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Retrospective Study

Stents combined with iodine-125 implantation to treat main portal vein tumor thrombus

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Abstract**AIM**

To evaluate the efficacy of main portal vein stents combined with iodine-125 (¹²⁵I) to treat main portal vein tumor thrombus.

METHODS

From January 1, 2010 to January 1, 2015, 111 patients were diagnosed with liver cancer combined with main portal vein tumor thrombus. They were non-randomly assigned to undergo treatment with transarterial chemoembolization (TACE)/transarterial embolization (TAE) + portal vein stents combined with ¹²⁵I implantation (Group A) and TACE/TAE + portal vein

stents only (Group B). After the operation, scheduled follow-up was performed at 6, 12 and 24 mo. The recorded information included clinical manifestations, survival rate, and stent restenosis rate. Kaplan–Meier curves, log-rank test and Cox regression were used for data analyses.

RESULTS

From January 1, 2010 to January 1, 2015, 54 and 57 patients were allocated to Groups A and B, respectively. The survival rates at 6, 12 and 24 mo were 85.2%, 42.6% and 22.2% in Group A and 50.9%, 10.5% and 0% in Group B. The differences were significant [log rank $P < 0.05$, hazard ratio (HR): 0.37, 95%CI: 0.24–0.56]. The rates of stent restenosis were 18.5%, 55.6% and 83.3% in Group A and 43.9%, 82.5% and 96.5% in Group B. The differences were significant (log rank $P < 0.05$, HR: 0.42, 95%CI: 0.27–0.63). Cox regression identified that treatment was the only factor affecting survival rate in this study.

CONCLUSION

Main portal vein stents combined with ^{125}I can significantly improve survival rate and reduce the rate of stent restenosis.

Key words: Iodine-125; Liver cancer; Stent; Main portal vein tumor thrombus; Transarterial chemoembolization/transarterial embolization

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Core tip: This study evaluated the efficacy of stents combined with iodine-125 (^{125}I) to treat main portal vein tumor thrombus and its complications. ^{125}I was placed between the stent and tumor thrombus, and not in the form of particle strands. In this way, the quantity and position of ^{125}I could be flexibly adjusted. Transarterial chemoembolization or transarterial embolization was used as basic treatment. Patients with liver cancer and main portal vein tumor thrombus were non-randomly assigned to undergo portal vein stents combined with ^{125}I implantation or portal vein stents only. Portal vein stent combined with ^{125}I significantly improved survival rate and reduced stent restenosis.

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INTRODUCTION

Liver cancer is a common malignant tumor^[1], and it decreases patient quality of life^[2,3]. Tumor thrombus

in the main portal vein indicates late-stage disease. The treatment for portal vein tumor thrombus includes surgery and radiotherapy^[4,5]. However, the overall effect is limited. In recent years, radioactive iodine-125 (^{125}I) particles have been used to treat portal vein tumor thrombus to effectively decrease tumor thrombus volume and improve patient survival rates^[6]. However, ^{125}I was implanted in particle strands in those studies. This limits the amount of ^{125}I implanted and the ability to reposition the ^{125}I , which restrains the clinical use of ^{125}I . We studied the clinical effect of ^{125}I combined with main portal vein stents when the ^{125}I was placed between the tumor thrombus and the stents. This method avoids the above disadvantages and has never been previously reported.

MATERIALS AND METHODS

Study design

This was a nonrandomized controlled trial in which we compared transarterial chemoembolization (TACE)/transarterial embolization (TAE) + main portal vein stents combined with ^{125}I implantation and TACE/TAE + main portal vein stents only for the treatment of liver cancer with main portal vein tumor thrombus and portal hypertension.

Criteria

Inclusion criteria were as follows: (1) Liver cancer according to histological, cytological, or clinical diagnostic standards that conformed to the rules of diagnosis and treatment of primary hepatocellular carcinoma, 2011; (2) Main stem tumor thrombus of portal vein confirmed through biopsy (70%) or imaging, without tumor thrombus in the branches; (3) Clear indication of percutaneous liver puncture and main portal vein stent implantation; (4) Clear TACE or TAE treatment indication; (5) Age 18–70 years; and (6) No serious complications of portal hypertension, and only a small amount of ascites without bleeding or other complications. Exclusion criteria were: (1) Patients with serious disorders of the heart, lung, kidney, brain, or other important organs; (2) Active infection; (3) Women in pregnancy or lactation; (4) Life expectancy < 3 mo; and (5) Patients who could not cooperate with treatment and observation.

Patients

One hundred and eleven patients with main portal vein tumor thrombus were non-randomly assigned to undergo treatment with TACE/TAE + main portal vein stents combined with ^{125}I implantation or TACE/TAE + main portal vein stents alone from January 1, 2010 to January 1, 2015. There were 73 cases of hepatitis B cirrhosis, 21 cases of hepatitis C cirrhosis, seven cases of alcoholic cirrhosis, three cholestatic cirrhosis cases, three autoimmune liver cirrhosis cases and four cases of cirrhosis from other causes. Twenty-three patients

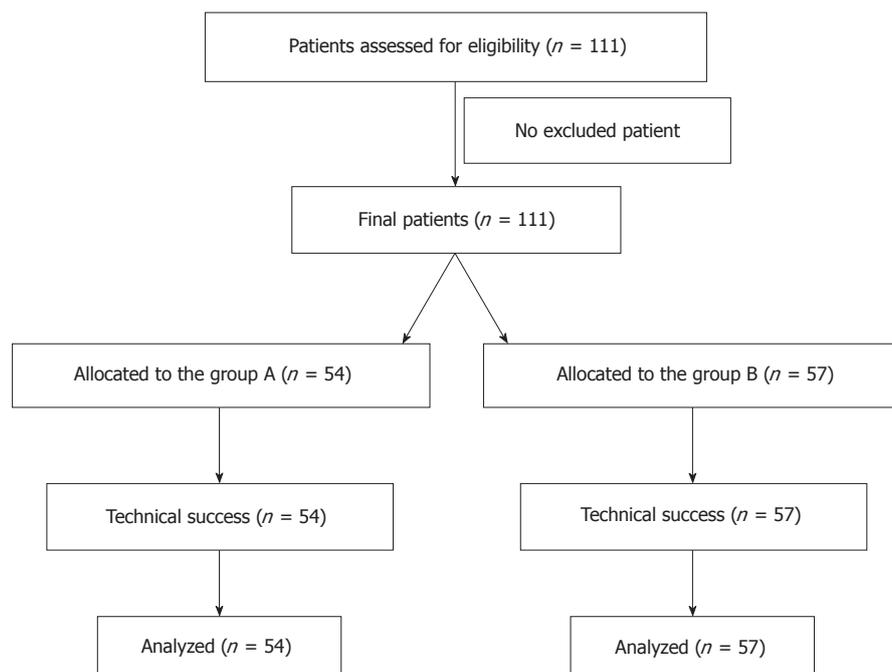


Figure 1 Study design and flow chart.

were diagnosed with primary carcinoma of the liver by percutaneous liver biopsy, whereas 88 patients were diagnosed by ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), serum α -fetoprotein levels and hepatic artery angiography. Imaging examination confirmed main portal vein tumor thrombus in all patients. According to the preoperative Child–Pugh classification, there were 49 cases of Class A, 62 cases of Class B, and zero class C cases. There were 20 patients with mild ascites and 91 without ascites. The flow chart is shown in Figure 1. Comparison between the two groups is shown in Table 1 and Figure 2.

Preoperative preparation

Before the operation, liver function tests, blood coagulation tests, routine blood tests, electrocardiography, CT, and/or MRI, color Doppler ultrasonography, and esophageal radiography were performed. In addition, gastroscopy was performed when necessary. Patients' coagulation function was corrected to the normal range. The operation-related concerns were explained to the patients and their family members, and they were asked to give signed informed consent. This study was approved by the Institutional Review Board of Beijing Shijitan Hospital and conducted in accordance with all current ethical guidelines.

Percutaneous transhepatic and portal vein stent implantation

Patients were assigned to receive percutaneous transhepatic and portal vein covered stents (Fluency, Bard, Tempe, AZ, United States) with local anesthesia at the puncture site. A puncture device (NPAS-100; Cook, Indianapolis, IN, United States), which included a

puncture needle, venous sheath and guide wire, was passed from the right hypochondriac region to the portal vein. After that, a pigtail catheter was advanced through the NPAS-100 to the distal end of the splenic vein or superior mesenteric vein to measure the portal vein pressure and conduct venography. The pigtail catheter was removed, and the stent was implanted through the vein sheath. A 10-mm covered stent was implanted. Portal vein pressure measurements before and after stent placement allowed assessment of the success of the procedure. The hepatic puncture passage was blocked during catheter removal to avoid intra-peritoneal or thoracic hemorrhage.

¹²⁵I implantation

In Group A, the patients received treatment with percutaneous transhepatic and portal vein covered stent implantation, like the patients in Group B. After measurement of portal vein pressure and conduction of venography, the pigtail catheter was removed, and a guide wire was inserted through the venous sheath of the NPAS-100. Because the NPAS-100 had one guide wire, there were two guide wires in the main portal vein. The venous sheath was drawn out and inserted into the portal vein again along one of the guide wires. Another guide wire was placed between the tumor thrombus and venous sheath. Stents were implanted through the venous sheath. A catheter was inserted through the guide wire that was between the tumor thrombus and venous sheath. The catheter between the stent and the tumor thrombus was linked to the particle release gun. The catheter was slowly retracted, and ¹²⁵I (Tong Fu, Beijing, China) was simultaneously

Table 1 Baseline characteristics, *n* (%)

	Group A (<i>n</i> = 54)	Group B (<i>n</i> = 57)	<i>P</i> value
Gender			0.693
Male	35 (64.8)	39 (68.4)	
Female	19 (35.2)	18 (31.6)	
Average age (yr)	43.6 ± 6.9	44.3 ± 5.2	0.697
Pathogenesis			0.788
Hepatitis B	35 (64.8)	38 (66.7)	
Hepatitis C	9 (16.7)	12 (21)	
Alcoholic	5 (9.3)	2 (3.5)	
Cholestasis	2 (3.7)	1 (1.8)	
Autoimmunity	1 (1.8)	2 (3.5)	
Others	2 (3.7)	2 (3.5)	
Child-Pugh classification			0.705
A	25 (46.3)	24 (42.1)	
B	29 (53.7)	33 (57.9)	
C	0 (0)	0 (0)	
Albumin (g/L)	34.5 ± 7.5	31.5 ± 11.5	0.880
Alanine aminotransferase (U/L)	62.5 ± 46.5	49.5 ± 37.5	0.396
Glutamyl transpeptidase (U/L)	73 ± 66	74 ± 62	0.647
Na ⁺	143.5 ± 8.5	140 ± 7	0.104
K ⁺	4.12 ± 1.08	4.75 ± 1.05	0.883
Direct bilirubin (μmol/L)	29.8 ± 25.2	24.5 ± 18.5	0.299
Aspartate aminotransferase (U/L)	39 ± 30	49 ± 39	0.349
MELD score	11.96 ± 1.68	12.76 ± 2.47	0.145
Ascites			0.624
Yes	11 (20.4)	9 (15.8)	
No	43 (79.6)	48 (84.2)	
Size of liver cancer (cm)			0.788
≤ 5	14 (25.9)	17 (29.8)	
5-8	31 (57.4)	29 (50.9)	
> 8	9 (16.7)	11 (19.3)	
No. of liver tumors			0.834
1	28 (51.9)	32 (56.1)	
2 or 3	19 (35.2)	17 (29.8)	
> 3	7 (12.9)	8 (14.1)	

MELD: Model for end-stage liver disease; Child-Pugh classification: Score for liver function.

released through the catheter up to the portal vein trunk and tumor thrombus. The radioactive particles were arranged as neatly as possible in all tumor thrombi. After implantation, portal vein pressure was measured and venography was conducted. These particles could emit characteristic electrons and photons through the recession of the electron capture surface. The electrons were absorbed by the titanium alloy wall of the sealed seeds of ¹²⁵I. The photons mainly emitted X rays of 27.4 and 31.4 keV as well as γ rays of 35.5 keV. The pictures taken during the operation are shown in Figure 3.

TACE/TAE

Patients in Group A were treated with TACE according to the position of the lesion and its blood supply. The embolization agent was 3–30 mL iodinated oil. The chemotherapeutics included 10–20 mg pirarubicin and 5–15 mg hydroxycamptothecine. Patients in Group B were treated with TAE to reduce damage to liver function. The embolization agent was 5–25 mL iodinated oil.

For the basic technical operation, a needle was passed from the right or left femoral artery to the hepatic artery followed by hepatic arteriography. A catheter was placed in the direct blood supply artery of the tumor

as close to the focus as possible, and embolization and infusion of chemotherapeutic drugs were performed. The interval and number of treatments depended on tumor size, arterial status and liver function status. The interval was usually once every 1–6 mo. In Group A, 25 and 29 patients were treated with TACE and TAE, respectively, while 24 and 33 patients in Group B were treated with TACE and TAE, respectively, with no significant difference in patient numbers (*P* = 0.705).

Patients with lesions ≤ 5 cm in size and with a rich blood supply underwent TACE or TAE first and radiofrequency ablation after 3–5 d. Patients whose lesion was > 5 cm underwent TACE or TAE once or several times and then radiofrequency ablation when the imaging showed that the lesions no longer had blood supply from the hepatic artery or when the catheter could not enter the artery supplying the lesion. Finally, all patients underwent radiofrequency ablation (WHK-IB; Weaver Electronics, Beijing, China).

Postoperative routine observation and treatment

Low molecular weight heparin (5000 IU, twice daily) was subcutaneously injected for 5 d, and then warfarin was administered for one year. Coagulation function of

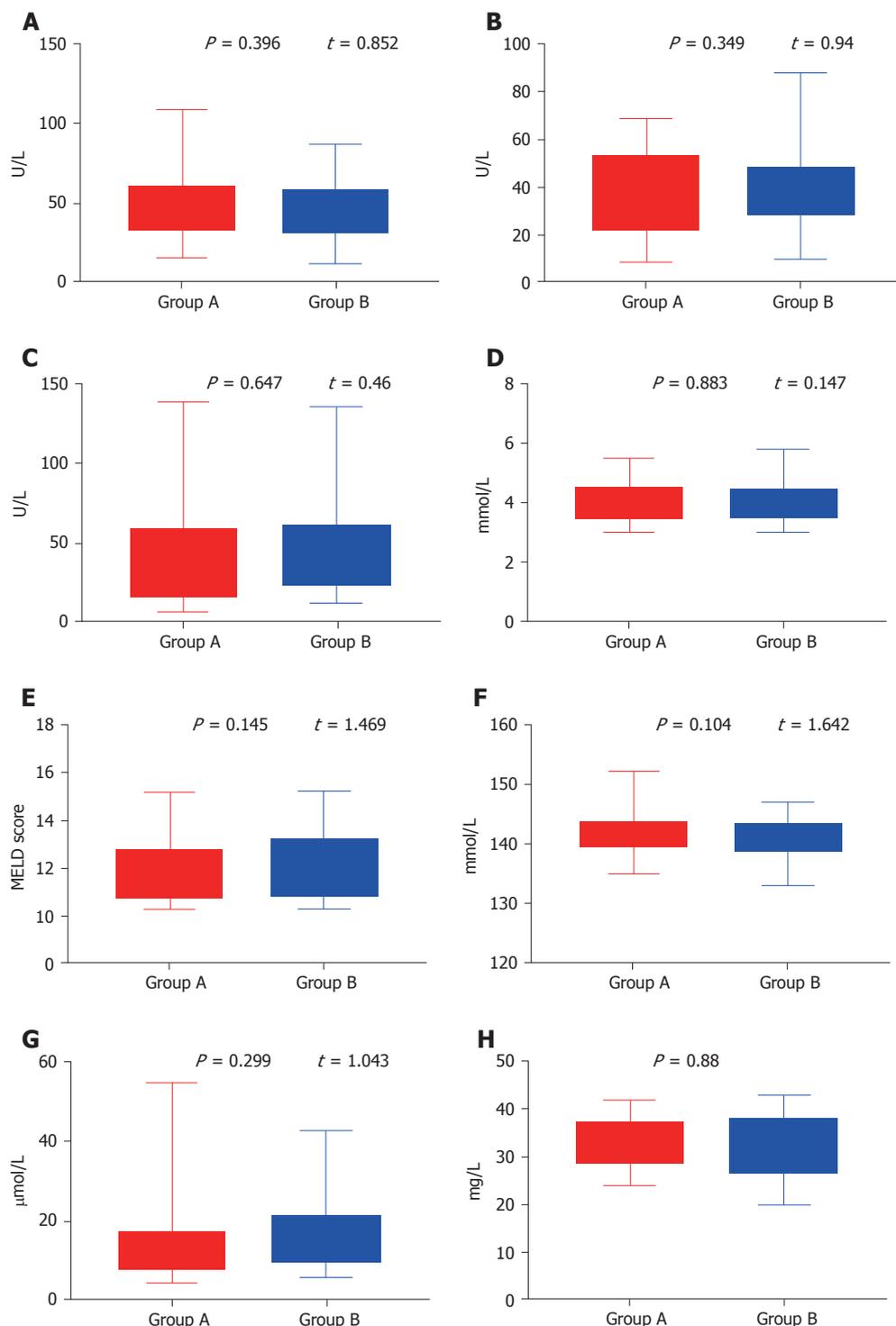


Figure 2 Boxplots of liver function. A: Alanine aminotransferase; B: Aspartate aminotransferase; C: Glutamyl transpeptidase; D: K⁺; E: Model for end-stage liver disease score; F: Na⁺; G: Direct bilirubin; H: Albumin (H) in Group A (red bars) and Group B (blue bars) were compared with Student's *t* test. MELD: Model for end-stage liver disease score.

each patient was examined every 15 d to ensure that the International Normalized Ratio ranged from 2 to 3.

Follow-up

Scheduled follow-up was performed at 6, 12 and 24 mo postoperatively. The recorded information included clinical manifestations, survival rate, physical exami-

nation, stent restenosis evaluation (through ultrasound and endoscopy) and laboratory tests. Telephone follow-up was performed to record patient conditions and details of relevant clinical events.

Statistical analysis

Continuous variables are presented as mean ± median

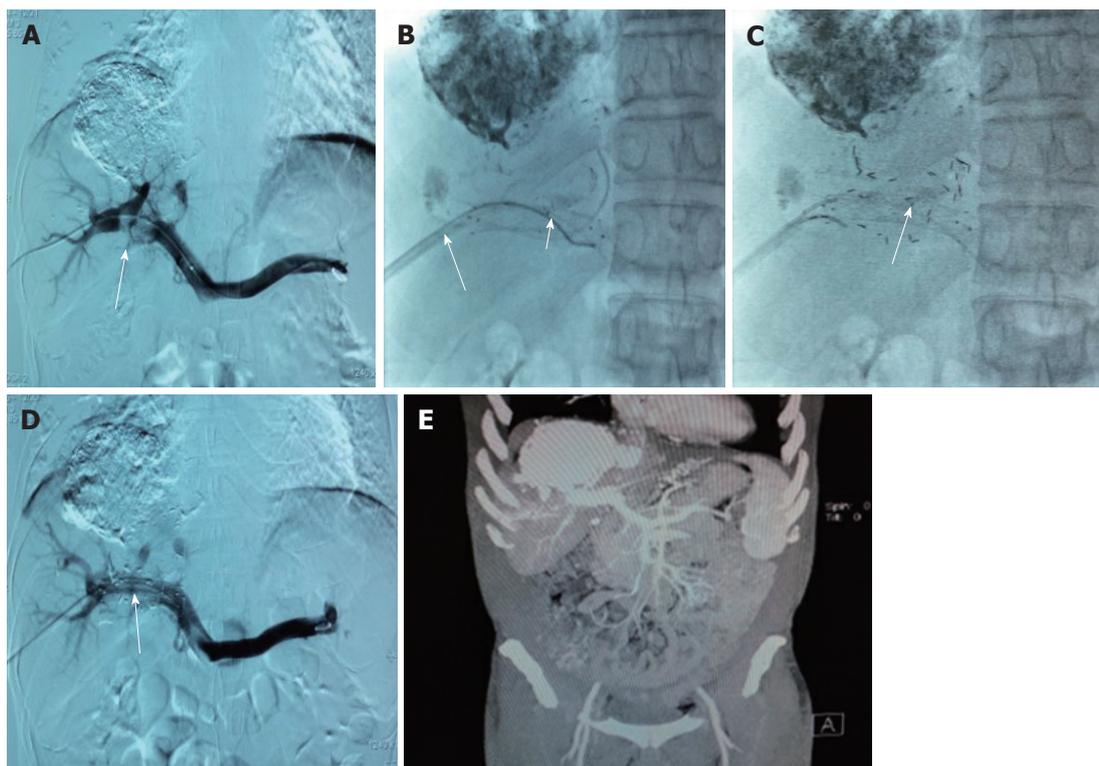


Figure 3 Pictures taken during operation of a 55-year-old male patient with hepatitis B cirrhosis and primary liver cancer with main portal vein tumor thrombus. The patient was treated with percutaneous liver puncture and ^{125}I implantation combined with portal vein stent implantation. A: Percutaneous transhepatic portal venography showing proximal and left branch of portal vein tumor thrombus (long white arrow); B: X-ray showing vein stent (short white arrow), catheter between the stent and tumor thrombus (long white arrow); C: X-ray showing ^{125}I between the stent and tumor thrombus (long white arrow); D: Postoperative portal vein angiography showing patency of stent blood flow (long white arrow); E: 18 mo after the operation, enhanced computed tomography showed that blood flow in the splenic vein, superior mesenteric vein, portal vein and stent was good.

and were compared by independent-sample or paired-sample *t* test. Categorical and ordinal variables are presented as frequencies or percentages and compared using χ^2 test. Time-to-event outcomes were evaluated with Kaplan–Meier curves and log-rank tests. Cox regression model was used to identify independent predictors. Unbalanced factors between groups were treated as covariates. Statistical analysis was performed using IBM SPSS Statistics version 22.0 (IBM, Chicago, IL, United States) and GraphPad Prism version 7.0 (GraphPad Software, La Jolla, CA, United States). Follow-up investigators and statisticians had access to all of the data and vouched for the integrity of the data analyses.

RESULTS

Portosystemic pressure gradient before and after operation

The portosystemic pressure gradient (PPG) in Group A decreased from 26.9 ± 6.22 to 13.6 ± 6.4 mmHg ($t = 18.11$, $P < 0.05$) after operation. The PPG before and after operation were significantly different. The PPG in Group B decreased from 26.77 ± 6.25 to 15.1 ± 7.2 mmHg ($t = 17.1$, $P < 0.05$). The PPG before and after operation were significantly different (Table 2). The pre-operative PPG was not significantly different

between the two groups ($t = 1.52$, $P = 0.132$). The post-operative PPG was also not significantly different between the two groups ($t = 1.20$, $P = 0.234$) (Figure 4).

Time-to-event outcomes

The rates of stent restenosis at 6, 12 and 24 mo were 18.5%, 55.6% and 83.3% in Group A and 43.9%, 82.5% and 96.5% in Group B, which differed significantly [log rank $P < 0.05$, hazard ratio (HR): 0.42, 95%CI: 0.27–0.63] (Figure 5A and Table 3). The rates of survival at 6, 12 and 24 mo were 85.2%, 42.6% and 22.2%, respectively in Group A and 50.9%, 10.5% and 0%, respectively in Group B, which differed significantly (log rank $P < 0.05$, HR: 0.37, 95%CI: 0.24–0.56) (Figure 5B and Table 3)

Cox regression

Cox regression showed that pathogenesis, tumor number and serum albumin had no significant effect on survival rate. Treatment was the only factor that affected survival rate (Table 4).

DISCUSSION

With a rapid increase in the number of patients with liver cancer, the incidence of portal vein tumor thrombus is gradually increasing. ^{125}I was reported to have a

Table 2 Differences of portosystemic pressure gradient in the two groups before and after operation

	PPG before operation (mmHg)	PPG after operation (mmHg)	<i>t</i>	df	<i>P</i> value
Group A	26.9 ± 6.22	13.6 ± 6.4	18.11	53	< 0.0001
Group B	26.77 ± 6.25	15.1 ± 7.2	17.10	56	< 0.0001

PPG: Portosystemic pressure gradient.

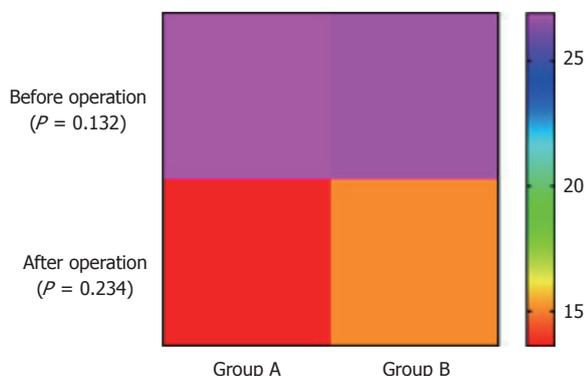


Figure 4 Heat map of comparison of portosystemic pressure gradient measurements before and after operation between Groups A and B. Student's *t* test was used to compare portosystemic pressure gradient at each time point, and no difference was found between the two groups.

good therapeutic effect^[7]. However, ¹²⁵I implantation has been in the form of particle strands. This has some disadvantages, such as implantation of a limited number of particles. In addition, the position of ¹²⁵I cannot be adjusted. No one has studied the clinical effect of ¹²⁵I combined with main portal vein stents in which the ¹²⁵I is placed between the tumor thrombus and stents. This procedure could make it easier to adjust the position and amount of ¹²⁵I. Thus, in the present study, we compared TACE/TAE + main portal vein stents combined with ¹²⁵I implantation and TACE/TAE + main portal vein stents alone for the treatment of liver cancer patients with main portal vein tumor thrombus and portal hypertension. Overall, our study suggested a benign outcome: (1) ¹²⁵I combined with stents implanted in the main portal vein significantly improved survival rate and reduced stent restenosis rate; (2) stents implanted in the main portal vein reduced portal vein pressure and relieved clinical symptoms; and (3) TACE/TAE + main portal vein stents combined with ¹²⁵I implantation was safe and feasible.

The incidence of portal vein tumor thrombus is high, and its treatment includes surgical resection, chemotherapy, and stent^[8-10]. Stent implantation of the main portal vein can quickly reduce portal vein pressure, relieve clinical symptoms and improve quality of life^[11,12]. In recent years, portal vein stenting combined with ¹²⁵I implantation has achieved significant effects in treating main portal vein tumor thrombus. Sun *et al.*^[13] conducted a study to evaluate the effect of ¹²⁵I. In their study, the median survival was 147 d. The cumulative survival rates and stent patency rates at 90, 180, and 360 d were 94.1%, 61.8%, and 32.4% and 97.1% (33/34), 76.9% (24/34), and 29.4% (10/34), respectively^[13]. However,

in previous studies, ¹²⁵I particles were implanted in the form of particle strands, which has some drawbacks. It is important to find a better method. In our study, the survival rate in Group A was higher than in Group B, and the stent restenosis rate was lower in Group A than in Group B. Cox regression was used to evaluate the effects of various factors on survival and stent restenosis. It showed that pathogenesis, tumor number and serum albumin had no significant effect on survival rate. Treatment was the only factor influencing survival rate. TACE/TAE + main portal vein stents combined with ¹²⁵I implantation can improve patient survival rate and reduce stent restenosis rate.

Our study had several limitations. First, the radiation dose was not uniformly distributed. Second, the number of patients was small, which may have influenced the accuracy of the results.

In summary, TACE/TAE + main portal vein stents combined with ¹²⁵I implantation is effective in treating main portal vein tumor thrombus and its complications, improving quality of life and reducing mortality.

ARTICLE HIGHLIGHTS

Research background

Tumor thrombus in the main portal vein indicates late-stage disease. Treatment for portal vein tumor thrombus includes surgery, chemotherapy, radiotherapy, targeted therapy, and proton beam radiation. In recent years, radioactive iodine-125 (¹²⁵I) particles have been used to treat portal vein tumor thrombus. However, seed implantation in recent studies had some disadvantages. We carried out the present study to explore a new method of seed implantation.

Research motivation

Previously, ¹²⁵I was implanted in the form of particle strands. This limits the number of ¹²⁵I particles implanted, and their position cannot be adjusted. In this study, we performed ¹²⁵I seed implantation combined with stent implantation, placing the particles between the stent and tumor thrombus. The stent could hold the ¹²⁵I particles, and the method can be widely used in clinical application.

Research objectives

¹²⁵I has been shown to be effective in treating portal vein thrombosis. The main objective of this study was to determine the efficacy of stents combined with ¹²⁵I implantation in the treatment of liver cancer accompanied by main portal vein tumor thrombus, as well as the technical feasibility of this method of seed implantation.

Research methods

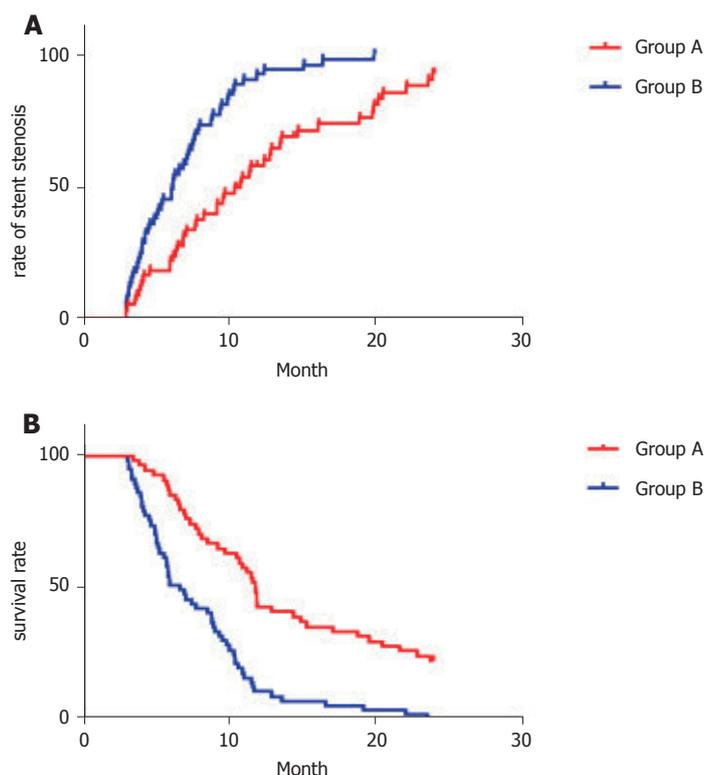
Patients were non-randomly assigned to undergo treatment with transarterial chemoembolization (TACE)/transarterial embolization (TAE) + portal vein stents combined with ¹²⁵I implantation (Group A) or TACE/TAE + portal vein stents only (Group B). It could show differences in treatment and outcomes between the two groups. After operation, scheduled follow-up was performed at 6, 12 and 24 mo. Follow-up included postoperative and preoperative portosystemic pressure gradient, postoperative stenting stenosis rate, and survival rate. Time-to-event outcomes were evaluated with Kaplan–Meier curves and log-rank test. Cox

Table 3 Time-to-event outcomes

	Group A (n = 54)	Group B (n = 57)	P value
Rate of stent stenosis			< 0.05
6 mo	18.5	43.9	
12 mo	55.6	82.5	
24 mo	83.3	96.5	
Survival rate			< 0.05
6 mo	85.2	50.9	
12 mo	42.6	10.5	
24 mo	22.2	0	

Table 4 Multivariate analysis of factors associated with postoperative outcomes

	Hazard ratio	95%CI	P value
Pathogenesis	1.227	0.773–1.948	0.385
Albumin (g/L)	1.266	0.829–1.932	0.275
Alanine aminotransferase (U/L)	1.222	0.798–1.872	0.357
Glutaryl transpeptidase (U/L)	0.821	0.509–1.224	0.419
Direct bilirubin (μmol/L)	2.262	0.270–18.96	0.452
Aspartate aminotransferase (U/L)	1.270	0.800–2.017	0.311
No. of liver tumors	1.238	0.232–19.41	0.330

**Figure 5** Kaplan–Meier curves of postoperative stent restenosis (A) and survival (B).

regression model was used to identify independent predictors. Kaplan–Meier curves and log-rank test clearly demonstrated the differences in survival rate and restenosis rate between the two groups, as well as the efficacy of ^{125}I in the treatment of main portal vein tumor thrombus. Cox analysis could take various factors into account to make the results more convincing.

Research results

Compared with stents alone, stents combined with ^{125}I implantation had a good therapeutic effect in liver cancer with main portal vein tumor thrombus. This method reduced the restenosis rate and improved survival rate. Stents

combined with ^{125}I implantation were safe and reliable in clinical application. In this study, the ^{125}I was placed between the stent and tumor thrombus and the stent could hold the particles. Using this method of ^{125}I implantation, the number and position of the particles could be adjusted, which is more flexible in clinical application. However, as the size of the liver cancer shrinks, the particles may drift to other parts of the body via blood flow, and this needs further study.

Research conclusions

Stents combined with ^{125}I implantation have a good therapeutic effect in the treatment of liver cancer with main portal vein tumor thrombus. The ^{125}I was

placed between the stent and the tumor thrombus, and the stent could hold the particles. The new method can avoid the drawbacks of particle strands and can be widely used in the clinic. Stents combined with ¹²⁵I implantation have a good therapeutic effect in the treatment of liver cancer with main portal vein tumor thrombus. The method is technically safe and reliable. Tumor thrombus in the main portal vein indicates late-stage disease. ¹²⁵I is an effective treatment for main portal vein thrombosis. Compared with stents alone, stents combined with ¹²⁵I implantation can reduce restenosis rates and improve survival rate. It is technically safe and reliable. ¹²⁵I has made great achievements in the treatment of main portal vein tumor thrombus, but there are drawbacks in the method of ¹²⁵I implantation, and new methods should be explored.

Research perspectives

Liver cancer with portal vein thrombosis seriously affects patient quality of life and should be treated in a timely manner. Stents combined with ¹²⁵I implantation have a good therapeutic effect in liver cancer with main portal vein tumor thrombus. Appropriate patients were selected for seed implantation treatment according to the inclusion criteria. The particle drift rate of the patients was followed up at 6, 12 and 24 mo after the operation.

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