

Stent insertion for inoperable hilar cholangiocarcinoma

Comparison of radioactive and normal stenting

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Abstract

To assess effectiveness and safety associated with radioactive stenting for hilar cholangiocarcinoma (HCCA) patients.

This single-center retrospective study compared baseline and treatment data of recruited consecutive patients with HCCA underwent either normal or radioactive stenting between January 2016 and December 2019. Clinical success was defined by total bilirubin (TBIL) levels falling below 70% of the preoperative baseline within 2 weeks post stent insertion.

Sixty-five patients with inoperable HCCA underwent normal (n=35) or radioactive (n=30) stenting at our center. Technical success of both types of the normal and radioactive stent insertion was 100%. Each patient received 1 stent. In the radioactive stent group, each patient received 1 radioactive seed strand (RSS), containing 10 to 12 radioactive seeds. Clinical success rates were 86.8% and 100% in normal and radioactive groups, respectively ($P=.495$). We observed stent dysfunction in 9 patients (normal group) and 7 patients (radioactive group) ($P=.824$). Median duration of stent patency was 165 days (normal group) and 226 days (radioactive group) ($P<.001$). During follow-up, all patients died from tumor progression, with respective median survival of 198 days (normal group) and 256 days (radioactive group) ($P<.001$). Seven and 5 patients in the normal and radioactive groups suffered from stent-related complications ($P=.730$).

Radioactive stenting is effective and safe for inoperable HCCA patient and may prolong stent patency and survival.

Abbreviations: CT = computed tomography, ECOG PS = Eastern Cooperative Oncology Group performance status, HCCA = hilar cholangiocarcinoma, MBO = malignant biliary obstruction, MHBO = malignant hilar biliary obstruction, MRI = magnetic resonance imaging, RSS = radioactive seed strand.

Keywords: hilar cholangiocarcinoma, radioactive, stent

1. Introduction

Malignant hilar biliary obstruction (MHBO) may arise in patients suffering from primary or metastatic hepatobiliary tumors.^[1–3] Approximately 80% of MHBO patients are not eligible for operative procedures, and as such palliative interventions are the only treatment currently available.^[1–3] Of available palliative treatments, percutaneous or endoscopic stenting is used most frequently to treat MHBO patients.^[1–3]

Hilar cholangiocarcinoma (HCCA) is the commonest disease causing MHBO.^[4,5] Some studies have focused on metal stenting for HCCA patients.^[2,4,5] Stent patency and survival are the principal endpoints in studies of stenting for MHBO or HCCA.^[1–5] Most such analyses have examined topics such as the comparative benefits of plastic versus metal stents, side-by-side versus stent-in-stent insertion, and unilateral versus bilateral stenting.^[1–6] However, none of these stenting strategies treats tumors directly.

To address this issue, Jiao et al^[7] used a radioactive stent to treat malignant biliary obstruction (MBO) patients: a normal metal stent was combined with a radioactive seed strand (RSS), which might prolong stent patency and survival. Chen et al^[8] also reported using radioactive stenting for MHBO patients. However, a clear need remains for a study comparing these 2 stenting strategies in patients with a single form of cancer.

Herein, we assessed the effectiveness and safety of radioactive stenting for HCCA patients.

2. Materials and methods

The Institutional Review Board at our center approved this retrospective study. As the study was retrospective, written informed consent from patients were waived.

2.1. Study design

Consecutive HCCA patients had either normal or radioactive stenting undertaken between January 2016 and December 2019. Patients treated before December 2017 had normal stenting, while those treated afterwards had radioactive stenting.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Inclusion criteria were: patients with a confirmed HCCA diagnosis, inoperable cases, patients showed evidence of obstructive jaundice, and Eastern Cooperative Oncology Group performance status (ECOG PS) < 4.

Exclusion criteria were: patients who had postoperative external radiotherapy, and patients who experienced severe cardiac, renal, lung, or dysfunctions of coagulation.

After stenting, patients in both groups were permitted to undergo chemotherapy.

2.2. Diagnosis

HCCA was diagnosed based on clinical symptoms and the results of abdominal computed tomography (CT) and magnetic resonance imaging (MRI) analyses. Pathological HCCA diagnosis was confirmed by biopsy.

2.3. Radioactive stents

A radioactive stent combined an uncovered metal stent (Micro-Tech, Nanjing, China) with an RSS.

An RSS combined a 4F catheter (Cook, IN) with multiple ^{125}I seeds (model 6711; Chinese Atomic Energy Science Institution, Beijing, China). The catheter was sealed at the distal end, and ^{125}I seeds placed linearly along the catheter to produce the RSS. Proximal portions of the catheter without seeds were removed. Finally, the proximal tip was sealed.

Individual ^{125}I seeds (dimensions: 4.5-mm long, 0.8-mm diameter) emitted low-energy 35.5-keV γ -rays with a 59.6-day half-life. The length of an observed obstruction was used to estimate the number of seeds added to the RSS.

2.4. Normal stenting

All procedures were performed using fluoroscopic guidance and all patients underwent unilateral stenting. Stent diameter and length were 8 mm and 50 to 70 mm. The right intrahepatic biliary tract was punctured using a 21G Chiba needle (Cook) under fluoroscopic and ultrasonic guidance. Obstructions were visualized using cholangiography. The extent of any obstruction was evaluated using a 4F VER catheter (Cordis, FL) and a 0.035-in. guide wire (Terumo, Tokyo, Japan). Once the catheter and guide wire were inserted past the obstruction, the guide wire was replaced with a 0.035-in. stiff guide wire (Cook), which was used to release the stent at the obstructed site.

2.5. Radioactive stenting

All patients underwent unilateral stenting. Cholangiography was used to visualize the obstruction. Two stiff guide wires (Cook) were inserted into the duodenum. One wire was used to insert a 6F-long sheath (Cook) across the obstruction and the other to insert the stent. The 6F-long sheath was then used to insert the RSS. Next, the sheath was removed, with the RSS being positioned between the stent and biliary tract (Fig. 1).

2.6. Postoperative treatment

Postoperatively, a temporary biliary catheter (Cook) was used to drain the bile for 3 days. All patients were given preventive anti-inflammatory medications and hemostasis for 5 days. The anti-inflammatory medicine was cefoxitin.



Figure 1. Radioactive stenting for a patient with HCCA. Arrows indicates the radioactive seeds. HCCA=hilar cholangiocarcinoma.

2.7. Assessment

Technical success for stenting was defined by the extent of obstruction elimination enabling smooth flow of contrast medium flow through the stent.^[9–11] For RSS insertion, technical success was defined by the exact placement of RSS between stent and biliary tract. Stent dysfunction was confirmed by recurrence of cases of cholangitis and/or jaundice resulting from reobstruction or migration.^[9–11] Clinical success was defined by total bilirubin (TBIL) levels falling below 70% of the preoperative baseline within 2 weeks post stent insertion.^[1–3] Stent patency was defined by the duration from stent insertion to patient death or stent dysfunction. Overall survival was defined as the time from stent insertion to patient death.

All patients had postoperative physical examination, CT examination, and liver function tests after 2 weeks, 1 month, 3 months, 6 months, and every 6 months thereafter.

2.8. Statistical analysis

SPSS v16.0 (SPSS, Inc., IL) was used for all statistical testing. Continuous and categorical variables are analyzed using *t* tests and Chi-squared tests. Patient survival and stent patency are compared using Kaplan–Meier curves and log-rank tests. A multivariate Cox regression analysis is used to identify factors relating to patient survival. All variables with a *P* value of < .1 in the initial univariate analysis are included into the subsequent multivariate model. *P* < .05 was used as the statistical significance threshold.

3. Results

3.1. Patients

Seventy patients with inoperable HCCA received either normal (*n* = 40) or radioactive (*n* = 30) stenting at our center. Five patients

Table 1**Patient characteristics in 2 groups.**

	Normal stent group	Radioactive stent group	P value
Patients number	35	30	-
Age, y	66.0±12.8	66.6±9.9	.827
Male/Female	21/14	18/12	1.000
ECOG PS	2.7±0.5	2.5±0.5	.217
Comorbidity			
Hypertension	7	4	.475
Diabetes	2	3	.857
Cerebrovascular diseases	5	3	.884
Tumor stage			.998
II	15	13	
III	14	12	
IV	6	5	
Bismuth type			.842
I	5	5	
II	11	12	
III	14	10	
IV	5	3	
TBIL, μmol/L			
Before	206.1±103.2	223.7±113.4	.518
After	96.3±61.0	99.7±53.4	.812
P value	<0.001	<0.001	-
AST, U/L			
Before	151.6±100.5	158.3±123.9	.811
After	71.0±46.4	61.9±35.9	.382
P value	<0.001	<0.001	-
ALT, U/L			
Before	139.1±89.7	169.3±125.2	.276
After	68.7±44.1	64.7±39.9	.701
P value	<0.001	<0.001	-
Albumin, g/L	34.6±4.0	35.3±4.1	.491
Carbohydrate antigen-199, U/L	963.6±1339.9	914.7±803.2	.377
Subsequent chemotherapy	6	5	.959

ALT=alanine aminotransferase, AST=aspartate transaminase, ECOG PS=Eastern Cooperative Oncology Group performance status, TBIL=total bilirubin.

in the normal stenting group were excluded as they underwent external radiotherapy after stenting. Thus, 65 patients (normal group: 35 patients; radioactive group: 30 patients) were included in this study (Table 1). Post-stenting chemotherapy was performed in 6 and 5 patients in normal and radioactive groups, respectively ($P=.959$). The protocol of chemotherapy was cisplatin (25 mg per square meter of body surface area) with gemcitabine (1000 mg per square meter of body surface area). The chemotherapy was performed on days 1 and 8, every 3 weeks.

3.2. Technical success

Technical success rates for the normal and radioactive stent insertions were both 100%. Neither group had procedure-related complications. Each patient received a single stent. In the radioactive stent group, each patient received 1 RSS, containing 10 to 12 radioactive seeds (Fig. 1).

3.3. Clinical success

Clinical success rates were 86.8% (normal group) and 100% (radioactive group) ($P=.495$). Changes in TBIL, aspartate transaminase (AST), and alanine aminotransferase (ALT) in both groups are shown in Table 1.

Table 2**Comparison of outcomes between 2 groups.**

	Normal stent group	Combined group	P value
Clinical success	33 (86.8%)	30 (100%)	.495
Stent dysfunction	9 (25.7%)	7 (23.3%)	.824
Adverse events			.730
Cholangitis	6 (17.1%)	4 (13.3%)	
Cholecystitis	1 (2.9%)	1 (3.3%)	
Median patency, d	165	226	<.001
Median overall survival, d	198	256	<.001

3.4. Patency

Stent dysfunction was observed in 9 patients (normal group) and 7 patients (radioactive group) ($P=.824$, Table 2). Tumor growth caused all stent dysfunction. In the normal group, 7 patients had a second stent inserted and 2 patients had an in-stent biliary drainage catheter inserted. In the radioactive group, all dysfunctions were revised by in-stent biliary drainage catheter insertion. Median stent patency duration was 165 days (normal group) and 226 days (radioactive group) ($P<.001$, Fig. 2A). Based on different tumor stages, median stent patency duration was 143 and 225 days, 165 and 229 days, and 134 and 189 days based on the stage II, III, and IV tumors in the normal and radioactive groups, respectively ($P=.043$, $<.001$, and $.415$, respectively).

3.5. Survival

Tumor progression resulted in the deaths of all patients during the follow-up period, with median survival duration of 198 days (normal group) and 256 days (radioactive group) ($P<.001$, Fig. 2B). Based on different tumor stages, the median survival duration was 216 and 256 days, 178 and 246 days, and 222 and 297 days based on the stage II, III, and IV tumors in the normal and radioactive groups, respectively ($P=.028$, $.001$, and $.346$, respectively).

At univariate Cox-regression analysis, Bismuth type III (hazard ratio: 1.983; 95% confidential interval; 0.893–4.405; $P=.092$) was associated with reduced survival and use of a radioactive stent (hazard ratio: 0.311; 95% confidential interval; 0.171–0.567; $P<.001$) was associated with longer survival. When these 2 factors were included in a multivariate analysis, it was found that the radioactive stenting was the only predictor of longer survival (hazard ratio: 0.330; 95% confidential interval; 0.180–0.604; $P<.001$). Post-stenting chemotherapy was not associated with longer survival ($P=.530$).

3.6. Complications

Seven patients (normal group) and 5 patients (radioactive group) suffered from stent-related complications ($P=.730$). The 12 complications were cholangitis ($n=10$) and cholecystitis ($n=2$, Table 2).

4. Discussion

We compared the effectiveness and safety in HCCA patients who received normal or radioactive stent insertion. High technical and clinical success rates were observed in both groups, suggesting that both normal and radioactive stents are reliable and safe when providing instant palliative relief to patients with inoperable HCCA.

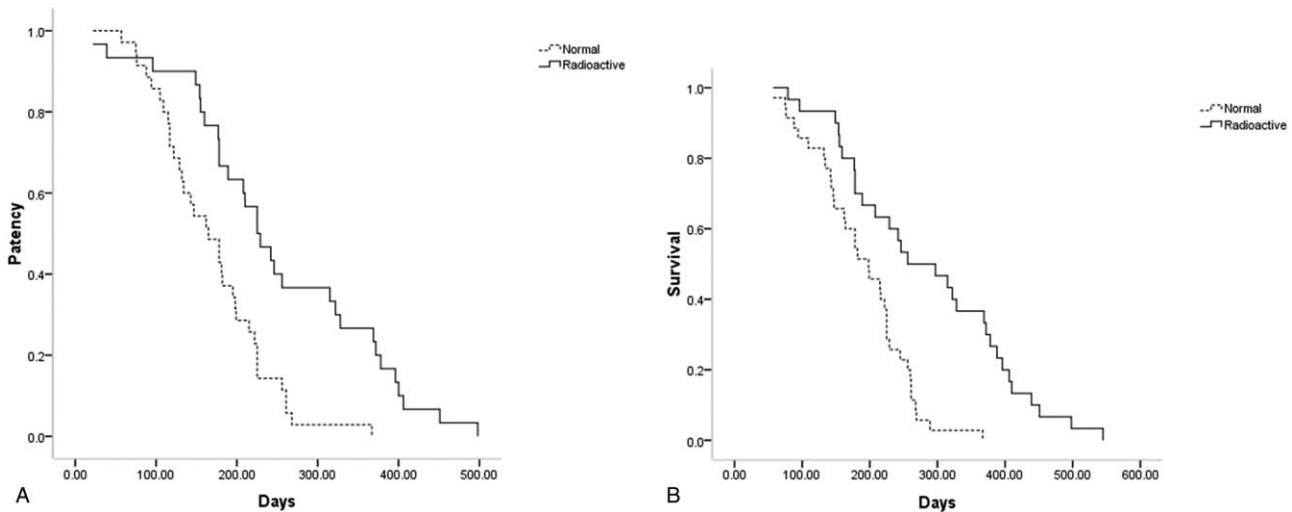


Figure 2. Kaplan–Meier curve demonstrated a significant longer patency (A) and survival (B) after radioactive stenting.

Two types of radioactive stents have been reported previously.^[7–9] We used one, the other being a normal metallic stent with several radioactive seeds directly attached to the stent.^[9] This second type of the stent has a more complex manufacturing process.

Unlike previous studies of bilateral stenting for MHBO or HCCA,^[10,11] we used unilateral stenting for HCCA. Although some meta-analyses have demonstrated that bilateral stenting can provide a longer stent patency than unilateral stenting, those meta-analyses both included percutaneous and endoscopic biliary stenting.^[12,13] The clinical effectiveness between percutaneous and endoscopic biliary stenting for MBO was different.^[4] This study used percutaneous approach to place the stents. Some recent studies and meta-analysis regarding of percutaneous unilateral versus bilateral stenting for MHBO demonstrated that percutaneous unilateral and bilateral metal stenting are similarly effective for treatment of patients with MHBO.^[1–3,14] Therefore, we believe that percutaneous unilateral stenting is sufficient to treat the patients with HCCA.

The most effective way to maintain stent patency is to prevent tumor growth.^[15] In this study, stent patency was significantly longer in the radioactive group when compared with the normal group (226 days vs 165 days; $P < .001$), with similar rates of overall stent dysfunction ($P = .824$). However, radioactive stents could not prevent tumor growth, as not all patients were consistently sensitive to intra-luminal radiotherapy. Radioactive stents did prolong the time to stent dysfunction.

Chemotherapy and radiotherapy are the most commonly used approaches to prevent tumor growth after stent insertion.^[15–17] Compared with the conventional chemotherapy and radiotherapy, radioactive stents offer several advantages, including ease of manipulation, direct contact with tumor surface, and sustained delivery of low-dose radiation to the tumor over an extended period of time.^[8,18] It is reported that ^{125}I seeds can continuously release X and γ rays to effectively kill tumor cells and inhibit tumorigenesis.^[18] After the implantation of ^{125}I seeds, the percentages of CD3 + T, CD4 + T, natural killer, and regulatory T cells significantly increased in peripheral blood of tumor patients.^[18] In addition, the concentrations of IgM, IgG, and IgA, and complements C3 and C4 also increased, indicating that

^{125}I seeds may stimulate not only cellular immunity but also humoral immunity.^[18]

We found that patients in the radioactive group survived significantly longer than patients in the normal group (256 days vs 198 days; $P < .001$). Although many factors, such as tumor stage, Bismuth type, ECOG PS, liver function, and subsequent chemotherapy, may influence overall survival, a multivariate analysis showed that use of a radioactive stent was independently associated with prolonged patient survival. This may be due to several reasons: first, this is a retrospective study, with a high risk of bias. Secondly, the sample size is limited. The median 256-day survival time in the radioactive group was consistent with previous reports of 202 to 355 days for MBO or MHBO patients who underwent radioactive stenting.^[7–9]

We further calculated the stent patency and survival duration based on the tumor stages. We found that both stent patency and survival were comparable between normal and radioactive groups based on the stage IV patients. These results might be attributed to the following factors: radioactive stents have limited ability to control the distant metastasis; and there were only 6 and 5 patients with stage IV tumors in normal and radioactive groups, and therefore, the statistical power was limited.

No significant difference in complication rates was observed between 2 groups, indicating that the radioactive stents did not give rise to additional complications. Only 15.4% (10/65) of patients experienced complications. This low rate was likely due to the temporary drainage catheter inserted for up to 5 days post-stenting.

We identified several limitations in this study. First, the sample size for the current investigation is small coupled with retrospective nature of the clinical study introduces numerous biases in the data analysis. Although the unique cancer type in this study might reduce the risk of bias, it is important to validate our findings in future prospective studies. Second, these patients came from a single-center, and therefore, there was not enough validations from several variables which are underplay in different clinical setting. Third, the clinical efficacy between 2 procedures in stage IV HCCA is not drastically different because the limited sample size. Fourth, we were unable to measure the radioactive stent dosimetry accurately due to a paucity of data on dedicated measurements in HCCA patients.

In conclusion, radioactive stenting is effective and safe for patients with inoperable HCCA and may prolong stent patency and survival. However, further prospective, multicenter clinical trials should be performed to validate the conclusions.

Author contributions

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References

- [1] Chang G, Xia FF, Li HF, Niu S, Xu YS. Unilateral versus bilateral stent insertion for malignant hilar biliary obstruction. *Abdom Radiol (NY)* 2017;42:2745–51.
- [2] Yin X, Li DM, Yang F, Liu TG, Xia FF, Fu YF. Self-expanded metallic stent insertion for hilar cholangiocarcinoma: comparison of unilateral and bilateral stenting. *J Laparoendosc Adv Surg Tech A* 2019;29:1501–6.
- [3] Fu YF, Zhou WJ, Shi YB, Cao W, Cao C. Percutaneous stenting for malignant hilar biliary obstruction: a randomized controlled trial of unilateral versus bilateral stenting. *Abdom Radiol (NY)* 2019;44:2900–8.
- [4] Zhao XQ, Dong JH, Jiang K, Huang XQ, Zhang WZ. Comparison of percutaneous transhepatic biliary drainage and endoscopic biliary drainage in the management of malignant biliary tract obstruction: a meta-analysis. *Dig Endosc* 2015;27:137–45.
- [5] Staub J, Siddiqui A, Murphy M, et al. Unilateral versus bilateral hilar stents for the treatment of cholangiocarcinoma: a multicenter international study. *Ann Gastroenterol* 2020;33:202–9.
- [6] Perdue DG, Freeman ML, DiSario JA, et al. Plastic versus self-expanding metallic stents for malignant hilar biliary obstruction: a prospective multicenter observational cohort study. *J Clin Gastroenterol* 2008;42:1040–6.
- [7] Jiao D, Wu G, Ren J, et al. Study of self-expandable metallic stent placement intraluminal 125I seed strands brachytherapy of malignant biliary obstruction. *Surg Endosc* 2017;31:4996–5005.
- [8] Chen G, Zhang M, Sheng YG, et al. Stent with radioactive seeds strand insertion for malignant hilar biliary obstruction. *Minim Invasive Ther Allied Technol* 2020;1–7. doi: 10.1080/13645706.2020.1735446. Epub ahead of print.
- [9] Zhu HD, Guo JH, Huang M, et al. Irradiation stents vs. conventional metal stents for unresectable malignant biliary obstruction: a multicentre trial. *J Hepatol* 2018;68:970–7.
- [10] Kanno Y, Ito K, Fujita N. Single session endoscopic bilateral Y-configured placement of metal stents for hilar malignant biliary obstruction. *Dig Endosc* 2011;23:91–6.
- [11] Law R, Baron TH. Bilateral metal stents for hilar biliary obstruction using a 6Fr delivery system: outcomes following bilateral and side-by-side stent deployment. *Dig Dis Sci* 2013;58:2667–72.
- [12] Ashat M, Arora S, Klair JS, et al. Bilateral vs unilateral placement of metal stents for inoperable high grade hilar biliary strictures: a systemic review and meta-analysis. *World J Gastroenterol* 2019;25:5210–9.
- [13] Li M, Wu W, Yin Z, et al. Unilateral versus bilateral biliary drainage for malignant hilar obstruction: a systematic review and meta-analysis. *Zhonghua Gan Zang Bing Za Zhi* 2015;23:118–23.
- [14] Fu YF, Xu YS, Shi YB, et al. Percutaneous metal stenting for malignant hilar biliary obstruction: a systematic review and meta-analysis of unilateral versus bilateral stenting. *Abdom Radiol (NY)* 2021;46:749–56.
- [15] Li TF, Chen C, Han XW, Zhen L, Jiao DC, Ma J. Clinical efficacy of metallic biliary stents combined with different anti-cancer treatments in the management of bile duct cancer. *Hepatogastroenterology* 2014;61:22–6.
- [16] Niu S, Cheng L, Qiao Y, Fu YF, Cao C. Combined stent insertion and high-intensity focused ultrasound ablation for patients with malignant obstructive jaundice. *Surg Laparosc Endosc Percutan Tech* 2016;26:488–92.
- [17] Boulay BR, Birg A. Malignant biliary obstruction: from palliation to treatment. *World J Gastrointest Oncol* 2016;8:498–508.
- [18] Pang Q, Zhou L, Hu XS, et al. Biliary stenting alone versus biliary stenting combined with 125I particles intracavitary irradiation for the treatment of advanced cholangiocarcinoma. *Sci Rep* 2019;9:1–7.