REVIEW

Interventional treatment for unresectable hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the sixth most common cancer and third leading cause of cancer-related death in the world. The Barcelona clinic liver cancer classification is the current standard classification system for the clinical management of patients with HCC and suggests that patients with intermediate-stage HCC benefit from transcatheter arterial chemoembolization (TACE). Interventional treatments such as TACE, balloon-occluded TACE, drug-eluting bead embolization, radioembolization, and combined therapies including TACE and radiofrequency ablation, continue to evolve, resulting in improved patient prognosis. However, patients with advanced-stage HCC typically receive only chemotherapy with sorafenib, a multi-kinase inhibitor, or palliative and conservative therapy. Most patients receive palliative or conservative therapy only, and approximately 50% of patients with HCC are candidates for systemic therapy. However, these patients require therapy that is more effective than sorafenib or conservative treatment. Several researchers try to perform more effective therapies, such as combined therapies (TACE with radiotherapy and sorafenib with TACE), modified TACE for HCC with arterioportal or arteriohepatic vein shunts, TACE based on hepatic hemodynamics, and isolated hepatic perfusion. This review summarizes the published data and data on important ongoing studies concerning interventional treatments for unresectable HCC and discusses the technical improvements in these interventions, particularly for advanced-stage HCC.

Core tip: Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide. Interventional treatments for intermediate-stage HCC patients such as transcatheter arterial chemoembolization (TACE), drug-eluting bead embolization, and radioembolization, continue to evolve, improving prognosis. However, advanced-stage HCC is typically treated only with sorafenib, with only a modest improvement in overall survival. More effective therapies such as combined TACE and radiotherapy, TACE with special techniques, and isolated hepatic perfusion have been studied extensively. This review summarizes data on published and important ongoing studies concerning interventional treatments for unresectable HCC and discusses technical improvements in these interventions, particularly for advanced-stage HCC.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related deaths in the world[1]. The Barcelona clinic liver cancer (BCLC) classification is the current standard classification system for clinical management of patients with HCC (Table 1)[2] and suggests that patients presenting with very early-stage and early-stage disease (20%-30% of HCC patients) are suitable for curative treatments, such as resection, liver transplantation, local ablation with percutaneous ethanol injection, or radiofrequency ablation (RFA)[3,4]. Typically, patients with intermediate-stage disease show a survival benefit with transarterial chemoembolization (TACE). Patients with advanced-stage HCC with macroscopic vascular invasion (portal vein invasion), extrahepatic spread (lymph nodes and metastases), or cancer-related symptoms (performance status 1-2) may have a modest improvement in prognosis from first-line treatment with sorafenib, a molecularly targeted drug[5], while patients with terminal-stage disease (10%-20% of HCC patients) receive only symptomatic treatment.

TACE is the current standard of care for patients with intermediate-stage disease and has been reported to prolong survival and allow control of HCC symptoms[6-8]. Patients with advanced-stage HCC receive first-line therapy with sorafenib, according to the BCLC treatment algorithm, and an increase in overall survival and time to progression has been shown in 2 major trials[5,9]. However, the median overall survivals in patients treated with sorafenib for advanced-stage disease were 10.7 and 6.5 mo in the SHARP and Asia-Pacific trials, respectively, and a better treatment modality is needed.

The aims of this review are to summarize the published data and important ongoing studies concerning interventional managements for HCC and to discuss the technical improvements in TACE, particularly for advanced-stage HCC.

UNRESECTABLE HCC

Intermediate-stage HCC

Patients presenting with Child-Pugh class A and B liver function and large or multinodular HCC without cancer-related symptoms, macrovascular invasion, or extrahepatic metastasis are diagnosed with intermediate-stage HCC. Transarterial intervention, particularly TACE, is the recommended BCLC classification treatment and is endorsed by the European Association for the Study of the Liver[10] and the American Association for the Study of Liver Diseases[11] guidelines.

TACE: The liver is a unique organ with a dual blood supply provided by the portal vein and hepatic artery. The portal vein delivers 80% of the blood supply to healthy liver tissue, while, the hepatic artery delivers 99% of the blood supply to hepatic tumors. Based on this observation, TACE for HCC is appropriate for patients for whom surgical or percutaneous ablative treatment is contraindicated. TACE involves the injection of anticancer drugs (doxorubicin, epirubicin, cisplatin or miriplatin) and iodized oil (Lipiodol Ultra Fluide, Laboratoires Guerber, Aulnay-sous-Bois, France) into the hepatic artery, followed by the administration of embolic agents[12,13]. The antitumor effect of TACE is greater than that of either anticancer drugs[14] or iodized oil[15,16] alone. Prognostic factors found to be associated with that a reduction in serum alpha fetoprotein levels after the intervention[17], the number of TACE procedures[18,19], a low model for end-stage liver disease score[20], the absence of diffuse disease[21,22], and small tumor size[23] have been shown to correlate with better survival.

Iodized oil is used as an embolic agent and carrier of anticancer drugs in TACE. Mixtures of anticancer drugs and iodized oil are classified as either emulsions (oil with saline and drugs) or suspensions (drugs in oil)[24,25]. Comparative studies of suspensions versus emulsions in TACE, with cisplatin powder[26] or epirubicin[27] as anticancer agents for the treatment of rabbit VX2 liver tumors, demonstrated that suspensions were superior to emulsions with regard to their antitumor effects. Several factors are thought to explain these findings. In an emulsion, most of the powdered drug is contained in the unstable aqueous phase[13,28], which undergoes rapid dilution in the blood, elimination from the hepatic tissue, and excretion by the kidneys. In a suspension, the powder is directly mixed in the oil phase and distributed in a similar fashion to iodized oil alone through the portal venules and sinusoids over a 24-h period[29,30]. As a result, suspensions show a longer anticancer drug release time at the tumor border and higher continuous drug concentrations. This longer tissue/drug activity period associated with the use of suspensions produces superior antitumor effects, as evaluated by changes to the growth ratio and results of histopathological investigations[24,25,31,32]. However, since most anticancer drugs are hydrophilic, it is hard to make stable drug suspensions in oil. Additionally, tumor uptake of suspensions is poor, most likely due to their high viscosity[33]. As

Table 1 Barcelona-clinic liver cancer classification in patients diagnosed with hepatocellular carcinoma

Stage	Description
Very early	PS 0, Child-Pugh A, single HCC < 2 cm
Early	PS 0, Child-Pugh A-B, single HCC or 3 nodules < 3 cm
Intermediate	PS 0, Child-Pugh A-B, multinodular HCC
Advanced	PS 1-2, Child-Pugh A-B, portal neoplastic invasion, nodal metastases, distant metastases
End-stage	PS > 2, Child-Pugh C

This classification is in accordance with that outlined in reference [2]. PS: Performance status; HCC: Hepatocellular carcinoma.

the viscosity of iodized oil has a negative correlation with temperature exceeding 50 mPa.s at 20° but decreasing to 22 mPa.s and 12 mPa.s, at 40° and 60°, respectively[34], we designed a syringe warmer to maintain suspensions at a high temperature. We have obtained significant antitumor effects without major adverse events when treating HCC patients with warmed drug suspensions since January of 2011 (article submitted for publication), and a prospective, comparative study of TACE with warmed suspension at 53° is currently under way.

Drug-eluting beads (DEB), which can be loaded with doxorubicin, represent a novel drug delivery system for chemoembolization. A slow and sustained release of drug is predicted after intra-arterial delivery of DEB, and several studies have reported this method to be safe and efficacious in the treatment of HCC[35,36]. DEB-TACE is proposed to have a better pharmacokinetic profile than conventional Lipiodol-TACE and result in decreased systemic adverse effects[37]. However, a recent study reported that liver/biliary injury was strongly associated with DEB-TACE irrespectively of the type of tumor and underlying liver disease. At least 1 liver/biliary injury was observed after 30.4%-35.7% of DEB-TACE sessions, whereas this event occurred after only 4.2%-7.2% of conventional Lipiodol-TACE ($P < 0.001$)[38]. Despite encouraging pharmacological and antitumor advantages, a recent large, phase Ⅱ randomized trial of HCC failed to demonstrate a better tumor response rate to DEB-TACE compared with conventional Lipiodol-TACE[39]. Further randomized, controlled, multicenter trials are necessary to explore the differences in adverse events and to assess the effects of DEB-TACE on short- and long-term outcomes.

Radioembolization involves the catheter-based delivery of yttrium-90 (^{90}Y)-embedded resin (SIR-Spheres®; Sirtex Medical, Sidney, New South Wales, Australia) or glass (TheraSphere®, MDS Nordion, Toronto, Ontario, Canada) microspheres into the hepatic artery[40] to distribute radioisotopes to the tumor. ^{90}Y is a pure beta-emitter, which generates high-energy radiation with a short half-life (2.67 d) and tissue penetration (mean 2.5 mm, maximum 11 mm)[41]. Once administered, these microspheres selectively emit high-energy, low-penetration radiation to the tumor, resulting in necrosis. Although there is currently a lack of sufficient prospective data comparing treatment efficacy in terms of response or survival between radioembolization and TACE for intermediate-stage HCC, a retrospective study[42] comparing the outcomes between radioembolization ($n = 38$) and TACE ($n = 35$) determined no significant difference in survival (median 8.0 mo *vs* 10.3 mo, $P = 0.33$). However, postembolization syndrome was significantly more severe in patients who underwent TACE[42]. Further evaluation of radioembolization, including direct comparisons with TACE, is needed.

Radioembolization may cause injury to the hepatic tissue and result in fibrotic changes and tissue atrophy[43,44]. The loss of liver function can be compensated for by non-treated liver segments, which tend to undergo hypertrophy after radioembolization (the atrophy-hypertrophy complex)[45]. A few studies have described the hepatic volume changes of treated and non-treated liver segments after radioembolization and report a 40%-55% loss in volume in treated segments and a 30%-40% increase in volume in non-treated segments[46,47].

Combination TACE and RFA: RFA is a curative treatment for very early- and early-stage HCC but is limited in the control of large tumors. The effectiveness of RFA is dependent on thermal necrosis, and blood flow through the tumor promotes heat loss and prevents proper heating. TACE can be performed strategically before RFA treatment to reduce this heat sink effect and increase the ablation volume of the tumor. A recently published, randomized study[48] showed that, when patients with tumors > 3 cm were randomized to receive either TACE, RFA, or TACE-RFA, the combination of TACE-RFA produced a superior median survival (TACE-RFA: 37 mo, TACE: 24 mo, and RFA: 22 mo) and rate of objective tumor response (TACE-RFA: 54%, TACE: 35%, and RFA: 36%). The results of TACE-RFA support the combining of locoregional modalities to improve the outcomes of patients with unresectable HCCs.

Modified TACE to obtain complete necrosis of the tumor: Histopathological investigations of HCCs resected after TACE have shown that the most viable tissue is located at the periphery of the tumor[49]. The efficacy of TACE is limited by the dual blood supply of liver tumors, which makes it impossible to deliver anticancer agents to the entire tumor area or achieve sufficient tumor ischemia without irreversible damage to surrounding normal liver parenchyma. Some studies[50,51] have reported superselective TACE to be useful for the treatment of small HCCs because it can embolize both the tumor and surrounding normal parenchyma. For large liver tumors, however, the therapeutic options are limited to techniques that result in complete necrosis of the tumor.

To obtain complete necrosis of a HCC, including the periphery, several reports[52-54] have investigated the hemodynamic changes occurring in the liver and tumors during hepatic vein balloon occlusion using computed tomography during hepatic arteriography (CTHA) and arterial portography, demonstrated that the occluded area is supplied with arterial blood alone[53,54], and suggested that sufficient embolization may be obtained during TACE with arterial control alone. Since balloon occlusion of the segmental hepatic vein eliminates the dual blood supply, leaving only the arterial supply, TACE performed using this technique can sufficiently embolize both the tumor and the surrounding liver parenchyma. We have performed TACE under balloon occlusion of the hepatic vein for more than 70 patients with advanced HCC, but only 30% of the patients benefited from the procedure due to the complex veno-venous communications in the liver[34,53]. The hepatic veins assume the role of draining
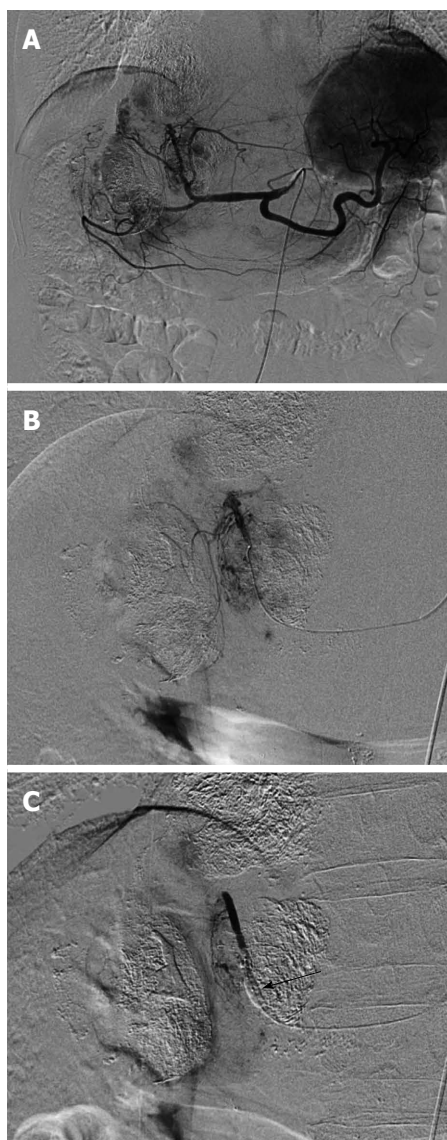
Figure 1 Selective arteriography with and without balloon-occluded feeding artery in a 72 year-old man with multiple hepatocellular carcinomas. A: Celiac arteriography revealed multiple hepatocellular carcinomas (HCCs) in the liver; B: Opacified HCCs were shown by medial segmental arteriography without balloon-occluded feeding artery; C: In contrast, the arteriography with balloon occlusion showed faint opacification of HCCs and nontumoral liver parenchyma was opacified. Arrow indicated an inflated microballoon.

veins despite single hepatic vein occlusion[53,55]; therefore, sufficient embolization of large liver tumors using the hepatic vein balloon occlusion technique is difficult.

When portal venous blood flow is decreased or stopped due to tumor thrombus, thromboembolus, or compression of the portal vein, the affected liver parenchyma appears as a hyperattenuated area with straight borders on contrast CT[56-62]. This appearance is similar to that seen with hepatic vein occlusion. One study[63] investigated the hepatic hemodynamic changes under acute balloon occlusion of the portal vein using single-level dynamic CTHA and reported several phenomena. First, a demarcated, hyperattenuated area of the liver parenchyma was noted in the distribution of the occluded portal vein branch, which was significantly higher than that of

the non-occluded area ($P < 0.01$). Second, the balloon-occluded portal branch enhancement appeared to result from arterioportal communications. These findings suggest that, when portal venous flow stoppage occurs, only the hepatic artery supplies the corresponding area and hepatic arterial blood flow is increased. This phenomenon is known as the hepatic artery buffer response. The observed variations in blood flow are due to the degree of adenosine clearance, to which the hepatic artery is very sensitive, as adenosine is a potent vasodilator of the hepatic artery[64-66]. Finally, there is little anatomical variation in portal veins or porto-portal venous anastomosis. Therefore, sufficient embolization may occur, even in large liver tumors, by TACE under the corresponding portal vein branch occlusion (TACE-PVO). We began using TACE-PVO for large HCCs 6 years ago and have seen promising antitumor effects, which will be reported in the near future.

In 1981, Yamada *et al*[67] first reported a balloon-occluded arterial infusion therapy for liver tumors. In the 1990s, compulsory, superselective, balloon-occluded arterial embolization using a 3-French microballoon catheter[68] was introduced for hypovascular liver tumors. The selective balloon-occluded TACE (B-TACE) method is currently a useful treatment for HCC because of preventing proximal migration and leakage of embolization materials[69]. This technique leads to dense lipiodol emulsion accumulation in the HCC nodule[69]; however, the effectiveness of this therapy for HCC is controversial.

CT arteriography under balloon occlusion of the sub- or segmental hepatic artery demonstrates a much higher attenuation in the corresponding liver parenchyma than in HCC tumors[70]. This phenomenon suggests that B-TACE leads to dense lipiodol emulsion accumulation in nontumorous liver parenchyma and not in HCC nodules. Indeed, arteriography *via* the balloon-occluded hepatic artery shows dense opacification in the liver parenchyma and faint opacification in the HCC, while arteriography *via* the non-occluded hepatic artery shows dense opacification in the HCC (Figure 1). Therefore, the effectiveness of B-TACE is controversial. To remedy this, we developed a two-step B-TACE method for liver tumor (Figure 2). First, tumors are sufficiently embolized by TACE, followed by the inflation of a microballoon catheter to occlude the feeding artery in the second step. B-TACE is then performed for full embolization of the peritumoral liver parenchyma. Following this two-step B-TACE procedure, CT images showed dense lipiodol accumulation in the HCC. The two-step B-TACE method has a great advantage for therapy in patients with liver dysfunction because it prevents proximal migration and leakage of embolization materials, the embolized area can be determined, and injury to the liver parenchyma can be prevented. A comparative study of the two-step B-TACE method with conventional TACE obtained promising results for two-step B-TACE.

Advanced-stage HCC
HCC patients with Child-Pugh class A and B liver func-
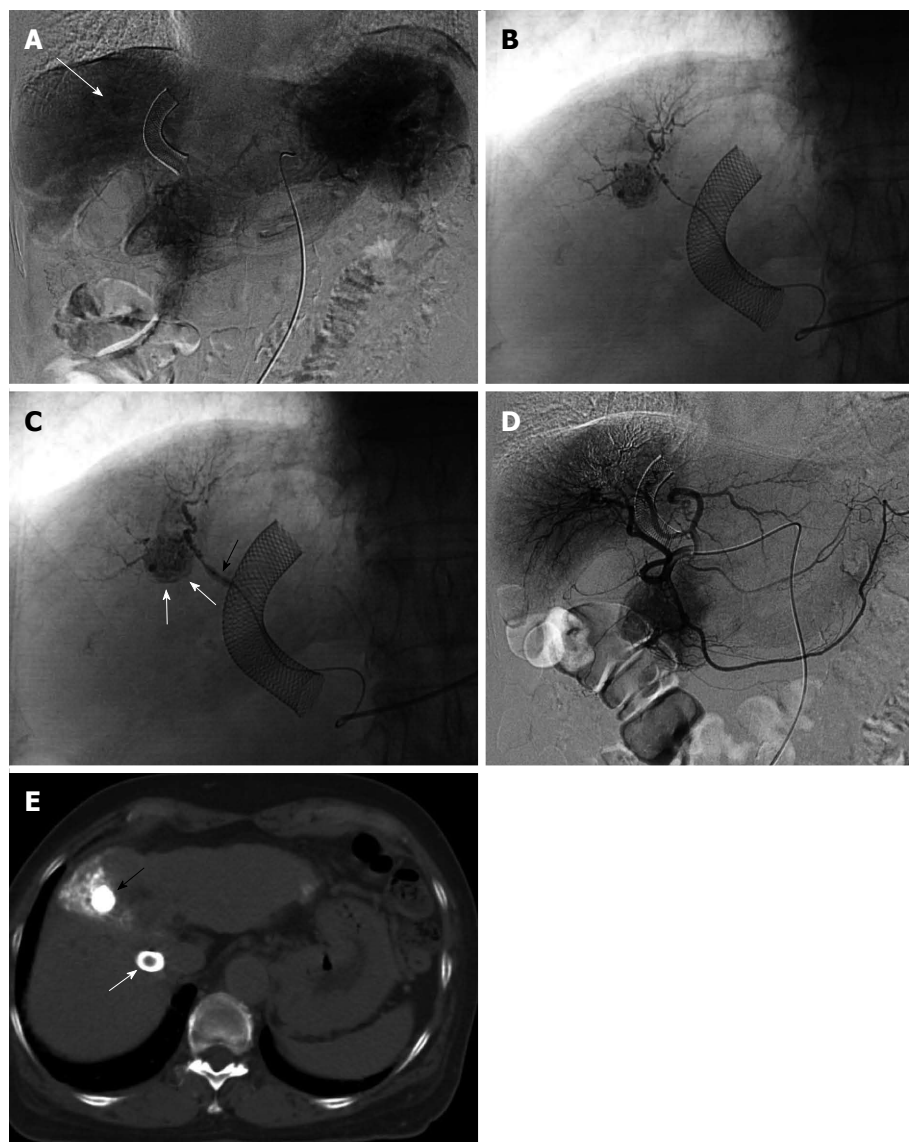
Figure 2 Two-step balloon-occluded transarterial chemoembolization. A 76-year old woman characterized as Child-Pugh class C underwent transjugular intrahepatic portosystemic shunt (TIPS) for massive ascites before several transarterial chemoembolization (TACE) sessions. Celiac arteriography in the venous phase (A) showed a small hepatocellular carcinoma (HCC) (arrow). A microballoon catheter was advanced into the tumor feeding artery. Then, two-step balloon-TACE (B-TACE) was performed. First, tumors were sufficiently embolized by TACE without balloon occlusion of the tumor feeding artery (B); Second, a microballoon catheter was inflated to occlude the feeding artery (C, black arrow), and B-TACE was performed to fully embolize the peritumoral liver parenchyma (C, white arrows). Common hepatic arteriography showed no proximal migration or leakage of embolization materials (D). Following the two-step B-TACE procedure, computed tomography showed dense lipiodol accumulation in the HCC (E, black arrow). There was no evidence of proximal migration or leakage of embolization materials. White arrows indicated a stent for TIPS.

tion who present with macroscopic vascular invasion, extrahepatic spread, or cancer-related symptoms (performance status 1-2) are diagnosed with advanced-stage HCC. First-line treatment with sorafenib is recommended for this stage of HCC according to the BCLC treatment algorithm based on the results of sorafenib therapy in randomized trials in Europe and Asia[5,9]. However, overall survival was only modestly improved by 2.8 mo[5]. Patients with advanced-stage HCC require more effective therapy than sorafenib or conservative treatment, and this is currently under consideration.

HCC with vascular invasion: In general, HCCs with portal venous tumor thrombus (PVTT) and significant

arterioportal or arteriohepatic vein shunts are contraindicated for TACE. Conventional TACE did not provide a survival benefit for advanced-stage patients with PVTT[71], potentially due to hepatic infarction and acute liver failure. Portal vein invasion is a major prognostic factor for reduced survival in patients with advanced HCC. Advanced HCC with PVTT in the major branches of the portal vein, particularly the main portal vein, has an extremely poor prognosis (3-4 mo without treatment[72]) because portal vein invasion may cause liver failure, massive esophageal variceal bleeding, or extensive tumor spreading throughout the liver[73]. The results of sorafenib therapy in randomized trials in Europe and Asia[5,9] did not provide a substantial survival improve-

ment in patients with PVTT. As the incidence of patients with HCC and PVTT was reported to be between 12.5% and 39.7% at the time of diagnosis using recent imaging techniques[74], effective therapies are needed for advanced HCC patients with vascular invasion.

Combined TACE and radiotherapy (TACE + RT) consists of TACE followed by radiation therapy to the vascular invasions and has shown an overall survival benefit in patients with PVTT[75-77]. Shirai *et al*[75] reported that HCC patients (*n* = 19) with PVTT ≥ 8 cm in the first branch or main trunk that received TACE + RT had 1- and 2-year survival rates of 47.4% and 23.7%, respectively. Although prospective data comparing the efficacy of TACE + RT and sorafenib therapy in terms of response or survival in advanced-stage HCC with PVTT are not sufficient, a retrospective study[78] comparing the outcomes of TACE + RT (*n* = 27) and sorafenib therapy (*n* = 27) in a propensity score-matched cohort determined that the TACE + RT group had prolonged overall survival compared to the sorafenib group (6.7 mo *vs* 3.1 mo, *P* < 0.001). To determine the efficacy of TACE + RT compared to sorafenib in locally advanced HCC, a randomized controlled multicenter trial is necessary.

HCC has a tendency to spread to the portal vein and, to a lesser extent, the hepatic vein[79], which allows the development of arteriovenous shunts. These shunts represent the main impediment to successful TACE because anticancer drugs or mixtures of iodized oil and anticancer drugs easily pass through them[80]. Conventional TACE is therefore not effective for HCC patients with hepatic arteriovenous shunts and may even be harmful, due to the possibility of pulmonary embolism[81-83]. These patients require an effective, low-risk alternative treatment option.

RFA may be a useful treatment for HCCs < 3 cm in diameter; however, most HCCs with intratumoral arteriohepatic vein shunts are large, and RFA cannot be performed. To overcome this limitation, we performed TACE of the HCC feeding arteries with balloon occlusion of the corresponding draining hepatic vein, which was monitored by angiography and CT[34]. If the target HCC is located in the lateral segment of the liver, we recommend TACE with balloon occlusion of the left hepatic vein. If the target HCC is located in the right or middle lobe of the liver, particularly the upper portion, we recommend TACE with balloon occlusion of 2 hepatic veins, typically the right and middle hepatic veins[55]. TACE with balloon occlusion of the corresponding hepatic vein results in both significant tumor growth control and elimination of the intratumoral shunts[34]. After this modified procedure, conventional TACE can be performed for the treatment of residual HCC.

As noted above, HCC is frequently associated with arteriovenous shunts, which typically present as arterioportal shunts. Kojiro[84] analyzed 106 resected HCCs < 2 cm in diameter and found that nodular-type HCC was associated with microscopic portal invasion in up to 25% of cases. Although the presence of small arterioportal shunts does not necessarily preclude TACE therapy for

unresectable HCC, larger arterioportal shunts caused by tumor invasion interfere with TACE because anticancer drugs, either alone or mixed with iodized oil, easily pass through the shunts[81,82]. Conventional TACE causes extensive embolization of the portal vein and can induce extensive ischemia of nontumorous liver parenchyma[80]. The presence of significant arterioportal shunts can also lead to liver dysfunction and portal hypertension, resulting in potentially life-threatening conditions such as rupture of the gastroesophageal varices[85-88], refractory ascites, or hepatic encephalopathy.

Several studies have treated significant arterioportal shunts by embolization of the hepatic arteries with materials such as gelatin sponges or coils, and these approaches have yielded good short-term results[89,90]. However, they do not eradicate the HCC and contribute little to patient survival[89,90]. We attempted to overcome this complication by performing TACE of tumor-feeding arteries with occlusion of the corresponding portal vein[91]. The intrahepatic portal branch was punctured under ultrasonographic guidance using an 18-gauge percutaneous transhepatic cholangiography needle. For TACE-PVO, a 5- or 8- French balloon catheter was advanced into the portal vein branch identified by direct portography and hepatic arteriography to contain the arterioportal shunt. The balloon catheter was inflated, and a mixture of lipiodol (up to 15 mL) and anticancer agents, as an emulsion or suspension, was injected *via* the target feeder artery until reflux into the hepatic artery was confirmed. Particles of gelatin sponge were immediately injected into the feeder artery until the target hepatic artery was occluded. If the target HCC concurrently invades the right and left branches of the portal vein, we recommend TACE with balloon occlusion of the 2 portal vein branches (Figure 3).

The effectiveness of TACE-PVO for arterioportal shunts was ascribed to balloon occlusion of the corresponding portal veins, resulting in adequate embolization of the entire tumor, including the portions involving arterioportal shunts. Consequently, TACE-PVO may prevent the development of collateral anastomoses to arterioportal shunts.

We performed a comparative, prospective, but not randomized study of standard transarterial embolization (TAE) or TACE versus TACE-PVO for HCC with significant arterioportal shunts[91]. Subjects differed fundamentally by patients' choice of treatment. We found that TACE-PVO was significantly better (*P* = 0.009) than standard TAE for arterioportal shunt treatment, and subsequent angiographic findings suggested the superiority of TACE-PVO (*P* = 0.028). Antitumor response (*P* = 0.002) and patient outcome (*P* = 0.032) were significantly better in the TACE-PVO group than in the standard treatment group. Furuse *et al*[90] reported that HCC patients with significant arterioportal shunts due to PVTT who underwent embolization had 1- and 2-year survival rates of 12% and 0%, respectively. In our study, 1- and 2-year survival rates in the standard treatment group were 28.6% and 0%, respectively, similar to that observed by
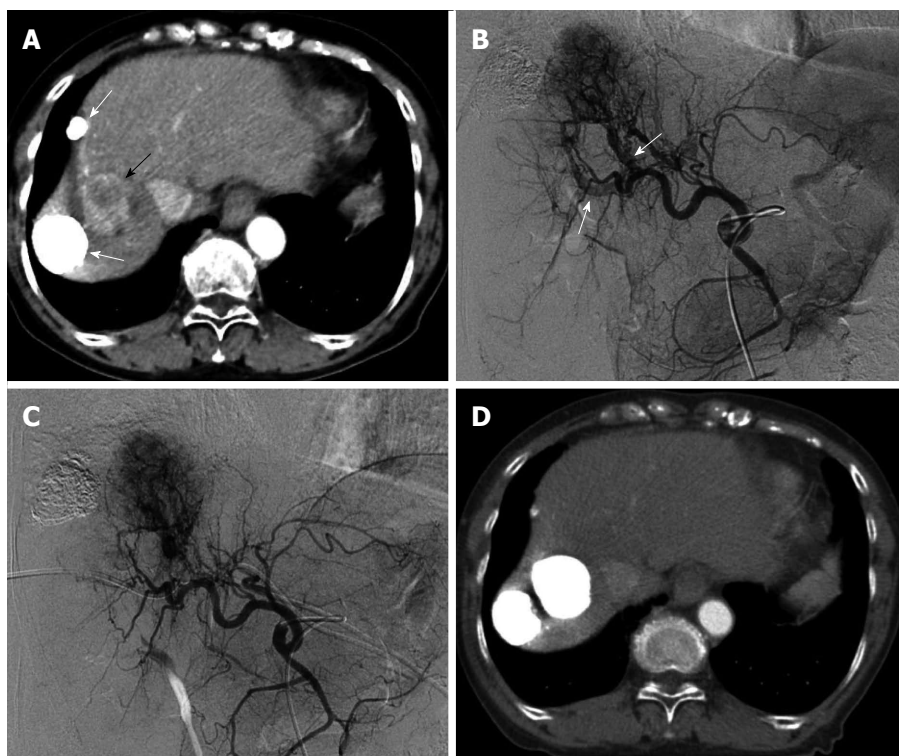
Figure 3 Multiple hepatocellular carcinomas with significant arterioportal shunts in a 71-year-old woman. Enhanced computed tomography (CT) imaging revealed viable hepatocellular carcinomas (HCCs) (A, black arrow) with lipiodol deposit HCCs (A, white arrows). Common hepatic arteriography in the arterial phase (B) demonstrated HCC with significant arterioportal shunts (B, arrows), consisting of P8 and P4. Common hepatic arteriography under balloon occlusion of the portal vein branches of P8 and P4 showed an opacified tumor with non-visualized arterioportal shunts (C). CT images 2 mo after transcatheter arterial chemoembolization under occlusion of the 2 portal vein branches (D) demonstrated a dense lipiodol deposit in the HCC and a complete response, according to modified Response Evaluation Criteria in Solid Tumors.

Furuse *et al*[90]. We obtained both a good target tumor response and dramatic improvement in arterioportal shunts with TACE-PVO therapy, with favorable 1-, 2-, and 3-year survival rates of 85.7%, 64.3%, and 42.9%, respectively[91]. This survival was markedly better than that in the previous series.

To our knowledge, no effective treatment for both HCC and significant arterioportal shunts has been previously reported. We have performed TACE-PVO on 37 patients with significant arterioportal shunts at our institution, resulting in good tumor responses and prolonged survival. Randomized controlled multicenter trials are necessary to further explore differences in quality of life and to assess the effects of TACE-PVO on short- and long-term outcomes.

Finally, we introduce a specialized embolization technique for HCC with arterioportal shunt. A patient presented to our institution with multiple HCCs and underwent several sessions of TACE. Following therapy, 1 HCC, fed by a cystic artery with an arterioportal shunt, remained. We attempted superselective TACE-PVO *via* the branch of the cystic artery, thus avoiding embolization; however, the procedure was not successful (Figure 4). We then performed chemoembolization *via* the portal vein branch with an arterioportal shunt during balloon occlusion of the portal vein (TPCE) and observed a dense accumulation of lipiodol in the tumor. Angiogra-

phy 3 mo after the TPCE procedure revealed no arterioportal shunt, and conventional TACE was performed for the residual HCC. To our knowledge, this is the first report of successful TPCE, and this technique may be a useful and safe method for selected patients with HCC and arterioportal shunts.

Isolated hepatic perfusion (IHP) is an attractive option for achieving higher tumor exposure to any given agent while avoiding systemic toxicity by decreasing systemic drug exposure. Surgical IHP has shown promising results[92-94]; however, this technique is therapeutically limited because it requires an aggressive surgical intervention that is associated with considerable morbidity and mortality. Further, this technique is not amenable to repeated interventions, mainly due to the formation of adhesions[92,94,95]. Therefore, several studies have attempted to develop safe and repeatable percutaneous IHP techniques without using laparotomy with balloon occlusion catheters. Ku *et al*[96] reported on advanced-stage HCC patients (*n* = 25) that underwent percutaneous IHP after reductive surgery and determined their 5-year overall survival rate to be 42%. However, percutaneous IHP techniques result in higher rates of leakage from the perfusion circuit into the systemic circulation[97-99], mainly because the distance between the right atrium and hepatic vein origins is often too short to allow balloon occlusion of the suprahepatic inferior vena cava (IVC) above the hepatic veins without
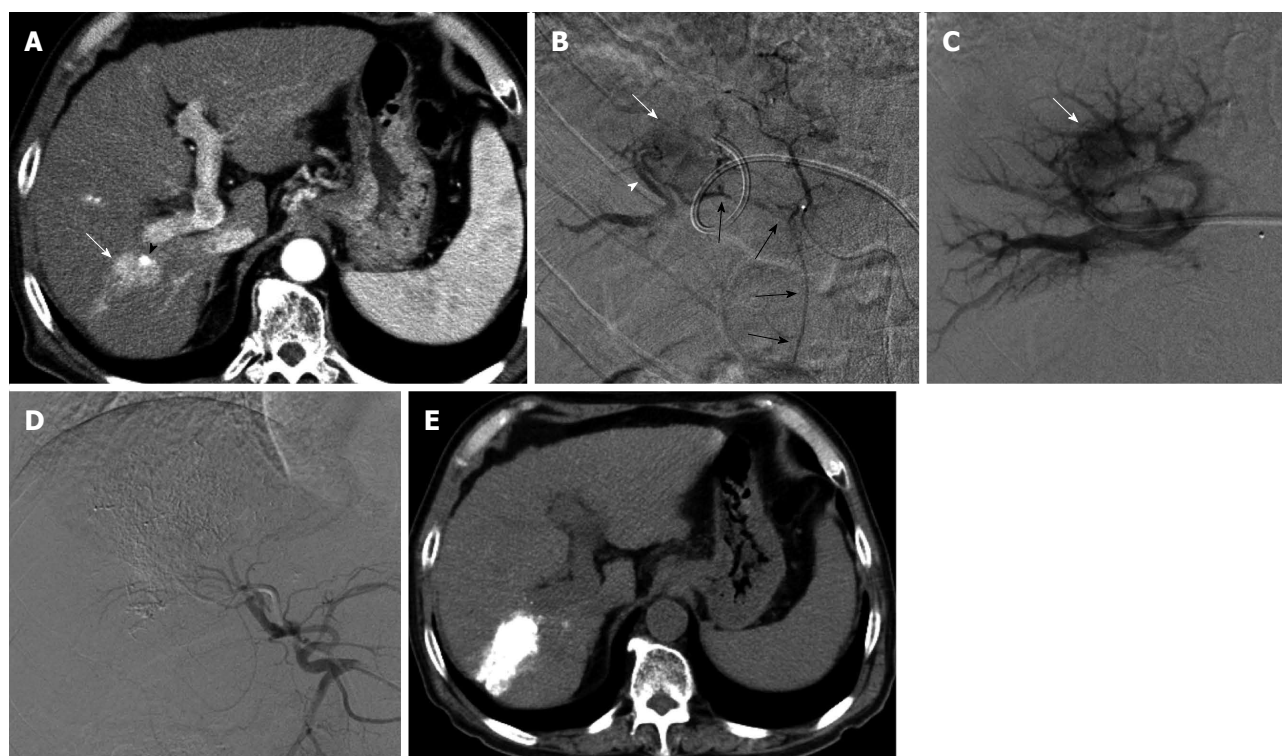
Figure 4 Transportal chemoembolization for hepatocellular carcinoma with an arterioportal shunt in a 70-year-old man. Enhanced abdominal computed tomography (CT) examination (A) demonstrated a recurrent hepatocellular carcinoma (HCC) (A, arrow) in the posterior segment with a lipiodol deposit (arrowhead). Hepatic arteriography *via* the anterior branch (B) revealed a HCC (B, white arrow) fed by the cystic artery (B, black arrows) and an intratumoral arterioportal shunt (B, arrowhead). A 5-French sheath was inserted into the portal vein *via* the lateral superior branch of the left portal vein. Direct portography *via* the portal vein branch contributed an arterioportal shunt showed a tumor stain (C, arrow). Following transcatheter portal chemoembolization, proper hepatic arteriography showed non-visualized tumor stain and arterioportal shunt (D). Non-enhanced CT 7 d after therapy (E) showed a dense accumulation of lipiodol in the tumor and peritumoral liver parenchyma.

occluding the hepatic veins themselves[97,99]. IHP involves an orthograde approach, employing inflow *via* the hepatic artery and outflow *via* the IVC through the hepatic veins. All non-surgical orthograde IHP techniques may be associated with this problem, including combinations of orthograde percutaneous and surgical IHP techniques that employ a double-balloon catheter for IVC occlusion.

To overcome this disadvantage, we developed a percutaneous IHP circulation system - retrograde-outflow percutaneous IHP (R-PIHP) - by redirecting hepatic outflow through the portal vein[100,101] based on hepatic circulation under hepatic vein occlusion[53,54]. This technique inhibits systemic leakage and maintains a high concentration of drug delivery to the liver. A phase I / II trial of R-PIHP for unresectable liver malignancies, including HCC, was begun 3 years ago, and we have obtained good tumor responses and survival benefits although R-PIHP recommends expert interventional techniques (Figure 5).

Unresectable HCC usually presents as a hypervascular tumor. TACE results in both tumor hypoxia and longer activity periods for anticancer drugs remaining in the tumor tissues. However, TACE also induces a post-treatment surge of angiogenic factors, such as vascular endothelial growth factor (VEGF), which can occur as early as a few hours post-TACE[102]. This process may contribute to the revascularization of the tumor, thus reducing the efficacy of TACE[103,104]. Sorafenib is an antiangiogenic drug that blocks tumor cell proliferation and angiogenesis by inhibiting the activity of VEGF receptors. Combining sorafenib with TACE may potentially improve the treatment outcome[105]. Several studies have evaluated the efficacy and safety of this combination treatment[106,107], and clinical trials investigating this therapeutic approach are currently ongoing. The dosing schedule of antiangiogenic drugs in relation to TACE is a key factor for this method of therapy. A randomized phase III study comparing the advent of sorafenib treatment with placebo 1-3 mo after TACE failed to show a survival benefit[106]. In contrast, a single-arm phase II study with sorafenib beginning 1 wk after TACE reported a disease control rate of 95%[107], according to the response evaluation criteria for solid tumors. Optimal scheduling of antiangiogenic agents with TACE is essential to improve the patient prognosis. Moreover, if locoregional treatments are superior to conventional TACE, the combination of sorafenib with these other interventional treatments, such as DEB-TACE or radioembolization, is also promising.

CONCLUSION

In this review, we have summarized the efforts of many studies to improve the treatment outcomes of patients with intermediate- or advanced-stage HCC. For intermediate-stage HCC patients, interventional treatments, such
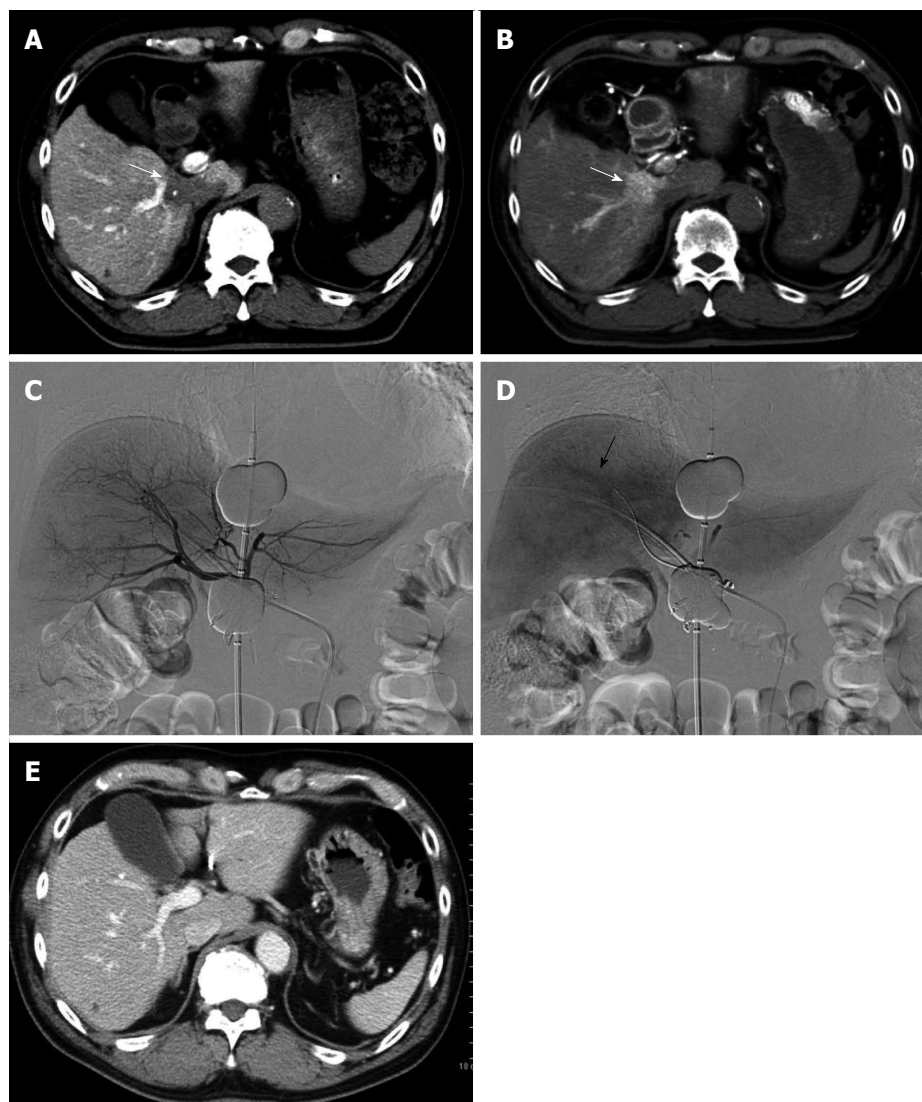
Figure 5 Retrograde-outflow percutaneous isolated hepatic perfusion for multiple hepatocellular carcinomas in a 64-year-old man. A patients received 2 sessions of transcatheter arterial chemoembolization for multiple hepatocellular carcinomas (HCCs) at other hospital. Computed tomography (CT) during arterial portography (A) and hepatic arteriography (B) demonstrated multiple HCCs with portal vein invasion (arrows). Retrograde-outflow percutaneous isolated hepatic perfusion (C, arterial phase; D, venous phase) was performed twice (arrow of D indicated a portal branch), and enhanced CT imaging 6 mo after therapy (E) revealed that the HCC was diminished.

as TACE, drug-eluting beads embolization, radioembolization, and combination therapies, for prognostic improvement are continually evolving. For advanced-stage HCC patients, sorafenib chemotherapy, TACE-based therapies combined with sorafenib treatment, TACE with radiotherapy, TACE based on hepatic hemodynamics, and IHP are all effective therapies. In conclusion, the evolution of therapy continues to improve the prognosis of patients with unresectable HCC.

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