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Radiotherapy Prolongs Biliary Metal Stent Patency in Malignant Pancreatobiliary Obstructions

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Background/Aims: Biliary stenting is the most effective decompressive method for treating malignant biliary obstructive jaundice. Although the main cause of stent occlusion is tumor growth, few studies have investigated whether stent patency is affected by the combination of cancer-treatment modalities. The aim of this study was to evaluate the effects of local radiotherapy on metal-stent patency in patients with malignant biliary obstruction. **Methods:** Patients who underwent self-expandable biliary metallic stenting for malignant biliary obstruction from 1999 to 2007 were included. Forty patients received chemotherapy and radiation therapy (radiation group, RG), and 31 patients received only chemotherapy (nonradiation group, NRG). **Results:** The cumulative median stent patency was significantly longer in the RG than in the NRG (17.7 months; 95% confidence interval [CI], 1.8 to 33.6 months vs 8.7 months; 95% CI, 4.9 to 12.5 months; p=0.025). Stent occlusion caused by tumor growth or stent migration occurred in two (5%) and three (7.5%) cases in the RG and in six (19.3%) and two (6.5%) cases in the NRG, respectively. **Conclusions:** The patency of biliary metal stents in pancreatobiliary cancer patients who receive chemoradiation therapy is significantly longer than that in patients who do not receive radiotherapy, which suggests that local cancer control significantly affects stent patency. **(Gut Liver 2013;7:480-485)**

Key Words: Biliary metal stent; Malignant biliary obstruction; Radiotherapy; Stent patency

INTRODUCTION

Despite advances in therapeutic options, the 5-year survival rate for pancreatobiliary cancer is reported less than 5%.[1] Most of these malignancies are inoperable at the time of diagnosis, and 70% to 90% of patients with pancreaticobiliary cancer have jaundice due to bile duct obstruction. The biliary obstruction exacerbates the clinical condition and quality of life by causing cholangitis, sepsis, and hepatic failure.[2] However, the general condition of most patients with inoperable pancreatobiliary cancers is usually too poor for them to endure a major operation.[2] Biliary stenting can relieve obstructive jaundice and improve the quality of life for patients with inoperable pancreatobiliary cancer. It has also been shown to be safer and as effective as decompressive bypass surgery.[3,4] So, biliary stent decompression is the preferred method of treatment. Factors influencing the patency of biliary metal stents include the type of metal stent (covered or uncovered), the various complications that occur as a result of stent occlusion or stent migration, and the cancer treatment modality used.[5-11] External radiotherapy with concurrent chemotherapy has been treatment of choice for inoperable locally advanced pancreatobiliary cancer.[9,10,12] Recent studies have also reported on the efficacy of local treatments for pancreatobiliary cancers consisting of external radiotherapy, intraluminal brachytherapy, or photodynamic treatment.[12-14] Among these reports, studies focusing on the effects of local treatments, especially external radiotherapy with concurrent chemotherapy to the metal stent patency were relatively few.

The aim of this study was to compare the patency of biliary metal stents in a radiation group (RG) with a nonradiation treatment group (NRG), and to determine if a local cancer treatment, such as radiotherapy, affects the patency of metal stents in ma-

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lignant biliary obstruction.

MATERIALS AND METHODS

1. Patients

Patients with biliary obstructions due to inoperable malignant causes at the Pancreatobiliary Cancer Clinic, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea between January 1999 and August 2007 were included in this study. Forty patients with unresectable pancreatobiliary cancer who had been treated with concurrent chemoradiation therapy were assigned to the RG and 31 patients who had received only systemic chemotherapy were assigned to the NRG. An inoperable malignant biliary obstruction was defined as an obstruction due to tumor at the intrahepatic or extrahepatic bile ducts that could not be curatively resected. In the RG, radiation therapy was administered to the primary tumor site and regional lymph nodes. The total radiation dose in the RG was 45 to 50.4 grays/28 fractions over 4 to 6 weeks by conventional radiation therapy. In the RG and NRG, five variable chemotherapy regimens and doses were used in pancreatic cancer patients as below. Gemcitabine plus cisplatin chemotherapy (gemcitabine 1,000 mg/m^2 intravenous administration (IV) on days 1, 8, and 15; and cisplatin 70 mg/m^2 IV on day 1 of each 4 weeks cycle), gemcitabine monotherapy (gemcitabine 1,000 mg/m^2 IV on days 1, 8, and 15 of each 4 weeks cycle), gemcitabine plus capecitabine combination therapy (gemcitabine 1,000 mg/m^2 IV on days 1, 8, and 15; and oral administration of capecitabine 1,660 mg/m^2 on days 1 to days 21 of each 4 weeks cycle), 5-fluorouracil plus cisplatin chemotherapy (5-fluorouracil 1,000 mg/m^2 IV on days 1, 2, and 3; and cisplatin 70 mg/m^2 IV on day 2 of each 4 weeks cycle), and taxol plus 5-fluorouracil combination therapy (taxol 175 mg/m^2 IV on day 1; and 5-fluorouracil 1,000 mg/m^2 IV on days 1, 2, and 3 of each 4 weeks cycle) were used. Furthermore, bile duct tract cancer patients including the ampulla of Vater cancer patients were treated according to the below regimens in both groups. Regimens of gemcitabine plus cisplatin chemotherapy and 5-fluorouracil plus cisplatin chemotherapy were the same as previously mentioned. Etoposide plus 5-fluorouracil plus ciplatin triple combination chemotherapy (Etoposide 100 mg/m^2 IV on days 1, 2, and 3; 5-fluorouracil 1,000 mg/m^2 IV on days 1, 2, and 3; and cisplastin 70 mg/m^2 IV on day 1 of each 4 weeks cycle), 5-fluorouracil monotherapy (5-fluorouracil 1,000 mg/m^2 IV on days 1, 2, and 3 of each 4 weeks cycle), and TS-1 monotherapy (oral administration of 70 mg/m^2 on days 1 to days 14 of each 3 weeks cycle) were used. This study is a restrospective analysis.

2. Biliary metal stent insertion

All 71 patients underwent metal stent insertion with 32 covered and 39 uncovered stents. At first, stent insertion was attempted endoscopically in included patients, after confirmation of unresectability and malignant biliary obstruction by imaging and pathologic studies. The endoscopic approach failed in nine cases including patients without a full expansion of metal stent, and then they performed by transhepatic approach percutaneously. A lumen diameter of metal stent just after stent placement and dilatation was about 10 mm in technically successful insertion. Functional success was defined as a relieving of obstructive jaundice due to malignant biliary obstruction by metal stent insertion. All biliary metal stents were commercially available and manufactured by various companies (Boston Scientific Co., Natick, MA, USA; Taewoong Medical Inc., Gimpo, Korea). Niti-S biliary covered and uncovered stent by Taewoong Medical Inc. were used in this study. They are made of nitinol, a nickel-titanium alloy with or without silicone covering. In this study, Wallstent bare and covered biliary stent by Boston Scientific Co. were also inserted. Wallstent is manufactured from medical stainless steel with or without covered silicone.[15]

Stent malfunction was defined as a nonfunctioning stent status with abnormal clinical parameters showing obstructive jaundice, after the endoscopic or transhepatic cholangiographic evaluations. Causes of stent malfunction were classified as tumor ingrowth, sludge impaction, extraluminal tumor compression due to cancer outgrowth, or stent migration. Stent patency was defined as the duration of time from stent insertion to stent malfunction.

3. Evaluation

Our primary aim was to compare the patency of metal stents between the RG and the NRG. Our secondary aim was to determine the complications and causes of stent malfunctions. And we also evaluated the affective factors on stent patency. A monthly patient follow-up was carried out according to the maintenance protocol of the Yonsei Pancreatobiliary Cancer Clinic, including laboratory test, clinical condition, and confirmation of stent patency.

4. Statistical analysis

Continuous variables were compared with the independent sample t-test and categorical variables with a chi-square test. Values were reported as mean±standard deviation (SD) or median with ranges. Data were expressed as median cumulative patency was estimated by Kaplan-Meier analysis. The associations between stent patency and risk variables were assessed by multivariate Cox regression analysis. Age, sex, stage of disease, location of the cancer (pancreatic cancer or biliary cancer), types of stent (covered or uncovered stent), cancer treatment modalities (RG or NRG), and chemotherapy regimens (gemcitabine-based, 5-fluorouracil-based, or taxane-based drugs) were included as parameters in the multivariate Cox regression analysis. All analyses were performed by SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). A p-value <0.05 was considered significant.

RESULTS

1. Patient characteristics

Seventy-one patients (44 men and 27 women) with malignant biliary obstructions were included in this study. The mean age of the patients was 65.8±8.04 years (range, 44 to 79 years). There were no differences in baseline characteristics between patients in the RG and NRG (Table 1). In the RG, a higher proportion of patients had locally advanced cancers than in the NRG (70% vs 22.6%, respectively; p<0.001). Pancreatic cancer was the most common cause of malignant biliary obstruction, occurring in 59% of all cases. The location of malignant tumors including the pancreas, gallbladder, bile duct, or ampulla of Vater, was also not significantly different between the two groups. For patients with pancreatic cancer, the chemotherapy regimens included gemcitabine-based (71%), 5-fluorouracil-based (11.9%), or taxane-based drugs (16.7%). In contrast, the chemotherapy regimens for cancers in the gallbladder and bile duct included gemcitabine (40%), a combination of 5-flourouracil with cisplatin (44%), or 5-flourouracil monotherapy (16%).

2. Stent patency

Cumulative median stent patency was significantly longer in the RG than in the NRG (17.7 months, 95% confidence interval [CI], 1.8 to 33.6 months; and 8.7 months, 95% CI, 4.9 to 12.5 months, respectively; p=0.025) (Fig. 1). Subgroup analysis revealed that the patency of covered stents (RG and NRG; 12.2 and 7.2 months, respectively) and uncovered stents (RG and NRG; 17.7 and 9.6 months, respectively) was also longer in the RG (p=0.023). We also evaluated the prognostic factors for stent patency. The only influencing factor for prolonged stent patency was cancer treatment modality (odds ratio, 12.4; 95% CI, 1.1 to 141.9; p=0.042). Stent patency was only influenced by combined chemotherapy and radiation therapy (RG) compared with chemotherapy (NRG). Stent patency was not affected by other risk variables such as age, sex, stage, location of the cancer, types of stent, and regimens of chemotherapy. Regimens of chemotherapy were divided by following three groups; gemcitabine-based, 5-fluorouracil-based, and taxane-based drugs. There was no significant difference in metal stent patency according to each chemotherapy regimen (p=0.348).

Table 1. Patient Characteristics

Characteristic	RG	NRG	p-value
No. of patients	40	31	
Sex, M/F	25/15 (62.5/37.5)	19/12 (61.3/38.7)	0.917
Age, yr	67.2±6.9	64.0±9.0	0.094
Cancer location			0.057
Pancreas	29 (72.5)	13 (41.9)	
Gallbladder	9 (22.5)	12 (38.7)	
Bile duct	1 (2.5)	3 (9.6)	
Ampulla of Vater	1 (2.5)	3 (9.6)	
Cancer stage			<0.001
Locally advanced	28 (70.0)	7 (22.6)	
Distant metastasis	12 (30.0)	24 (77.4)	
Procedure for stent insertion			0.165
Endoscopic	37 (92.5)	25 (80.6)	
Transhepatic	3 (7.5)	6 (19.4)	
Types of stent			0.810
Covered stent	19 (47.5)	13 (41.9)	
Uncovered stent	21 (52.5)	18 (58.1)	
Biochemical profiles			
AST, IU/L	133.1±128.3	123.0±98.5	0.719
ALT, IU/L	171.6±155.7	127.3±109.3	0.182
Alkaline phosphatase, IU/L	567.3±343.2	514.8±406.2	0.560
Total bilirubin, mg/dL	12.3±8.5	9.8±11.3	0.280
Bilirubin after stenting, mg/dL	2.9±3.9	2.3±2.3	0.489

Data are presented as mean±SD or number (%).
RG, radiation group; NRG, nonradiation group; M, male; F, female; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 2. Stent Patency and Causes of Stent Malfunction

	RG (n=40)	NRG (n=31)	p-value
Median stent patency (95% CI), mo	17.7 (1.8-33.6)	8.7 (4.9-12.5)	0.025
Covered	12.2 (8.7-15.7)	7.2 (6.5-7.9)	
Uncovered	17.7 (4.9-30.5)	9.6 (7.5-11.7)	
Stent malfunction	10 (25.0)	9 (29.0)	0.790
Covered stent	6 (15)	6 (19.3)	0.721
Obstruction by tumor growth	1 (2.5)	3 (9.7)	
Sludge or cholangitis	2 (5.0)	1 (3.2)	
Stent migration	3 (7.5)	2 (6.4)	
Uncovered stent	4 (10.0)	3 (9.7)	0.539
Obstruction by tumor growth	1 (2.5)	3 (9.7)	
Sludge or foods	3 (7.5)	0 (0)	
Stent migration	0 (0)	0 (0)	

Data are presented as number (%).
RG, radiation group; NRG, nonradiation group; CI, confidence interval.

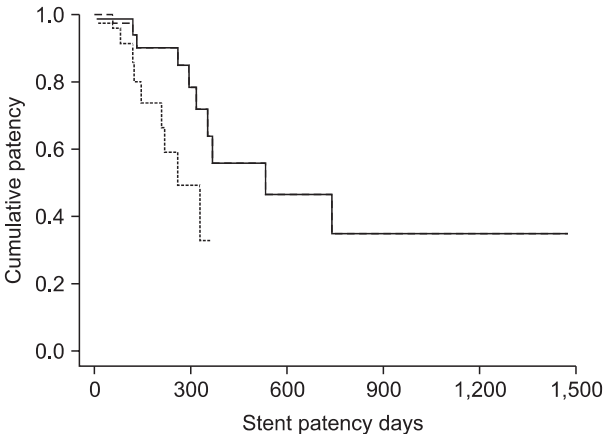

Fig. 1. Median patency of metal stents in the radiation group (RG; solid line) and nonradiation group (NRG; dotted line). Stent patency in the RG was longer than that in the NRG (17.7 and 8.7 months, respectively; p=0.025).

3. Stent complications

There were no stent insertion-related serious complications such as perforation or death. Stent occlusion occurred in seven patients (17.5%) in the RG and was caused by tumor growth (n=2, 5%) or sludge and foods (n=5, 12.5%). In the NRG, stent occlusion also occurred in seven patients (22.6%) and was caused by tumor growth (n=6, 19.3%) or sludge (n=1, 3.2%). Stent migration was observed only in covered stents with three cases (7.5%) in the RG and two cases (6.5%) in the NRG. There were no significant differences in the causes of stent malfunction between the two groups (Table 2).

DISCUSSION

This study shows that the patency of biliary metal stents in patients with malignant biliary obstruction receiving chemoradiation therapy was significantly longer than in patients without radiotherapy. It is suggested that local cancer control significantly affects stent patency.

Endoscopic stent placement using self-expandable metal stents (SEMS) is an established method of palliative treatment for relieving obstructive jaundice in patients with unresectable pancreatobiliary malignancies.[7,16] SEMS were introduced at the end of the 1980s to overcome the disadvantages of plastic stents with respect to patency and durability.[17-20] Although plastic stenting provides adequate drainage, late complications with stent occlusion from biliary infection and sludge formation have limited the clinical benefits of plastic stents. Therefore, biliary SEMS should be used if the expected survival is greater than 6 months.[21] Factors reported to influence the patency of biliary stents include the type of metal stent (covered or uncovered), the type of complication following stent occlusion, the presence of duodenobiliary reflux (especially for plastic stents),[22] and the cancer treatment modality.[8-11,13] Takasawa *et al*.[23] reported that gemcitabine chemotherapy resulted in longer patency with metal stents than with plastic stents in patients with unresectable pancreatic cancer. Other study by Bowling *et al*.[9] has shown that the number of stent changes per patient was not statistically different between the control group and the radiotherapy group in patients with unresectable cholangiocarcinoma. This also means that radiation treatment does not reduce stent changes. The authors showed that these results were due to longer hospitalization stays, better medical care, and more timely interventions for complications for patients in the radiotherapy group, which resulted in more frequent stent changes than in the control group. Therefore, related studies on patients treated with local radiation therapy in pancreatobiliay cancers were focused on the survival benefit not the biliary metal stent

patency.

In this study, the two treatment groups had similar clinical characteristics including treatment of systemic chemotherapy except cancer stage and location. Actually, this retrospective cohort study showed a mismatch of cancer stage in each group and heterogenous cancer types. Pancreatic cancers and biliary tract cancers like gallbladder cancer, intrahepatic cholangiocarcinoma, common bile duct cancer, or ampulla of Vater cancer had different tumor behavior, median overall survival and prognosis of disease, respectively.[24-28] Especially, advanced stage of disease might influence stent patency caused by less active treatments or early death or follow-up loss. Hence, we tried to analyze the influencing factors on the stent patency for statistical compensating the mismatch of cancer stage and various types of cancer. As a result, the single factor for prolonged stent patency was cancer treatment modality; RG versus NRG.

This study was mainly focused on stent patency influenced by local control of tumors. Up to the present, a study on the effect of cancer local treatment, especially radiation therapy on the biliary stent patency was rarely reported. Therefore, we were able to demonstrate that local radiation treatment combined with systemic chemotherapy rather than chemotherapy alone can prolong the patency of biliary metal stents in unresectable malignant obstruction and potentially improve the quality of life for cancer patients with terminal stage. In subgroup analysis, the overall patency of uncovered stents was similar with that of covered stents in both groups (RG and NRG) (p=0.14).

The strength of this study was that it was a clinical study focused to the relation between active multimodality treatment, especially local cancer control, and the prolongation of metal stent patency in advanced cancer patients with poor prognosis. Consequently, this prolongation could cause the improvement of quality of life in terminally ill patients. However, our study had some limitations. It was not a large-scale, randomized, prospective study, even though the follow-up protocol was predefined. There would be a selection bias due to nonrandomized controlled trial. Additionally, there were significant differences in cancer stages between the two groups, in spite of statistical adjustment on the effects of stent patency. And, heterogenous cancer types, especially small number of cases with a part of biliary tract cancers, were one of the difficult factors to analyze. Placement of not unified stents from various manufacturers' covered or uncovered stent were also an obstacle to perform a precise analysis. Although the minimal tendency to have a better survival was showed in the RG, median overall survival days were not significantly different between two groups in this study (p=0.906). Subgroup analysis dividing disease stage (locally advanced versus distant metastasis) in patients with pancreatic cancer had similar findings without statistical difference.

In conclusion, the patency of metal stents was significantly prolonged in the RG compared to the NRG. Therefore, the patency of stents can be prolonged by local cancer treatment in unresectable malignant biliary obstruction. Comparisons of stent patency should be interpreted carefully with consideration of treatment modalities. Future prospective studies involving larger numbers of patients are required to further elucidate the effects of local treatment of pancreatobiliary cancer on the improvement of metal stent patency.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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