

Radioactive stent insertion for inoperable hilar cholangiocarcinoma: a prospective randomized controlled trial

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Abstract

Introduction: Hilar cholangiocarcinoma (HC) is the leading cause of hilar biliary obstruction. Radioactive stent insertion has been utilized extensively for inoperable HC patients.

Aim: To assess the relative clinical outcomes of inoperable HC patients who underwent either normal or radioactive stent insertion.

Material and methods: This single-center, prospective, randomized, open-label study enrolled 90 inoperable HC patients from April 2021 to March 2022 and randomly assigned them to normal or radioactive stent groups ($n = 45$ /group), with clinical data then being compared between these groups.

Results: Technical success rates in the normal and radioactive stent insertion groups were 93.3% and 97.9%, respectively ($p = 1.000$), and clinical success rates were similarly consistent in both groups (95.3% vs. 97.7%, $p = 0.983$). Individuals in the radioactive stent group exhibited significantly longer median stent patency as compared to the normal stent group (195 days vs. 115 days, $p < 0.001$), and median overall survival (OS) was also significantly increased in the normal stent group (242 days vs. 125 days, $p = 0.002$). In the normal stent insertion group, 6 (14.3%) and 5 (11.9%) patients experienced early and late postoperative complications, respectively. Additionally, early and late postoperative complications impacted 7 (16.3%) and 8 (18.6%) patients in the radioactive stent insertion group, respectively. Complication rates were comparable in these 2 patient groups.

Conclusions: Radioactive stent insertion represents a safe and effective strategy for patients with inoperable HC, potentially contributing to prolonged stent patency and OS relative to normal stent insertion.

Key words: stent, radioactive, hilar cholangiocarcinoma, randomized controlled trial.

Introduction

Hilar cholangiocarcinoma (HC) is the leading cause of hilar biliary obstruction [1–3]. When patients with HC experience jaundice and related symptoms, their disease is generally inoperable, and their prognosis and expected overall survival (OS) are relatively poor [4]. Biliary stent insertion is often

conducted in inoperable HC patients as it can provide rapid relief of jaundice while allowing patients to undergo radiotherapy or chemotherapy to prolong their survival [4].

Bilateral stent insertion in patients suffering from hilar biliary obstruction has been established by the Asia-Pacific consensus criteria and a series of meta-analyses as superior to unilateral stent inser-

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tion concerning both rates of clinical success and the duration of stent patency [5–8]. Bilateral stenting is associated with lower re-stenosis rates of 7–12% compared to unilateral stenting [7, 8]. As these bilateral stents lack intrinsic antitumor properties, they fail to extend the OS of treated patients [6–8]. Undergoing external radiotherapy or systemic chemotherapy, while common treatments for individuals with HC, can result in particularly severe toxic treatment-related effects [4].

Given the above challenges, researchers and clinicians have increasingly explored the deployment of radioactive stent systems consisting of a metal stent and a strand of ^{125}I seeds to protect patients with HC against re-stenosis and thereby extend their survival [4]. In this method, a radioactive stent is implanted at the obstruction site so that the ^{125}I seeds are fixed between the tumor and the inserted stent, enabling the delivery of persistent, localized radiotherapeutic treatment [4]. Critically, these ^{125}I seeds can simultaneously deliver a high radiation level to the tumor while mainly avoiding the irradiation of surrounding healthy tissue [4]. A few reports have assessed the relative clinical efficacy of traditional and radioactive stent insertion procedures in patients with HC [9–11], but prospective studies on this topic are lacking.

Aim

The present study was designed as a prospective randomized controlled trial (RCT) to compare the clinical outcomes of inoperable HC patients following the insertion of either a normal or a radioactive stent.

Material and methods

Study design

The Ethics Committee of Xuzhou Central Hospital approved this open-label, prospective RCT, with all enrolled patients have provided written informed consent. This trial has been registered at <https://clinicaltrials.gov/>, No. NCT04779788.

Between April 2021 and March 2022, 90 patients with HC were randomly assigned to either a normal or a radioactive stent insertion group ($n = 45/\text{group}$). Patient baseline data are summarized in Table I, while a flowchart of the study process is provided in Figure 1. To be eligible for inclusion, patients had to: (1) have a definitive diagnosis of HC, (2) have inoperable HC, and (3) exhibit symptoms consistent with obstructive jaundice. Patients were excluded if they (1) had Bismuth I type IC, (2) had undergone perioperative external radiotherapy, (3) had any prior history of biliary stent insertion or drainage,

Table I. Baseline data of enrolled patients

Parameter	Normal stent ($n = 45$)	Radioactive stent group ($n = 45$)	<i>P</i> -value
Age [years]	64.2 \pm 14.5	67.0 \pm 8.4	0.273*
Gender (male/female)	25/20	24/21	0.832
Tumor stage (II/III/IV)	11/21/13	17/18/10	0.385
Bismuth type (II/III/IV)	20/17/8	21/17/7	0.955
ECOG PS	1.5 \pm 0.5	1.6 \pm 0.5	0.295*
TBIL [$\mu\text{mol/l}$]			
Before/after	210.2 \pm 89.3/116.8 \pm 77.9	215.6 \pm 118.6/99.2 \pm 53.7	0.809/0.217*
AST [U/l]			
Before/after	138.3 \pm 81.4/62.5 \pm 41.7	163.1 \pm 128.4/65.6 \pm 37.1	0.277/0.713*
ALT [U/l]			
Before/after	158.5 \pm 137.4/62.2 \pm 40.0	155.2 \pm 120.1/64.6 \pm 43.0	0.905/0.783*
Albumin [g/l]	34.3 \pm 4.4	34.9 \pm 4.3	0.506*
CA19-9 [U/ml]	384 (Q1: 147; Q3: 1147)	278 (Q1: 147; Q3: 1042)	0.806#
Post-operative chemotherapy	14	12	0.642

ALT – alanine aminotransferase, AST – aspartate aminotransferase, ECOG PS – Eastern Cooperative Oncology Group performance status, TBIL – total bilirubin. *Independent *t*-test. #Mann-Whitney *U* test.

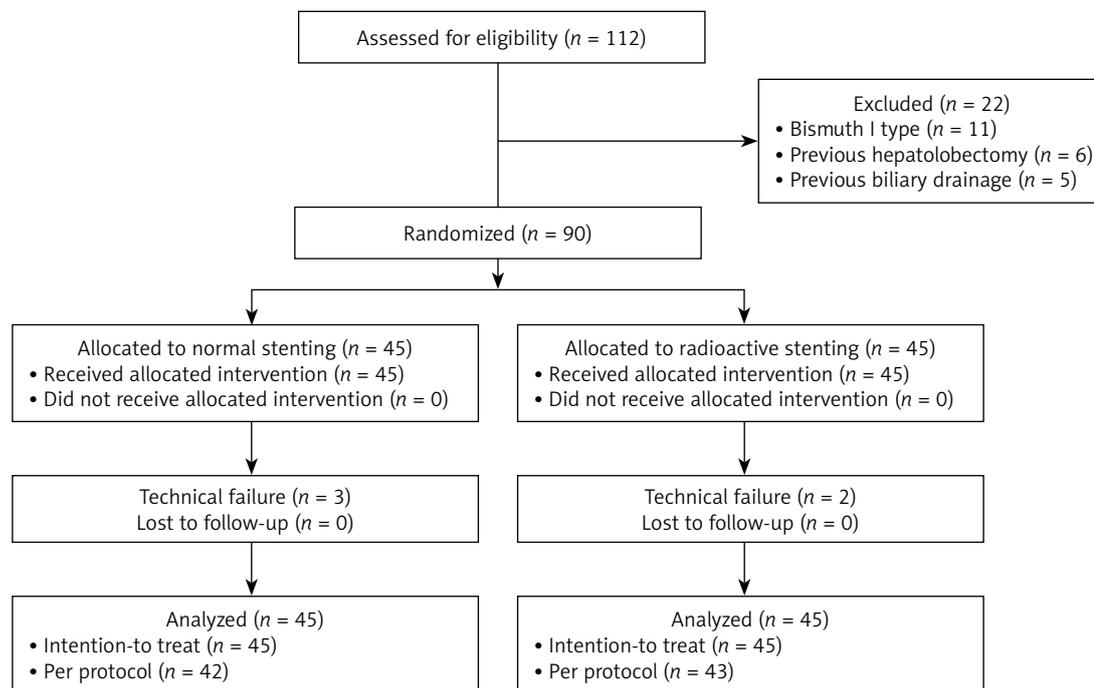


Figure 1. Study flowchart

(4) had any history of prior hepatectomy, (5) exhibited an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥ 4 , or (f) were unable to provide informed consent.

The definitive diagnosis of HC was established based on the results of intraductal biopsy analyses. Bismuth type determinations were made based on the results of abdominal computed tomography (CT) and magnetic resonance imaging (MRI) scans. The inoperable criteria were as follows: (a) extensive infiltration to the adjacent tissues; (b) distant metastasis; and (c) poor physical condition [12].

Randomization

Patients were randomized to normal and radioactive stent groups at a 1 : 1 ratio via block randomization with a block size of four. Random numbers were generated with a computer and placed in sealed, opaque, sequentially numbered envelopes. Before stent insertion, a member of the Science and Education Department with no other role in this RCT opened the randomly assigned envelopes.

Stents

Self-expanded metal stents (Micro-Tech, Nanjing, China) that were 8 mm in diameter and 50–70 mm

long were used for stent insertion in all patients. Radioactive stenting was performed by combining these stents with a ^{125}I seed strand prepared by sealing ^{125}I seeds (Chinese Atomic Energy Science Institution, Beijing, China) within a 4F catheter (PBN MEDICALS Denmark A/S, Stenlose, Denmark). Individual seeds were 0.8 mm in diameter and 4.5 mm long, and released low-energy 35.5-keV γ -rays with a 59.6-day half-life. The number of seeds was selected based on the obstruction length: $N = \text{length of stent (mm)}/4.5 + 4$ [11].

Normal stent insertion

A side-by-side percutaneous approach was used for the insertion of bilateral stents. Following the simultaneous puncture of the left and right intrahepatic biliary tracts, two VER catheters were introduced via a 0.035-inch Radifocus guide wire (Terumo, Tokyo, Japan) to detect the obstruction. After the catheters had reached the obstruction and entered the duodenum, stiff guide wires (Cook, IN, USA) were used to replace the Radifocus guide wires. Two delivery systems were then introduced with the stiff guidewires to the site of the obstruction and simultaneously released in a Y shape (Photo 1 A).

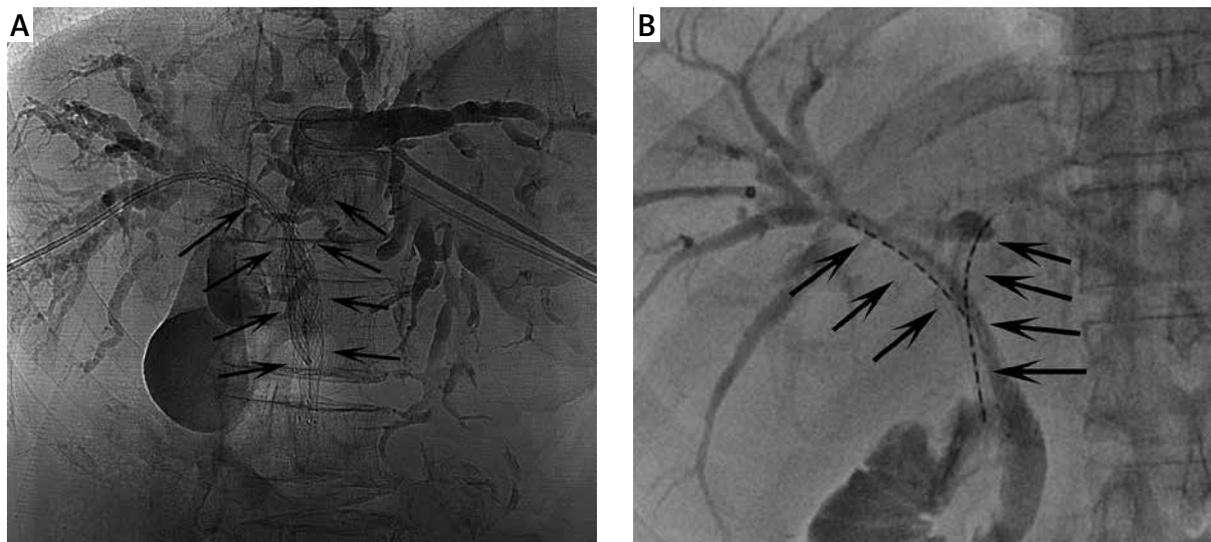


Photo 1. A – Normal bilateral stent insertion. Arrows show the 2 stents. **B** – Radioactive bilateral stent insertion. Arrows show the 2 I-125 seed strands

Radioactive stent insertion

A side-by-side percutaneous approach was used for the insertion of bilateral radioactive stents. Briefly, two stiff guidewires were initially introduced, with two additional guidewires being used to pass two 6F sheaths across the obstructed sites. Stents were placed at the center of the obstructed site with a 0.035-inch stiff guidewire. Then, ¹²⁵I seed strands were placed within 6F sheaths; with these sheaths removed the seed strands were positioned between the stent and the biliary wall. These two stents were positioned in a Y shape (Photo 1 B).

Follow-up

Patients were followed for 2 weeks, 1, 3, and 6 months, and every 6 months after that until death or September 30, 2022. Blood tests, physical examinations, and abdominal CT scans were part of the follow-up examinations.

Definitions

Technical success for stent insertion procedures was defined by the release of stents precisely at the site of the obstruction so that the contrast medium could smoothly pass through the stent [12]. Clinical success was defined by a $\geq 30\%$ reduction in total bilirubin (TBIL) levels within 2 weeks following stent placement [12]. Stent patency was defined by the period from stent insertion to jaundice recurrence

[12]. When patients died without evidence of re-stenosis, stent patency and OS were identical, and results were not censored. OS was the period from stent insertion to all-cause death. Early and late postoperative complications were defined based on whether they occurred less than or more than 30 days after stenting.

Statistical analysis

The primary endpoint of this study was stent patency. When we registered this study, the primary endpoint was OS. However, we read many studies regarding biliary radioactive stent insertion and found that the primary function of biliary radioactive stent was reducing the re-stenosis rate [4, 11]. Therefore, we changed the primary endpoint to stent patency. According to results of a prior study comparing normal and radioactive stenting in malignant hilar biliary obstruction patients [13], a 30% higher 6-month stent patency rate was expected following radioactive stenting as compared to normal stenting (85% vs. 55%). Accordingly, power calculations indicated that a minimum of 76 patients (38 patients in each group) were necessary with a power of 0.8 and an α of 0.05 when taking a dropout rate of 10% into consideration.

This study was conducted using intention-to-treat (ITT) and per-protocol (PP) analytical approaches, with the former being conducted based on the total number of enrolled patients and the latter being based on the number of patients in whom stent in-

sersion procedures were technically successful. ITT analyses were employed when assessing baseline data and rates of technical success, whereas rates of clinical success, stent patency, OS, and complications were compared via PP analyses.

Continuous data are given as medians or means \pm standard deviation and were compared via the Mann-Whitney *U* test or *t*-test. Categorical data were compared with the χ^2 test or Fisher's exact test. Kaplan-Meier curves and log-rank tests were used to compare OS and stent patency. Predictors of OS and stent patency were assessed through Cox regression analyses, with those variables exhibiting $p < 0.1$ in univariate analyses being included in a multivariate analysis. $P < 0.05$ served as the significance threshold, and SPSS 16.0 (SPSS Inc., IL, USA) was used for all statistical testing.

Results

Technical success rates

A total of 5 patients in the normal stent group did not undergo bilateral stenting, 2 underwent unilateral stenting, and 3 underwent an extra-biliary drainage catheter placement. After drainage for 1 week, stent insertion was again attempted in these patients but without technical success. Similarly, bilateral stent insertion failed in 5 radioactive stent patients, of whom 3 and 2 underwent unilateral stenting and extra-biliary drainage catheter placement, respectively. Following drainage for 1 week, stent insertion was again attempted, without technical success. Thus, the respective technical success rates in the normal and radioactive stent insertion groups were 93.3% and 97.9% ($p = 1.000$, Table II).

Clinical success

Similar clinical success rates were seen in patients who underwent normal and radioactive stent-

ing (95.3% vs. 97.7%, $p = 0.983$, Table II). The TBIL, aspartate transaminase (AST), and alanine aminotransferase (ALT) levels of patients in the normal stenting group declined from pre-stenting values of $210.2 \pm 89.3 \mu\text{mol/l}$, $138.3 \pm 81.4 \text{ U/l}$, and $158.5 \pm 137.4 \text{ U/l}$, respectively, to $116.8 \pm 77.9 \mu\text{mol/l}$ ($p < 0.001$), $62.5 \pm 41.7 \text{ U/l}$ ($p < 0.001$), and $62.2 \pm 40.0 \text{ U/l}$ ($p < 0.001$) following stent placement. Similarly, the TBIL, AST, and ALT values of individuals who underwent radioactive stent insertion declined from $215.6 \pm 118.6 \mu\text{mol/l}$, $163.1 \pm 128.4 \text{ U/l}$, and $155.2 \pm 120.1 \text{ U/l}$ prior to stenting to $99.2 \pm 53.7 \mu\text{mol/l}$ ($p < 0.001$), $65.6 \pm 37.1 \text{ U/l}$ ($p < 0.001$), and $64.6 \pm 43.0 \text{ U/l}$ ($p < 0.001$) following stent placement.

Stent patency

Similar re-stenosis rates were found in the normal and radioactive stent insertion groups (26.2% vs. 23.2%, $p = 0.754$, Table II). All patients in the normal stenting group who experienced re-stenosis were treated via biliary drainage catheter placement, while 9/10 patients with re-stenosis in the radioactive stent group also underwent biliary drainage catheter placement. The remaining patient had originally undergone unilateral radioactive stent insertion and was therefore treated by placing a second stent from the contralateral intrahepatic biliary tract.

Radioactive stent insertion was associated with significant prolongation of stent patency relative to the normal stent group (195 days vs. 115 days, $p < 0.001$, Figure 2 A). Cox regression analyses revealed that factors related to increased stent patency included Bismuth III HC ($p = 0.027$) and radioactive stent use ($p = 0.018$) (Table III).

OS

Following stent placement, a transarterial chemo-infusion was conducted in 14 and 12 patients in the normal and radioactive groups. Postoperative

Table II. Treatment effectiveness

Variable	Normal stent ($n = 42$)	Radioactive stent group ($n = 43$)	<i>P</i> -value
Technical success rate (%)	93.3% (42/45)	97.9% (43/45)	1.000
Clinical success rate (%)	95.3% (40/42)	97.7% (42/43)	0.983
Stent re-stenosis rate (%)	26.2% (11/42)	23.2% (10/43)	0.754
Stent patency (median) [days]	115	195	< 0.001
Overall survival (median) [days]	125	242	0.002

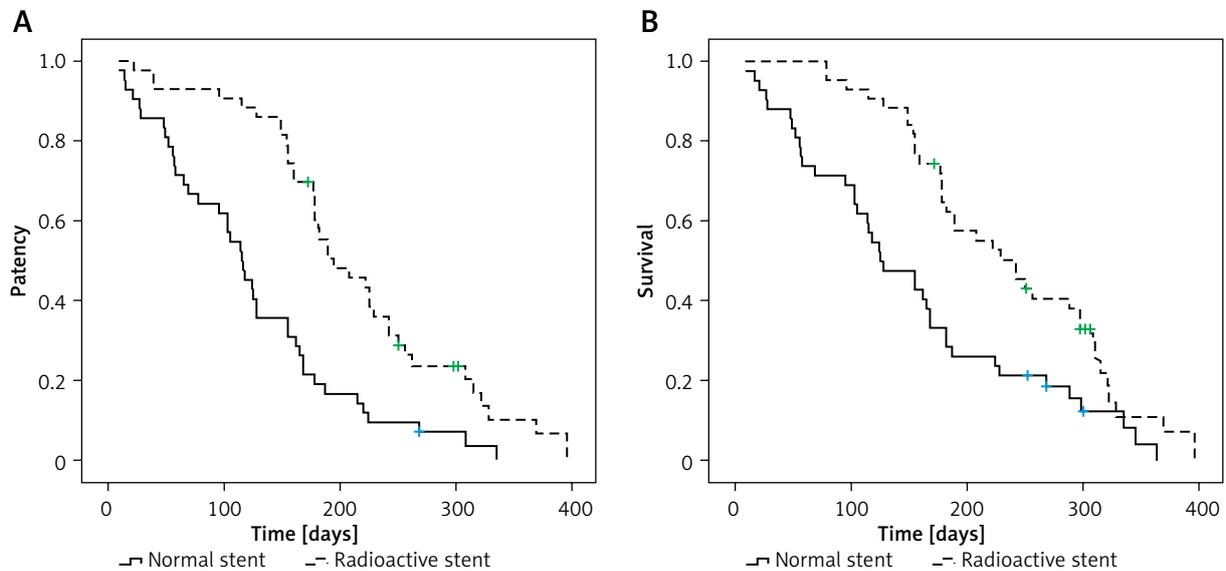


Figure 2. Photos of the (A) stent patency and (B) OS curves

chemotherapeutic treatment was based on each patient's condition and approval. During the follow-up period, 39 and 37 patients in these two groups died, with 65 patients succumbing to tumor progression, 8 to severe abdominal infection, and 3 to acute renal failure.

Individuals who underwent radioactive stent insertion survived significantly longer than those who underwent normal stenting (242 days vs. 125 days, $p = 0.002$, Figure 2 B). Higher ECOG PS ($p = 0.043$), post-operative TBIL ($p = 0.014$), radioactive stent use ($p < 0.001$), and postoperative chemotherapy use ($p = 0.003$) were all associated with longer OS according to Cox regression analyses (Table IV).

Postoperative complications

Of the patients in the normal stent group, early and late postoperative complications developed in 6 (14.3%) and 5 (11.9%) patients, respectively, with these complications including cholangitis ($n = 7$) and cholecystitis ($n = 4$). Similarly, 7 (16.3%) and 8 (18.6%) radioactive stent group patients, respectively, experienced early and late postoperative complications, including cholangitis ($n = 8$), cholecystitis ($n = 6$), and self-limited biliary bleeding ($n = 1$). Complication rates in these groups were not significantly different (Table V).

The 15 cases of cholangitis were managed through medical treatment ($n = 10$) or percutaneous

catheter drainage ($n = 5$), with medical treatment ($n = 8$) or percutaneous catheter drainage ($n = 2$) also being used for the treatment of the 10 cases of cholecystitis.

Discussion

The present RCT was performed to examine the relative safety and efficacy of traditional and radioactive stenting in patients with HC. These two groups' overall technical and clinical success rates were similar, suggesting that these stenting strategies are well-suited to provide rapid jaundice relief in individuals with HC. The technical (97.9%) and clinical (97.7%) success rates for individuals who underwent radioactive stenting in this study were also similar to those in prior reports focused on radioactive stent placement in patients with HC [3, 10, 13].

A percutaneous stent insertion approach may explain the high technical and clinical success rates. While endoscopic approaches are often used by groups inserting stents to treat distal biliary obstructions [14–16], the percutaneous approach is more appropriate in cases of hilar biliary obstruction [17, 18], improving respective technical and clinical success rates by 17.6% and 15.4% as compared to the endoscopic approach [17, 18].

Stent re-stenosis often results from tumor growth, sludge formation, and the proliferation of biliary epithelial cells [14–16], with stent re-ste-

Table III. Predictors of stent patency

Variables	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Age	0.973	0.932–1.014	0.196			
Gender:						
Male	1					
Female	1.545	0.641–3.726	0.333			
Tumor stage:						
II	1					
III	1.311	0.466–3.688	0.608			
IV	1.801	0.576–5.630	0.312			
ECOG PS	0.784	0.328–1.871	0.583			
Bismuth type:						
II	1			1		
III	0.347	0.112–1.079	0.067	0.264	0.081–0.857	0.027
IV	1.337	0.466–3.835	0.589	1.264	0.440–3.631	0.663
TBIL before	1.000	0.996–1.005	0.828			
TBIL after	0.999	0.991–1.007	0.783			
AST before	1.000	0.996–1.003	0.825			
AST after	1.004	0.993–1.014	0.480			
ALT before	0.999	0.995–1.003	0.628			
ALT after	0.996	0.985–1.008	0.528			
Albumin	0.931	0.819–1.059	0.277			
Ca19-9	1.000	0.999–1.000	0.619			
Stent insertion:						
Normal	1			1		
Radioactive	0.428	0.178–1.032	0.059	0.322	0.126–0.826	0.018
Post-operative chemotherapy:						
No	1					
Yes	1.731	0.727–4.123	0.215			

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

nosis as the most common cause [19]. Antitumor treatments are thus the most effective option for minimizing rates of re-stenosis. Since radioactive stenting allows for the simultaneous delivery of brachytherapy and stent dilation [20], it is ideally suited to use in this context. ¹²⁵I seeds are effective radioactive sources capable of continuously releasing X and γ rays capable of killing tumor cells and slowing tumor growth [10] while surrounding normal tissue received a radioactive dose < 25% of that received by tumor cells [21].

Here, the insertion of radioactive stents did not contribute to any significant reduction in the rate of

re-stenosis, although it was associated with significant prolongation of stent patency. Strikingly, radioactive stenting was associated with more prolonged patient OS. Since radioactive stent insertion was predictive of both longer stent patency and OS, and postoperative chemotherapy was also predictive of prolonged OS, chemotherapy may represent a practical option for the simultaneous adjuvant treatment of HC patients undergoing radioactive stent insertion.

Here, bilateral radioactive stent insertion was performed, whereas many prior studies have performed unilateral radioactive stenting in patients

Table IV. Predictors of overall survival

Variables	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Age	0.973	0.932–1.014	0.196			
Gender:						
Male	1					
Female	1.545	0.641–3.726	0.333			
Tumor stage:						
II	1			1		
III	1.000	0.581–1.721	1.000	0.648	0.361–1.163	0.146
IV	1.713	0.955–3.074	0.071	1.605	0.871–2.957	0.129
ECOG PS	1.746	1.090–2.799	0.021	1.660	1.016–2.713	0.043
Bismuth type:						
II	1					
III	0.865	0.519–1.440	0.576			
IV	1.223	0.640–2.340	0.542			
TBIL before	1.002	0.999–1.004	0.126			
TBIL after	1.006	1.001–1.010	0.012	1.006	1.001–1.011	0.014
AST before	1.000	0.998–1.002	0.787			
AST after	0.999	0.993–1.006	0.874			
ALT before	1.000	0.999–1.002	0.721			
ALT after	1.000	0.994–1.006	0.992			
Albumin	0.969	0.907–1.036	0.361			
Ca19-9	1.000	1.000–1.000	0.565			
Stent insertion:						
Normal	1			1		
Radioactive	0.487	0.306–0.775	0.002	0.354	0.216–0.579	< 0.001
Post-operative chemotherapy:						
No	1			1		
Yes	0.553	0.334–0.917	0.022	0.440	0.253–0.763	0.003

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

Table V. Post-operative complications

Variable	Normal stent (n = 42)	Radioactive stent group (n = 43)	P-value
Cholangitis (%)	16.7% (7/42)	18.6% (8/43)	0.815
Cholecystitis (%)	9.5% (4/42)	14.0% (6/43)	0.766
Self-limited biliary bleeding (%)	0% (0/42)	2.3% (1/43)	1.000
Early complication (%)	14.3% (6/42)	16.3% (7/43)	0.799
Late complication (%)	11.9% (5/42)	18.6% (8/43)	0.391

with HC [9, 10, 13]. Wang *et al.* [3] additionally reported comparable rates of technical (100% vs. 100%) and clinical success (100% vs. 100%), stent patency (208 days vs. 222 days), and OS (250 days vs. 246 days) when comparing unilateral and bilateral radioactive stent insertion in patients with HC. These results, however, were derived from a retrospective study [3]. Additional RCTs will thus be essential to test this possibility.

In this study, we found that Bismuth type III HC was another factor for increased stent patency. This finding is unexpected because Bismuth type III HC is more extensive infiltration of the biliary tree than Bismuth type II HC. The possible reason is that post-operative chemotherapy was mainly used for the Bismuth type III and IV patients.

The current findings demonstrated that the use of radioactive stents did not contribute to any incidence of postoperative complications. This is likely because the ¹²⁵I seed strand has a diameter of only 1.33 mm (4F) and thus is unlikely to exert significant pressure on the biliary tract.

There are some limitations to these analyses. While this was an RCT, patients were not randomized with stratification based on tumor staging or Bismuth type, potentially contributing to selection bias. The open-label nature of this study may have also influenced the risk of bias. However, as different stent types were used for this study, achieving effective blinding was challenging. Third, exact radioactive stent dosimetry could not be calculated as the treatment planning system is unsuitable for lumen-shaped tumors [22]. Finally, using RECIST criteria to assess tumor responses to treatment was challenging given that the stent pressed directly on the tumor, thus limiting efforts to assess the ability of radioactive stent insertion to inhibit the tumor [4].

Conclusions

Radioactive bilateral stent insertion represents a safe and effective therapeutic option for individuals diagnosed with inoperable HC. Radioactive stenting may contribute to the prolongation of both stent patency and patient OS when compared to conventional stenting.

Acknowledgments

Tao Song and An-Qiang Feng contributed equally to this study.

Conflict of interest

The authors declare no conflict of interest.

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