patients were treated in the First Department of Surgery, Shimane University School of Medicine between 1997 and 2006. Their profiles are summarized in Table I. They were 6 male and 8 female patients, and the mean age (years±SD) was 68.5±6.2. The 4 patients with recurrent cancer had previously received 3 pylorus-preserving pancreatoduodenectomy and 1 distal pancreatectomy.

Method for portal stenting. To place the PV stent, an expandable metallic stent (Bird Lumine: 6-2 mm in diameter and 4-8 cm in length) was used. The patients received a mini-laparotomy at the ileocecal region and the ileocecal vein was cut. Under guidance with image roentgenography, the stenotic portion of the PV was dilated by a balloon catheter and then the expandable metallic stent was placed. In one case, 3 stents were placed, and in the other 13 cases, a single stent was placed (Table I).

Anti-coagulation therapy. The patients were given heparin continuously at 5,000 U/day for 7 days, and then biaspirin or warfarin for 1-3 months.

Chemotherapy and radiotherapy. Under the universal coverage of the Japanese Health Insurance System, the chemotherapeutic agents available for clinical use are specified strictly according to their indications by the Japanese Ministry of Health, Welfare and Labor. In the present study, according to their indications for pancreatic cancer, the patients were treated with CT. The CT included oral uracil and tegafur (UFT) at 300-400 mg/day daily, oral cyclophosphamide (CPA) at 50 mg/day every other day, and/or gemcitabine (GEM) at 200-400 mg/body weekly or biweekly in combination or singly. The regimens administered were decided according to the performance status of the patients with fully informed consent of the patients and/or their families. The CT regimens are summarized in Table I. Six patients were given a UC (UFT + CPA) regimen orally in combination with GEM, and the other 7 patients received other regimens: 2 UC, 2 GEM alone, 1 UC + cisplatin + epirubicin, 1 UFT alone, and one GEM + TS-1. However, 1 patient died without receiving any CT.

Radiotherapy. RT was performed using LINAC (ML-15MDX, 10MVX; Mitsubishi Electric Co. Ltd., Tokyo, Japan) at 40-60 Gy (2 Gy × 20-30 times).

Evaluation of the objective tumor response to the therapies. The objective response (OR) of the tumor was assessed using roentgenography, computed tomography, or ultrasonography using the following criteria: i) a complete response (CR) indicated a total disappearance of the tumor for at least 4 weeks, during which time the patient was free of all symptoms related to pancreatic cancer; ii) a partial response (PR) was defined as a 50% or greater reduction in the sum of the products of the two perpendicular diameters of all measurable tumor lesions as compared to their original size for at least 4 weeks. During this time, there must have been no increase of >25% in the size of any single lesion or the appearance of any new lesion; iii) progressive disease (PD) was defined as a greater than a 25% increase in the sum of the products of the diameters of all measurable lesions, the appearance of any new lesion, or a deterioration in the clinical status that was consistent with disease progression; and iv) stable disease (SD) was indicated for those patients who failed to meet the criteria for a CR, PR or PD, and who remained in the study for at least 8 weeks. The response was initially evaluated by an investigator at the department, and then re-evaluated by the Ethics Committee. The duration of the response was measured from the first day of injection of the agents to the day of the increase in tumor size.

Evaluation of side-effects. The National Cancer Institute Common Toxicity Criteria were used (4). All of the patients were followed by physical examination, routine hematological and biochemical examinations, and serum tumor marker assays for evaluating side-effects.

Statistics. The effects of the therapies were evaluated with respect to the response rate (RR) of the tumor and the survival rate after
therapy. The overall survival (OS) was calculated by the Kaplan-Meier method. Multivariate analysis of the maximum likelihood estimates using Cox’s proportional hazard model was used to obtain the conditional risk of carcinoma-related death. All analyses were performed using StatView software (SAS Institute Inc., Cary, NC, USA) and a p-value less than 0.05 was considered statistically significant.

Results

The effects of the PV stent are summarized in Table II. In 4 cases, the PV stent was very effective, and the ascites and/or hemorrhagic tendency was improved. Furthermore, the cancer lesions also responded to CT and RT, and 3 CRs and 3 PRs were observed, while the overall RR (CR + PR) was 42.9%, and SDs were observed in 3 patients. However, in the 2 remaining cases, the PV stent was not effective: one patient died of gastrointestinal bleeding 17 days after stent placement and the other died of liver dysfunction and cachexia due to increased liver metastasis.

The survival curves after the initiation of treatment and the placement of the PV stent are shown in Figure 1. The MST and 1-year OS rate were 9.5 months and 35.1%, respectively, after PV-stent placement. B, Survival curve after the initiation of therapy. The MST and 1-year survival rate were 13.0 months and 54.5%, respectively, after the initiation of the treatment.

Discussion

In the present study, 14 patients received placement of a PV stent and adjuvant CT or RT, and the RR was 43%. This RR is quite high, as compared with previous reports in which the RR of a combination regimen with 5-FU, GEM and their combinations ranged between 5% and 25%, and the MST ranged between 4 and 10 months (2, 5-16), although the sample size of the present study was too small to draw any conclusive interpretations. However, it is very difficult to obtain an RR higher than 30% in advanced or recurrent pancreatic cancer. This is one of the reasons for the low efficacy of CT and RT against advanced or recurrent pancreatic cancer; obstructive jaundice, which is usually followed by liver dysfunction, and PV obstruction, which is usually followed by PH-associated symptoms, are major obstacles for CT and RT. Accordingly, we believe that the PV stent was beneficial for improving the efficacy of CT or CRT. There may be several reasons for the high RR achieved by the PV stent. In those patients with liver dysfunction and PH, a dose of CT or RT sufficient to regress the tumor cannot be administered. The PV stent improves the portal circulation and PH-associated symptoms, which cause liver

Table II. Objective response and clinical benefits.

| I. Objective response: |  
|-----------------------|---|  
| CR                    | 3 |  
| PR                    | 3 |  
| SD                    | 3 |  
| PD                    | 5 |  
| Overall RR (CR+PR)    | 42.9% (6/14) |  
| II. Other clinical benefits |  
| Pain relief            | 2 |  
| Decrease or disappearance of ascites | 2 |  
| Improvement in hyperglycemia | 1 |  
| Improvement in thrombocytopenia | 1 |  

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease; RR, response rate.
dysfunction and pancytopenia, especially thrombocytopenia and leucocytopenia (due to hypersplenism), and gastrointestinal bleeding. Since the liver dysfunction and pancytopenia can be easily exacerbated by CT and RT, they are major difficulties for the administration of a dose of CT or RT sufficient to induce regression of the pancreatic cancer. Therefore, placement of a PV stent improves the efficacy of adjuvant therapies by removing any PH-associated co-morbidities. Furthermore, in the present study, pain and other PH-associated symptoms such as ascites and hyperglycemia were also improved.

In the present study, an expandable metallic mesh stent was used as the PV stent. In general, for a vascular stent, a wall stent is used. The reason for using a metallic stent is that the PV is joined to the splenic vein. In the case of an intrahepatic PV stenosis, a wall stent can be used, but in the
case of an extrahepatic PV stenosis, it cannot be used because it occludes the splenic vein and may lead to serious complications. Furthermore, in the case of an intrahepatic PV stenosis, a percutaneous transhepatic procedure is usually applied to place the wall stent in the PV. However, we placed an expandable metallic stent into the PV via the ileocecal vein using laparotomy because it is very difficult to define the occlusive site from the distal PV under image roentgenography, and a percutaneous transhepatic procedure carries various risks such as intra-abdominal bleeding and perforation, which can be easily managed by laparotomy.

One of the disadvantages of placing a metallic stent is that the tumor can invade through the mesh into the lumen, resulting in re-obstruction. Accordingly, RT and/or CT are essential to inhibit invasion into the lumen. The other disadvantage is that anti-coagulation therapy is necessary, and we typically used heparin at 5,000U/day by intravenous drip infusion for 1 week and then aspirin or warfarin orally for 3 months. Fortunately, there were no side-effects due to the anti-coagulation therapy in this series.

In the present study, we administered UFT, CPA, and GEM as the CT regimen in most patients. After the introduction of

Figure 4. Procedure for placing an expandable metallic stent. A, Expandable metallic stent (Ruminnex). B, Venogram of the portal vein: the arrow A indicates a portion of the stricture and B indicates the collateral circulation. C, Dilatation of the stenotic portion with a balloon catheter. D, Three metallic stents were placed into the portal vein and the blood flow became smooth and the collateral circulation disappeared.
GEM against advanced pancreatic cancer, various combination regimens have been attempted, but no optimal or standard combination regimen has been established yet. A previous study using this combination regimen with UFT, CPA and GEM resulted in a 27% RR and 23% clinical benefit response (CBR), and a 10.7 month MST (17). The present study used a low dose of GEM at 200 - 400 mg (almost equivalent to 150-300 mg/m²), although most studies used standard doses of GEM at 800-1,000 mg/m². However, this low dose was used in order to reduce the side-effects in combination with RT because our previous preliminary study on RT in combination with GEM at standard doses for inoperable pancreatic cancer resulted in serious myelosuppression, especially thrombocytopenia (data not published).

The present study used oral UFT instead of i.v. 5-fluorouracil (5-FU). In Japan, UFT has been used as a substitute for i.v. 5-FU for various malignancies such as gastric, colorectal, lung and breast cancer (18), and several studies in other countries have demonstrated that UFT was as effective as i.v. 5-FU, with a better toxicity profile (19, 20). However, UFT did not show any significant antitumor activity against metastatic pancreatic cancer in a phase II study (21). Recently, several groups have studied a combination of GEM at standard doses (1,000-1,200 mg/m²) and oral UFT at 300-400 mg/m² against pancreatic cancer, and the RR ranged between 16% and 33%, with a MST between 5.8 and 11 months (22-24).

The present study combined CPA in addition to GEM and UFT. As reported previously (21), UFT alone is not very effective against pancreatic cancer in our experience, and UFT plus CPA showed higher antitumor activity than UFT alone (25). Several previous clinical reports have suggested that this combination regimen of UFT + CPA (UC) showed antitumor activity against breast cancer, sometimes in combination with anthracyclines (26, 27). In addition, it has been reported that CPA augments the activity of ribonucleotide dehydrogenase, CPA plus 5-FU or its derivatives. However, the role of CPA in chemotherapy against pancreatic cancer will need to be clarified in future studies.

As discussed above, conventional CT, RT, or CRT resulted in a 5%-25% RR and a 4-10 month MST in advanced or recurrent pancreatic cancer. However the present series resulted in a higher RR and longer MST. These results suggest that placement of a PV stent is very beneficial for managing PH-associated symptoms as well as improving the efficacy of CT and CRT in pancreatic cancer with malignant PV stenosis or obstruction.

Conclusion

Placement of a PV stent was beneficial for improving PH-associated symptoms, such as ascites and pancytopenia, as well as in terms of compliance for CT and RT.

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References


