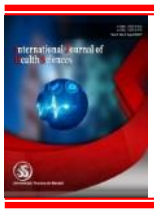

International Journal of Health Sciences
Available online at www.sciencescholar.us
Vol. 7 No. 3, December 2023, pages: 76-85
e-ISSN: 2550-696X, p-ISSN: 2550-6978
https://doi.org/10.53730/ijhs.v7n3.14563

Clinical Application of Transarterial Chemoembolization Combined with Terminal Branches Portal Vein Embolization in Planned Hepatectomy

Guoqing Zhu [a], Wenhao Hu [b], Wei Xiang [c], Junwei Ni [d], Liyang Dong [e]

Manuscript submitted: 09 July 2023, Manuscript revised: 27 August 2023, Accepted for publication: 18 Sept 2023

Corresponding Author [a]

Keywords

hepatectomy;
hepatocellular carcinoma;
portal vein embolization;
terminal branches;
transarterial chemoembolization;

Abstract

This study aimed to investigate the clinical efficacy of transarterial chemoembolization (TACE) in conjunction with terminal branches portal vein embolization (TBPVE) in the context of planned hepatectomy. A cohort of five patients afflicted by primary hepatocellular carcinoma who were deemed unsuitable candidates for primary surgical resection was gathered from August 2019 to December 2021. Following the application of TACE in combination with TBPVE as a therapeutic intervention, we observed postoperative general reactions, alterations in tumor biomarkers, hyperplasia of future liver remnant (FLR), and subsequent surgical resection. All patients successfully underwent the combined TACE and TBPVE procedure, achieving a technical success rate of 100%. One week after TACE, alpha-fetoprotein (AFP) levels decreased from 38.52±49.21 to 25.27±37.94 μg/L, and Protein Induced by Vitamin K Absence or Antagonist (PIVKA) levels decreased from 1689.30±1663.83 to 219.03±228.10 μg/L. Two weeks post-TBPVE, FLR exhibited an increment from 350.80±41.17 to 476.00±57.91 mL. The ratio of FLR to standard liver volume (SLV) increased from 30.94%±3.63% to 42.03%±5.62%. The combined application of TACE and TBPVE not only effectively manages tumor progression but also augments the FLR, thereby affording patients with a limited future liver remnant an opportunity for surgical resection of hepatocellular carcinoma.

Contents

[a] Department of Interventional Radiology, The First Affiliated Hospital of Wenzhou Medical University, 325000 Wenzhou, China
[b] Department of Interventional Radiology, The First Affiliated Hospital of Wenzhou Medical University, 325000 Wenzhou, China
[c] Department of Interventional Radiology, The First Affiliated Hospital of Wenzhou Medical University, 325000 Wenzhou, China
[d] Department of Interventional Radiology, The First Affiliated Hospital of Wenzhou Medical University, 325000 Wenzhou, China
[e] Department of Interventional Radiology, The First Affiliated Hospital of Wenzhou Medical University, 325000 Wenzhou, China

1 Introduction

For hepatic tumors, standardized surgical resection remains the preferred therapeutic approach (Moris et al., 2018). However, insufficient postoperative residual liver volume (FLR) leading to postoperative hepatic insufficiency or even mortality constitutes a significant limiting factor for surgical resection (Makuuchi et al., 1990; Adam et al., 2000). Therefore, enhancing FLR preoperatively holds paramount significance in preventing postoperative hepatic dysfunction or mortality (Reddy et al., 2011; Menon et al., 2006).

Associating liver partition and portal vein ligation staged hepatectomy (ALPPS), a novel technical approach involving a two-step liver resection through hepatic parenchymal separation and portal vein ligation, swiftly augments residual liver volume. Nonetheless, this procedure is technically demanding and carries a high risk, rendering it unsuitable for all medical centers^4. Portal vein embolization (PVE), on the other hand, can also increase FLR. Compared to ALPPS, PVE entails significantly lower risks, but its effect on augmenting FLR is less pronounced. Hence, in light of the advantages of combining ALPPS and PVE, Professor Peng Shuyou in our country has proposed the application of terminal branches portal vein embolization (TBPVE) (Peng et al., 2016).

Following portal vein embolization, there is a possibility of tumor tissue proliferation due to hepatic arterial overperfusion (Imamura et al., 2008). Therefore, concurrently with TBPVE, we employ transcatheter arterial chemoembolization (TACE) to prevent tumor progression, collectively creating conditions for a two-stage surgery. In this article, we retrospectively review five cases of primary hepatocellular carcinoma patients who were admitted to our department in recent years due to anticipated inadequate FLR for a one-stage surgical resection. Through the utilization of hepatic artery chemotherapy embolization in conjunction with terminal branches portal vein embolization, we controlled tumor progression while increasing FLR in preparation for the second-stage surgery (Llovet & Beaugrand, 2003; Song et al., 2004).

2 Materials and Methods

Patient and tumor characteristics

We retrospectively reviewed five cases of primary hepatocellular carcinoma patients admitted to our institution between August 2019 and December 2021. Among them, there were four males and one female, aged between 39 and 66 years, with an average age of (48.40±10.29) years. All five patients presented with concurrent hepatitis B and liver cirrhosis, with Child-Pugh class A liver function. The tumors were all located in the right lobe of the liver, with four cases exhibiting multiple lesions. The maximum tumor diameter ranged from 5.3 to 15 cm, with an average of (9.08±3.66) cm. This study has obtained informed consent from the patients and their families and has received approval from the hospital's ethics committee. For further details, please refer to Table 1.

Table 1
Demographic and pathological characteristics

Patient	1	2	3	4	5
Age (Year)	45	47	66	45	39
Sex	male	male	female	male	male

Tumor Maximum Diameter (cm)	15	5.3	7.3	9.6	8.2
Tumor Number	solitary	*multiple*	*multiple*	*multiple*	*multiple*
Tumor location	Right liver	Right liver	Right liver	Right liver	Right liver
Liver cirrhosis	Yes	Yes	Yes	Yes	Yes
Hepatitis B	Yes	Yes	Yes	Yes	Yes
FLR (ml)	378	408	308	324	336
SLV (ml)	1189	1104	1086	1124	1168

TACE Treatment Protocol

The Seldinger technique was employed to puncture the right femoral artery, followed by selective catheterization into the celiac trunk and superior mesenteric artery to perform angiography. This procedure aimed to delineate details about the number, size, vascular supply, and extent of intrahepatic tumors. Subsequently, super-selective catheterization into the tumor-feeding arteries was carried out, and chemotherapy drugs, specifically oxaliplatin (100-150 mg), irinotecan (10-30 mg), and emulsified iodized oil (8-20 ml), were infused through the catheter to embolize the tumor vasculature. This process continued until stasis of blood flow within the tumor vessels was achieved, with some patients receiving embolization with absorbable gelatin sponge particles (Lesurtel et al., 2006; Kothary et al., 2007).

TBPVE Treatment Protocol

Approximately 1-2 weeks after TACE treatment, based on liver-enhanced CT imaging and 3D reconstruction, a plan for the second-stage surgical resection of liver cancer was devised. Accordingly, a TBPVE treatment protocol was developed. Under local anesthesia and B-mode ultrasound guidance, a puncture was made into the left portal vein branch. Upon successful puncture, a 5F catheter was advanced into the main portal vein, and a microcatheter was introduced into the targeted branch for embolization. Using fluoroscopy, an appropriate mixture of surgical glue (α-cyanoacrylate butyl ester adhesive) and iodized oil emulsion (mixed at a 1:4 ratio) was slowly injected for embolization. First, the peripheral portal vein branches were embolized, followed by gradual retraction to embolize the main portal vein branches until the target vessel's blood flow ceased. Subsequently, portal vein angiography was performed to confirm complete embolization of the target vessel (Thanassi et al., 1998; Pastell et al., 2008).

Surgical Procedure

The decision to undergo surgical intervention was based on individual patient circumstances and patient/family preferences. All surgeries were performed within 4-8 weeks following PVE. Patients who declined surgery were followed up every 1-3 months until their demise.

Observation Parameters

Following TACE and TBPVE, observations were made regarding patients' systemic reactions and biochemical results. CT scans before and after TBPVE were utilized to create three-dimensional liver reconstructions, including tumor volumes, using 3D-DOCTOR 5.0 software. In line with the method described in previous study Wakabayashi et al. (2004), the future liver remnant (FLR) and standard liver volume (SLV) were calculated. Surgical outcomes and postoperative follow-ups were recorded.

Statistical Analysis

Statistical analysis was conducted using SPSS V25.0 software, and numerical data were expressed as mean ± standard deviation (sd).

3 Results and Discussions

Systemic Reactions Following TACE Combined with TBPVE

All five patients underwent successful TACE combined with TBPVE treatment, achieving a technical success rate of 100%. After TACE, two patients experienced mild right upper abdominal pain, while two others developed a fever (all with temperatures below 39°C), and the remaining patients did not exhibit significant discomfort. Following TBPVE, all five patients were devoid of notable adverse symptoms. Three days after TBPVE, blood biochemical examinations indicated slight elevations in bilirubin and transaminases. However, with necessary supportive measures, including hepatic protection, these elevations generally resolved within approximately one week. Please refer to Table 2 for further details.

Table 2
Changes in Blood Biochemical Parameters Before and After TBPVE

Patient	ALT(U/L)		TBIL(μmol/L)		DBIL(μmol/L)	
	Pre-TBPVE	Post-TBPVE	Pre-TBPVE	Post-TBPVE	Pre-TBPVE	Post-TBPVE
1	67	85	15	48	6	40
2	88	85	13	13	5	5
3	12	22	10	12	4	5
4	16	134	8	7	4	4
5	86	58	35	12	17	5
Average	53.80±37.27	76.80±41.12	16.20±10.85	18.40±16.71	7.20±5.54	11.80±15.77

Note: TBPVE, terminal branches portal vein embolization, ALT, Alanine aminotransferase; TBIL, total bilirubin; DBIL, direct Bilirubin.

Tumor Marker Changes

Prior to TACE, the average AFP level in four patients (excluding one patient with values exceeding the detection limit) was (38.52±49.21) μg/L. One week after TACE, the average AFP level in these four patients was (25.27±37.94) μg/L. Before TACE, the average PIVKA level in four patients (with one missing data point) was (1689.30±1663.83) mAu/ml. One week after TACE, the average PIVKA level in these four patients was (219.03±228.10) mAu/ml. Please refer to Table 3 for detailed information.

Table 3
Postoperative Tumor Markers and FLR Changes

Patient	AFP (μg/L)		PIVKA (mAu/ml)		FLR (ml)			SLV (ml)	FLR/SLV (%)	
	Pre-TACE	Post-TACE	Pre-TACE	Post-TACE	Pre-TBPVE	Post-TBPVE	Hyperplasia (%)		Pre-TBPVE	Post-TBPVE
1	7.18	7.08	-	-	378	488	110(29.10)	1189	31.79	41.04
2	>54000	9188	3471	458	408	572	164(40.20)	1104	36.96	51.81
3	2.4	2.4	23.2	15.1	308	432	124(40.26)	1086	28.36	39.78
4	109	82	548	370	324	450	126(38.89)	1124	28.83	40.04
5	35.5	9.6	2715	33	336	438	102(30.36)	1168	28.77	37.50
Average	38.52±49.21	25.27±37.94	1689.30±1663.83	219.03±228.10	350.80±41.17	476.00±57.91	35.76±5.55	1134.2	30.94±3.63	42.03±5.62

Note: AFP, alpha-fetoprotein; PIVKA, Protein induced by vitamin K absence or antagonist; FLR, future liver remnant; SLV, standard liver volume

Pre- and Post-Volume Changes

FLR Changes Before and After TBPVE: Prior to TBPVE, the average FLR was (350.80±41.17) mL, with an average FLR/SLV ratio of 30.94%±3.63%. Two weeks after TBPVE, the average FLR increased to

(476.00±57.91) mL, with an average FLR/SLV ratio of 42.03%±5.62%. The FLR exhibited an average increase of 35.76%±5.55%, and the FLR/SLV ratio increased by an average of 42.03%±5.62%. Please refer to Table 3 for detailed data.

Surgical Results and Postoperative Follow-Up

Among the five patients, one patient declined surgical intervention, while four underwent curative surgical resection. The average interval between TBPVE and surgery for the four operated patients was (37.5±8.22) days. Postoperatively, the pathological examination confirmed hepatocellular carcinoma in all four cases, with clear surgical margins achieving R0 resection. One of the four postoperative patients experienced mild bile leakage during the perioperative period, which improved with symptomatic treatment and drainage. There were no complications such as acute liver failure, severe ascites, or bleeding. Unfortunately, one patient passed away 8 months after surgery, and the patient who did not undergo surgery due to tumor progression succumbed 7 months after TBPVE (Pandanaboyana et al., 2015; Glantzounis et al., 2017).

Discussion

ALPPS was first formally reported by Schnitzbauer and colleagues from Germany in 2012 (Schnitzbauer et al., 2012). Over the past few decades, ALPPS has emerged as one of the most promising new techniques in liver surgery. It rapidly and effectively increases FLR, improving the resectability of liver cancer lesions that were previously deemed inoperable (Baili et al., 2019). However, ALPPS remains a subject of considerable controversy due to its higher rate of surgical complications. Moreover, a critical question is whether the increased rate of tumor resection translates into improved patient survival (Moris et al., 2018). Reported complication rates after ALPPS range from 16% to 64%, with mortality rates between 12% and 23% (Baili et al., 2019). Major complications following ALPPS include bile leakage and sepsis, with postoperative liver failure being the primary cause of mortality. According to Eftratia's research, ALPPS should be performed in experienced surgical centers, and patient selection should be carefully evaluated by a multidisciplinary team (Baili et al., 2019).

To mitigate the risks associated with ALPPS complications, some have proposed using PVE to induce liver regeneration and increase FLR Makuuchi et al. (1990), with the goal of achieving a two-stage resection. Overall, PVE is considered safe and effective Azoulay et al. (2000); Brouquet et al. (2011), with a high technical success rate (van Lienden et al., 2013). PVE provides the opportunity for liver resection in nearly 80% of patients who require it (Shindoh et al., 2014). PVE can increase FLR by an average of 8%-27% in various types of malignant liver tumors (Abulkhir et al., 2008; Yamashita et al., 2017).

However, the regenerative effect of PVE in promoting FLR growth is weaker compared to ALPPS, and approximately 2.8% of patients may not be eligible for surgery due to inadequate FLR growth after PVE (Alvarez et al., 2018). Thus, Professor Peng Shuyou's team in China proposed the method of terminal branches portal vein embolization (TBPVE) (Peng et al., 2016). TBPVE excels in promoting residual liver regeneration compared to PVE, while avoiding the injuries associated with ALPPS.

Excessive hepatic arterial perfusion following portal vein embolization can lead to increased tumor tissue proliferation (Imamura et al., 2008). Therefore, we concurrently employed TACE during TBPVE to prevent tumor progression. In our study, TACE combined with TBPVE was successfully performed in all cases without significant postoperative complications, indicating the overall safety of this approach. One week after TACE, monitoring of tumor markers revealed decreases in both AFP and PIVKA levels, with two patients experiencing reductions of more than 50%. Coupled with postoperative follow-up CT results, this suggests that TACE combined with TBPVE effectively inhibits tumor progression.

Two weeks after TBPVE, the average FLR increased by 35.76%±5.55%, and the FLR/SLV ratio increased from 30.94%±3.63% before PVE to 42.03%±5.62%. A study by Professor Peng reported that TBPVE led to average FLR increases of 56.2% and 57.8% at 7 and 14 days after TBPVE, respectively Peng et al. (2021), which were higher than our center's results. The researchers suggested that this difference may be due to all five patients in our study having concomitant liver cirrhosis, which could have limited the degree of FLR growth. This calls for further clinical research to determine the specific reasons.

Our study data indicate an average waiting time of 26.25±1.71 days (median 26.5 days) for surgery after TBPVE. A single-center study from Japan reported a median time of 25 days between PVE and surgery for hepatocellular carcinoma Yamashita et al. (2017), ALPPS significantly shortens the waiting time before surgery to 7-9 days (Schelotto & Gondolesi, 2017). However, for patients with concomitant liver cirrhosis, it is generally recommended to wait at least 4-6 weeks after PVE before performing surgery (Aoki & Kubota, 2016).

Our study has several limitations, with the most significant being the small sample size. Due to the limited number of patients and various technical considerations, we currently lack a sufficiently large sample size. Another limitation is the relatively incomplete data collection. For ethical and patient preference reasons, we did not collect data frequently, as doing so may have had an unnecessary impact on patients. Nevertheless, our single-center experience still provides valuable insights. TACE combined with TBPVE offers a new option for the treatment of advanced liver cancer, and our research contributes our own experiences to the application of this procedure.

4 Funding

This work was supported by Wenzhou Science and Technology Bureau Project (Y2020809).

Acknowledgments
We are grateful to two anonymous reviewers for their valuable comments on the earlier version of this paper.

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Biography of Authors

Guoqing Zhu
Born on March 7, 1981 in Zhejiang Province. He graduated from Wenzhou Medical College in 2010 and received a master's degree in oncology. He has been working as an attending physician at the First Affiliated Hospital of Wenzhou Medical University since 2019. Young member of the Hepatobiliary and Pancreatic Committee of the Chinese Anti-Cancer Rehabilitation Association. Participated in the third level of the "Wenzhou 551 Talent Project" in 2012. Young member of the Interventional Branch of the Zhejiang Medical Association. Young member of the Interventional Tumor Committee of the Zhejiang Anti-Cancer Association. Wenzhou Interventional Radiology Deputy Chairman of the Youth Committee of the Professional Committee.
Email: zhuguoqing2007@wzhospital.cn

Wenhao Hu
Born in Zhejiang Province on March 8, 1968. He graduated from Wenzhou Medical University with a bachelor's degree in clinical medicine in 1992. He received a master's degree in biomedical engineering from Wenzhou Medical University in November 2017. Since 2015, he has served as the affiliated department of Wenzhou Medical University. Deputy director of the interventional department of a hospital (in charge of work). The society serves as Chairman of the Interventional Radiology Branch of Wenzhou Medical Association, Vice Chairman of the Interventional Physician Branch of Zhejiang Medical Doctor Association, Vice Chairman of Interventional Branch of Zhejiang Anti-Cancer Association, Standing Committee Member of Interventional Branch of Zhejiang Medical Association, and Interventional Physician Branch of Chinese Medical Doctor Association. He is a member of the Emergency Intervention Professional Committee, the Particle Therapy Branch of the Cancer Professional Treatment Committee of the Chinese Anti-Cancer Association, and the Vascular Intervention Branch of the Minimally Invasive Oncology Society of the Chinese Anti-Cancer Association.
Email: wzhwh9@163.com

Wei Xiang
Born on November 4, 1979 in Zhejiang Province. He graduated from Medical College of Xiamen University in 2004 with a bachelor's degree in clinical medicine. He graduated from Wenzhou Medical University in 2014 with a master's degree in imaging and nuclear medicine. Since then, he has been working in the Interventional Department of the First Affiliated Hospital of Wenzhou Medical University.
Email: 29573716@qq.com

Junwei Ni
Born on March 14, 1986 in Zhejiang Province. 2013-06 to 2018-12, Wenzhou Medical University, majoring in medical imaging and nuclear medicine, equivalent master's degree. 2005-8 to 2010-8, Wenzhou Medical University, Bachelor of Medical Imaging. From 2010 to now, worked as chief resident physician in the Department of Interventional Surgery, the First Affiliated Hospital of Wenzhou Medical University.
Email: jw138066@163.com

Liyang Dong
Born on October 13, 1975 in Shandong Province. Graduated fromMedical College of Jiamusi University in 2002 with a master's degree in clinical medicine.