Review

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Advances in endovascular therapy to treat primary hepatocellular carcinoma

Zhi Guo*, Haipeng Yu, Changfu Liu, Tongguo Si, Xueling Yang, Weihao Zhang, Yan Xu, Yong Li

Department of Interventional Therapy, Tianjin Medical University Cancer Institute & Hospital, National Clinical Cancer Research Center, Key Laboratory of Cancer Prevention and Therapy, Tianjin, China.

Summary **Transcatheter arterial chemoembolization (TACE) is a minimally invasive procedure to restrict a tumor's blood supply, and TACE has an established role in cancer therapy. An embolic material in the form of microspheres (such as drug-eluting beads) and transarterial radioembolization is effective at treating hepatocellular carcinoma (HCC). Endovascular therapy offers promise for the treatment of tumor thrombi in the portal vein. Many researchers are anticipating an era of TACE with microspheres. This review aims to provide an overview of advances in endovascular therapy to treat primary HCC.**

Keywords: Endovascular therapy, primary hepatocellular carcinoma, transcatheter arterial chemoembolization, microsphere, drug-eluting beads, transarterial radioembolization

1. Introduction

Transcatheter arterial chemoembolization (also called transarterial chemoembolization, or TACE) is a minimally invasive procedure to restrict a tumor's blood supply. Small embolic particles coated with chemotherapeutic agents are injected selectively into an artery directly supplying a tumor (*1*). Most investigative efforts are now focused on local control, with transarterial embolization (TAE) and TACE playing an established role in therapy. TACE is used as an effective means of palliation for unresectable tumors (*2-4*). TACE was first successfully performed for liver tumors by Doyon *et al*. in 1974 (*5,6*). Over the past few years, biological materials have consistently advanced and endovascular treatment of primary hepatocellular carcinoma (HCC) has improved with advances in medical science and technology. An embolic material in the form of microspheres (such as drug-eluting beads) and transarterial radioembolization is effective at treating HCC. Endovascular therapy offers promise for the treatment of tumor thrombi in the portal vein. Many researchers are anticipating an era of TACE with microspheres instead of conventional TACE involving lipiodol mixed with chemotherapeutic agents in combination with gelfoam. This review aims to provide an overview of advances in endovascular therapy to treat primary HCC.

**Address correspondence to:*
Dr. Zhi Guo, Department of Interventional Therapy, Tianjin Medical University Cancer Institute & Hospital, Huan-Hu-Xi Road, He-Xi District, Tianjin 300060, China.
E-mail: cjr.guozhi@vip.163.com

2. Drug-eluting beads (DEBs)

DEBs are microspheres copolymerized from polyvinyl alcohol and the monomer 2-acrylamido-2-methylpropane sulfonate (AMPS). This new system of drug delivery overcomes the drawbacks of a conventional system since anti-tumor drugs adsorb to the spheres. DEBs are widely used in the West to deliver drugs. The main DEBs on the market were DC Beads and Hepasphere microspheres. The former consists of a biocompatible polymer such as polyvinyl alcohol hydrogel while the latter consists of a super-absorbent polymer. DC Beads (the brand name in Europe) were approved by the FDA under the name LC Beads (*7,8*). Hepasphere microspheres were approved by the European Union in 2004 and by the FDA in 2006.

2.1. *Chemo-drugs and loading doses*

Doxorubicin and irinotecan were approved for elution by DEBs. Doxorubicin-eluting beads can release doxorubicin for 14 days or longer after they are

injected. Theoretically, the maximum loading dose of doxorubicin can reach 45 mg. In fact, the recommended safe dose is from 25 mg to 37.5 mg per ml to assure optimum elution. The dose of doxorubicin ranges from 100 mg to 150 mg depending on the patient's bilirubin levels. Another way to determine the dose is based on tumor size. For a tumor smaller than 5 cm, a dose of 75 mg is recommended, otherwise, a dose of 150 mg is suggested (*9*). A point worth noting is that all DEBs are made of a non-biodegradable material that absorbs chemotherapy drugs. In other words, beads degrade in a controlled manner to release drugs into a tumor. This is why DEBs are referred to as sustained-release drug-loaded beads. The ideal drug-loaded beads would consist of a biodegradable material and allow independent control of drug release.

2.2. *The diameter of DEBs*

Hepasphere microspheres come in sizes (dry) of 50-100 μm, 100-150 μm, and 150-200 μm. After hydration and loading, sphere sizes are 200-400 μm, 400-600 μm, and 600-800 μm. DC Beads come in sizes of 70-100 μm, 100-300 μm, 300-500 μm, and 500-700 μm. A size of 100-300 μm is recommended for optimum embolization in a clinical setting (*3*). DC Beads (M1) in a new size of 70-150 μm have appeared in Europe. New evidence suggests that small DC Beads provide a better objective response, downstage the tumor, and produce less tumor necrosis than beads 300-500 μm in size (*9*). DEBs 40 μm in size (Tandem; CeloNova BioSciences, Newnan, GA) have been used in clinical practice (*11*). However, beads 300-500 μm in size are common in clinical research.

2.3. *Clinical efficacy of drug-loaded microspheres*

Numerous studies have examined the use of TACE with drug-loaded microspheres in comparison to conventional TACE with iodized oil as a drug carrier, but they have failed to reach a uniform conclusion. A multi-center phase II prospective randomized controlled study has confirmed that doxorubicin-loaded microspheres were more efficient and caused less tumor necrosis than conventional TACE. Prajapati *et al*. (*12*) used the RECIST, WHO, EASL, and mRECIST guidelines to assess the efficacy of drug-eluting microspheres for the treatment of HCC, and they found that the WHO and RECIST1.1 guidelines had no obvious correlation with survival but that the EASL and mRECIST guidelines could indicate patient prognosis. Of the latter 2 guidelines, mRECIST was more effective. This finding indicates that TACE with drug-loaded microspheres needs to be evaluated in a substantially different manner from conventional TACE with iodized oil as a drug carrier.

PRECISION V, a phase IV trial of 212 patients with HCC (*12*), has indicated that the use of microspheres results in a higher rate of tumor necrosis at 6 months but no significant difference in the overall survival rate (51.6% vs. 43.5%). Research has shown that drug-loaded microspheres are effective in the short term, they are better tolerated, and they significantly decrease the incidence of severe hepatotoxicity events. TACE with these microspheres can partially replace conventional TACE with iodized oil as a drug carrier.

In a multi-center study by Malagari *et al*. (*7*) with a follow-up of 5 years, 41% of 173 patients had Barcelona Clinic Liver Cancer (BCLC) stage B unresectable HCC, and the 5-year survival rate was 22.5%. Patients with Child-Pugh grade A liver disease had a survival rate of 29.4% while patients with Child-Pugh grade B liver disease had a survival rate of 12.8%, and the median survival time was 43.8 months. Huang *et al*. (*15*) performed a meta-analysis comparing TACE with drug-loaded microspheres to conventional TACE. Their analysis included 7 clinical studies and 700 patients and they found that TACE with microspheres resulted in a significantly higher tumor response rate compared to conventional TACE (OR = 1.92, 95% CI (1.34, 2.77), $p = 0.0004$) and a lower risk (0.15 (0.07, 0.24) ($p = 0.0003$). The 1-year and 2-year survival rates increased significantly, but the 6-month and 3-year survival rates were 0.72 (0.46, 1.14) ($p = 0.16$) and 0.77 (0.55, 1.06) ($p = 0.11$), so there has no significant difference in survival rates.

Ferrer Puchol *et al*. (*16*) used the RECIST criteria to compare clinical outcomes of TACE with DEBs to conventional TACE. In their study, group A served as the control group ($n = 25$) and group B underwent TACE with DEBs ($n = 47$). The RECIST criteria were used to determine patient prognosis. A CR was achieved in 5.6% of patients in group A and 13.9% of patients in group B, and group A had a mean overall survival time of 686.24 days while group B had a mean overall survival time of 765.32 days. There were no significant differences in the rate at which a CR was achieved or in the mean overall survival time. Kalva *et al*. (*17*) noted that drug-loaded microspheres can prolong overall survival especially for patients with advanced liver cancer and that overall survival was correlated with the number of times DEB-TACE was undergone.

Some studies have found that drug-loaded microspheres have no obvious advantages compared to iodized oil. Scartozzi *et al*. (*18*) studied TACE with drug-loaded microspheres and TACE with iodized oil as a drug carrier in 150 patients with HCC. Patients who underwent TACE with drug-loaded microspheres had a median survival time of 46 months while patients who underwent TACE with iodized oil as a drug carrier had a median survival time of 19 months. The difference in median survival time was statistically significant. The time to progression was 30 months for patients who underwent TACE with drug-loaded microspheres

and 16 months for patients who underwent TACE with iodized oil as a drug carrier, indicating that drug-loaded microspheres are less effective than iodized oil.

Han *et al*. (*19*) performed a meta-analysis of literature from 1979 and 2013 on drug-eluting microspheres. They analyzed included 5 reports, 3 multi-center studies, and 2 case-control studies, and they found that drug-eluting microspheres had no advantages in terms of the rate of disease control and treatment-related complications. In a statistical analysis of numerous clinical studies, Tsuji *et al*. (*20*) found that TACE with drug-loaded microspheres had efficacy on par with that of conventional TACE. Kloeckner *et al*. (*21*) noted no significant difference between conventional TACE and DEB-TACE in terms of overall survival but they noted that TACE with microspheres required significantly less time than conventional TACE. This means that drug-loaded microspheres are crucial to the treatment of advanced liver cancer.

2.4. *Complications of drug-loaded microspheres*

According to clinical reports on embolization with drug-loaded microspheres (mainly DC Beads), the incidence of complications ranges from 4.2 to 11.4%. Complications mainly include pleural effusion, gastric ulcers, esophageal variceal bleeding, liver failure, cholangitis, and abscess formation (*22,23*). Aminotransferase levels also rise but they are generally believed to return to normal after a few days. The small diameter of the microspheres significantly increased the incidence of adverse reactions to drug-loaded microspheres, which were mainly high levels of alanine transferase and alkaline phosphatase. A point worth noting is that existing clinical studies of DC Beads loaded with doxorubicin have not found those beads to be associated with symptoms of doxorubicin-related systemic toxicity.

2.5. *Trends in research and development of drug-loaded microspheres*

Drug-loaded microspheres have become a focus of clinical research into TACE. Whether drug-loaded microspheres are used in combination with radiotherapy or liver transplantation, they have become the gold standard for TACE (*22*). A study by Xing *et al*. (*24*) found that drug-loaded microspheres can sustain quality of life for patients with advanced liver cancer while conventional TACE decreases their quality of life. From a health economics perspective, Vadot *et al*. (*26*) noted that TACE with drug-loaded microspheres cannot improve overall survival but that it can reduce drug toxicity and adverse reactions to TACE during hospitalization and ultimately reduce medical expenses. Thus, Vadot *et al*. consider TACE with drug-loaded microspheres to have benefits in terms of medical economics. These studies indicate that drug-loaded microspheres are in fact on par with or better than conventional TACE in clinical settings.

Recently, some researchers have begun to develop drug-loaded microspheres that are visually apparent in imaging studies (*27,28*). A contrast agent is added to beads with a porous structure or bonds in bead materials are chemically modified. During embolization, the beads can be observed in real-time, allowing the distribution of drug-loaded microspheres to be adjusted. These new materials may usher in a new generation of embolization agents.

2.6. *Existing problems and prospects for the future*

Almost all of the clinical studies that have compared drug-loaded microspheres with iodized oil as a drug carrier have found that drug-loaded microspheres resulted in a higher rate of tumor necrosis and fewer adverse reactions in the short term. However, there is still a lack of evidence regarding the efficacy of those microspheres over the long term. Conventional TACE is still the treatment of choice in treatment guidelines for HCC. A point worth noting is that almost all of the trials on drug-loaded microspheres thus far were not balanced and had too small a sample. Randomized, controlled prospective multicenter clinical studies are needed.

The appearance of drug-loaded microspheres has changed the nature and form of TACE (*7,9*). However, there is disparity in the development and use of those microspheres due to social and economic factors in various countries. The use of DEBs in Europe and the United States differs substantially from that in developing countries. In 2014, only 31% of Asian experts on the EPOIHCC expert committee regularly performed TACE with DEBs (*29*). This suggests that experts need to focus on the characteristics of the beads and procedure as well as conditions in different countries and use of the procedure in combination with other treatments. In other words, TACE with microspheres need to be studied clinically in light of conditions in China and the efficacy of that treatment in treating HCC needs to be compared to conventional TACE with iodized oil as a drug carrier.

Multicenter, randomized, controlled clinical trials with a large sample need to be conducted in order to further evaluate the advantages of TACE with drug-loaded microspheres in comparison to conventional TACE. This is essentially the consensus view of all experts in interventional oncology.

3. Transarterial radioembolization (TARE)

In 1962, Kim, Lafave, and MacLean successfully treated a tumor by local and transarterial injection of colloidal yttrium 90 (Y-90), marking the start of local irradiation to treat tumors (*30,31*). However, limitations

in materials science meant that, the only radioactive microspheres available were made of a colloid or resin since the microspheres could easily enter the blood. Radiation can cause myelosuppression and systemic radiation can cause severe reactions such as pulmonary fibrosis, limiting the development of local radiation to treat tumors.

In 1992, Gray *et al*. (*32*) reported using Y-90 to treat liver cancer. Yan *et al*. reported details on the experimental and clinical use of Y-90 glass microspheres to treat HCC (*33*), creating a new field involving radioactive microspheres. As materials science developed, the clinical use of stable radioactive microspheres has become a focus of attention in the endovascular treatment of liver cancer over the last 10 years.

3.1. *The principles and features of treatment with radioactive microspheres*

Y-90 is a pure beta-ray emitter with a half-life of 64.2 h (2.67 days); its beta particles have a maximum energy of 2.27 MeV (average: 0.937 MeV), a maximum range of 11 mm in soft tissue, and penetrate an average of 2.5 mm (*34,35*). Because of their structure and diameter, radioactive microspheres are primarily used to provide treatment through radiation rather than embolization. This differs from conventional embolization, which uses iodized oil and gelatin sponge particles.

Two types of nuclide microspheres have been approved for use. The first type is the Y-90 glass microsphere produced by the Canadian company Nordion. Marketed under the trade name TheraSphere, these microspheres contain Y-90 and have a diameter from 20 to 300 μm. TheraSphere appeared on the market in 1999 and its use in the palliative treatment of unresectable HCC was approved by the FDA.

The second type of nuclide microsphere is the Y-90 resin microsphere produced by the Australian company Sirtex Medical. Marketed under the trade name Sir-Spheres, these microspheres are coated with a Y-90 resin and have a diameter from 20 to 60 μm. Sir-Spheres appeared in 2002 for use in combination with chemotherapy to treat metastases of colorectal cancer liver. According to existing data, 4 million TheraSphere microspheres are used to deliver a radiation dose of 2,500 bq. Forty million Sir-Spheres microspheres are used to deliver a radiation dose of 50 bq. Since more Sir-Spheres microspheres are administered per dose, they can target a large or extensive lesion, but their administration requires more careful control.

3.2. *Evaluation of the curative effect of TARE and the rounds of treatment required*

Like TACE, the RECIST criteria are being used to evaluate the efficacy of radioactive microspheres in treating HCC, and TARE is reported to have an efficacy of 25-60%. When the EASL guidelines are used, TARE is reported to have an efficacy of 80% (*36,37*). Recent studies have indicated that the mRECIST criteria may be more objective.

Although a change in lesion size may be evident 1 month after TARE, most experts tend to evaluate the efficacy of TARE based on lesion size after 3-4 months and then decide whether a second round of TARE is needed (*35*).

3.3. *Clinical efficacy of TARE*

The characteristics of radioactive microspheres are responsible for the obvious differences between TARE and TACE. A tumor takes time to shrink after radiotherapy, so the maximum tumor shrinkage is generally observed after 3 to 6 months, with a mean time of 6.6 months. Thus, there are differences in the efficacy of treatment with radioactive microspheres. The shrinkage of a tumor is associated with the dose of Y-90, and this also causes differences in efficacy. The absorption of radiation depends on the rays emitted, the mechanics of hepatic arterial blood flow, tumor vascular density, and other factors (*36*).

3.3.1. *TARE as a treatment to downstage early HCC or as a bridging therapy prior to liver transplantation*

Due to the limited source of livers, the effective control of HCC prior to liver transplantation is a key factor affecting the prognosis for the patients with early HCC who are eligible for liver transplantation. Lewandowski *et al*. (*37*) retrospective analyzed 43 patients who underwent TARE and 43 patients who underwent TACE before liver transplantation. HCC was downstaged in 58% of the patients who underwent TARE, and patients had a median survival time of 42 months. These outcomes were markedly better than those for patients who underwent TACE (HCC was downstaged in 31% of patients, and patients had a median survival time of 42 months). Similar studies have found that using Y-90 microspheres can extend the time patients can await liver transplantation compared to patients who do not receive bridging therapy. There is no significant difference in the survival rate of the two groups of patients after liver transplantation.

3.3.2. *TARE as a treatment for unresectable advanced HCC*

Numerous studies have found that interventional therapy plays an important role in the treatment of advanced HCC, and it is the most effective treatment besides surgery. Such therapy can effectively reduce the tumor load, control or decrease the incidence of complications, prolong survival, and improve quality of life. TARE is gradually being used as an emerging

interventional treatment in advanced liver cancer. Research suggests that TARE with Y-90 microspheres can treat advanced liver cancer. Morosi *et al*. (*38*) reported the results of a phase II clinical study involving TARE with Y-90 microspheres. They found that patients had a median survival time of 15 months and a median time to progression of 11 months. A study by Hilgard *et al*. (*39*) found that patients with BCLC stage B HCC who underwent TARE with Y-90 microspheres had a median survival time of 16.4 months. In a prospective study, Salem *et al*. (*40*) analyzed the use of TARE with Y-90 microspheres to treat patients with BCLC stage B liver cancer, and they noted that patients had a median survival time of 17.2 months.

3.3.3. *TARE as a rescue treatment for recurrence after liver resection*

Recurrence after radical resection of liver cancer is one of the important factors affecting the prognosis of liver cancer. Related studies have found that the rate of recurrence within five years is 50-80%. Lau *et al*. (*41*) used Y-90 microspheres to treat 51 patients who were ineligible for resection of HCC and 20 patients in whom HCC recurred after resection. They compared the two groups in terms of the curative effect of treatment and prognosis, and they found that both treatments had a similar curative effect and that none of the patients had serious adverse reactions. These results suggest that TARE can be used as a rescue treatment for recurrent live cancer.

3.3.4. *TARE as a treatment for HCC and portal vein tumor thrombosis*

Literature since 2014 has focused mostly on portal vein tumor thrombosis (PVTT) in patients with HCC, so experts in interventional radiology are eagerly anticipating the use of TARE to treat PVTT (*42-44*). A study of the use of TARE to treat PVTT found that TARE can extend the overall survival time of patients with HCC and PVTT to 10-10.4 months (*40*). Patients with grade A liver function and a tumor thrombus in a branch of the portal vein who underwent TARE had an overall survival time of 16.6 months, but patients with grade B liver function and a tumor thrombus in a branch of the portal vein who underwent TARE had an overall survival of just 4.5 months (*41,42*).

3.4. *Adverse reactions to TARE*

The adverse reactions to radioembolization are relatively mild and include fatigue, mild abdominal pain or discomfort, cachexia, elevated bilirubin, and similar flu-like symptoms, which some experts have termed post-radioembolization syndrome (PRS) (*27,45*). PRS has an incidence of 12% to 54% and resolves spontaneously within ten hours. TARE combines embolization with radiation therapy, so adverse reactions to the treatment are mild. In Europe and the United States, TARE does not require hospitalization but only 1 day of observation. Due to the abnormal distribution of radioactive microspheres, adverse reactions often manifest as radiation injuries in the form of liver damage, pneumonia, and biliary complications. Although these adverse reactions are rare, they may be serious and even require surgical intervention. Lambert *et al*. (*46*) investigated the urinary excretion of Y-90 following treatment. They used a gamma counter to estimate urinary excretion of Y-90 in urine collected for 12 h after injection. Only 0.0025% of the administered Y-90 was excreted in the urine within the first 12 h following injection of TheraSpheres. Four of the patients in that study experienced clinically severe adverse events. One patient developed grade 4 hyperbilirubinemia and ascites and received a liver transplant. Another patient died 58 days after treatment due to spontaneous bacterial peritonitis and subsequent liver failure. Two patients presented with a subacute GI bleeding. Strigari (*47*) reported toxicity related to treatment of HCC with Y-90 SIR spheres. With a median liver dose of 36 Gy (range, 6-78 Gy), liver toxicity that was ≥ grade 2 (G2) was observed in 32% of patients (23/73), liver toxicity that was ≥ grade 3 (G3) was observed in 21% (15/73), and liver toxicity that was ≥ grade 4 (G4) was observed in 11% (8/73). This suggests that TARE still has certain risks. Preoperative assessment needs to be enhanced and modalities involving a multi-disciplinary team (MDT) need to be explored to ensure the safety of treatment.

3.5. *Clinical studies of radioactive microspheres and TARE*

P-32 and Y-90 microspheres are commonly used to perform local radiation and embolization. Radioactive microspheres containing ^{32}p are currently used in China. An emitter of β-rays, ^{32}p has a half-life of 14.28 ± 0.02 days. β particles penetrate an average of 3.2 mm and a maximum of 8 mm, though these figures vary depending on the tissue. The latest nucleotides to be studied are ^{166}Ho and ^{188}Re, both of which emit γ rays. Both have therapeutic value in nuclear imaging to facilitate follow-up after treatment. In the future, these nucleotides may display practical value in clinical settings.

TARE is the latest technique for endovascular treatment of liver cancer. TARE is often combined with drug therapy or other treatments.

PREMIERE (NCT00956930), a large randomized study, is currently underway in the United States (*48*). This study is comparing the value of radioactive microspheres to that of RFA, TACE, or a combination therapy to treat unresectable HCC. The SIRveNIB trial

(NCT01135056) in the Asian Pacific region is directly comparing radioactive microspheres and sorafenib. The SORAMIC trial (NCT01126645) in Europe is evaluating radioactive microspheres in combination with sorafenib and sorafenib alone for treatment of advanced HCC, but the results have yet to be published.

3.6. *Problems with TARE and areas for research*

Overall, studies of radioactive microspheres for treatment of HCC have been retrospective and non-randomized, providing evidence that is grade II-2 or II-3. No studies have provided quality evidence as to whether TARE or TACE is better. In a retrospective study with a large sample, 104 patients with HCC underwent TACE with radioactive microspheres and 100 underwent TACE alone. Patients with Child-Pugh A grade A liver disease who underwent TACE with radioactive microspheres had a median survival time of 22.1 months while patients who underwent TACE alone had a median survival time of 15.6 months (p = 0.24). Patients with Child-Pugh grade B liver disease who underwent TACE with radioactive microspheres had a median survival time of 13.5 months while patients who underwent TACE alone had a median survival time of 12.8 months (p = 0.64). Thus, TARE is comparable to TACE.

This is actually a disadvantage of evaluating TARE. Since there is a lack of quality evidence, TARE does not appear in the guidelines of the American Society of Clinical Oncology (ASCO). However, the European Society of Medical Oncology and the National Comprehensive Cancer Network (NCCN) recommend TARE as complementary treatment for liver metastasis in patients with HCC. Thus, randomized, controlled, multi-center studies need to be performed to study TARE further.

Currently, only two companies offer radioactive microspheres that are approved for clinical use. The cost of treatment per patient is about 50,000 US dollars, or about 300,000 RMB. This imposes a heavy burden on the patient or insurance company in developed European countries despite the fact that there medical insurance systems are better. Therefore, how to benefit more patients in Asian countries such as China, how to optimize treatment, its indications, local production of radioactive microspheres, and the health economics of those treatments all need to be studied further.

4. Interventional therapy for hepatic cancer and PVTT

PVTT results in a poor prognosis for patients with HCC and often indicates advanced liver disease with portal hypertension, acute upper digestive tract bleeding, refractory ascites, and even liver failure. The median survival time without any intervention is about 2-4 months since PVTT can lead to the wide dissemination of tumors throughout the liver and cause a marked deterioration in hepatic function (*49*). Based on the anatomical features of the portal vein in the liver and the way in which a tumor thrombus develops in HCC, PVTT can be classified into four types: Type I, with a tumor thrombus located in or above the segmental branches (secondary branches) of the portal vein; Type II, with a tumor thrombus in the right or left branch of the portal vein (primary branches); Type III, with a thrombus in the main trunk of the portal vein; and Type IV, with a tumor thrombus in the superior mesenteric vein or inferior vena cava. The classification system helps to evaluate the progression of disease, to guide therapy selection, and to improve the survival rate of patients with HCC and PVTT (*50*).

TACE has been the preferred palliative treatment for patients with HCC and type I-II PVTT (*51*), though other treatments (*52-54*) include transhepatic portal vein chemoembolization (PVCE), percutaneous ethanol injection (PEI), microwave coagulation therapy (MCT), radiofrequency ablation (RFA), and 1aser ablation (LA). In addition, radioactive seeds (iodine-125) can be directly implanted into a localized tumor thrombus to improve the local control rate (*55,56*) .

For patients with HCC and type III-IV PVTT, a portal vein stent (PVS) should be placed across stenosis caused by a tumor thrombus in order to reduce portal vein pressure, to alleviate esophageal varices and ascites, to improve portal vein blood supply to normal liver tissue, to prevent liver failure and hepatic encephalopathy, and to reduce the risk of upper gastrointestinal bleeding. The duration of stent placement depends on the control of tumor, and other treatments to eliminate the tumor, such as radiotherapy, brachytherapy, and TACE, should be considered. In a study of 27 patients with HCC and PVTT who underwent PVS and TACE, the median duration of stent patency was 6 months and the survival rates at 3, 6, and 12 months were 51.85%, 29.63%, and 18.52%, respectively (*57*). Recently, Luo *et al*. (*58*) reported on 32 patients with HCC and PVTT who were treated with a stent. 125I seeds were placed in the obstructed main portal vein and patients then underwent TACE. The 90-day, 180-day, and 360-day cumulative survival rates were 96.4%, 67.4%, and 39.3%, respectively, and the cumulative stent patency rates were 96.7%, 83.4%, and 83.4%, respectively.

Thus far, primary HCC and PVTT has been a challenging condition to treat with a poor prognosis. Combinations of multiple interventional techniques, such as RFA + TACE + PVS and TACE + PVS + 125I seeds are being explored, but the long-term efficacy of these combination needs to be studied further. Moreover, the combination of interventional therapy with other treatments such as radiotherapy, molecularly targeted therapy (such as sorafenib), immunotherapy, and other organic combinations also warrant further study (*59*).

5. Interventional treatment of HCC and portal hypertension

About 80% of patients with hepatocellular carcinoma have a history of liver cirrhosis along with portal hypertension. Of these, about 15% to 28% die due to bleeding from esophageal or gastric varices, accounting for the second cause of mortality in HCC. Interventional treatment of portal hypertension seeks to relieve portal pressure and reduce the rate of bleeding. Common treatments are described below.

5.1. *Interventional embolization of varices*

Esophageal and gastric varices are embolized in different ways in order to prevent or stop bleeding. Percutaneous transhepatic variceal embolization (PTVE) achieves the embolization of gastroesophageal varices via percutaneous transhepatic puncture of the intrahepatic branch of the portal vein. PTVE stops active bleeding with an efficacy of 82.2% to 100%, and a better level of liver function results in greater efficacy (*60*). Since PTVE cannot reduce portal pressure, it only reduces the mortality rate of patients with bleeding and it cannot guarantee long-term efficacy. For patients with PVTT or tumor at the puncture site, percutaneous transsplenic variceal embolization (PTSVE) represents a treatment alternative. This procedure is relatively difficult has more complications because of the fragility of the spleen. At present, PTSVE is the only alternative to PTVE. Balloon-occluded retrograde transvenous obliteration (BRTO) seeks to achieve embolization of gastric varices through the left renal vein (or a left gastric vein-inferior vena cava shunt). This procedure can be used in patients with gastric varices and refractory hepatic encephalopathy in conjunction with a left gastric vein-left renal vein shunt or a left gastric vein-inferior vena cava shunt (*61*).

5.2. *Interventional creation of a shunt*

A shunt is created between the portal vein and the inferior vena cava in order to decrease pressure in the portal vein. Transjugular intrahepatic portosystemic shunt (TIPS) has emerged over the past 20 years as an effective and minimally invasive way to treat portal hypertension and its associated complications. There is a dearth of literature on the use of percutaneous portosystemic shunting in patients with hepatic malignancies. Generally, a patient undergoes TACE to shrink the tumor and a shunt is placed such that it traverses the malignancy. According to the MD Anderson Cancer Center TIPS did not increase the risk of bleeding or tumor metastasis even though the shunt traversed the malignancy. However, TIPS had a high incidence of early stenosis or occlusion of the stent that may be due to damage from tumor tissue. A covered stent designed specifically for TIPS would reduce the rate of stenosis, extend long-term patency, and reduce the risk of tumor seeding within the liver, especially when the shunt traverses the malignancy, but the long-term efficacy of this treatment needs to be evaluated further. There is some dispute about whether patients with PVTT should be eligible for TIPS (*62,63*). A direct intrahepatic portacaval shunt (DIPS) is a modified form of TIPS that seeks to create an intrahepatic shunt between the inferior vena cava behind the liver and the portal vein. This technique was initially conceived to increase the duration of shunt patency and to extend the spectrum of patients with portal hypertension who would be eligible for endovascular portocaval shunting. DIPS is a reasonable choice for patients with hepatic veins that are not suitable for TIPS or patients with an occluded shunt after TIPS (*64*).

5.3 *Partial splenic arterial embolization*

Portal hypertension in cirrhosis commonly leads to splenomegaly and is frequently associated with decreased hematologic indices, including thrombocytopenia and anemia. Partial splenic arterial embolization (PSE) is an effective procedure that increases circulating platelet and leukocyte levels and that alleviates hepatic encephalopathy. Some authors set their initial target at embolization of 50-70% of the splenic blood volume. Others, however, embrace a more conservative approach and will target 30-40% of the spleen with the expectations of repeating the embolization with a higher target area (up to 70%) if clinical symptoms do not respond to initial treatment (*65*). However, patients with HCC may have a different degree of symptom improvement after PSE from non-cancer patients since patients with HCC have diminished liver function. The specific causes of and factors influencing these differences need to be studied further.

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