Randomised Controlled Trial

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Radiation-emitting metallic stent for unresectable Bismuth type III or IV perihilar cholangiocarcinoma: a multicenter randomized trial

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Background and Aims: Self-expandable metallic stents (SEMSs) have been recommended for patients with unresectable malignant biliary obstruction, while radiation-emitting metallic stents (REMSs) loaded with ^{125}I seeds have recently been approved to provide longer patency and overall survival in malignant biliary tract obstruction. This trial is to evaluate the efficacy and safety of REMS plus hepatic arterial infusion chemotherapy (REMS-HAIC) versus SEMS plus HAIC (SEMS-HAIC) for unresectable perihilar cholangiocarcinoma (pCCA).

Materials and Methods: This multicenter randomized controlled trial recruited patients with unresectable Bismuth type III or IV pCCA between March 2021 and January 2023. Patients were randomly assigned (1:1 ratio) to receive either REMS-HAIC or SEMS-HAIC using permuted block randomization, with a block size of six. The primary endpoint was overall survival (OS). The secondary endpoints were time to symptomatic progression (TTSP), stent patency, relief of jaundice, quality of life, and safety.

Results: A total of 126 patients were included in the intent-to-treat population, with 63 in each group. The median OS was 10.2 months versus 6.7 months ($P = 0.002$). The median TTSP was 8.6 months versus 5.4 months ($P = 0.003$). The median stent patency was longer in the REMS-HAIC group than in the SEMS-HAIC group ($P = 0.001$). The REMS-HAIC group showed better improvement in physical functioning scale ($P < 0.05$) and fatigue symptoms ($P < 0.05$) when compared to the SEMS-HAIC group. No significant differences were observed in relief of jaundice (85.7% vs. 84.1%; $P = 0.803$) or the incidence of grade 3 or 4 adverse events (9.8% vs. 11.9%; $P = 0.721$).

Conclusion: REMS plus HAIC showed better OS, TTSP, and stent patency compared with SEMS plus HAIC in patients with unresectable Bismuth type III or IV pCCA with an acceptable safety profile.

Keywords: Bismuth type III or IV, hepatic arterial infusion chemotherapy, perihilar cholangiocarcinoma, radiation-emitting metallic stent

Introduction

Cholangiocarcinoma (CCA) encompasses a heterogeneous group of malignancies arising from biliary epithelium, which can be categorized as intrahepatic CCA (iCCA), perihilar CCA (pCCA), and distal CCA. Among them, pCCA involves the bifurcation of bile ducts, accounting for ~50–60% of all CCAs[1–3]. Surgical resection remains the cornerstone of the radical regimen[4].

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Patients commonly present with advanced-stage or unresectable diseases and are ineligible for resection due to their intrinsic aggressive nature and insidious growth pattern[5].

For patients with unresectable or advanced-stage diseases, systemic chemotherapy of gemcitabine-cisplatin with or without durvalumab is the first-line regimen recommended by clinical guidelines[5,6]. However, in patients with pCCA complicated with obstructive jaundice, biliary drainage is often required before the initiation of chemotherapeutics. Stent implantation has been an established palliative treatment to relieve jaundice and improve quality of life (QoL). Nevertheless, the life expectancy of pCCA patients after conventional self-expandable metallic stent (SEMS) was suboptimal and associated with a high incidence of stent restenosis[7]. Although upgraded stent designs have been proposed over the past years, substantially improved clinical benefits have not yet been achieved[8].

Recently, a novel radiation-emitting metallic stent (REMS) loaded with iodine-125 (^{125}I) seeds has been demonstrated to offer significantly longer stent patency and survival in patients with unresectable malignant biliary obstruction than the conventional SEMS in randomized controlled trials[9,10]. Despite the promising outcomes in the whole spectrum of malignant biliary obstruction, it remains unclear if REMS is efficacious for Bismuth type III or IV pCCA.

Hepatic arterial infusion chemotherapy (HAIC) is well established for treating unresectable liver neoplasms, such as iCCA, hepatocellular carcinoma, and colorectal liver metastases, by increasing the local drug concentration through arterial administration of chemotherapeutic agents[11–13]. A recent study on HAIC has shown promising outcomes for advanced pCCA with high tumor control, survival benefit, and low toxicity, given that the blood supply of the perihilar region derives from the hepatic artery[14].

This randomized, open-label, multicenter trial aimed to investigate the efficacy and safety of REMS combined with HAIC for patients with unresectable Bismuth type III or IV pCCA.

HIGHLIGHTS

- Patients in the REMS plus HAIC group obtained longer survival time.
- Patients in the REMS plus HAIC group obtained longer time to symptomatic progression and stent patency.
- REMS plus HAIC group showed better improvement in physical functioning scale and fatigue symptoms.
- The use of REMS did not increase the incidence of treatment-related adverse events.

Materials and methods

Study design and patients

This multicenter, randomized, controlled trial was conducted in nine high-volume institutions in China from March 2021 to January 2023 following the Declaration of Helsinki and Good Clinical Practice. The protocol and any amendments were approved by the ethics committee at each center. Written informed consent was obtained from all patients.

The main inclusion criteria were as follows: clinical or histopathological diagnosis of cholangiocarcinoma; with jaundice caused by biliary obstruction; biliary obstruction of Bismuth-Correlate classification type III or IV; mass $\leq$ 3 cm in maximum diameter; Child–Pugh class A or B disease; aged $\geq$18 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; life expectancy of $\geq$3 months; and unresectable cholangiocarcinoma. Unresectability was determined based on the presence of distant metastases, the patient's medical fitness and ability to tolerate surgery, and locoregional factors after a discussion with a multidisciplinary team, including hepatobiliary surgeons, medical oncologists, radiologists, hepatologists, and pathologists. The main exclusion criteria were concomitant malignancy other than cholangiocarcinoma; the presence of distant metastases; history of biliary stent implantation; concomitant receipt of other antitumor drugs; severe ascites (ascites with a Child–Pugh score of 3); and presence of a biliary perforation. This study has been registered with ClinicalTrials.gov and followed the Consolidated Standards of Reporting Trials (CONSORT, Supplemental Digital Content 1; http://links.lww.com/JS9/D466 Supplemental Digital Content 2, http://links.lww.com/JS9/D467) Guidelines[15].

Randomization and masking

Prior to recruitment, the study statistician utilized SAS version 9.4 (SAS Institute Inc.) software to generate permuted block randomization sequences with a block size of 6. Randomization was performed centrally promptly upon admission by staff members in the trial office. Patients were randomly assigned in a 1:1 ratio to receive REMS-HAIC combination or SEMS-HAIC combination. Due to the necessity of radiation protection for REMS, neither the participants nor the investigators were masked to the randomization results.

Procedures

Details on the structural design of REMS have been described in previous studies[9,10,16]. Briefly, the REMS was composed of two isolated parts, including the inner SEMS (Cordis Corporation, Florida, USA) and the outer one carrying ^{125}I seeds (CIAE-6711; Chinese Atomic Energy Science Institution, Beijing, China), which were preloaded on the surface immediately before the procedure. The numbers, prescription dose, and distribution of ^{125}I seeds were programmed and determined using the Treatment Planning System (Qilin Co., Ltd). The median calculated surface radiation dose at the dose prescription point was 48.0 Gray (range, 29.7–60.8).

In the REMS-HAIC group, the expanded intrahepatic bile duct was punctured under ultrasonic and fluoroscopic guidance. A cholangiogram was conducted to confirm the location and extension of the stricture. After coaxial dilation of the passage using a balloon catheter, the outer seed-loaded stent was implanted and released to cover the stricture, and then the inner SEMS was immediately deployed to overlap the outer one (Fig. 1). In the SEMS-HAIC group, an uncovered SEMS was inserted into the targeted lesion following coaxial dilation. Then, a cholangiogram was performed to confirm the successful flow of contrast medium into the intestine through the stent. Ultimately, an external drainage catheter (Cook Medical, Bloomington, Indiana, USA) was placed for 7 days to reserve a passage for monitoring stent dysfunction and handling adverse events, if any. Radiation safety and management with regard to the irradiation stents were carried out according to the criteria recommended by

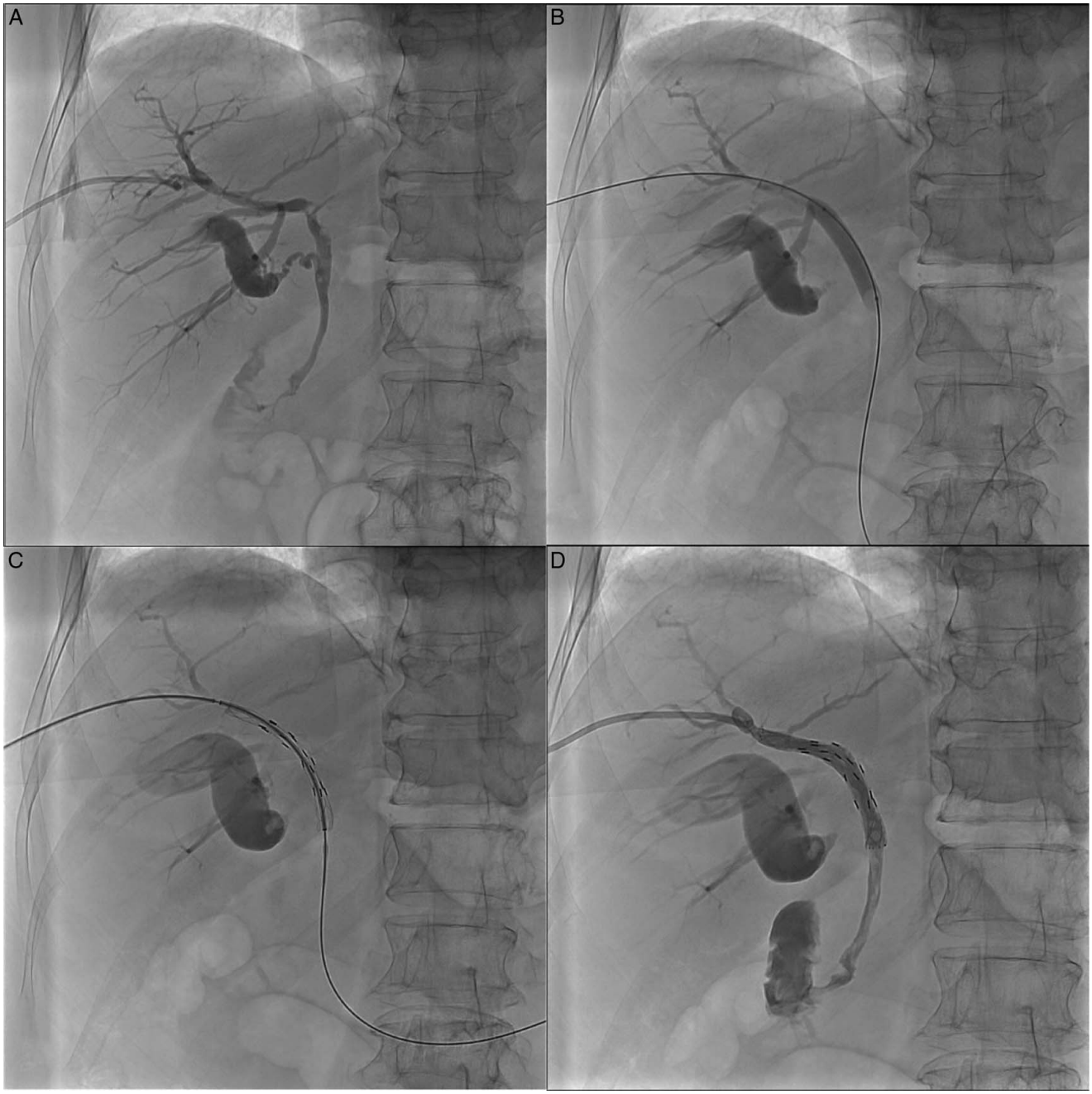

Figure 1. Representative images of a 75-year-old male patient who received a radiation-emitting metallic stent for unresectable perihilar cholangiocarcinoma. (A) Cholangiogram showing tumor involving the common hepatic duct, bifurcation, left primary branch, and right primary branch opening (Bismuth type IV). (B) The balloon catheter was used for coaxial dilation of the passage. (C) The outer seed-loaded stent was implanted and released to cover the stricture. (D) The inner stent was immediately deployed to overlap the outer one, and then the cholangiogram showed the successful flow of contrast medium into the intestine through the stent. pCCA, perihilar cholangiocarcinoma; REMS, radiation-emitting metallic stent.

the International Commission on Radiological Protection[17].

If successful relief of jaundice following stent placement was achieved, patients underwent fluoroscopy-guided HAIC. After successful percutaneous femoral artery puncture, the celiac trunk, superior mesenteric artery, or common hepatic artery was catheterized for selective arteriography. Then, a microcatheter was superselectively inserted into the distal part of the common hepatic artery. The chemotherapeutic regimen contained gemcitabine (1000 mg/m^2 given over 30 min) followed by cisplatin (25 mg/m^2 given over 2 h) every 3 weeks. All procedures were performed by well-trained interventional radiologists with over 10 years of experience.

Endpoints

The primary endpoint was overall survival (OS), defined as the time from randomization to death due to any cause or the data cutoff (15 July 2023). The secondary endpoints included time to

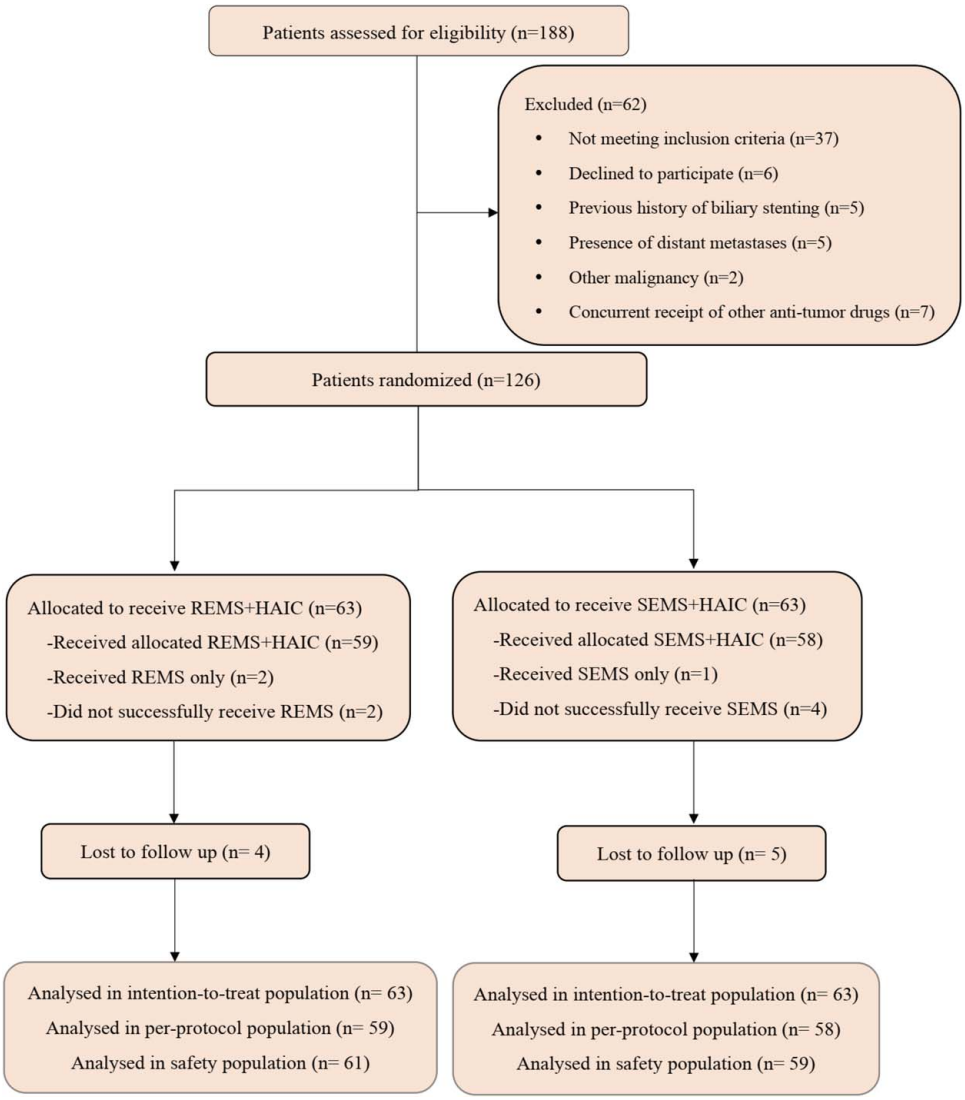

Figure 2. Trial profile. HAIC, hepatic arterial infusion chemotherapy; REMS, radiation-emitting metallic stent; SEMS, self-expandable metallic stent.

symptomatic progression (TTSP), stent patency, relief of jaundice, QoL, and safety. TTSP was defined as the duration from randomization to the first episode of symptom progression. Symptom progression was reported when the ECOG performance status score increased to 4 or 5. Stent patency was determined as the period to the first onset of recurrent biliary obstruction. Recurrent biliary obstruction was determined to be the occurrence of clinical symptoms indicating obstructive jaundice with increased bilirubin level, along with imaging findings of new dilation of bile ducts. Relief of jaundice was defined as a reduction in the total bilirubin (TB) level at least 20% from baseline within one week after stent implantation. QoL was evaluated by the European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (QLQ-C30). Raw scores of QoL were standardized on a scale of 0–100, with higher scores indicating better QoL on functional scales but worse QoL on the symptom scales. Follow-up visits, consisting of routine clinical assessment and radiographic examination, were conducted at 1 week, 1 month, 3 months, and 6 months after stent implantation, and every 3 months thereafter. In addition, QoL questionnaires were assessed at different time points: baseline, 4 weeks, 12 weeks, and 24 weeks after stent placement. The incidence and severity of adverse events were evaluated and classified following the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Statistical analyses

The assumption was that OS in the SEMS-HAIC group would be 6 months, while the REMS-HAIC group would ameliorate it to 10 months[16,18]. The duration of enrollment lasted for 12 months. The minimum period of follow-up was 6 months. For both groups, the estimated yearly dropout rate was 5%. To evaluate this significant difference with the 80% power and an alpha level of 0.05, the sample size was estimated to be 126 participants, with 63 patients in each group, using the PASS11 software (NCSS, LLC).

All analyses were completed using R (version 4.1.3; R Project for Statistical Computing, http://www.r-project.org) and Stata 17.0 (Stata Corporation, College Station, TX, USA). Efficacy was analyzed on an intention-to-treat (ITT) basis, which consisted of

all patients undergoing randomization and in a per-protocol (PP) set, which included patients who successfully received the allocated stent and completed at least one cycle of HAIC regimen. A safety set was applied to analyze all safety results, which included patients who successfully underwent at least one assigned treatment. Baseline characteristics are presented as mean [standard deviation (SD)], median with interquartile range (IQR) or range, and *n* (%) for continuous and categorical parameters, respectively. The Student *t* test or Mann–Whitney *U* test was performed for continuous, and Chi-square test or Fisher exact test was performed for categorical variables. Comparisons of liver function at baseline and 1-month posttreatment were analyzed using the Wilcoxon signed rank test or paired *t* test. Survival analyses for OS, TTSP, and patency time were presented using the Kaplan–Meier method and compared with the log-rank test. Pearson correlation coefficient was calculated between patency time and OS. The proportional hazards assumption was tested based on Schoenfeld residuals, and the Cox proportional hazards model was then utilized to determine hazard ratios (HRs) and 95% confidence interval (CI) for survival analysis. The differential changes in all QoL scales were assessed between the two groups at 4, 12, and 24 weeks compared with baseline based on statistical models for longitudinal data using generalized estimation equations. Cox models were used for univariate and multivariate analyses to identify independent risk factors for overall survival. $P < 0.05$ was considered to indicate statistical significance.

Results

Patient characteristics and treatment

A total of 188 patients were screened between March 2021 and January 2023. After excluding ineligible patients (Fig. 2), 126 patients were enrolled and randomly designated to either the REMS-HAIC group ($n = 63$) or the SEMS-HAIC group ($n = 63$) in the ITT population. No significant heterogeneity of the baseline characteristics was found between the two groups (Table 1). In the REMS-HAIC group, irradiation stents were successfully placed in 61 participants, while in the remaining two participants, the stent was unable to pass through the tumor blockage. In the SEMS-HAIC group, SEMS was successfully inserted in 59 participants, whereas stent placement failed in the remaining four participants. In the REMS-HAIC group, the mean number of HAIC cycles per participant was 3.1 (range, 0–6) compared to 3.0 (range, 0–6) in the SEMS-HAIC group ($P = 0.769$).

Primary endpoint

At the data cutoff (15 July 2023), the median follow-up time was 17.2 months (IQR: 14.9–25.9) in the ITT population. A total of 48 (76%) of the 63 participants in the REMS-HAIC group and 56 (89%) of the 63 participants in the SEMS-HAIC group died. The median OS was significantly longer in the REMS-HAIC group (median, 10.2 mo; 95% CI: 7.2–12.3) when compared with the SEMS-HAIC group (median, 6.7 mo; 95% CI: 5.4–8.7; HR: 0.53; 95% CI: 0.36–0.79; $P = 0.002$) (Fig. 3). The estimated survival rates at 3, 6, and 12 months in the REMS-HAIC group were 87.1% (95% CI: 75.9–93.4), 73.7% (95% CI: 60.7–83.0), and 36.5% (95% CI: 24.1–48.9) versus 77.8% (95% CI: 65.4–86.2), 55.8% (95% CI: 42.4–67.2), and 16.3% (95% CI: 8.1–27.1) in the SEMS-HAIC group. Subgroup analyses of OS are shown in Figure 4, showing consistent clinical benefits for OS across all the subgroups.

Secondary endpoints

Symptomatic progression was observed in 54 (86%) out of 63 participants in the REMS-HAIC group and in 59 (94%) out of 63

Table 1

Demographic and clinical characteristics of patients at randomization.

		Stent type		
Variable	**Total (*N* = 126)**	**REMS+HAIC (*n* = 63)**	**SEMS+HAIC (*n* = 63)**	***P***
Age, years, median (IQR)	69.0 (60.0–75.0)	69.0 (61.0–75.0)	70.0 (59.0–76.0)	0.711
Gender, *n* (%)				0.591
Female	57 (45.2%)	27 (42.9%)	30 (47.6%)	
Male	69 (54.8%)	36 (57.1%)	33 (52.4%)	
BMI, kg/m^2, median (IQR)	21.5 (19.9–22.9)	21.4 (19.5–22.9)	22.0 (20.5–23.2)	0.201
Duration of symptoms, days, median (IQR)	34.5 (15.0–50.0)	34.0 (14.0–49.0)	35.0 (15.0–51.0)	0.794
ECOG performance status, *n* (%)				0.440
0	6 (4.8%)	4 (6.3%)	2 (3.2%)	
1	70 (55.5%)	37 (58.7%)	33 (52.4%)	
2	50 (39.7%)	22 (35.0%)	28 (44.4%)	
Child–Pugh classification, *n* (%)				0.434
A	17 (13.5%)	7 (11.1%)	10 (15.9%)	
B	109 (86.5%)	56 (88.9%)	53 (84.1%)	
Bismuth classification, *n* (%)				0.717
Type III	52 (41.3%)	25 (39.7%)	27 (42.9%)	
Type IV	74 (58.7%)	38 (60.3%)	36 (57.1%)	
Extent of disease, *n* (%)				0.154
Locally advanced	66 (52.4%)	37 (58.7%)	29 (46.0%)	
Lymph node metastasis	60 (47.6%)	26 (41.3%)	34 (54.0%)	
CA19-9, U/ml, median (IQR)	616.3 (174.5–1000.0)	548.6 (169.0–1200.0)	755.2 (176.3–1000.0)	0.811
Total bilirubin level, μmol/l, median (IQR)	154.9 (74.6–270.3)	131.3 (72.8–228.5)	167.9 (83.2–306.5)	0.170

BMI, body mass index; CA, carbohydrate antigen; ECOG, Eastern Cooperative Oncology Group; HAIC, hepatic arterial infusion chemotherapy; REMS, radiation-emitting metallic stent; SEMS, self-expandable-metallic-stent.

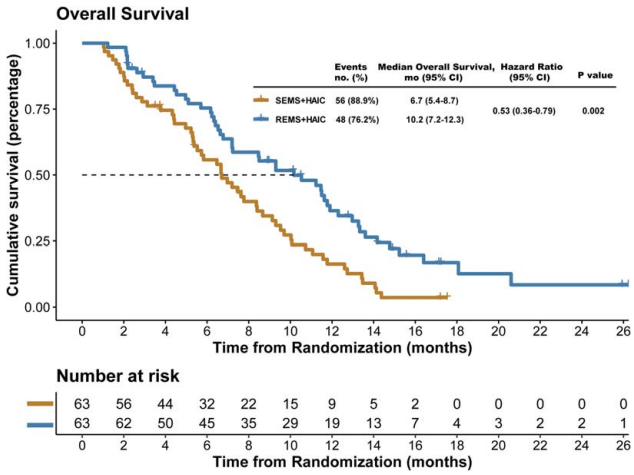

Figure 3. Kaplan–Meier estimate of overall survival.

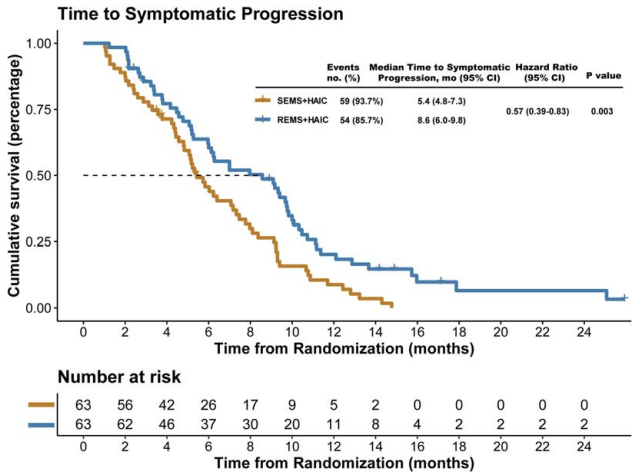

Figure 5. Kaplan–Meier estimate of time to symptomatic progression. HAIC, hepatic arterial infusion chemotherapy; REMS, radiation-emitting metallic stent; SEMS, self-expandable metallic stent.

participants in the SEMS-HAIC group. TTSP of patients in the REMS-HAIC group was significantly longer than that of patients in the SEMS-HAIC group (median, 8.6 mo; 95% CI: 6.0–9.8; vs. median, 5.4 mo; 95% CI: 4.8–7.3; HR: 0.57; 95% CI: 0.39–0.83; $P = 0.003$) (Fig. 5).

Stent restenosis was recorded in 18 (29%) of 63 patients in the REMS-HAIC group and 30 (48%) of 63 patients in the SEMS-HAIC group. The median stent patency time was significantly longer in the REMS-HAIC group than in the SEMS-HAIC group [median, not reached (NR); 95% CI: 11.5–NR; vs. median, 6.9 mo; 95% CI: 5.5–9.6; HR: 0.37; 95% CI: 0.21–0.68; $P = 0.001$) (Fig. 6). The first quartile patency time (when 25% of patients developed stent restenosis) was 7.4 months in the REMS-HAIC group compared to 4.1 months in the SEMS-HAIC group. The correlation coefficient showed that a longer patency time is correlated with longer OS ($r = 0.869$; $P < 0.001$) (Fig. 7).

The relief of jaundice within one week was 85.7% (54/63) in the REMS-HAIC group and 84.1% (53/63) in the SEMS-HAIC group ($P = 0.803$) (Fig. 8). After stent placement, various symptoms related to biliary obstruction, including pruritus, cholangitis, and pain, are alleviated to different extents.

For the comparative outcomes of QoL domains, there was no significant difference in baseline between the two groups. The REMS-HAIC group was as effective as the SEMS-HAIC group in maintaining most of the QoL domains, with the additional benefits of improvement in physical functioning scale (time-by-group interaction, 12 wk: β, 3.84 [95% CI, 0.85–6.83; $P = 0.012$]; 24 wk: β, 10.98 [95% CI, 5.69–16.26; $P < 0.001$]) and fatigue symptom (4 wk: β, −3.26 [95% CI, −6.37 to −0.15; $P = 0.040$]; 12 wk: β, −4.22 [95% CI, −8.12 to −0.32; $P = 0.034$]; 24 wk: β, −13.48 [95% CI, −19.85 to −7.11; $P < 0.001$]) (Tables 2, 3). QoL assessment after any study treatment at randomization is shown in Supplementary Table S1 (Supplemental Digital Content 3, http://links.lww.com/JS9/D468).

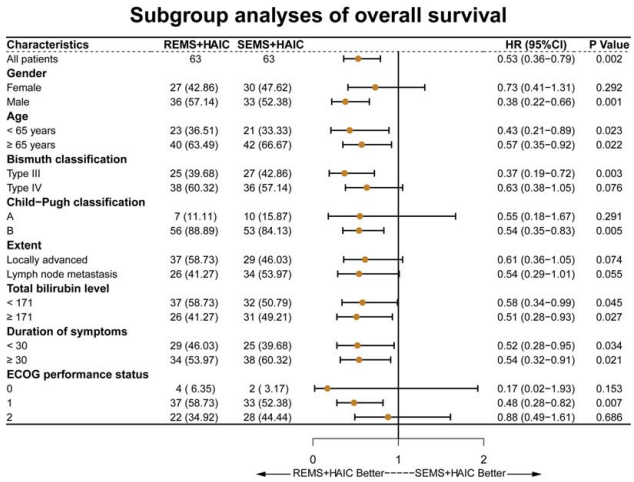

Figure 4. Subgroup analysis of overall survival. CI, confidence interval; HAIC, hepatic arterial infusion chemotherapy; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; REMS, radiation-emitting metallic stent; SEMS, self-expandable metallic stent.

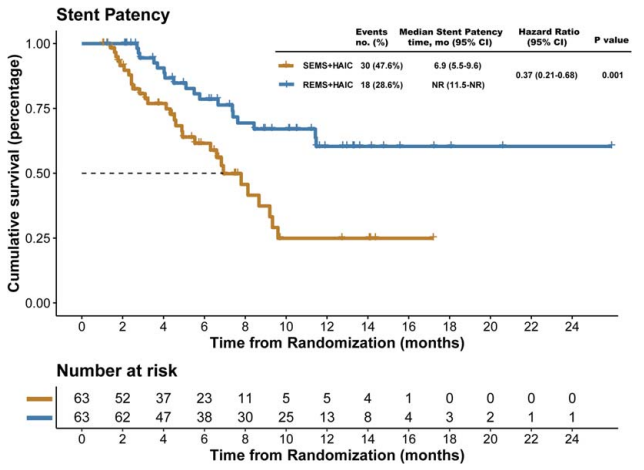

Figure 6. Kaplan–Meier estimate of stent patency. HAIC, hepatic arterial infusion chemotherapy; REMS, radiation-emitting metallic stent; SEMS, self-expandable metallic stent.

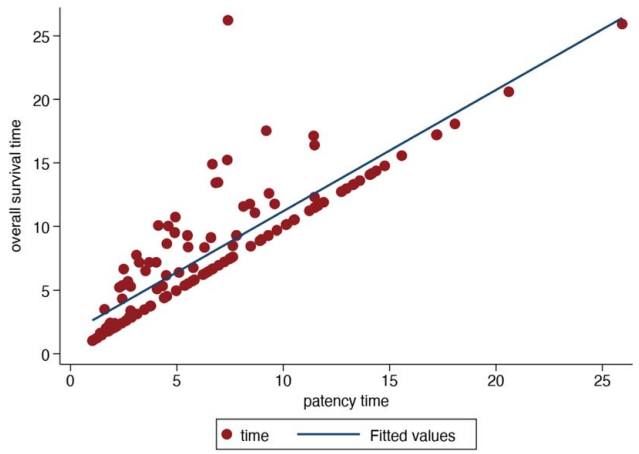

Figure 7. Correlation of stent patency with survival time.

After adjusting the covariates, multivariate Cox regression analyses showed that the REMS-HAIC treatment, ECOG performance status, and age were independent prognostic indicators for survival (Supplementary Table S2, Supplemental Digital Content 3, http://links.lww.com/JS9/D468). When further performing analyses based on the PP population, the results were largely similar to those of the ITT analyses (Supplementary Tables S3–S7, Supplemental Digital Content 3, http://links.lww.com/JS9/D468 and Supplementary Figs S1–S5, Supplemental Digital Content 3, http://links.lww.com/JS9/D468).

There was no mortality related to devices or procedures observed during the follow-up period. The incidence of grade 3 or 4 adverse events was comparable between the two groups (13.1% vs. 15.3%; $P = 0.798$) (Table 4). Abdominal pain, elevated alanine aminotransaminase (ALT), and elevated aspartate aminotransferase (AST) were the most common grade 3 or 4 adverse events (all were 3.3%) in the REMS-HAIC group, while elevated ALT and elevated AST were the most common grade 3 or 4 adverse events (all were 5.1%) in the counterpart group. For changes in liver function at 1-month posttreatment, no significant differences were recorded in the level of albumin compared to baseline values for either group. In contrast, the levels of AST, ALT, and TB decreased significantly in both groups (Table 5). No procedure-related liver failure was recorded in either group.

Discussion

This present trial showed the advantages of REMS plus HAIC over SEMS plus HAIC focusing on unresectable Bismuth type III or IV pCCA. It demonstrated that REMS plus HAIC significantly prolonged OS in patients with unresectable Bismuth type III or IV pCCA compared to those treated with SEMS plus HAIC. In addition, TTSP and stent patency were significantly prolonged in the REMS-HAIC group compared to those in the SEMS-HAIC group. The patients in the REMS-HAIC group benefited more from the improvement in physical functioning and fatigue symptoms. The rate of relief of jaundice and the incidence of grade 3 or 4 adverse events were comparable between the two groups.

In unresectable pCCA complicated with obstructive jaundice, SEMS placement is a well-established modality for biliary drainage. Percutaneous stent implantation is preferred over the endoscopic approach for palliation of Bismuth type III or IV hilar cholangiocarcinoma[19,20]. However, stent restenosis and limited patency time of uncovered SEMS have been the main intractable problems[21]. To improve biliary drainage, stent combination regimens, including ablation, photodynamic therapy, and brachytherapy, have emerged to address malignant biliary obstruction[22–24]. REMS was designed to provide immediate biliary recanalization and persistent brachytherapy against the tumor, which has been proven to extend the duration of stent patency and survival in various malignant tumors, such as malignant biliary obstruction, portal vein tumor thrombosis, and esophageal cancer[9,10,25–27]. In this present study, the restenosis rate of REMS-HAIC (29%) was significantly lower than that of SEMS-HAIC (48%). Moreover, the median stent patency time in the REMS-HAIC group was not reached, while the first quartile patency time (when 25% of patients developed stent restenosis) was 7.4 months when compared to 4.1 months in the SEMS-HAIC group, which was similar to previous studies[16].

Attributed to long-term patency, patients' liver function can be maintained, and the patients can continue receiving antitumor HAIC under the premise of relief of jaundice. In addition, patency time was positively correlated with survival time, and the REMS-HAIC group was an independent risk factor for survival. Based on the patient's characteristics balanced between the two groups, it can be speculated that adding brachytherapy could potentially improve survival by decelerating tumor growth. The survival advantages of REMS-HAIC over SEMS-HAIC are justified,

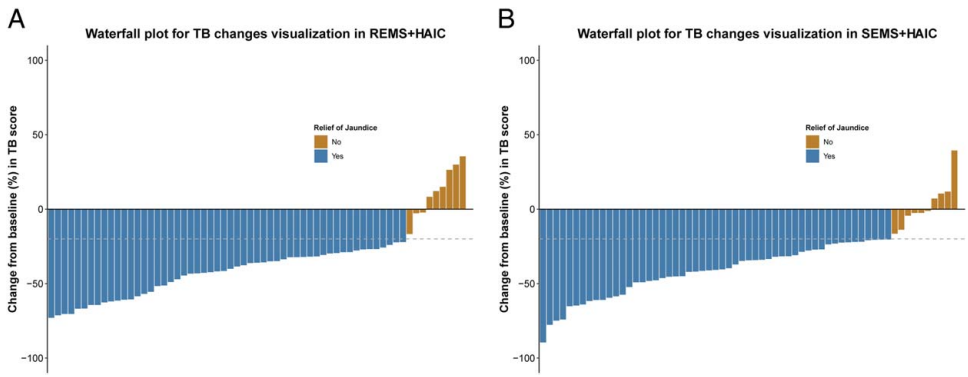

Figure 8. Waterfall plot for total bilirubin changes visualization. (A) REMS-HAIC group. (B) SEMS-HAIC group. HAIC, hepatic arterial infusion chemotherapy; REMS, radiation-emitting metallic stent; SEMS, self-expandable metallic stent; TB, total bilirubin.

Table 2

Generalized estimating equation analysis in QoL among intervention and control group.

EORTC QLQ-C30	Mean score		Group effect[a]		Time effect (SEMS+HAIC)[b]		Group×time effect[c]	
Outcome	REMS+HAIC	SEMS+HAIC	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Global health status[d]								
Global health status/QoL								
T0	53.3 (10.9)	50.7 (12.4)	2.57 (−1.68 to 6.81)	0.236	NA		NA	
T1	54.5 (10.8)	51.0 (13.4)			0.14 (−1.13 to 1.41)	0.828	0.95 (−1.01 to 2.92)	0.342
T2	59.4 (11.2)	58.1 (11.2)			3.70 (1.25–6.15)	0.003	0.66 (−2.67 to 3.99)	0.697
T3	63.5 (12.3)	60.1 (12.3)			3.59 (−0.01 to 7.19)	0.051	3.39 (−1.25 to 8.03)	0.152
Functioning scales[d]								
Physical functioning								
T0	63.8 (15.0)	61.3 (15.4)	2.01 (−3.43 to 7.45)	0.469	NA		NA	
T1	66.3 (13.4)	62.8 (14.4)			0.79 (−0.65 to 2.24)	0.283	1.50 (−0.36 to 3.37)	0.113
T2	72.7 (11.8)	68.7 (12.8)			4.38 (2.58–6.17)	< 0.001	3.84 (0.85–6.83)	0.012
T3	79.0 (12.5)	66.7 (17.2)			2.09 (−2.27 to 6.45)	0.347	10.98 (5.69–16.26)	< 0.001
Role functioning								
T0	55.0 (19.1)	50.0 (19.4)	4.32 (−2.14 to 10.77)	0.190	NA		NA	
T1	54.9 (15.3)	51.1 (14.8)			−0.56 (−3.61 to 2.48)	0.716	−0.53 (−4.89 to 3.83)	0.812
T2	62.3 (14.3)	57.5 (12.5)			3.46 (−0.04 to 6.97)	0.053	1.95 (−3.20 to 7.11)	0.457
T3	65.4 (14.3)	59.8 (13.0)			4.95 (−0.10 to 9.99)	0.055	3.73 (−3.09 to 10.55)	0.284
Cognitive functioning[e]								
T0	77.0 (13.9)	74.6 (13.3)	0.02 (−0.05 to 0.10)	0.515	NA		NA	
T1	76.2 (13.8)	73.0 (13.4)			−0.03 (−0.07 to 0.01)	0.137	0.02 (−0.03 to 0.06)	0.423
T2	79.9 (11.3)	76.3 (13.6)			0.00 (−0.04 to 0.05)	0.821	0.03 (−0.02 to 0.09)	0.230
T3	80.0 (13.2)	75.3 (13.8)			−0.02 (−0.08 to 0.03)	0.366	0.05 (−0.02 to 0.12)	0.146
Emotional functioning[e]								
T0	65.1 (15.3)	61.1 (15.5)	0.05 (−0.07 to 0.16)	0.422	NA		NA	
T1	68.3 (12.3)	63.4 (15.1)			0.02 (−0.02 to 0.06)	0.293	0.05 (−0.01 to 0.11)	0.114
T2	73.0 (9.7)	66.7 (13.1)			0.07 (0.02–0.12)	0.008	0.05 (−0.02 to 0.13)	0.175
T3	71.0 (11.6)	64.9 (17.5)			0.03 (−0.07 to 0.12)	0.612	0.07 (−0.05 to 0.20)	0.231
Social functioning[e]								
T0	73.3 (14.8)	70.9 (12.0)	0.03 (−0.05 to 0.10)	0.481	NA		NA	
T1	67.8 (15.2)	65.7 (14.2)			−0.09 (−0.13 to −0.05)	< .001	0.00 (−0.06 to 0.06)	0.956
T2	69.4 (14.0)	70.0 (12.6)			−0.04 (−0.10 to 0.02)	0.225	−0.04 (−0.12 to 0.04)	0.306
T3	68.8 (16.9)	67.2 (11.3)			−0.07 (−0.15 to 0.00)	0.057	−0.02 (−0.13 to 0.09)	0.780

Data are presented as mean (SD); T0 represents baseline; T1 represents 4 weeks posttreatment; T2 represents 12 weeks posttreatment; T3 represents 24 weeks posttreatment.

[a]Group effect was defined as group differences at baseline between the two groups.

[b]Time effect at T1 defined as change of scores for SEMS-HAIC group at T1 compared with T0; T2 defined as change of scores for SEMS-HAIC group at T2 compared with T0; T3 defined as change of scores for SEMS-HAIC group at T3 compared with T0.

[c]Group×time effect at T1 defined as additional change of scores for REMS-HAIC group compared with SEMS-HAIC group at T1; T2 defined as additional change of scores for REMS-HAIC group compared with SEMS-HAIC group at T2; T3 defined as additional change of scores for REMS-HAIC group compared with SEMS-HAIC group at T3.

[d]Scores range from 0 to 100, with a higher score representing a higher level of functioning.

[e]With log transformation in the generalized estimating equation model.

EORTC QLQ-C30, the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30; HAIC, hepatic arterial infusion chemotherapy; REMS, radiation-emitting metallic stent; SEMS, self-expandable-metallic-stent.

which may come as follows: first, the longer stent patency provides continuous biliary drainage following long-term continuous brachytherapy; second, since the synergistic effects of selective internal radiation therapy combined with chemotherapy, such as gemcitabine, in cholangiocarcinoma have been uncovered[28,29], the combination of radiation emitted by iodine-125 seeds and locally high-concentration chemotherapy may also potentially be synergistic. Although the treatment response of the lesion could not be directly evaluated due to the presence of metal artifacts after stent implantation and the unclear perihilar structure in some patients, long-term stent patency showed that radioactive ^{125}I particles could kill or inhibit the growth of lesions at the obstruction site, delaying restenosis induced by lesion growth into the stent or at ends, increasing patient's tolerability for subsequent HAIC treatment. A previous study reported a median survival of 155 days after administering SEMS plus systemic chemotherapy for unresectable pCCA[30], and the treatment strategy in the current study seems to be more beneficial given its longer median OS of 10.2 months.

In patients with biliary malignancies combined with impaired liver function, a bilirubin level of < 2 mg/dl was the endpoint level in most chemotherapy protocols. In addition, jaundiced patients (defined as bilirubin at the time of starting chemotherapy higher than 1.5 times the upper limit of normal) were excluded from the randomized ABC-02[31] and KEYNOTE-966 clinical trials[32]. Successful decompression is the precondition of chemotherapy[6]. For Bismuth types I and II, it is relatively easy to relieve hyperbilirubinemia after stent implantation, and the rate of clinical success is high, while for Bismuth type III or IV perihilar cholangiocarcinoma, bilateral stent implantation is technically complex and has a high incidence of adverse events, but unilateral approach may lead to inadequate relief of jaundice and biliary tract infection. In this present study, the contralateral hilar lesion without stent

Table 3

Generalized estimating equation analysis in QoL among intervention and control group.

EORTC QLQ-C30	Mean score		Group effect[a]		Time effect (SEMS+HAIC)[b]		Group×time effect[c]	
Outcome	REMS+HAIC	SEMS+HAIC	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Symptom scales[d]								
Fatigue								
T0	50.3 (14.67)	49.7 (13.7)	0.94 (−4.01 to 5.90)	0.709	NA		NA	
T1	46.1 (14.9)	48.4 (15.3)			−0.56 (−2.75 to 1.62)	0.613	−3.26 (−6.37 to −0.15)	0.040
T2	41.7 (13.7)	42.2 (14.3)			−3.75 (−6.30 to −1.21)	0.004	−4.22 (−8.12 to −0.32)	0.034
T3	38.9 (14.9)	47.1 (15.9)			3.08 (−1.83 to 8.00)	0.219	−13.48 (−19.85 to −7.11)	<0.001
Nausea and vomiting[e]								
T0	17.5 (21.1)	19.6 (22.7)	−0.03 (−0.65 to 0.60)	0.935	NA		NA	
T1	10.1 (12.7)	13.0 (19.6)			−0.54 (−0.99 to −0.09)	0.019	0.04 (−0.51 to 0.59)	0.883
T2	11.6 (15.3)	10.0 (15.0)			−0.41 (−0.88 to 0.06)	0.086	−0.04 (−0.72 to 0.65)	0.920
T3	7.9 (11.3)	12.1 (15.4)			−0.24 (−0.83 to 0.34)	0.420	−0.51 (−1.29 to 0.27)	0.199
Pain[e]								
T0	25.9 (23.7)	30.4 (25.0)	−0.13 (−0.73 to 0.47)	0.672	NA		NA	
T1	17.2 (18.0)	21.5 (19.1)			−0.27 (−0.52 to −0.01)	0.040	−0.18 (−0.56 to 0.20)	0.360
T2	18.0 (18.9)	20.8 (17.6)			−0.30 (−0.72 to 0.13)	0.168	−0.13 (−0.66 to 0.41)	0.642
T3	20.8 (19.2)	24.1 (20.2)			0.10 (−0.39 to 0.59)	0.684	−0.26 (−0.86 to 0.33)	0.387
Dyspnea[e]								
T0	20.6 (22.7)	23.8 (22.7)	−0.25 (−0.91 to 0.41)	0.455	NA		NA	
T1	15.3 (19.8)	14.1 (18.8)			−0.66 (−1.14 to −0.17)	0.008	0.33 (−0.30 to 0.97)	0.303
T2	10.2 (15.5)	15.8 (18.5)			−0.40 (−0.97 to 0.18)	0.176	−0.26 (−1.02 to 0.49)	0.495
T3	12.5 (20.9)	16.1 (21.1)			−0.47 (−1.19 to 0.25)	0.204	−0.12 (−1.13 to 0.89)	0.816
Insomnia								
T0	31.8 (21.1)	33.9 (15.3)	−2.75 (−9.35 to 3.85)	0.414	NA		NA	
T1	25.7 (19.6)	31.6 (15.7)			−2.26 (−5.73 to 1.21)	0.202	−3.20 (−9.55 to 3.14)	0.322
T2	25.2 (21.0)	29.2 (21.6)			−4.40 (−10.87 to 2.06)	0.182	0.02 (−9.41 to 9.44)	0.997
T3	25.0 (24.8)	27.6 (25.3)			−4.14 (−13.44 to 5.17)	0.383	0.73 (−11.61 to 13.08)	0.907
Appetite loss[e]								
T0	45.0 (17.1)	45.5 (17.3)	−0.01 (−0.13 to 0.11)	0.895	NA		NA	
T1	37.7 (14.2)	39.0 (20.7)			−0.43 (−0.71 to −0.15)	0.003	0.23 (−0.09 to 0.54)	0.158
T2	33.3 (15.2)	36.7 (18.2)			−0.34 (−0.64 to −0.04)	0.024	−0.17 (−0.60 to 0.26)	0.445
T3	28.3 (26.7)	33.3 (33.3)			−1.31 (−2.00 to −0.63)	<0.001	−0.01 (−0.90 to 0.88)	0.983
Constipation[e]								
T0	17.5 (20.6)	20.1 (24.4)			NA		NA	
T1	18.0 (25.5)	18.1 (22.6)	−0.11 (−0.77 to 0.55)	0.740	−0.08 (−0.53 to 0.36)	0.717	−0.03 (−0.65 to 0.59)	0.927
T2	17.0 (21.7)	20.0 (23.6)			0.04 (−0.59 to 0.66)	0.905	−0.05 (−0.82 to 0.72)	0.892
T3	14.2 (18.3)	14.3 (19.1)			−0.43 (−1.27 to 0.41)	0.314	0.19 (−0.79 to 1.17)	0.705
Diarrhea[e]								
T0	21.8 (24.0)	19.1 (21.4)	0.12 (−0.54 to 0.79)	0.715	NA		NA	
T1	16.4 (18.9)	16.4 (19.9)			−0.26 (−0.73 to 0.21)	0.271	−0.07 (−0.68 to 0.54)	0.820
T2	17.0 (20.6)	14.2 (19.8)			−0.51 (−1.13 to 0.11)	0.106	0.15 (−0.60 to 0.91)	0.689
T3	19.2 (22.5)	18.4 (22.9)			−0.15 (−0.94 to 0.64)	0.711	−0.08 (−1.05 to 0.88)	0.864
Financial difficulties[e]								
T0	10.1 (15.4)	9.0 (14.9)	0.08 (−0.49 to 0.66)	0.772	NA		NA	
T1	11.5 (16.0)	10.7 (15.7)			0.18 (−0.02 to 0.38)	0.077	−0.01 (−0.28 to 0.27)	0.967
T2	7.5 (14.1)	9.2 (15.1)			0.30 (−0.04 to 0.64)	0.080	−0.13 (−0.55 to 0.28)	0.529
T3	10.8 (17.5)	6.9 (13.7)			0.32 (−0.19 to 0.84)	0.221	−0.01 (−0.63 to 0.61)	0.971

Data are presented as mean (SD); T0 represents baseline; T1 represents 4 weeks posttreatment; T2 represents 12 weeks posttreatment; T3 represents 24 weeks posttreatment.

[a]Group effect was defined as group differences at baseline between the two groups.

[b]Time effect at T1 defined as change of scores for SEMS-HAIC group at T1 compared with T0; T2 defined as change of scores for SEMS-HAIC group at T2 compared with T0; T3 defined as change of scores for SEMS-HAIC group at T3 compared with T0.

[c]Group×time effect at T1 defined as additional change of scores for REMS-HAIC group compared with SEMS-HAIC group at T1; T2 defined as additional change of scores for REMS-HAIC group compared with SEMS-HAIC group at T2; T3 defined as additional change of scores for REMS-HAIC group compared with SEMS-HAIC group at T3.

[d]Scores range from 0 to 100, with a higher score representing a greater degree of symptoms.

[e]With log transformation in the generalized estimating equation model.

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implantation can be irradiated by ^{125}I seeds, leading to shrinkage of the tumor and long-term decompression.

In our study, the median level of bilirubin was 84.4 (range 9.9–290.5) (4.9 [range 0.8–16.9] mg/dl) in patients receiving HAIC within 1 week after stent placement, and the majority of patients (95.2%) had an ECOG performance status of 1–2. Generally, in clinical practice, the patient's bilirubin level remains elevated even with effective drainage, especially in complex Bismuth type IV

Table 4

Grade 3 or 4 adverse events.

	Patients at randomization		
Variable	REMS+HAIC ($n=61$)	SEMS+HAIC ($n=59$)	*P*
Abdominal pain	2 (3.3)	1 (1.7)	> 0.999
Hemobilia	1 (1.6)	2 (3.4)	0.616
Cholangitis	1 (1.6)	1 (1.7)	> 0.999
Liver abscess	1 (1.6)	0	> 0.999
Acute renal failure	0	1 (1.7)	0.492
Elevated ALT	2 (3.3)	3 (5.1)	0.677
Elevated AST	2 (3.3)	3 (5.1)	0.677
Leukopenia	0	1 (1.7)	0.492
Neutropenia	0	1 (1.7)	0.492
Thrombocytopenia	1 (1.6)	0	> 0.999

Data are noted in *n* (%).

The sum of the percentages may not equal the total percentage because of rounding.

ALT, alanine aminotransaminase; AST, aspartate aminotransferase; HAIC, hepatic arterial infusion chemotherapy; REMS, radiation-emitting metallic stent; SEMS, self-expandable-metallic-stent.

lesions, which may delay the initiation of chemotherapy. Interestingly, in this prospective study, HAIC with cisplatin and gemcitabine can be concluded as effective and safe for jaundiced patients even though the ECOG performance status was 2. This result suggested that HAIC can be applied sooner for Bismuth type III or IV pCCA without the need for bilirubin normalization.

Arteriovenous injury during percutaneous stent placement may lead to significant bleeding and represents a major concern[33]. In the REMS-HAIC group, the stents are designed as a double-layer structure, which can be delivered through a 10 F sheath. If the stent was designed to be all-in-one, the delivery sheath would be larger, thus requiring a wider puncture passage and potentially increasing complications, such as bleeding, or even making the percutaneous approach impossible. Therefore, REMS was designed to carry radioactive particles in such a way. No deaths related to devices or procedures, stent-related perforation, or radiation-related complications occurred in this study. The incidence of grade 3 or 4 adverse events was comparable between the two groups without increasing the risk of bleeding. These results suggested that the placement of REMS with radioactive ^{125}I seeds is well tolerated.

Table 5

Comparison of liver function at baseline and 1-month posttreatment.

	Baseline value	1-month value	*P*[a]
	AST(U/l)	AST(U/l)	
REMS+HAIC	70.0 (53.0–92.0)	44.0 (31.0–67.0)	0.001
SEMS+HAIC	66.0 (49.0–94.0)	46.0 (35.0–62.0)	< 0.001
	ALT(U/l)	ALT(U/l)	
REMS+HAIC	76.0 (48.0–93.0)	50.0 (28.0–73.0)	0.014
SEMS+HAIC	60.8 (39.0–90.0)	43.0 (29.0–65.0)	< 0.001
	TB (μmol/l)	TB (μmol/l)	
REMS+HAIC	131.1 (72.8–228.5)	32.1 (20.9–75.3)	< 0.001
SEMS+HAIC	167.9 (83.2–306.5)	46.1 (20.7–110.4)	< 0.001
	Albumin (g/l)	Albumin (g/l)	
REMS+HAIC	34.7 (32.6–39.0)	35.1 (30.8–38.3)	0.223[b]
SEMS+HAIC	34.6 (31.4–37.7)	34.9 (32.2–37.4)	0.835

[a]Using Wilcoxon signed rank test unless otherwise specified.

[b]Using paired *t* test.

ALT, alanine aminotransaminase; AST, aspartate aminotransferase; HAIC, hepatic arterial infusion chemotherapy; REMS, radiation-emitting metallic stent; SEMS, self-expandable-metallic-stent; TB, total bilirubin.

There remain some limitations to this study. First, the sensitivity of some tissue acquisition modalities was low. As a result, some patients received designated treatment without histological confirmation. However, biliary strictures were considered to be malignant from the clinical courses for these patients. In years to come, it will be necessary to increase the sensitivity in a variety of joint methods. Second, clinical data on the comparison between REMS plus HAIC and REMS followed by subsequent systemic chemotherapy are insufficient in the current study, which is worthy of further exploration. Third, the protocol of this study was designed in an era before the advent of immunotherapy, and the United States Food and Drug Administration approved the combination of the PD-L1 inhibitor duvalumab with gemcitabine and cisplatin as the first-line treatment of locally advanced or metastatic biliary tract cancer on September 2022. This time point is well beyond our preset initiatory date for enrollment. In this case, novel front-line systemic, locoregional, and combination regimens will be included in our future studies.

Conclusion

In conclusion, REMS plus HAIC significantly improved survival and stent patency compared with SEMS plus HAIC in patients with unresectable Bismuth type III or IV pCCA, with comparable safety profiles. REMS plus HAIC might be a promising treatment strategy for patients with unresectable Bismuth type III or IV pCCA. Additional trials in conjunction with novel systemic treatment are warranted.

Ethical approval

This randomized controlled trial was approved by the clinic trial ethics committee of Southeast University Zhongda Hospital. The relevant Judgement's reference number was 2021ZDSYLL008-P01.

Consent

Written informed consent was obtained from the patients. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

J.L., G.-J.T., and J.-H.G.: conceived the study idea and planned the study; Q.C., N.-J.G., Y.-L.L., and M.H.: collected the data; Q.C., N.-J.G., Y.-L.L., M.H., W.-H.L., D.L., N.W., and P.-H.L.: have directly accessed and verified the data; J.L., G.-J.T., J.-H.G., J.-F.T., C.-J.H., W.-J.W., R.D., B.P., X.-J.W., and F.-A.W.:

supervised the data collection; Q.C., G.-Y.Z., Y.W., and L.C.: analyzed and interpreted the data; J.M.: performed the statistical analysis; Q.C., N.-J.G., Y.-L.L., and M.H.: wrote the first draft. All authors contributed to the review and critical revision of the manuscript and approved the final version of the manuscript.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

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Guarantor

Jin-He Guo, Gao-Jun Teng, and Jian Lu.

Data availability statement

All relevant data are available within the manuscript and its supplementary material files. Further inquiries can be directed to the corresponding author (Jian Lu).

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