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Clinical Implications of an Expandable Metallic Mesh Stent for Malignant Portal Vein Stenosis in Management of Unresectable or Recurrent Pancreatic Cancer

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1. Introduction

Pancreatic cancer (PC) remains one of the most lethal common malignancies. More than 80% of patients with PC cannot be cured by surgical resection (Li D et al., 2004); the actuarial 5-year survival rate after curative resection is approximately 20% (Crist et al., 1987), and the median survival time (MST) after surgical resection ranges between 11 and 24 months (Nitecki et al., 1995). In other words, most patients develop recurrent disease in the near future even after curative resection.

Advanced or recurrent PC frequently invades the surrounding organs or tissues, and the patients require substantial palliative interventions, especially against biliary obstruction, gastric or duodenal outlet obstruction, and severe abdominal or back pain. In addition, when the portal vein (PV) is invaded and occluded, the patient suffers from various portal hypertension (PH)-associated symptoms and liver dysfunction, including jaundice, ascites, and bleeding tendencies, which disturb chemotherapy (ChT) or radiotherapy (RT).

PC-associated portal obstruction is classified into two categories, intrahepatic obstruction and extrahepatic obstruction. In the case of intrahepatic or hilar PV stenosis, a wall-stent is usually applied (Tsukamoto et al., 2003); however, a wall-stent cannot be used for the extrahepatic PV stenosis, because it may occlude the splenic vein, which joins the extrahepatic PV, leading to serious complications. In patients with extrahepatic PV obstruction, we placed an expandable metallic mesh (EMM) stent into the PV *via* the ileocecal vein following a mini-laparotomy. A total of 14 patients with inoperable or recurrent PC were given an EMM-PV-stent and received subsequent ChT and/or RT, and the treatment results were retrospectively compared with patients without an EMM-PV-stent.

2. Patients and methods

2.1 Patients

We treated a total of 97 patients with inoperable or recurrent PC. Of 97 patients, 68 received ChT, 28 received RT using LINAC at 40 - 60Gy (2Gy × 20 - 30 times) and 14 were given an

EMM-PV-stent. All patients were treated in the Department of Surgery, Shimane University School of Medicine.

2.2 Methods

A Bird Luminex EMM-stent (6 - 12 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-down. Under guidance with image roentgenography, the stenotic portion of the PV was dilated by a balloon catheter and the EMM-stent was placed. In one case, 3 stents were placed, and in the other 13 cases, a single stent was placed. All patients were given heparin continuously at 5,000 U/day for 7 days, and then biaspirin or warfarin for 1 - 3 months.

2.3 Chemotherapy (ChT) and radiotherapy (RT)

The ChT included oral UFT (uracil and tegafur) 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 with fully informed consent of the patients and/or their families. Six patients were given a UC (UFT and 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 ChT.

RT was performed using LINAC at 40 - 60Gy (2Gy × 20 - 30 fractions).

2.4 Evaluation of the objective response (OR) to the therapies

The OR of the tumor was assessed using roentgenography, computed tomography (CT), or ultrasonography (US) using the following standard criteria: i) a complete response (CR) indicated 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; and 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 duration of the response was measured from the first day of injection of the agents to the day of the increase in tumor size.

2.5 Evaluation of side-effects

The National Cancer Institute - Common Toxicity Criteria were used for evaluation of side-effects (NCI-CTC version 2.0). All of the patients were followed by physical examination,

routine hematological and biochemical examinations, and serum tumor marker assays to evaluate side-effects.

2.6 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.

3. Treatment results

The effects of the EMM-PV-stent are summarized in **Table 1**. In 4 cases, the EMM-PV-stent was very effective, and the ascites and/or hemorrhagic tendency were improved. Furthermore, ChT and RT were also effective and 3 CRs and 3 PRs were observed: the overall RR (CR + PR) was 42.9%, and SDs were observed in 3 patients. However, in the 2 remaining cases, the EMM-PV-stent was not effective: one patient died of gastrointestinal bleeding and the other died of liver dysfunction and cachexia due to increased liver metastasis.

I. Objective response	
Complete response (CR)	3
Partial response (PR)	3
Stable disease (SD)	3
Progressive disease (PD)	5
Overall response rate (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

Table 1. Objective response and clinical benefits

The procedure for an EMM-PV-stent is shown in the treatment course of one representative case in **Figure 1 - 4.** The patient had a pancreatic head carcinoma causing obstructive jaundice, and the PC was diagnosed as inoperable because splenic metastasis and PV occlusion were observed (**Figure 1A,1B and 1C**).

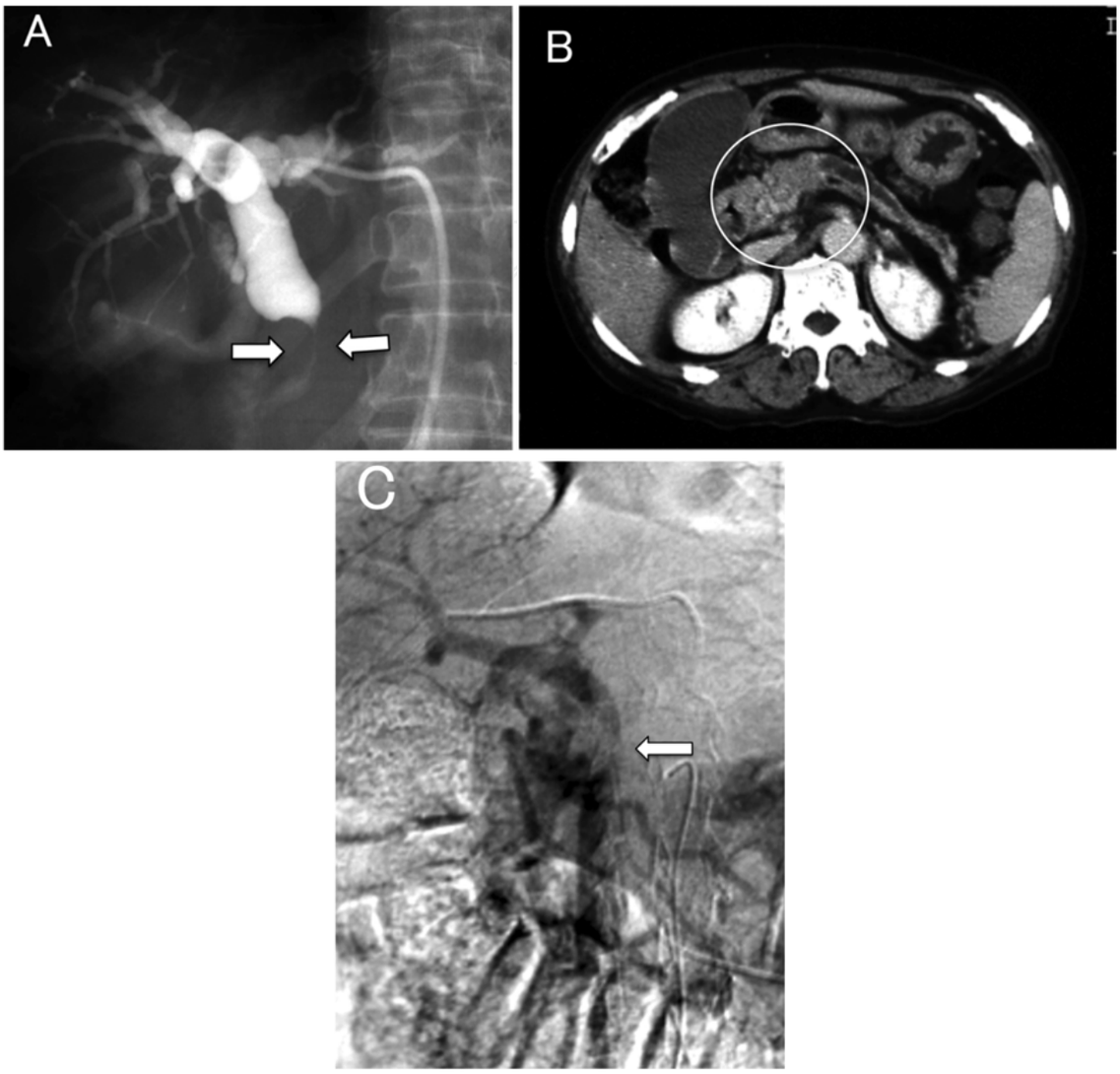

Fig. 1. A representative case with portal stenosis
A. Percutaneous transhepatic cholangiography. Arrows indicate stenosis.
B. CT. Circle indicates a pancreatic head cancer
C. Portography. Arrow indicates extrahepatic portal stenosis

The patient underwent a laparotomy, but peritoneal dissemination and malignant ascites were also seen. In order to release the obstruction of the bile duct and duodenum, the patient received bypass surgeries with a cholecysto-jejunostomy and a gastro-jejunostomy. In addition, she received placement of an EMM-PV-stent with three metallic stents, as shown in **Figure 2A,2B,2C,2D and 2E**.

After surgery, she was treated with ChT consisting of oral UFT plus CPA with intravenous GEM, and RT to a total of 50 Gy. The tumor responded well to the therapies, and the splenic metastasis and primary lesion disappeared completely 4 months after the surgery (**Figure 3**). Finally, she died of malignant ascites 21 months after the initiation of treatment. **Figure 4** summarizes the treatment course.

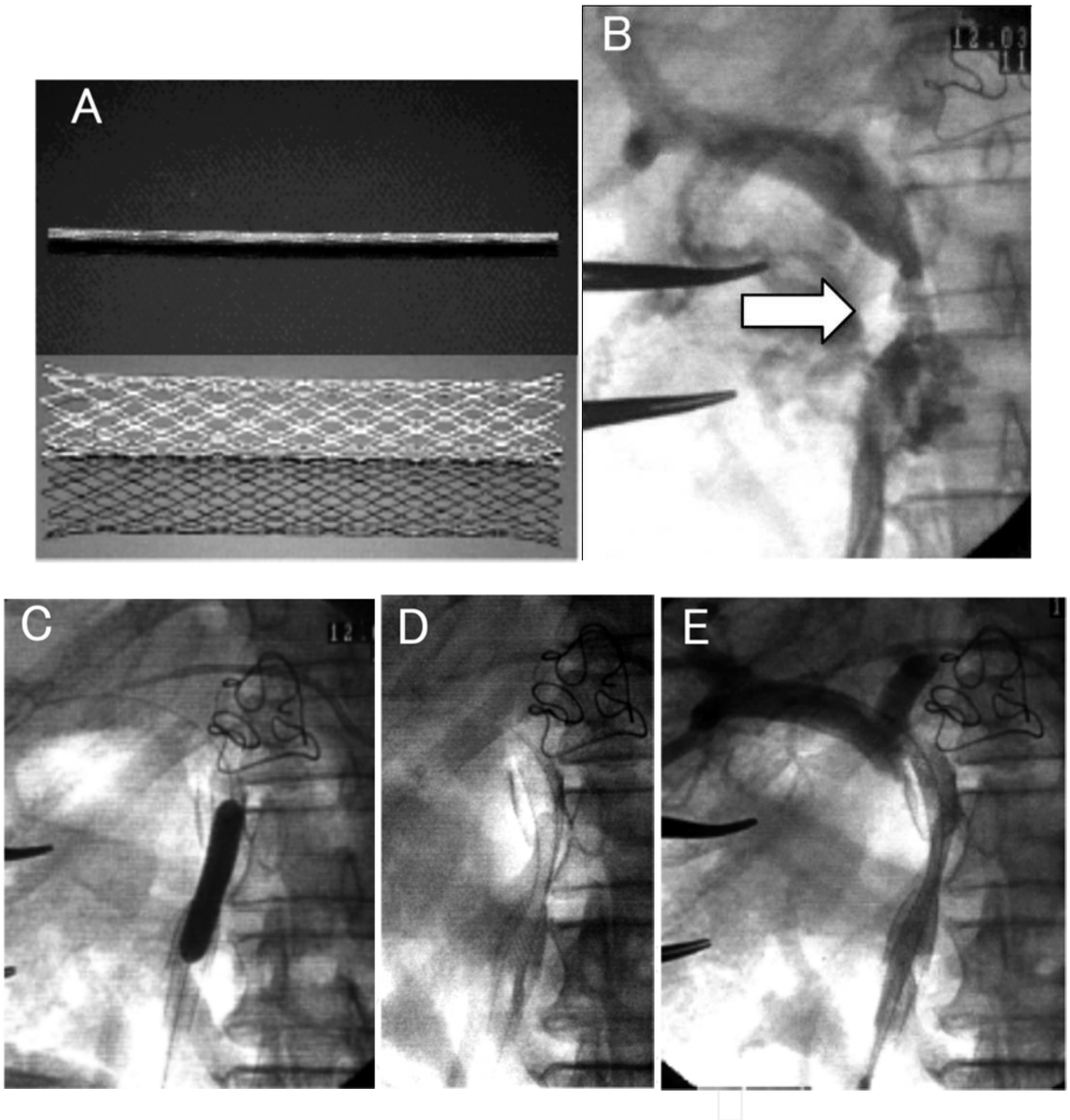

Fig. 2. Procedure of portal stent
A. An expandable metallic mesh stent (Bird Luminex)
B. Arrow indicates portal stenosis
C. Balloon dilatation
D. Insertion of three stents
E. Portography after portal stent

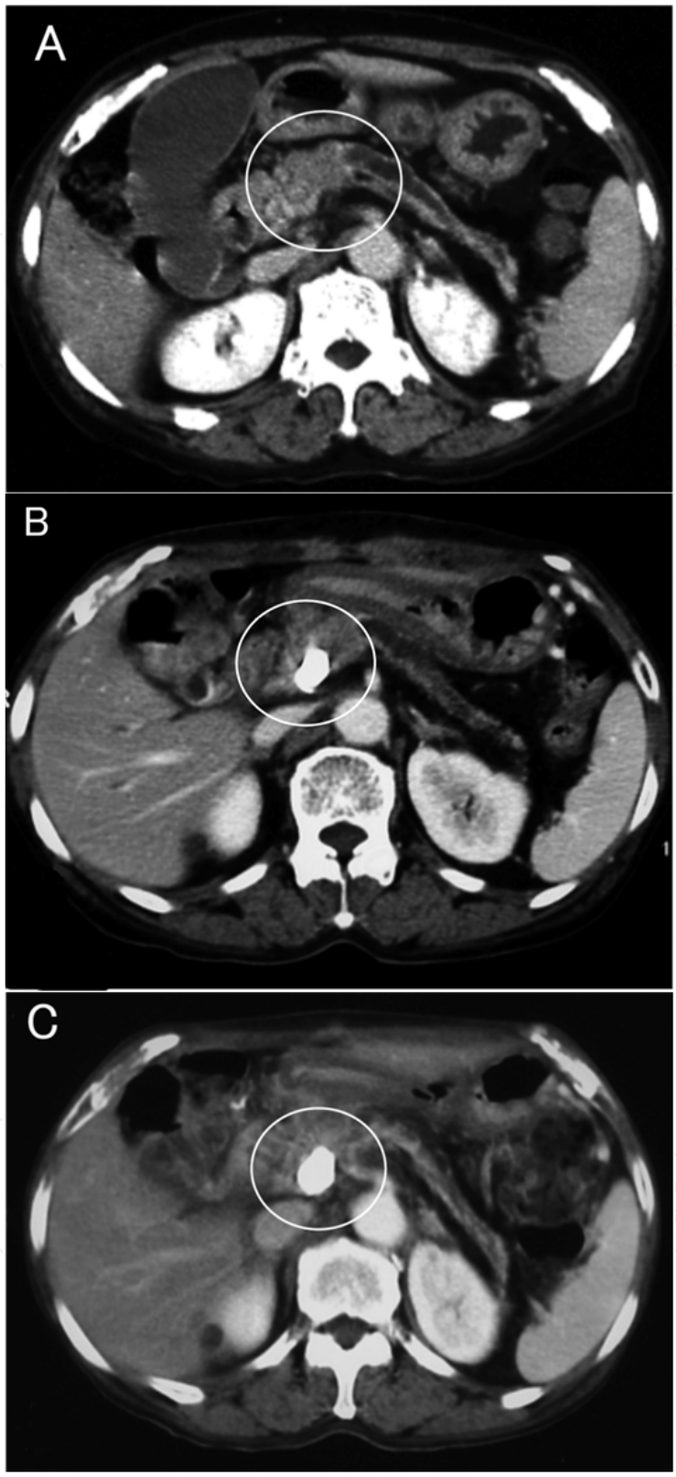

Fig. 3. Comparative CT before and after PV-stent
A. Before PV-stent
B. Two months after PV-stent
C. Six months after PV-stent

Circles indicate pancreas head and portal vein.

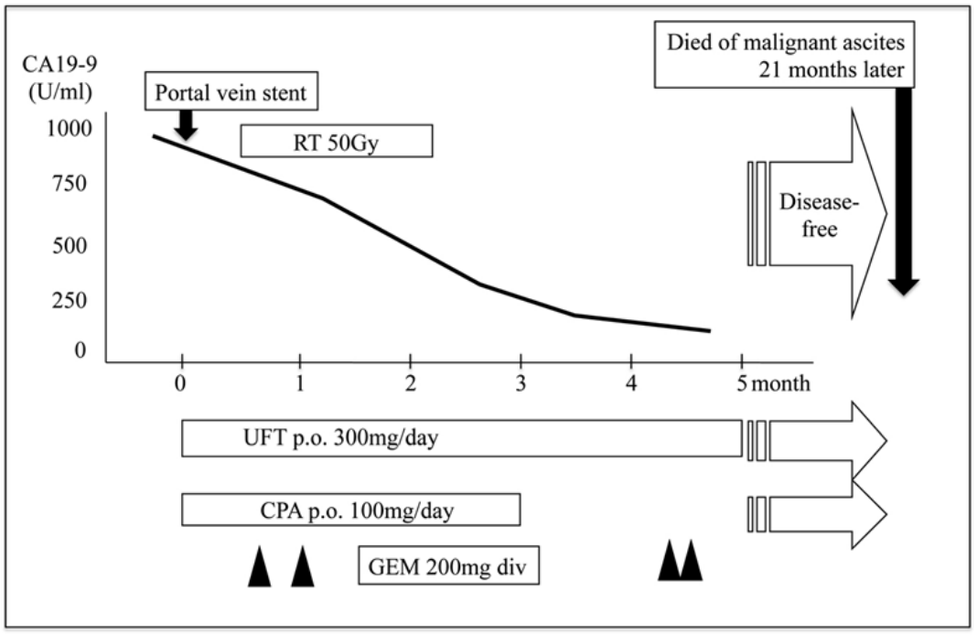

Fig. 4. Treatment course

The survival curves after the initiation of treatment and placement of the EMM-PV-stent are shown in **Figure 5**.

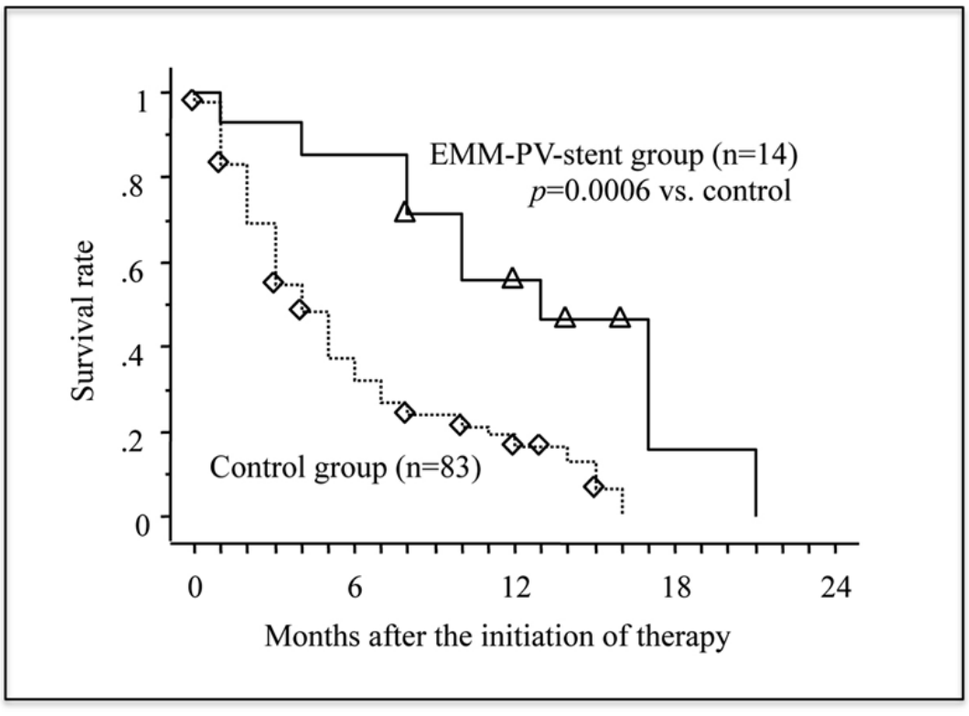

Fig. 5. Comparative survival curves.

The survival curve of the EMM-PV-stent group was significantly higher than that of the remaining patients (control group, n=83) (p=0.0006 by Cox-Mantel): the 6 months and 1-year survival rates were 85.7% and 54.5% for the EMM-PV-stent group vs. 32.0% and 16.2% for the control group, respectively, while the MSTs were 13.0 vs. 4.0 months, respectively (**Table 2**).

Group	Survival rate (%)		Median survival (months)	*p*-value
	6-month	1-year		
Control	32.0	16.2	5.9	0.0006
EMM-PV-stent	85.7	54.5	12.7	

Table 2. Comparative survival between the control and EMM-PV-stent groups

The implications of EMM-PV-stenting in the treatment results were analyzed by multivariate analysis (**Table 3**), but this demonstrated that an EMM-PV-stent was not a significant factor, while RT and ChT were significant prognostic factors. This suggests that an EMM-PV-stent itself does not improve the patients' survival, but it is beneficial for improving the efficacy of ChT or RT by reducing the risk of liver failure or hemorrhagic tendency.

Variables	Conditional risk ratio (95% confidence limit)	*p*-value
Age	1.000 (0.978 – 1.022)	0.9718
Palliative surgery	0.830 (0.485 – 1.423)	0.4986
PV-stent	0.537 (0.195 – 1.481)	0.2298
Chemotherapy	0.349 (0.206 – 0.590)	<0.001
Radiotherapy	0.427 (0.220 – 0.830)	0.012

Table 3. Multivariate analysis by Cox's proportional hazard risk model

4. Discussion

In the present study, we used an EMM-stent as the PV-stent, although in general, for a vascular stent, a wall stent is used. The reason for using an EMM-stent is that a wall stent occludes the splenic vein, which is joined to the PV, and may lead to serious complications. In intrahepatic PV stenosis cases, a wall stent can be used, but pancreatic cancer usually causes extrahepatic PV stenosis. Furthermore, in intrahepatic PV stenosis, a percutaneous transhepatic procedure is usually applied to place the wall stent into the PV. However, we placed an EMM-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 more easily managed by laparotomy.

One of the disadvantages of placing an EMM-stent is that the tumor frequently invades through the mesh into the lumen, resulting in re-obstruction. Accordingly, RT and/or ChT are essential to inhibit tumor invasion into the lumen.

The present study included 14 patients who received placement of an EMM-PV-stent and adjuvant ChT or RT, and the RR was 43%: the 1-year survival rate was 54.5% for the EMPV-

stent group vs. 16.2% for the control group, and the MSTs were 13.0 vs. 4.0 months, respectively (p=0.0006). These RR and survival rates are high and long for PC, 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%, while the MST ranged between 4 and 10 months (Van Cutsem et al., 2004; Okusaka & Kosuge, 2004; Pasetto et al., 2004; Heinemann, 2002; Novarino et al., 2004; Berlin et al., 2002), although the sample size of the present study was too small to draw any conclusive interpretations.

The present study also demonstrated that an EMM-PV-stent was not a significant prognostic factor, although the survival rate was significantly higher in the EMM-PV-stent group than the control group. However, ChT and RT were significant prognostic factors by multivariate analysis ($p<0.001$ and 0.0120, respectively). These results indicate that the EMM-PV-stent itself does not improve prognosis, but that ChT and RT may play important roles in regressing the tumor, and that an EMM-PV-stent helps to improve the efficacy of ChT and RT in patients with PH-associated complications that cause liver dysfunction and pancytopenia, especially thrombocytopenia and leucocytopenia (due to hypersplenism), and gastrointestinal bleeding. However, in order to achieve clinically beneficial treatment results, ChT and RT at a sufficient dose to regress the tumor are very important in patients with PH, as a dose of ChT or RT sufficient to regress the tumor cannot be administered. Since liver dysfunction and pancytopenia can easily be exacerbated by ChT and RT, there are major difficulties for the administration of a dose of ChT or RT sufficient to induce regression of PC. Therefore, placement of a PV-stent improves the efficacy of these 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.

We administered UFT, CPA, and GEM as the ChT regimen in most patients. These regimens were unique to our team. GEM now plays a core role in ChT for advanced PC, and various combination regimens have been attempted. The present study used a low dose of GEM at 200 - 400 mg (almost equivalent to 150 - 300 mg/m^2), although most studies used standard doses of GEM at 800 - 1000 mg/m^2. 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 PC resulted in serious myelosuppression, especially thrombocytopenia. Our previous study using this combination regimen with UFT, CPA and GEM at low doses resulted in a 27% RR and 23% clinical benefit response (CBR), and a 10.7 month MST (Nio et al., 2005.).

Here, we oral UFT instead of *iv* 5-fluorouracil (5-FU). In Japan, UFT has been used as a substitute for *iv* 5-FU for various malignancies such as gastric, colorectal, lung and breast cancer, and several studies in other countries have demonstrated that UFT was as effective as *iv* 5-FU, with a better toxicity profile (Sulkes et al., 1998; Van Cutsem & Peeters, 2000). Furthermore, the present ChT combined CPA in addition to GEM and UFT because previous reports including ours demonstrated that CPA augments the antitumor activity of fluoropyrimidines by modulating the activity of various enzymes, which are associated with pyrimidine metabolism, such as augmenting ribonucleotide reductase, inducing thymidine phosphorylase and inhibiting intratumoral activity of dihydropyrimidine dehydrogenase (Haga et al., 1999; Endo et al., 1999; Nio et al., 2007).

As discussed above, the treatment results of advanced or recurrent PC are not satisfactory, and the EMM-stent itself has no effect to regress the tumor; it only improves the PH-

associated symptoms. Recently, various new agents have been introduced to the ChT for advanced PC, including TS-1, capecitabine, oxaliplatin, irinotecan, erlotinib, and taxanes, and these should help to improve the poor outcomes for patients with PC.

5. Conclusion

The placement of an EMM-PV-stent is very beneficial for managing PH-associated symptoms, as well as improving the efficacy of ChT and RT in pancreatic cancer with malignant PV stenosis or obstruction.

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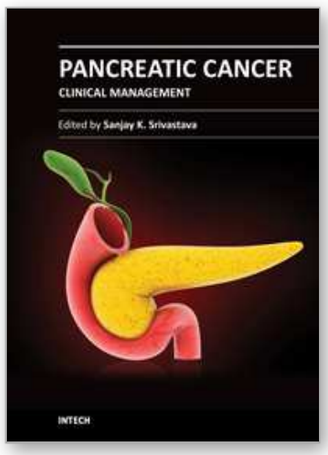

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This book covers pancreatic cancer risk factors, treatment and clinical procedures. It provides an outline of pancreatic cancer genetic risk factors, biomarkers and systems biology for the better understanding of disease. As pancreatic cancer suffers from lack of early diagnosis or prognosis markers, this book encompasses stem cell and genetic makers to identify the disease in early stages. The book uncovers the rationale and effectiveness of monotherapy and combination therapy in combating the devastating disease. As immunotherapy is emerging as an attractive approach to cease pancreatic cancer progression, the present book covers various aspects of immunotherapy including innate, adaptive, active, passive and bacterial approaches. Management of anesthesia during surgery and pain after surgery has been discussed. Book also takes the reader through the role of endoscopy and fine needle guided biopsies in diagnosing and observing the disease progression.

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