



Endoscopic biliary drainage for patients with unresectable pancreatic cancer with obstructive jaundice who are to undergo gemcitabine chemotherapy

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Abstract

AIM: To assess optimum endoscopic biliary drainage (EBD) in cases with unresectable pancreatic cancer in the era of gemcitabine (GEM).

METHODS: Thirty patients with unresectable pancreatic cancer, who presented with jaundice and underwent chemotherapy using GEM after EBD were included in this study (GEM group). Fifteen cases with the same clinical manifestation and stage of pancreatic cancer treated with EBD alone were also included as controls. A covered metallic stent (CMS) or a plastic stent (PS) was used for EBD. The mean survival time (MST) in each group, risk factors of survival time, type of stent used and associated survival time, occlusion rate of stent, patency period of stent, and risk factors of stent occlusion were evaluated.

RESULTS: MST in the GEM group was longer than that in the control (9.9 mo vs 6.2 mo). In the GEM group, the survival time was not different between those who underwent metallic stenting and those who underwent plastic stenting. Stent occlusion occurred in 60% of the PS group and 7% of the CMS group. The median stent patency in the PS-GEM group and the CMS-GEM group was 5 mo and 7.5 mo, respectively. Use of a PS was the only risk factor of stent occlusion.

CONCLUSION: A CMS is recommended in cases presenting with jaundice due to unresectable pancreatic cancer, since the use of a CMS makes it possible to continue chemotherapy using GEM without repetition of stent replacement.

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Key words: Gemcitabine chemotherapy; Endoscopic

INTRODUCTION

Pancreatic cancer is one of the most intractable malignancies of the digestive tract and has a dismal prognosis. Such cancer in most patients is in an advanced stage when they first visit medical facilities, and management of obstructive jaundice caused by the tumor is of great concern in the treatment. Endoscopic biliary drainage (EBD) is the mainstay in the control of jaundice^[1-5]. Due to a relatively short survival time after establishment of the diagnosis, placement of a plastic stent is considered to be reasonable from the viewpoint of cost-effectiveness^[2,3,6-8]. The development of anticancer agents, however, has necessitated reassessment of the optimal choice of stents in this patient group. We evaluated the optimum EBD in cases with unresectable pancreatic cancer in the era of gemcitabine (GEM) chemotherapy.

MATERIALS AND METHODS

Subjects

One hundred and twelve patients with unresectable pancreatic cancer presented with obstructive jaundice at our medical center during the period from May 2001 to March 2005. Of those, 30 patients (age, 80 years or less; Karnofsky performance status, 60% or greater; stage IV or greater) who achieved successful decompression of the biliary tree by EBD and underwent chemotherapy with GEM were included in this study (GEM group). Fifteen cases that fulfilled the same criteria and were treated by EBD and the best possible supportive care without chemotherapy during an earlier period (May 1997 to November 2000) were selected as a control. The demographics of the two groups are shown in Table 1.

Table 1 Patients characteristics

	GEM group <i>n</i> = 30	Control group <i>n</i> = 15	<i>P</i>
Age (yr)	61 ± 10	67 ± 8	0.06
Male/Female	21/9	7/8	0.13
Stage (IVa/IVb)	22/8	7/8	0.08
PS/CMS	¹ 15/15	11/4	0.32

GEM: gemcitabine; PS: plastic stent; CMS: covered expandable metallic stent.

¹The PS was exchanged to CMS after occlusion in 4 patients.

Table 2 Prognostic factors of survival by univariate analysis

	OR	95% CI	<i>P</i>
Age	1.03	1.00-1.06	0.08
Gender (Female)	1.56	0.81-2.99	0.18
Stage (IVb)	2.36	1.15-4.84	0.02
Liver metastasis (+)	2.55	1.24-5.22	0.01
Gemcitabine (-)	2.72	1.35-5.48	0.01

Methods

GEM was administered in a standard manner, i.e., a drip infusion of 1000 mg/m² at a stable speed was given once per week for three consecutive weeks with an interval of one week between courses. After confirming a decrease in the serum total bilirubin level of 20 mg/L or less, administration of GEM was started. When some adverse events occurred, administration of GEM was postponed or its dose was reduced. Adverse effects were evaluated following National Cancer Institute Common Terminology Criteria for Adverse Events ver.3.0 (CTCAE)^[9]. The stents used were covered expandable metallic stents 10 mm in caliber (covered biliary Wallstent, Boston Scientific Co.) (CMS) and plastic stents 10 Fr in diameter (Double Layer Biliary Stent, Olympus Co.) (PS). In the GEM group, CMS was placed in 15 patients (CMS-GEM group) and PS was applied in the remaining 15 (PS-GEM group). In the control group, CMS was deployed in 4 patients (CMS-alone group), while PS was applied in the remaining 11 (PS-alone group). The period of stent patency was measured from the day of stenting to the day when the initial occlusion was diagnosed. Stent occlusion was defined as development of cholangitis or jaundice with abnormalities in laboratory tests indicating bile stasis. When a PS has clogged and was replaced with a CMS, the duration from placement of PS to its occlusion was regarded as the patency period of PS. As for survival time, the total period was counted as PS in such cases. In the CMS group, when the stent was occluded and was replaced with a PS, the duration between the initial stenting and the second stenting was measured as the patency period of CMS, and the total time until death was regarded as the survival time for this group. The median survival time (MST) was calculated based on the definition of survival time as the time from the day of hospitalization to that of death or the last date of confirmed survival. The following were evaluated: (1) MST of the GEM group and the control, (2) prognostic factors, (3) correlation between the stent applied and survival time,

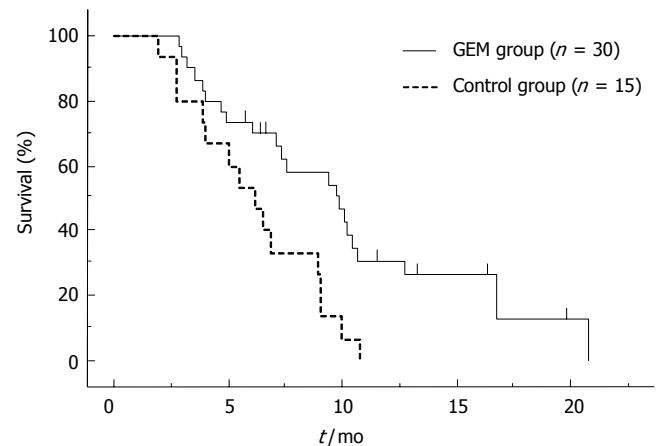


Figure 1 Survival time in GEM and control groups (9.87 ± 0.33 vs 6.23 ± 0.93 , $P = 0.004$).

(4) occlusion rate and patency of stents, (5) risk factors of stent occlusion, and (6) complications of stenting and adverse events of GEM.

Statistical analysis

Stat View v5.0 was used for statistical analysis. Comparison of the two groups was carried out using the Chi-square test, the unpaired *t* test (Student's *t*-test), or the Mann-Whitney *U* test, MST and the median patency time of stents were evaluated by the Mantel-Cox log rank test of the Kaplan-Meier curves. For the analysis of the risk factors of stent patency and survival, univariate analysis by Cox's proportional hazard model followed by multivariate analysis was performed.

RESULTS

The mean survival time in the GEM group and the control was 9.9 mo and 6.2 mo, respectively (9.87 ± 0.33 vs 6.23 ± 0.93 , $P = 0.004$, Figure 1). The following were listed as prognostic factors of survival by univariate analysis: clinical stage of pancreatic cancer (IVa vs IVb, $P = 0.02$; OR = 2.36; 95% CI, 1.15-4.84), liver metastasis (+ vs -, $P = 0.01$; OR = 2.55; 95% CI, 1.24-5.22), and GEM treatment (+ vs -, $P = 0.01$, OR = 2.72; 95% CI, 1.35-5.48) (Table 2). Multivariate analysis, however, revealed that none of these prognostic factors had reached the level of significance. The survival curves of the PS group and the CMS group with/without GEM are shown in Figures 2 and 3. There were significant difference between the PS-alone group and the PS-GEM group (5.53 ± 0.94 vs 10.1 ± 2.70 , $P = 0.02$), as well as between the PS alone group and the CMS-GEM group (5.53 ± 0.94 vs 9.87 ± 0.43 , $P = 0.001$). The difference between the CMS-GEM group and the PS-GEM group was not significant (9.87 ± 0.43 vs 10.1 ± 2.70 , $P = 0.26$, Figure 4). Stent obstruction was observed more frequently in the PS group than in the CMS group (PS vs CMS, $P = 0.0002$; OR = 26.4; 95% CI, 11.4-14.6). Only one patient developed stent occlusion (1/15, 7%), which was due to overgrowth of the tumor in the CMS-GEM group; this was treated by additional PS stenting. The stent patency in the PS-GEM group and PS-alone group was 5.0 mo and

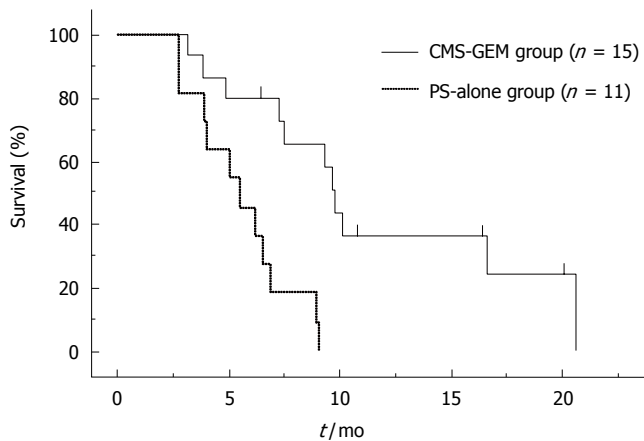


Figure 2 Survival curves of CMS-GEM and PS-alone groups (9.87 ± 0.43 vs 5.53 ± 0.94 , $P = 0.001$).

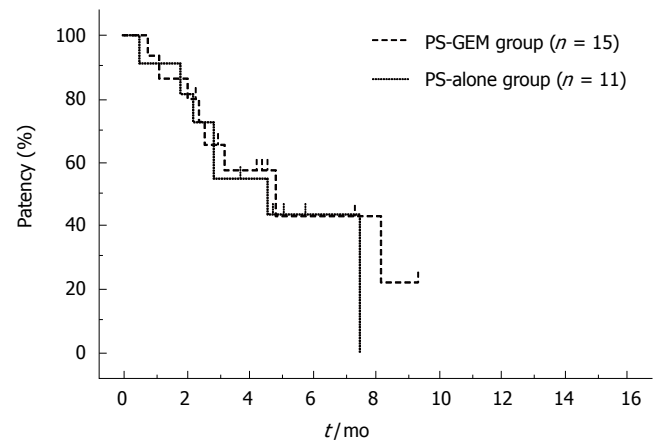


Figure 5 Stent patency in PS-GEM and PS-alone groups (5.00 ± 2.26 vs 4.53 ± 1.31 , $P = 0.59$).

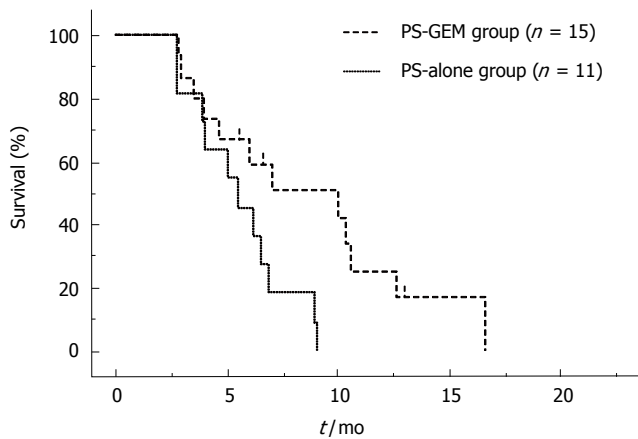


Figure 3 Survival curves of PS-GEM and PS-alone groups (10.1 ± 2.70 vs 5.53 ± 0.94 , $P = 0.02$).

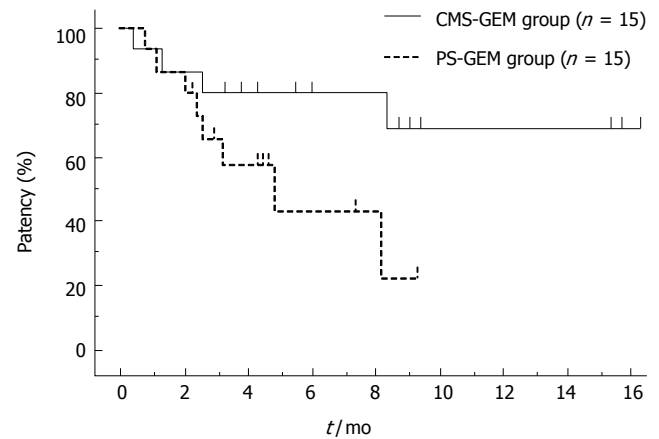


Figure 6 Stent patency in CMS-GEM and PS-GEM groups (7.49 ± 0.82 vs 5.0 ± 2.26 , $P = 0.03$).

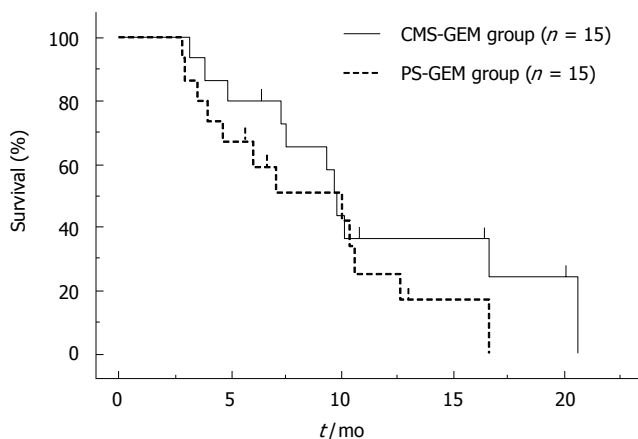


Figure 4 Survival curves of CMS-GEM and PS-GEM groups (9.87 ± 0.43 vs 10.1 ± 2.70 , $P = 0.26$).

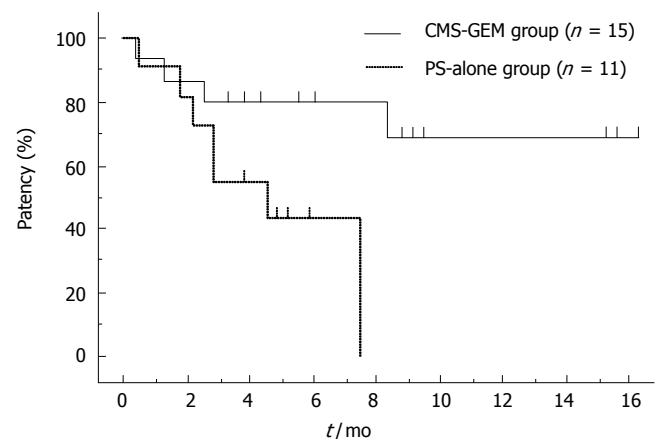


Figure 7 Stent patency in CMS-GEM and PS-alone groups (7.49 ± 0.82 vs 4.53 ± 1.31 , $P = 0.01$).

4.5 mo, respectively (5.00 ± 2.26 vs 4.53 ± 1.31 , $P = 0.59$, Figure 5). Compared with these two groups, the CMS-GEM group showed a patency of 7.5 mo (not reached) (5.00 ± 2.26 vs 7.49 ± 0.82 , $P = 0.03$ and 5.00 ± 4.53 vs 1.31 ± 0.82 , $P = 0.01$, respectively, Figures 6 and 7). Univariate

analysis revealed use of a plastic stent to be the only risk factor of stent occlusion ($P = 0.01$; OR = 4.7; 95% CI, 1.48-15.4, Table 3). One patient each in the CMS-GEM and the CMS-alone groups developed acute cholecystitis. Either dislodgement of a stent or development of acute

Table 3 Risk factors of stent occlusion by univariate analysis

	OR	95% CI	P
Age	1.00	0.95-1.05	1.00
Gender (Male)	2.01	0.72-5.60	0.18
Stage (IVb)	1.30	0.57-3.31	0.59
Liver metastasis (+)	1.46	0.57-3.74	0.43
Stent (PS)	4.76	1.48-15.4	0.01
Gemcitabine (-)	1.30	0.51-3.33	0.59

Table 4 Adverse effects of GEM chemotherapy n (%)

	Grade		
	1	2	3
Bone marrow 24 (89) (n = 27)			
Leukocytes 17 (71)	5 (21)	10 (42)	2 (8)
Hemoglobin 17 (71)	10 (42)	7 (29)	
Platelets 6 (25)	3 (13)	1 (4)	2 (8)
Gastrointestinal 6 (20) (n = 30)			
Anorexia 3 (9)		1 (3)	2 (6)
Nausea 5 (15)	2 (6)	2 (6)	1 (3)

Administration of gemcitabine (GEM) was abandoned due to adverse effects in 4 patients.

pancreatitis after stent placement was observed. In the GEM group, 24 patients (89%) showed adverse effects of GEM on the bone marrow system, these effects benign grade 3 or greater in 4 patients. Reduction of the dose of GEM was necessary in 3 patients due to bone marrow suppression and in 7 due to digestive symptoms such as nausea and anorexia. Finally, administration of GEM was abandoned due to adverse effects in 4 patients (Table 4).

DISCUSSION

Before starting chemotherapy, biliary drainage is mandatory in patients with unresectable pancreatic cancer who present with obstructive jaundice. Endoscopic biliary drainage (EBD) is now widely used for such purpose. Many studies have been published on the selection of stents in EBD^[1-5]. With regard to PS, development of Teflon stents^[4,10] has not been able to prolong the patency period much longer than that of polyethylene stents^[5,11-13]. Many a study has revealed the patency of metallic stents to be longer than that of PS^[1-3]. The reported patency is 3-5 mo for PS^[1-3,5,7,14] and nearly 9 mo for metallic stents^[1-3,14]. In current clinical practice, stent selection is based on the stage of malignancy and expected prognosis. Distant metastasis, tumor size, and local extension are considered to be prognostic factors^[15-17]. In cases with short life expectancy (4-6 mo or less), such as in advanced pancreatic cancer, occlusion of PS usually does not occur before death, and application of PS is considered to be adequate from the viewpoint of cost-effectiveness as well^[2,3,6-8]. Thus far, chemotherapy, radiation and chemoradiotherapy have been performed for patients with unresectable pancreatic

cancer, which necessitates hospitalization. However, the results have been quite unsatisfactory. Development of GEM has had an impact on the treatment. Rothenburg *et al*^[18] reported significant prolongation of survival with GEM in their phase II study of patients in whom 5-FU was not effective. Burris *et al*^[19] carried out a randomized controlled trial on the comparison of GEM with 5-FU in cases without previous chemotherapy, and reported that although mass reduction was observed in only 5.4% of the cases, alleviation of symptoms was achieved in 23.8% with a significant difference. The survival time was also significantly prolonged in the patient group treated with GEM compared with that in the 5-FU group. GEM is given to patient by drip infusion at a stable speed that requires a relatively short time without critical side effects, enabling its administration on an outpatient basis. Shortening of the period of hospitalization is quite meaningful for patients with poor prognoses. In this study, prolongation of MST by GEM in patients with stage IV pancreatic cancer was confirmed. With respect to MST, there was no difference between the CMS-GEM group and the PS-GEM group. However, stent occlusion developed more frequently in the PS-GEM group than in the CMS-GEM group (60% *vs* 7%). Stent occlusion may necessitate postponement of administration of GEM and requires additional intervention or hospitalization, which leads to deterioration of the patient's QOL. Possible influences of GEM on the patency of stents are prolongation of patency by controlling the tumor mass and shortening of patency by clogging subsequent to biliary infection induced by bone marrow suppression. As the comparison of stent patency in the PS-GEM group and that in the PS-alone group showed no difference, GEM may have no or only a subtle effect on the stent patency. Acute cholecystitis, which was managed conservatively, was the only complication relevant to stenting. Discontinuance of GEM due to adverse effects was necessary in only 16% of the patients. When compared to that of the PS group, the stent patency of the CMS-GEM group was longer. It is expected that those patients who are to undergo GEM will have a longer survival than that before GEM was available. The significance of the maintenance of stent patency is much greater than before as it can eliminate readmission due to stent occlusion and postponement of GEM. Development of effective chemotherapy, including a combination of some agents, will further extend the significance of longer stent patency further. The selection of stents should be reassessed from this point of view. Based on the data shown here, we suggest that the use of CMS should be considered in patients with unresectable pancreatic cancer presenting with jaundice that are to undergo GEM. Further studies including cost-benefit assessment and a randomized, prospective comparison trial with metallic and plastic stents are necessary.

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