Radiotherapy Prolongs Biliary Metal Stent Patency in Malignant Pancreatobiliary Obstructions

Semi Park*,†, Jeong Youp Park‡, Seungmin Bang*,§, Seung Woo Park*,†, Jae Bock Chung‡, and Si Young Song*,†

*Department of Internal Medicine, Graduate School, Yonsei University College of Medicine, †Center for Health Promotion, Samsung Medical Center, Sungkyunkwan University School of Medicine, ‡Division of Gastroenterology, Department of Internal Medicine, Yonsei Institute of Gastroenterology, Yonsei University College of Medicine, and §Brain Korea 21 Project for Medical Science, Yonsei University College of Medicine, Seoul, Korea

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 pancreaticobiliary cancer is reported less than 5%. 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. However, the general condition of most patients with inoperable pancreaticobiliary cancer is usually too poor for them to endure a major operation. Biliary stenting can relieve obstructive jaundice and improve the quality of life for patients with inoperable pancreaticobiliary cancer. It has also been shown to be safer and as effective as decompressive bypass surgery. 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. External radiotherapy with concurrent chemotheraphy has been treatment of choice for inoperable locally advanced pancreaticobiliary cancer. Recent studies have also reported on the efficacy of local treatments for pancreatobiliary cancers consisting of external radiotherapy, intraluminal brachytherapy, or photodynamic treatment. Among these reports, studies focusing on the effects of local treatments, especially external radiotherapy with concurrent chemotheraphy 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-
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 pancreaticobiliary 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/m² intravenous administration (IV) on days 1, 8, and 15; and cisplatin 70 mg/m² IV on day 1 of each 4 weeks cycle), gemcitabine monotherapy (gemcitabine 1,000 mg/m² IV on days 1, 8, and 15 of each 4 weeks cycle), gemcitabine plus capecitabine combination therapy (gemcitabine 1,000 mg/m² IV on days 1, 8, and 15; and oral administration of capecitabine 1,660 mg/m² on days 1 to days 21 of each 4 weeks cycle), 5-fluorouracil plus cisplatin chemotherapy [5-fluorouracil 1,000 mg/m² IV on days 1, 2, and 3; and cisplatin 70 mg/m² IV on day 2 of each 4 weeks cycle], and taxol plus 5-fluorouracil combination therapy (taxol 175 mg/m² IV on day 1; and 5-fluorouracil 1,000 mg/m² 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 cisplatin triple combination chemotherapy [Etoposide 100 mg/m² IV on days 1, 2, and 3; 5-fluorouracil 1,000 mg/m² IV on days 1, 2, and 3; and cisplatin 70 mg/m² IV on day 1 of each 4 weeks cycle], 5-fluorouracil monotherapy (5-fluorouracil 1,000 mg/m² IV on days 1, 2, and 3 of each 4 weeks cycle), and TS-1 monotherapy (oral administration of 70 mg/m² 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-fluourouracil-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-fluorouracil with cisplatin (44%), or 5-fluorouracil 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    | 19/12    | 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.
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. SEMS were introduced at the end of the 1980s to overcome the disadvantages of plastic stents with respect to patency and durability. 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. 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), and the cancer treatment modality. Takasawa et al. 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. 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 pancreatobiliary cancers were focused on the survival benefit not the biliary metal stent.

**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.
In conclusion, the patency of metal stents was significantly prolonged 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.

REFERENCES

1. Moss AC, Morris E, Leyden J, MacMathuna P. Malignant distal biliary obstruction: a systematic review and meta-analysis of endoscopic and surgical bypass results. Cancer Treat Rev 2007;33:213-221.

2. Conio M, Demarquay JF, De Luca I, Marchi S, Dumas R. Endoscopic treatment of pancreatico-biliary malignancies. Crit Rev Oncol Hematol 2001;37:127-135.

3. Kahaleh M, Brock A, Conaway MR, et al. Covered self-expandable metal stents in pancreatic malignancy regardless of resectability: a new concept validated by a decision analysis. Endoscopy 2007;39:319-324.

4. Cipolletta L, Rotondano G, Marmo R, Bianco MA; Italian Evidence-Based Gastroenterology & Hepatology Club. Endoscopic palliation of malignant obstructive jaundice: an evidence-based review. Dig Liver Dis 2007;39:375-388.

5. Brountzos EN, Prochis N, Panagiotou I, Malagari K, Tzavara C, Kelekis D. A survival analysis of patients with malignant biliary strictures treated by percutaneous metallic stenting. Cardiovasc Intervent Radiol 2007;30:66-73.

6. Schmassmann A, von Gunten E, Knuchel J, Scheurer U, Fehr HF, Halter F. Wallstents versus plastic stents in malignant biliary obstruction: effects of stent patency of the first and second stent on patient compliance and survival. Am J Gastroenterol 1996;91:654-659.

7. Leung J, Rahim N. The role of covered self-expandable metallic stents in malignant biliary strictures. Gastrointest Endosc 2006;63:1001-1003.

8. Eschelman DJ, Shapiro MJ, Bonn J, et al. Malignant biliary duct obstruction: long-term experience with Gianturco stents and combined-modality radiation therapy. Radiology 1996;200:717-724.

9. Bowling TE, Galbraith SM, Hatfield AR, Solano J, Spittle MF. A retrospective comparison of endoscopic stenting alone with stenting and radiotherapy in non-resectable cholangiocarcinoma. Gut 1996;39:852-855.

10. Miura Y, Endo I, Togo S, et al. Adjuvant therapies using biliary stenting for malignant biliary obstruction. J Hepatobiliary Pancreat Surg 2001;8:113-117.

11. Qian XI, Zhai RY, Dai DK, Yu P, Gao L. Treatment of malignant
biliary obstruction by combined percutaneous transhepatic biliary drainage with local tumor treatment. World J Gastroenterol 2006;12:331-335.
12. Hong SP, Park JY, Jeon TJ, et al. Weekly full-dose gemcitabine and single-dose cisplatin with concurrent radiotherapy in patients with locally advanced pancreatic cancer. Br J Cancer 2008;98:881-887.
13. Valek V, Kysela P, Kala Z, Kiss I, Tomásek J, Petera J. Brachytherapy and percutaneous stenting in the treatment of cholangiocarcinoma: a prospective randomised study. Eur J Radiol 2007;62:175-179.
14. Simmons DT, Baron TH, Petersen BT, et al. A novel endoscopic approach to brachytherapy in the management of Hilar cholangiocarcinoma. Am J Gastroenterol 2006;101:1792-1796.
15. Yang KY, Ryu JK, Seo JK, et al. A comparison of the Niti-D biliary uncovered stent and the uncovered Wallstent in malignant biliary obstruction. Gastrointest Endosc 2009;70:45-51.
16. Judah JR, Draganov PV. Endoscopic therapy of benign biliary strictures. World J Gastroenterol 2007;13:3531-3539.
17. Isayama H, Komatsu Y, Tsujino T, et al. A prospective randomised study of “covered” versus “uncovered” diamond stents for the management of distal malignant biliary obstruction. Gut 2004;53:729-734.
18. Yoon WJ, Lee JK, Lee KH, et al. A comparison of covered and uncovered Wallstents for the management of distal malignant biliary obstruction. Gastrointest Endosc 2006;63:996-1000.
19. Piñol V, Castells A, Bordas JM, et al. Percutaneous self-expanding metal stents versus endoscopic polyethylene endoprostheses for treating malignant biliary obstruction: randomized clinical trial. Radiology 2002;225:27-34.
20. Soderlund C, Linder S. Covered metal versus plastic stents for malignant common bile duct stenosis: a prospective, randomized, controlled trial. Gastrointest Endosc 2006;63:986-995.
21. Srikureja W, Chang KJ. Endoscopic palliation of pancreatic adenocarcinoma. Curr Opin Gastroenterol 2005;21:601-605.
22. Dua KS, Reddy ND, Rao VG, Banerjee R, Medda B, Lang I. Impact of reducing duodenobiliary reflux on biliary stent patency: an in vitro evaluation and a prospective randomized clinical trial that used a biliary stent with an antireflux valve. Gastrointest Endosc 2007;65:819-828.
23. Takasawa O, Fujita N, Kobayashi G, Noda Y, Ito K, Horaguchi J. Endoscopic biliary drainage for patients with unresectable pancreatic cancer with obstructive jaundice who are to undergo gemcitabine chemotherapy. World J Gastroenterol 2006;12:7299-7303.
24. Wang J, Wang X, Xie S, et al. p53 status and its prognostic role in extrahepatic bile duct cancer: a meta-analysis of published studies. Dig Dis Sci 2011;56:655-662.
25. Singh P, Srinivasan R, Wig JD. Major molecular markers in pancreatic ductal adenocarcinoma and their roles in screening, diagnosis, prognosis, and treatment. Pancreas 2011;40:644-652.
26. Choi SB, Kim WB, Song TJ, Suh SO, Kim YC, Choi SY. Surgical outcomes and prognostic factors for ampulla of Vater cancer. Scand J Surg 2011;100:92-98.
27. Shakla PJ, Barreto SG. Systematic review: should routine resection of the extra-hepatic bile duct be performed in gallbladder cancer? Saudi J Gastroenterol 2010;16:161-167.
28. Jiang BG, Ge RL, Sun LL, Zong M, Wei GT, Zhang YJ. Clinical parameters predicting survival duration after hepatectomy for intrahepatic cholangiocarcinoma. Can J Gastroenterol 2011;25:603-608.