Bilateral versus unilateral radioactive stent insertion for hilar cholangiocarcinoma

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Abstract

Introduction: *Radioactive stent insertion (RSI) is widely used for patients with obstructive hilar cholangiocarcinoma (HC) to increase the stent patency and overall survival (OS). However, one controversy of treating HC patients is determining whether to use unilateral or bilateral stenting. General knowledge on unilateral and bilateral RSI efficacy is still lacking.*
Aim: *To evaluate the clinical efficacy and long-term prognoses of unilateral and bilateral RSI in HC patients.*
Material and methods: *Between January 2016 and December 2020, all HC patients who received unilateral and bilateral RSI at our hospital were selected for this study. We compared the treatment efficacy and long-term prognosis of patients undergoing these two procedures.*
Results: *Overall, 65 HC patients received either unilateral (n = 33) or bilateral (n = 32) RSI. There were no significant differences in the technical (both 100%) and functional (97.0% vs. 90.6%, p = 0.584) success rates between the 2 groups. Stent re-obstruction occurred in 6 and 9 patients in the unilateral and bilateral groups, respectively (p = 0.341). Median stent patency was 214 and 233 days in the unilateral and bilateral groups, respectively (p = 0.650). Median OS was 240 and 281 days in the unilateral and bilateral groups, respectively (p = 0.068). Lastly, the total complication rate was significantly lower in the unilateral group, as compared to the bilateral group (12.1% vs. 34.4%, p = 0.033).*
Conclusions: *Unilateral and bilateral RSI provided comparable clinical efficacy and long-term prognoses of HC patients. However, unilateral stenting exhibited a markedly lower complication rate.*

Key words: *hilar cholangiocarcinoma, radioactive stent, unilateral, bilateral.*

Introduction

Hilar cholangiocarcinoma (HC) is a prevalent malignant tumor involving the hepato-biliary system [1–3]. Unfortunately, HC is asymptomatic in the early stages. Therefore, it is mostly diagnosed at a late stage of disease, when the opportunity for surgical resection is lost [4]. Moreover, HC patients typically cannot tolerate chemo- or radiotherapy, due to jaundice, which occurs in the late stage of disease [5]. Given these challenges, stent insertion is the first-line treatment for late stage inoperable HC [5].

However, the stent does not treat the tumor, and, in about 50% of cases, stent re-obstruction occurs, due to tumor growth or biliary epithelial cell proliferation [6]. To reduce the stent re-obstruction rate, many anticancer treatments, including chemotherapy (ChT), photodynamic therapy (PdT), and endobiliary radiofrequency ablation (ERA), are typically used after relieving jaundice [7–9]. In recent years, many researchers have used a radioactive stent technique to treat HC [10–12]. A radioactive stent contains a normal metal stent that is attached to I-125 seeds [10–12]. Compared to ChT, PdT, and ERA, the major

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advantage of the radioactive stent is its persistent brachytherapeutic effect [10–12].

Another controversy in treating HC patients is determining whether to use unilateral and bilateral stenting [5]. Although multiple studies have assessed the clinical efficacy of unilateral or bilateral stenting, these assessments were primarily done on the normal metal stent, but not on the recently developed radioactive stent [13–15]. Therefore, general knowledge on unilateral and bilateral radioactive stent insertion (RSI) efficacy is still lacking.

Aim

Our goal in this study was to compare the clinical efficacy and long-term prognoses of unilateral and bilateral RSI in the treatment of HC patients.

Material and methods

Study design

This study was based on a retrospective design, and it received ethical approval from our hospital. Owing to our retrospective design, documented informed consent was not necessary for our study.

Between January 2016 and December 2020, all HC patients who received unilateral or bilateral RSI at our hospital were selected for this study. Between January 2016 and December 2018, we employed the unilateral RSI technique. From January 2019 onwards, we employed the bilateral RSI technique.

The inclusion criteria were as follows: (a) HC patients; (b) inoperable cases; (c) patients with obstructive jaundice; and (d) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2. The exclusion criteria were as follows: (a) patients who had previously undergone hepatectomy; (b) Bismuth type I patients; and (c) life expectancy < 3 months.

Diagnosis

HC was initially diagnosed via abdominal computed tomography (CT) and magnetic resonance imaging (MRI). The Bismuth types were diagnosed via abdominal CT and MRI. The pathological diagnosis of HC was made via intraductal biopsy.

Radioactive stent

A radioactive stent was combined with a normal metal stent (Micro-Tech, Nanjing, China) and an I-125 seed strand. Each I-125 seed strand was designed by sealing I-125 seeds (Chinese Atomic Energy Science Institution, Beijing, China) onto a 4F catheter (PBN MEDICALS Denmark A/S, Stenlose, Denmark). Each I-125 seed (4.5 mm long, 0.8 mm in diameter) released low-energy 35.5-keV γ-rays, carrying a half-life of 59.6 days. The number of required I-125 seeds in each strand was decided according to the obstruction length: N = length of stent (mm)/4.5 + 4 [10].

Unilateral RSI

The radioactive stent was inserted via the percutaneous trans-hepatic approach. In short, the intrahepatic bile duct was penetrated with a 22-G needle under fluoroscopic and ultrasonic intelligence. Next, a 4F single-curved catheter, with a 0.035-inch loach guide wire, was used to detect the obstruction. The length of the obstruction was measured via cholangiography. Once the catheter and guide wire crossed the obstruction, they were guided into the duodenum, and the loach guide wire was replaced with a 0.035-inch stiff guide wire. Next, a 6F sheath was sent across the obstruction via another guide wire. The stent was deployed at the center of the obstruction using a 0.035-inch stiff guide wire. Subsequently, the I-125 seed strand was placed inside the 6F sheath, and the 6F sheath was removed carefully so that the I-125 seed strand was deposited between the biliary wall and the stent (Photo 1 A).

Bilateral RSI

The bilateral RSI was performed via the left and right intrahepatic bile duct approach, and the stents were placed employing the side-by-side technique (Photo 1 B).

Follow-up and definitions

After surgery, all patients were followed up at 1 week; 1, 3, and 6 months; and once every 6 months after that. During these follow-ups, patients underwent abdominal CT, a liver function test, and body examination. The follow-ups lasted either until patients' death or until 31 December 2021.

Technical success was described as the successful recanalization of the biliary obstruction, with good contrast passage via the stent and into the duodenum [10, 11]. Functional success was described as 20% lowering of the serum total bilirubin (TB) at

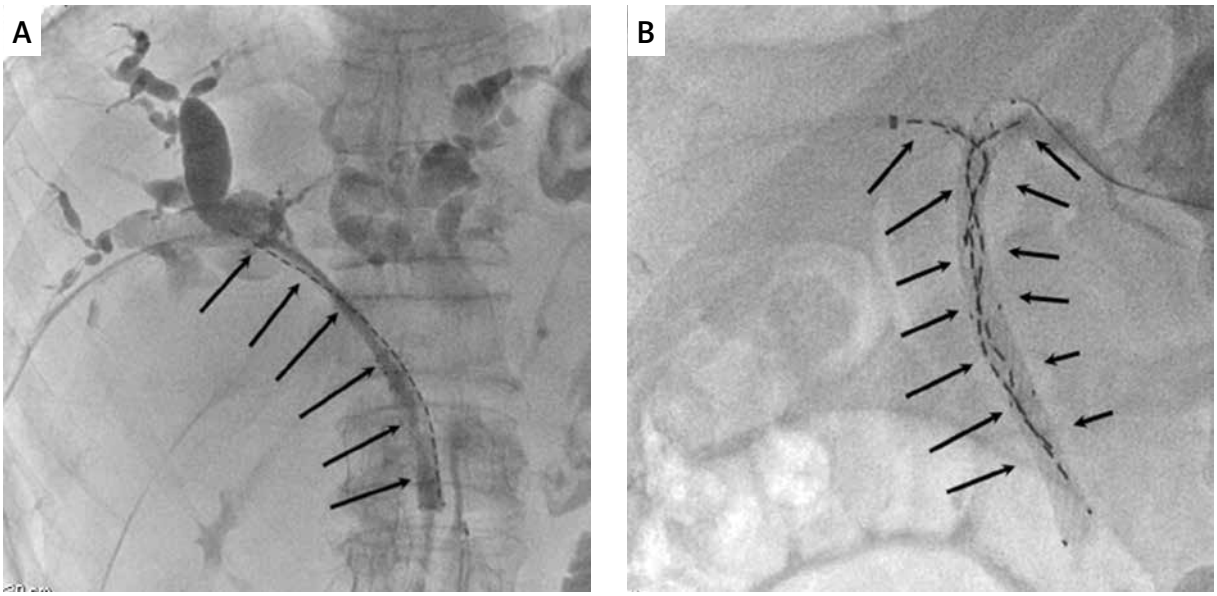

Photo 1. Images for unilateral (arrows) (**A**) and bilateral (arrows) (**B**) radioactive stent insertion for HC patients

< 1 week after surgery [16]. Stent patency was defined as the duration between the stent deployment and the first recurrence of jaundice, the most recent follow-up, or death in the absence of jaundice [10, 11]. Overall survival (OS) was defined as the duration between the stent deployment and death [10, 11]. Early complication was defined as a complication occurring within 30 days of stent placement [16].

Statistical analysis

Inter-group continuous variables were analyzed via the Mann-Whitney *U* test, and the data before and after stent placement were compared via the paired *t*-test. Categorical data are presented as number and percentage (%), and were analyzed using the χ^2 or Fisher's exact test. The intergroup stent patency and OS were analyzed via Kaplan-Meier curves with the log-rank test. Uni- and multivariate Cox regression analyses were employed to examine the associations between predictors and OS. $P < 0.05$ was considered significant. All analyses were carried out with the SPSS v16.0 software (SPSS, Inc., Chicago, Illinois, USA).

Results

Patients

Overall, 65 HC patients, who underwent unilateral ($n = 33$) or bilateral ($n = 32$) RSI at our hospital, were selected for analysis (Table I). The baseline data were comparable between the two groups. Moreover, a total of 14 and 12 patients underwent ChT after unilateral and bilateral RSI, respectively ($p = 0.685$).

Treatment effect

The technical success rate was 100% in both groups. No intra-operative complications occurred. The diameter of all stents was 8 mm, and the length of all stents ranged between 50 and 70 mm. A total of 452 (mean 13.7 per patient) and 786 (mean 24.6 per patient) I-125 seeds were utilized in the unilateral and bilateral groups, respectively. The functional success rates were 97.0% (32/33) and 90.6% (29/32) after unilateral and bilateral RSI, respectively, and there was no significant difference between the two groups ($p = 0.584$). In the unilateral group, the average TB decreased from the preoperative value of 230.1 µmol/l to the postoperative value of 98.1 µmol/l ($p < 0.001$). In the bilateral group, the average TB decreased from the preoperative value of 181.3 µmol/l to the postoperative value of 81.0 µmol/l ($p < 0.001$).

Follow-up

No patients were lost to follow-up. Stent re-obstruction was observed in 6 (18.2%) and 9 (28.1%) patients after unilateral and bilateral RSI, respec-

Table I. Patient characteristics in the 2 groups

Parameter	Unilateral group	Bilateral group	*P*-value
Number of patients	33	32	–
Age [years]	65.5	63.2	0.247
Gender (male/female)	17/16	17/15	0.897
Tumor stage (II/III/IV)	13/11/9	10/11/11	0.750
Bismuth type (II/III/IV)	12/14/7	17/10/5	0.397
Obstruction length [mm]	40.2	37.3	0.163
ECOG PS (0/1/2)	16/11/6	17/11/4	0.813
TB [μmol/l]:			
Before	230.1	181.3	0.084
After	98.1	81.0	0.242
Ca19-9 (≤/> 37 U/l)	1/32	2/30	0.978

ECOG PS – Eastern Cooperative Oncology Group performance status, TB – total bilirubin.

Table II. Post-operative complications and re-obstruction

Parameter	Unilateral group	Bilateral group	*P*-value
Total complications	4	11	0.033
Cholangitis	3	9	
Cholecystitis	1	2	
Early/late complications	2/2	8/3	0.930
Re-obstruction	6	9	0.341

tively (p = 0.341, Table II). All stent re-obstructions were caused by tumor invasion. The median stent patency periods were 214 and 233 days following unilateral and bilateral RSI, respectively (Figure 1 A), and there was no significant difference between the two groups (p = 0.650). In the unilateral group, 6 re-obstruction patients underwent percutaneous transhepatic cholangial drainage (PTCD) (n = 5) or

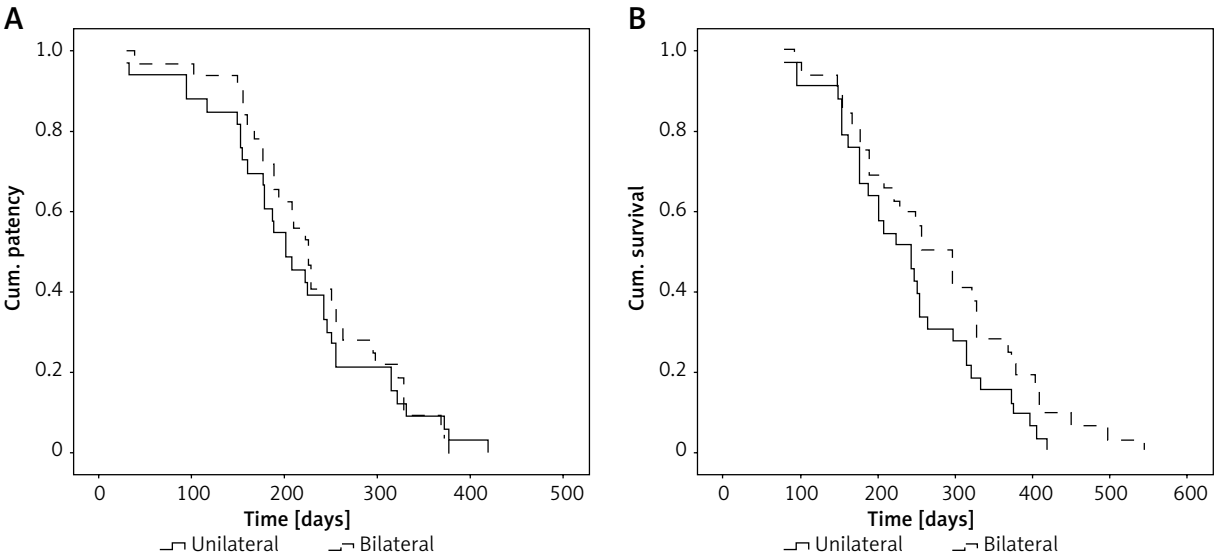

Figure 1. Comparison of stent patency duration (**A**) and OS (**B**) between the 2 groups

deployment of a second metal stent (n = 1). In the bilateral group, all 9 re-obstruction patients underwent PTCD.

All patients expired during follow-up. The median OS periods were 240 and 281 days after the unilateral and bilateral RSI, respectively (Figure 1 B), and there was no significant difference between the two groups (p = 0.068). Our univariate Cox regression analysis revealed that the Bismuth type III HC (p = 0.035) was correlated with reduced OS, while the post-operative ChT (p = 0.012) and bilateral RSI (p = 0.076) were correlated with prolonged OS. We next entered the above significant variables into the multivariate model. We found that the Bismuth type III HC (p = 0.035) was associated with shorter OS, while the post-operative ChT (p = 0.033) was associated with longer OS (Table III).

Post-operative complications

The total complication rate was significantly lower among the unilateral RSI-treated patients versus the bilateral RSI-treated patients (12.1% vs. 34.4%, p = 0.033, Table II). In the unilateral RSI-treated patients, cholangitis and cholecystitis were detected in 3 and 1 patients, respectively. In the bilateral RSI-treated patients, cholangitis and cholecystitis were detected in 9 and 2 patients, respectively. Moreover, 2 and 8 patients in the unilateral RSI- and bilateral RSI-treated patients experienced early complications.

Table III. Predictors of overall survival

Parameter	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Age	0.995	0.964–1.026	0.995			
Gender:						
Male	1					
Female	1.382	0.833–2.293	0.211			
Tumor stage:						
II	1					
III	0.695	0.378–1.276	0.695			
IV	1.237	0.671–2.279	0.496			
Obstruction length	1.058	0.806–1.390	0.685			
ECOG PS	1.163	0.846–1.599	0.352			
Bismuth type:						
II	1			1		
III	2.547	1.422–4.562	0.035	1.932	1.047–3.564	0.035
IV	0.924	0.459–1.859	0.824	0.808	0.397–1.644	0.556
TB before	1.000	0.997–1.002	0.921			
TB after	1.004	0.998–1.009	0.192			
Ca19-9:						
≤ 37 U/l	1					
> 37 U/l	0.988	0.566–1.723	0.965			
Post-operative chemotherapy:						
No	1					
Yes	0.520	0.312–0.867	0.012	0.553	0.320–0.995	0.033
Types of stent:						
Unilateral	1			1		
Bilateral	0.632	0.381–1.049	0.076	0.637	0.376–1.018	0.095

ECOG PS – Eastern Cooperative Oncology Group performance status, TB – total bilirubin.

Subgroup analyses

We also performed subgroup analyses, based on the different tumor stages and Bismuth types (Table IV). Patient stratification by tumor stages showed no significant differences in stent patency duration. A significantly longer OS period was observed in the bilateral RSI-treated patients only, depending on tumor stage III ($p = 0.037$). Patient stratification by Bismuth types also showed no significant differences in stent patency or the OS period.

Discussion

Herein, we evaluated the clinical efficacy and long-term prognoses of unilateral and bilateral RSI in treating HC patients. Compared to previous studies involving RSI insertion for malignant hilar obstruction [10, 11], the advantage of this study was that we only included HC patients. Our results were also quite positive. Based on our analyses, both procedures exhibited high technical and functional success rates. Therefore, both procedures can be effectively used to relieve jaundice in HC patients.

The observed high technical success rates (both 100%) in our study may be attributed to the percutaneous trans-hepatic stenting approach. At present, endoscopic biliary stent insertion is still employed in patients with malignant obstructive jaundice [17, 18]. The main advantages of the endoscopic approach are the physiological drainage of the biliary tract into the intestine and the avoidance of liver puncture. However, endoscopic biliary stenting was usually used for patients with distal biliary or Bismuth type I/II hilar obstruction [17–21]. In Bismuth type III and IV HC, the obstruction pattern is more complex because it is tighter, longer, and more tortuous, and it involves more liver segments. Endoscopic biliary stenting is not suitable for Bismuth type III and IV HC because the endoscopic approach has only one retrograde direction and manipulation of devices is more difficult through the long channel [21]. Percutaneous trans-hepatic stenting is used over endoscopic biliary stenting in advanced HC because the precise lobe can be selected for drainage [21]. In the case of HC patients, the percutaneous stenting approach achieves both higher technical (100% vs. 72.4%) and functional (92.7% vs. 77.3%) success rates, as compared to the endoscopic stenting approach [20, 21]. Therefore, percutaneous stenting is the obvious rescue procedure after a failed endoscopic stenting attempt [20].

Table IV. Subgroup analyses of patency and OS

Parameter	Unilateral group	Bilateral group	*P*-value
Tumor stage II:			
Patency (d)	217	230	0.912
OS (d)	253	253	0.824
Tumor stage III:			
Patency (d)	211	222	0.935
OS (d)	234	330	0.037
Tumor stage IV:			
Patency (d)	212	244	0.449
OS (d)	227	257	0.435
Bismuth type II:			
Patency (d)	228	242	0.678
OS (d)	265	306	0.106
Bismuth type III:			
Patency (d)	187	209	0.400
OS (d)	207	209	0.946
Bismuth type IV:			
Patency (d)	242	245	0.685
OS (d)	261	340	0.298

OS – overall survival.

In this study, bilateral RSI did not show any superiority in terms of the functional success over unilateral RSI. In fact, it was previously demonstrated that unilateral RSI also effectively relieves jaundice in HC patients by draining more than 25% of the liver bile, thereby achieving functional success [22].

A recent meta-analysis also demonstrated that the side-by-side stent technique achieves a significantly reduced stent re-obstruction rate, compared to the unilateral stent insertion technique [14]. However, our analysis did not detect any marked differences in stent re-obstruction rates or stent patency duration. These results may be attributed to the fact that we employed the radioactive stent, which can also inhibit tumor growth [6]. Our re-obstruction rate (18.2%) after unilateral RSI was lower, compared to the 26.0% in the previous meta-analysis that employed normal unilateral stent insertion to treat HC patients [14]. Nevertheless, the dose of each I-125 seed strand was not calculated by the treatment plan system (TPS) because TPS may not be suitable for luminal cancers [23]. Furthermore, the main purpose of RSI is to decrease the re-obstruction rate and prolong the stent patency duration [10, 11]. We did not expect that RSI usage would cure HC. Therefore, we calculated the number of I-125 seeds in each strand using the formula: N = length of stent (mm)/4.5 + 4 [10].

The OS duration was also comparable between the unilateral and bilateral RSI patient populations. This result may be attributed to the comparable stent patency duration between the two groups. While bilateral RSI resulted in the insertion of two I-125 seed strands, such brachytherapy only inhibited regional tumor growth. However, in patients with stage III and IV tumors, such brachytherapy is unable to influence distant or lymph node metastases [24]. Furthermore, we observed that the post-operative ChT was associated with longer OS. This corroborated some previous studies involving stent insertion in HC patients [11, 25]. In such cases, post-operative ChT was shown to play an essential role in treating distant or lymph node metastases. However, in this study, the post-operative ChT was performed based on patient consent and condition; therefore, the effectiveness of the post-operative ChT should be further confirmed by prospective clinical trials.

The total complication rate was significantly reduced in our unilateral RSI patient population. It is possible that, with the use of side-by-side stenting, the placement of two stents into the common biliary tract may promote a rise in the biliary wall compressive stress. This, in turn, can potentially increase the risk of cholangitis [14, 26].

Furthermore, we conducted subgroup analyses, based on distinct tumor stages and Bismuth types. Our results revealed that bilateral RSI significantly prolonged OS duration in patients with stage III tumors. However, this result may not be very reliable since we did not compare the baseline data among stage III tumor patients. Additionally, our subgroup analyses were performed based on a subset of patients with limited sample size.

At present, transarterial radio-embolization (TARE) using yttrium-90 (Y90) is widely employed in treating inoperable intra-hepatic cholangiocarcinoma [27]. Compared to transarterial chemoembolization, TARE provides similar good outcomes with significantly reduced adverse event rates in patients with intra-hepatic cholangiocarcinoma [27]. However, TARE is usually used for mass-like intra-hepatic cholangiocarcinoma. In this study, the HCs were presented as the luminal cancer and TARE was not suitable.

Our research has certain limitations. First, the major limitation was the retrospective nature of the study. Second, the analyzed groups of patients were from different time intervals. Nevertheless, the unique cancer type and comparable baseline data may reduce the risk of bias. Third, the number of I-125 seeds was decided by the length of obstruction, without any treatment planning dedicated to the luminal organs. Under this condition, the radioactive dosimetry may not be able to accurately assess each patient. Fourth, the post-operative ChT was conducted based on patient consent and condition. This may also have introduced selection bias. Nevertheless, the comparable ratio of patients with post-operative ChT between the two groups may have potentially reduced the risk of bias.

Conclusions

Our results revealed that unilateral and bilateral RSI can provide comparable clinical efficacy and long-term prognoses when treating HC patients. However, unilateral RSI is associated with a markedly lower complication rate.

Conflict of interest

The authors declare no conflict of interest.

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