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ORIGINAL RESEARCH

TACE Combined with Portal Vein Tumor Thrombus ^{125}I Seed Implantation in the Treatment of HCC with Hepatic Arterioportal Shunts

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Background and Objectives: Transarterial chemoembolization (TACE) and ^{125}I seed implantation are methods used to treat hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT), PVTT often associated with arterioportal shunts(APS), there are few reports on the combined use of TACE and ^{125}I seed implantation for such patients. This study aimed to evaluate the efficacy and safety of TACE combined with PVTT ^{125}I seed implantation in the treatment of HCC patients with APS.

Methods: Forty-two patients diagnosed with HCC combined with PVTT and APS between January 2020 and December 2021 were included. Appropriate materials were selected to transarterial embolization of the APS, and ^{125}I seeds were implanted into the PVTT. The occlusion effect was observed and recorded after 3 months, the efficacy of intrahepatic lesions and PVTT was evaluated, and the patient survival, prognostic factors affecting APS recanalization were analyzed.

Results: All 42 patients completed the follow-up three months after treatment. The immediate APS improvement rate was 100%, and the APS improvement rate at the three-month follow-up was 64.29%. The disease control rates of PVTT and intrahepatic lesions were 81.00% and 78.60%, respectively. The patients' 6-month and 12-month survival rates were 78.6% and 46.8%. The median OS for all patients was 11.90 months, and the median OS was 13.30 months in the APS effective treatment group and 8.30 months in the ineffective group. The PVTT type is the only independent factor affecting APS recanalization. (P=0.02).

Conclusion: For HCC patients with PVTT and APS, TACE combine with ^{125}I seed implantation in PVTT is a potentially effective and safe method that contributes to prolonging patient survival.

Keywords: hepatocellular carcinoma, transarterial chemoembolization, portal vein tumor thrombus, ^{125}I seed, arterioportal shunts

Introduction

Advanced hepatocellular carcinoma (HCC) accompanied by portal vein tumor thrombosis (PVTT) and arterioportal shunts (APS) is common.[1–3] The presence of moderate to severe APS can exacerbate portal hypertension, leading to life-threatening complications such as gastroesophageal variceal rupture, refractory ascites, and hepatic encephalopathy. Transarterial chemoembolization (TACE) is commonly used topical treatments for intermediate and advanced HCC.[4–6] However, in HCC patients with PVTT and APS, Lipiodol may flow into normal liver tissue through the shunt, potentially diminishing the effectiveness of TACE by reducing its ability to concentrate within the tumor and target the tumor thrombus effectively.[7] Therefore, effective treatment of APS is crucial, as shunt occlusion is an essential initial step in managing portal hypertension and performing TACE.

For HCC patients with APS, according to the "Chinese clinical practice guidelines for transarterial chemoembolization of hepatocellular carcinoma"[8], the shunts should be embolized with an appropriate particle size material according to the degree and volume of APS.[9,10] However, TACE alone has been reported to have limited efficacy in the treatment of patients with PVTT.[11] Studies have also shown that PVTT ^{125}I seed implantation has a good curative effect.[10,12,13] To our knowledge, there are few

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reports on TACE combined with ^{125}I seed implantation for the treatment of APS in HCC patients with PVTT, we retrospectively evaluated the efficacy and safety of this therapy in the treatment of such patients.

Methods

Patient Information

Clinical records for patients with HCC treated with TACE and portal vein tumor thrombus ^{125}I seed implantation from January 2020 to December 2021 were collected and analyzed retrospectively. The study was approved by the Ethics Committee of the Affiliated Cancer Hospital of Zhengzhou University (approval number: 2016ct005). Informed consent was waived due to the retrospective study nature.

Inclusion criteria: (1) Diagnosed with HCC and PVTT in accordance with the Guidelines for the Diagnosis and Treatment of Hepatocellular Carcinoma (2019 Edition);[14] (2) APS confirmed by digital subtraction angiography (DSA) of the hepatic artery; (4) Child-Pugh class A or B<8; (5) No previous antineoplastic treatment such as surgery, radiofrequency or microwave ablation, chemotherapy, or radiotherapy. (6) No contraindications to TACE or ^{125}I seed implantation. The exclusion criteria were: (1) Complete occlusion of the main portal vein without collateral circulation; (2) Central nervous system metastasis; (3) Other malignant tumors; and (4) The presence of severe complications, including severe cardiac, pulmonary, renal, or coagulation disorders.

TACE Procedure Combined with ^{125}I Seed Implantation

As described in previous report on TACE procedures,[5,12,15] Hepatic arteriography were used to clarify the diagnosis of HCC and the specifics of APS. An appropriate embolic material was selected according to the APS, and included a gelatin sponge, PVA particles, and an ethanol-soaked gelatin sponge. A 2.7 F coaxial microcatheter (Terumo, Japan) was inserted into the corresponding artery for super-selective angiography. After hepatic arteriography, according to whether the microcatheter could pass through the APS region, two categories were considered: (1) if the microcatheter could pass through the APS region, tumor embolization was performed first. In addition, 4–20 mL lipiodol plus epirubicin (30–60mg/m^2) was mixed to prepare an iodized oil emulsion. After tumor chemoembolization was completed, the microcatheter was returned to the APS region, and gelatin sponge particles, PVA particles, or an ethanol-soaked gelatin sponge was used to occlude the shunt; (2) If the microcatheter could not pass through the APS area, the target tumor and APS could be embolized at the same time. Figure 1 shows the whole therapy process before and post procedure containing APS embolization and PVTT 125I seeds implantation.

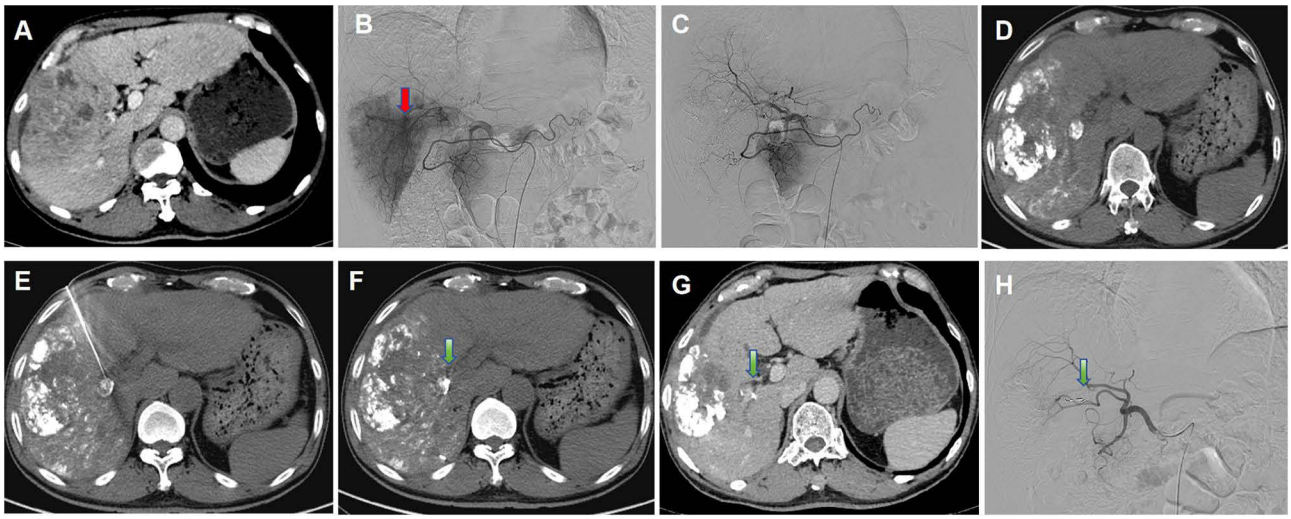

Figure 1 The whole therapy process before and after procedure containing APS embolization and PVTT ^{125}I seeds implantation.
Notes: This is a treatment process of a 55-year-old male HCC patient with PVTT (IIa) and APS. (**A**)CT image with a filling defect in the right branch of the portal vein, which was considered portal vein tumor thrombus. (**B**) Hepatic artery angiography shows early enhancement of portal vein branches (the red arrow indicates APS). (**C**) The shunt is seen to be occluded after TACE. (**D-F**) show the process of CT-guided PVTT ^{125}Iseed implantation seven days later. (**D**) Lipiodol deposition in the PVTT. (**E**) The puncture process during ^{125}I seed implantation. (**F**) high-density ^{125}I seeds are visible in PVTT after procedure (green arrow indicates ^{125}I seeds). (**G**)Three months later, CT showed a reduction in portal vein tumor thrombus. (**H**)Hepatic angiography confirmed the absence of APS.

Three to seven days after TACE, if the patient had good liver function and no contraindications, ^{125}I seed implantation was performed using a computerized particle implantation planning system (treatment planning system, TPS, Beijing KELINZHONG Institute of Medical Technology). We aimed to achieve a prescribed dose of 95% volume of the PVTT target area and a target volume ratio of 1.5–2.0. According to the TPS system, an 18 G needle was used to puncture the target lesion, ^{125}I seeds were implanted in different layers and positions of the tumor in sequence, and the source was distributed according to a spacing of 5 mm (Figure 1). A computed tomography scan was performed postoperatively to observe the seed distribution.

Evaluation Index

We classified PVTTs into three subgroups based on Cheng's classification as follows:[16] (a) type III was defined as a PVTT in the main portal vein; (b) type II was divided into IIa and IIb subtypes, with type IIa defined as a PVTT in a first-order portal vein branch (the right or left portal vein only) and type IIb defined as a PVTT in both the left and right first-order portal vein branches; and (c) type I defined as a PVTT in a second- or lower-order portal vein branch. All eligible patients with a type II PVTT (IIa or IIb) were included in this study.

APS can be divided into three categories:[10] (1) mild: the morphology of the shunt cannot be seen on angiography, while the small branches of the portal vein can; (2) moderate: in the middle and late stages of tumor staining, the main vein or branches can be visualized; (3) severe: when the trunk and branches of the hepatic artery are visualized, the veins can be visualized, and tumor staining does not appear or is in the early stage.

The criteria for evaluating the treatment effect of APS follow the recommendations by Kim, Zhou et al[17,18] and have been modified by us as follows: changes in APS grade: (1) cured, APS disappears completely; (2) alleviated, the degree of APS is alleviated, or the onset time is delayed; (3) stable, the degree of APS remains unchanged; (4) progress, the degree of APS is aggravated, or there is an increased flow rate. All patients underwent re-examination of DSA angiography images three months after the first treatment, and the effect of shunt closure was observed according to the arteriography images. Among them, (1) and (2) were considered effective, and (3) and (4) were considered ineffective. APS recanalization was defined as fellows: reappearance of blood flow through previously occluded shunts, new shunt formations, or significant changes in blood flow patterns (such as increased APS grade). Changes in liver function indicators, including the Child-Pugh score and total bilirubin and albumin levels, were also evaluated.

Efficacy evaluation of tumor embolization: The modified response evaluation criteria in solid tumors (mRECIST) were used to evaluate the efficacy of tumor embolization three months after the first treatment, including complete response, partial response, stable disease, and disease progression (PD).[19] Intrahepatic tumor lesions and portal vein tumor thrombi were evaluated separately. The patient's systemic treatment plan, as well as medication adjustments after disease progression, are determined based on multidisciplinary discussion and the patient's wishes.

Statistical Analysis

SPSS version 25.0 (SPSS, Chicago, IL, USA) was used for the statistical analysis. Continuous variables that conformed to a normal distribution were expressed using the mean ± standard deviation (x±s), and those that did not conform to a normal distribution were expressed using the median and interquartile spacing [M (P25, P75)]. Comparisons between groups were made using the two independent samples *t*-test or the Mann–Whitney *U*-test, respectively. Count data are expressed as the number of cases (percentage, %), and the Chi-square test was used to compare the groups. The difference in media OS between the two groups was evaluated using the Kaplan-Meier method. Univariate and multivariate analyses were used to analyze the prognostic factors affecting APS recanalization. A P-value of < 0.05 was considered statistically significant.

Results

Baseline Characteristics

From January 2020 to December 2021, 168 HCC patients with PVTT and were treated by TACE at our department. Forty-two patients were found to have APS during hepatic arteriography, and after transarterial embolization of the APS, PVTT was implanted with ^{125}I seeds. The average age of patients was 54.64±8.76 years, and among the patients, 35 (83.3%) were male. According to the general information of the patients before treatment, the APS categories was mainly mild to moderate (88.10%), and the embolic materials were mostly gelatin sponge and PVA particles (81.00%). Detailed baseline characteristics, including gender, age, Cirrhosis, Child-Pugh score, ascites, tumor number, maximum tumor diameter, PVTT type (IIa or IIb), APS Flow categories (Mild, Moderate, or Severe), AFP level, TBIL and ALB level are shown in Table 1.

Evaluation of the Effect of APS Occlusion

During the initial procedures, the immediate APS improvement rate was 100% (42/42), APS disappears completely in 40 patients and alleviated in two patients. All 42 patients completed the follow-up at three months. According to the above criteria, APS disappeared or decreased in 27 patients, APS flow remained unchanged in 11 patients, and APS flow increased in four patients. The effective rate was 64.29% (27/42). There were statistically significant differences in the APS grade (P<0.001) and ascites (P=0.005) before treatment and three months after treatment. However, there were no significant differences in the Child-Pugh score, total bilirubin, and albumin levels (P>0.05) (Table 2).

Efficacy Evaluation of Intrahepatic Lesions/PVTT and Follow-Up

After three months of treatment, the disease control rate (DCR) of PVTT and intrahepatic lesions in all patients was 81.00% and 78.60%, respectively (Table 3). The patients' 6-month and 12-month survival rates were 78.6% and 46.8%,

Table 1 Baseline Characteristics of the Patients

Characteristics	Level	N=42
Gender	Male	35 (83.3%)
	Female	7 (16.7%)
Age (years)		54.64±8.76
Cirrhosis	None	35 (83.3%)
	Have	7 (16.7%)
Child-Pugh score	5	18 (42.9%)
	6	21 (50.0%)
	7	3 (7.1%)
Ascites	None	26 (61.9%)
	Have	16 (38.1%)
Tumor number	Single	11 (26.2%)
	Multiple	31 (73.8%)
Maximum tumor diameter (cm)		7.38±3.81
PVTT type	IIa	31 (73.8%)
	IIb	11 (26.2%)
APS Flow	Mild	19 (45.2%)
	Moderate	18 (42.9%)
	Severe	5 (11.9%)
Embolisation materials	Gelatin sponge	20 (47.6%)
	PVA particles	14 (33.3%)
	Ethanol-soaked gelatin sponge	8 (19.1%)
AFP (ng/mL)	≤400	22 (52.4%)
	>400	20 (47.6%)
TBIL (g/L)		18.42±8.54
ALB (μmol/L)		39.90±4.97

Abbreviations: AFP, alpha-fetoprotein; TBIL, total bilirubin; TBIL, total bilirubin; ALB, albumin.

Table 2 Comparison of APS Grades and Liver Indicators Before Treatment and 3 Month After Treatment

Variables	Number of Cases		χ^2	*P* value
	Before Treatment	After Treatment		
APS Flow				
None	0	23	38.005	<0.001
Mild	19	9		
Moderate	18	6		
Severe	5	4		
Child-Pugh score				
5	18	23	1.775	0.436
6	21	18		
7	3	1		
Ascites				
None	26	38	7.941	0.005
Have	16	4		
TBIL (g/L)	18.42±8.54	20.75±10.00	−1.265	0.213
ALB (μmol/L)	39.90±4.97	39.25±5.80	0.566	0.575

Table 3 Efficacy Evaluation of PVTT and Intrahepatic Lesions

Tumor Response	PVTT	Intrahepatic Lesions
CR	0	0
PR	10	8
SD	24	25
PD	8	9
DCR	81.00%	78.60%

respectively. The median OS (mOS) for all patients was 11.90 months (95% CI: 8.46–15.34) (Figure 2A). Based on treatment at three months, patients were divided into APS treatment effective and ineffective groups, with an mOS of 13.30 months (95% CI: 11.39–16.21) and 8.30 months (95% CI: 3.88–12.72), with a statistically significant difference (*P*<0.001) (Figure 2B).

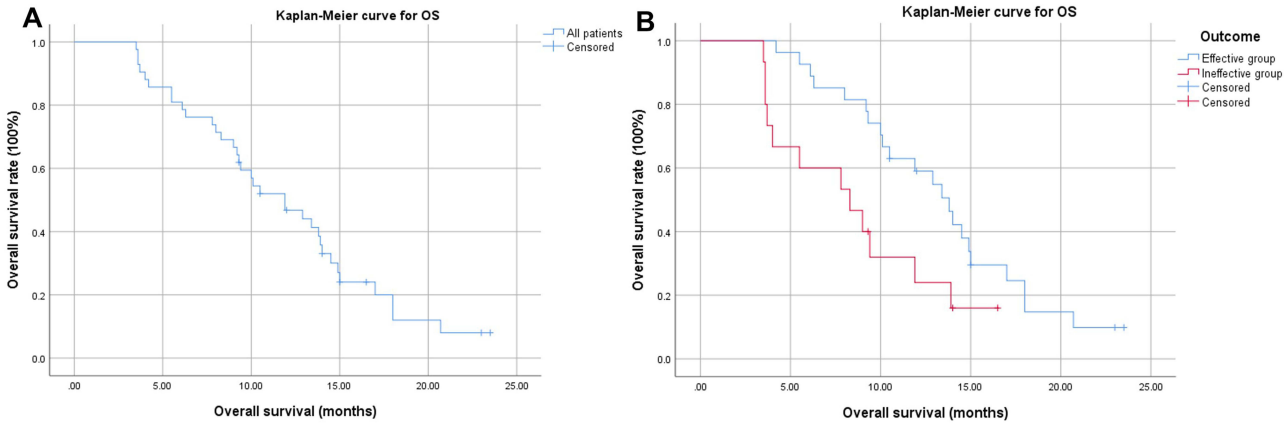

Figure 2 Kaplan-Meier curve for OS for all patients(**A**) and treatment effective group, ineffective group (**B**).

Table 4 Prognostic Analysis Affecting APS Recanalization After 3 Months

Variables	Univariate Logistic		Multivariate Logistics	
	OR (95% CI)	P value	OR (95% CI)	P value
Gender (M/F)	0.25 (0.03–2.31)	0.22		
Age	1.02 (0.95–1.10)	0.59		
Cirrhosis (None/Have)	1.44 (0.28–7.50)	0.67		
Child-Pugh score				
5:6	1.00 (0.26–3.80)	1		
5:7	4.00 (0.30–53.47)	0.29		
Ascites (None/Have)	1.13 (0.31–4.14)	0.85		
Tumor number (Single/Multiple)	3.25 (0.6–17.62)	0.17		
Maximum tumor diameter	1.14 (0.97–1.36)	0.12		
PVTT type (IIa/IIb)	9.14 (1.90–44.01)	0.01	7.34 (1.32–10.69)	0.02
APS Flow				
Mild:Moderate	4.27 (0.91–19.99)	0.07	4.09 (0.77–21.86)	0.99
Mild:Severe	21.33 (1.73–263.68*)	0.02	14.16 (0.95–211.78*)	0.06
Embolisation materials				
Gelatin sponge:PVA particles	0.62 (0.10–3.92)	0.61		
Gelatin sponge:ethanol-soaked gelatin sponge	1.39 (0.34–5.66)	0.64		
AFP	0.94 (0.27–3.34)	0.93		
TBIL	0.99 (0.92–1.07)	0.8		
ALB	1.03 (0.91–1.18)	0.62		

Notes: *Indicates that the 95% CI interval of the OR value is relatively large due to the small number of patients in a group of classified samples.

Prognostic Analysis Affecting APS Recanalization

Univariate and multivariate logistic analyses were performed to analyze the risk factors for APS recanalization. Univariate analysis showed that the factors significantly associated with prognosis were PVTT type (OR=9.14, 95% CI: 1.90–44.01, *P*=0.01), and APS flow categories (OR=21.33, 95% CI: 1.73–263.68, *P*=0.02). In the multivariate analysis, only the PVTT type (OR=7.34, 95% CI: 1.32–10.69, *P*=0.05) was founded to be an independent risk factor for APS recanalization (Table 4).

Adverse Reactions

TACE-related adverse events occurred in 76.19% of patients (32/42), including abdominal pain (59.5%, 25/42), fever (47.6%, 20/42), nausea and vomiting (28.6%, 12/42). All symptoms were resolved with symptomatic treatment. Few acute adverse events were reported with ^{125}I seed implantation. The adverse effects of ^{125}I seed implantation were mainly caused by the puncture and included bleeding and pneumothorax. Five patients (5/42) had minor subcapsular liver hemorrhages, treated successfully conservatively. Two patients (2/42) developed pneumothoraxes with less than 30% lung collapse, which resolved with conservative treatment. Seed migration to normal liver parenchyma was observed in one case (1/42), but required no medical intervention. No other severe adverse events and ^{125}I seed implantation procedure-related deaths were observed.

Discussion

APS is considered an independent predictor of poor prognosis and is a typical complication of PVTT.[20,21] Although the exact cause is unknown, some studies have found that radiotherapy can reduce or cure APS.[22] This study used TACE combined with PVTT ^{125}I seed implantation to treat APS, with an effective efficiency of 64.28% and manageable adverse effects. Our findings indicate that ^{125}I seed implantation into PVTT can lead to a good APS response. Several studies have been conducted on TACE combined with PVTT ^{125}I seed implantation for treating patients with advanced HCC;

however, few studies have been conducted on APS. In the present study, not only did APS improve, but liver function was also effectively relieved, similar to previous reports.[12]

Previous studies have shown varying efficacies of different materials for the treatment of APS.[20,23,24] For example, a mixture of anhydrous ethanol and gelatin sponges was reported to be more effective than polyvinyl alcohol pellets/gelatin sponges. This may due to anhydrous ethanol has good mobility and penetrates into capillaries and venous shunts, destroying adjacent tumor cells. The gelatin sponge slows the blood flow, allowing anhydrous ethanol to cause complete damage to the vessel wall.[18] However, this advantage was not observed in the present study. Univariate logistic regression analysis showed that the material was not a risk factor for shunt recanalization. However, it is worth noting that all patients in this study had PVTT, which may have contributed to the poorer efficacy of APS. Therefore, further understanding of the relationship between PVTT and APS is needed.

The relationship between hepatic artery-portal shunts and PVTT is more complex, and the formation of PVTT is mainly associated with portal venous reflux. Approximately 47%-63% of hepatocellular carcinomas are combined with hepatic arteriovenous shunts,[25] which are mainly hepatic artery-portal vein traffic branches. The formation of PVTT causes obstruction of the portal vein, resulting in the opening of extensive anastomotic branches between the hepatic artery and portal vein in normal liver tissue, ultimately resulting in the development of APS, which further aggravating the incidence of intrahepatic failure. Therefore, for HCC patients with PVTT and APS, it is even more important to control the progression of PVTT after APS occlusion.

Previous studies have shown that treating APS resulted in a mOS of 129 to 382 days, with cumulative survival rates at 6 months, 1 year, and 2 years reported to vary between 45% and 79%, 12% and 50%, 7.8% and 25%, respectively.[17,20,26,27] In this study, the mOS for patients with effective APS occlusion was approximately 13.3 months, which is significantly better than previous treatments. The better effective in this study could be related to the effective control of tumor thrombus. ^{125}I seed implantation has a good effect on the control of tumor thrombus; therefore, it also controls the occurrence of shunt recanalization to a large extent. The occurrence and recanalization of the shunt can be reduced by controlling tumor thrombus and avoiding direct invasion or compression of the portal vein vessels. The complete or near-complete occlusion of the APS can alleviate portal venous pressure and reduce the incidence of complications associated with portal hypertension, thereby improving patient survival. Additionally, this improved outcome may also be related to the lower proportion of patients with cirrhosis enrolled in this study.

This study has several limitations. First, This was a small retrospective study, so patient selection bias could have occurred. Second, despite using the TPS planning system, uneven seed distribution, due to local anesthesia and lack of a 3D-printed template during implantation, may have introduced variability in treatment efficacy. Furthermore, TACE combined with targeted therapy and immunotherapy has been reported as effective in treating APS,[28] but this study did not include data from patients who received such treatments.

Conclusions

For HCC patients with PVTT and APS, TACE combined with ^{125}I seed implantation in PVTT is a potentially effective and safe method that can control tumor thrombus, reduce the occurrence of shunt recanalization, and improve patient survival.

Data Sharing Statement

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

Ethics Statement

This study was a retrospective study in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Affiliated Cancer Hospital of Zhengzhou University (approval number: 2016ct005). Informed consent was waived due to the retrospective study nature. All patient data were strictly confidential and used solely for the purpose of this study. During the data usage process, patient personal information was anonymized, in compliance with relevant privacy protection regulations.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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