

# The Current Practice of Transarterial Chemoembolization for the Treatment of Hepatocellular Carcinoma

Sung Wook Shin, MD

Despite remarkable advancement in the surveillance and treatment of hepatocellular carcinoma (HCC) and the availability of novel curative options, a great proportion of HCC patients are still not eligible for curative treatment due to an advanced tumor stage or poor hepatic functional reserve. Therefore, there is a continuing need for effective palliative treatments. Although practiced widely, it has only recently been demonstrated that the use of transarterial chemoembolization (TACE) provides a survival benefit based on randomized controlled studies. Hence, TACE has become standard treatment in selected patients. TACE combines the effect of targeted chemotherapy with the effect of ischemic necrosis induced by arterial embolization. Most of the TACE procedures have been based on iodized oil utilizing the microembolic and drug-carrying characteristic of iodized oil. Recently, there have been efforts to improve the delivery of chemotherapeutic agents to a tumor. In this review, the basic principles, technical issues and complications of TACE are reviewed and recent advancement in TACE technique and clinical applicability are briefed.

## Index terms :

Carcinoma, hepatocellular  
Chemoembolization, therapeutic  
Iodized oil  
Doxorubicin  
Gelatin sponge, absorbable

DOI:10.3348/kjr.2009.10.5.425

## *Korean J Radiol 2009; 10: 425-434*

Received February 26, 2009; accepted after revision April 3, 2009.

Department of Radiology and Center for Imaging Science, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul 135-710, Korea

## Address reprint requests to:

Sung Wook Shin, MD, Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Ilwon-dong, Gangnam-gu, Seoul 135-710, Korea.  
Tel. (822) 3410-2518  
Fax. (822) 3410-2559  
e-mail: swshin@skku.edu

The liver has a unique dual blood supply from both the portal vein and the hepatic artery. The normal parenchyma of the liver receives two-thirds of its necessary blood supply from the portal vein and receives the remaining one-third from the hepatic artery. However, it is well-known that vascularization of hepatocellular carcinoma (HCC) is mostly dependent on the hepatic artery (1, 2). This characteristic of HCC not only justifies the diagnostic use of contrast enhanced CT and MRI, but also provides a basic rationale for transarterial therapy as an effective treatment of HCC (3).

Though a variety of techniques and agents have been used to treat HCC with transarterial therapy (4), transarterial chemoembolization (TACE) and transarterial embolization (TAE) are the most widely accepted transarterial techniques to treat HCC. TACE is a combination therapy of TAE and regional chemotherapy. Selective arterial obstruction induces ischemic tumor necrosis while minimizing damage to the liver tissue. The blood supply to the liver tissue is still maintained by dominant blood flow from the portal vein minimizing damage to the liver. In addition, chemotherapeutic agents concomitantly administered remain in a tumor for a longer period at a higher concentration. The embolotherapy interrupts the arterial blood flow to a tumor and prevents washout of the injected chemotherapeutic agents from a tumor. Therefore, this combination of embolotherapy and regional chemotherapy has synergistic, anti-tumor effects with a high objective response rate (Fig. 1). Another added benefit is that the use of combination therapy results in lower systemic drug levels and therefore less toxicity.

### Basic Principles of Transarterial Chemoembolization

The selection of the most appropriate treatment option for HCC patients depends not only on tumor burden but also on liver function and the general performance status of the patient. TACE is usually done in a selected group of patients with multinodular HCCs who cannot benefit from curative treatment (5). TACE is not done for patients with a severely compromised liver function such as Child-Pugh

classification C or late B. Though superselective TACE may be attempted in a patient with compromised liver function, if the patient has a diffuse or massive HCC or an HCC involving the major portal veins, this precludes the practice of safe TACE. Therefore, residual liver function should be evaluated through the use of laboratory tests and clinical examinations, and the extent and characteristics of a tumor need to be evaluated through the use of imaging studies when TACE is planned.

As correct anatomical evaluation is essential to perform

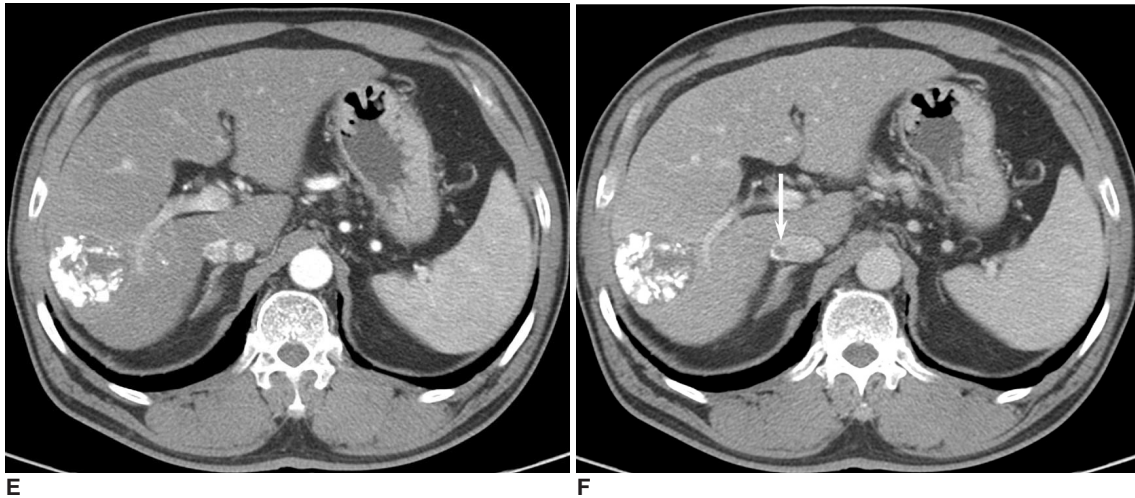


**Fig. 1.** 66-year-old man with hepatocellular carcinoma.

**A, B.** Early (**A**) and delayed (**B**) phases of contrast enhanced CT scans show large mass (arrowheads) in right hepatic lobe. Note filling defect in inferior vena cava (arrow) that is tumor thrombus extending from right hepatic vein.

**C.** Hepatic arteriogram shows infiltrative tumor staining in right hepatic lobe with formation of extensive arteriovenous shunt (arrowheads). Transarterial chemoembolization was performed with mixture of 15 ml of Lipiodol and 50 mg of doxorubicin followed by gelfoam embolization. This patient underwent four sessions of transarterial chemoembolization over period of five months.

**D.** Five months later, follow-up angiogram shows almost complete disappearance of tumor vascularity and only trace of arteriovenous shunt is noted (arrowheads).



**Fig. 1.** 66-year-old man with hepatocellular carcinoma.

**E, F.** One year later, follow-up CT scan shows shrunken tumors without any evidence of viable tumor. Size of tumor thrombus in inferior vena cava has markedly decreased as well (arrow in **F**). Initial serum level of  $\alpha$ FP was 917.0 ng/ml and it returned to normal (2.6 ng/ml).

segmental or subsegmental TACE, CT or MRI examinations should be done prior to TACE. A thorough angiographic examination is mandatory to locate all of the feeding arteries of a tumor including any possible extrahepatic arteries that may feed the tumor. The possibility of whether or not tumors will be supplied by extrahepatic arteries can be predicted from CT or MRI findings. These findings include the presence of a large tumor located at the surface or a bare area, a peripheral area of a tumor with no Lipiodol retention and visualization of hypertrophied extrahepatic arteries (6, 7).

Though TACE implementation is tailored according to the liver function of each patient as well as the extent of the tumor and portal vein involvement, the use selective TACE more often can result in a better outcome with less adverse effects. There is increasing evidence that selective TACE achieves better antitumoral effects and reduces both the dosage of drugs used for TACE and the number of TACE sessions needed to achieve extensive tumor necrosis as compared to the use of conventional TACE (8–11).

### Embolic Agents

Commonly used embolic agents include gelatin sponges, polyvinyl alcohol (PVA) particles and microspheres. The use of steel coils, autologous blood clots and degradable starch microspheres as embolic agents has also been reported. Among these, PVA, microspheres and steel coils are considered permanent embolic agents while the other agents only embolize temporarily. Each of these agents can be prepared in various sizes and each agent has different characteristics; therefore, it is difficult to determine which

embolic agent is the most appropriate especially as each tumor has a different size and vascularity. In general, the use of agents that can embolize as much as possible the peripheral portions of the hepatic artery for the effective interruption of hepatic arterial flow would be favored as the agents can prevent the development of collateral arterial flow to a tumor. However, it has been found that embolic agents such as gelatin powder that are able to reach far smaller vessels can damage extratumoral liver tissue. This damage results in biliary strictures and bile duct cysts, and such agents are no longer used for TACE (12–14). A gelatin sponge is the most widely used embolic agent that can be prepared in various forms such as particles, pellets or fragments, and the use of a gelatin sponge results in temporary occlusion of an artery with recanalization taking place within two weeks (15, 16). Hepatic artery embolization done with a gelatin sponge alone has been shown to cause no damage to the liver in an experimental study (17).

A novel system combining PVA beads and doxorubicin as drug-eluting beads (DEB) is supposed to release doxorubicin in a slow and controlled manner. A recent study of TACE using DEB has shown that DEB could further improve the pharmacokinetics of the injected doxorubicin and reduce drug-related side effects maintaining the same therapeutic efficacy as TACE (18). The clinical benefits of DEB need to be confirmed with randomized controlled studies (RCTs) that compare the use of DEB to TACE.

### Lipiodol

Lipiodol (iodized oil; Guerbet Laboratories, Roissy,

France), an iodinated ethyl ester of poppy seed oil, is an oily contrast medium and has been used for lymphangiographic studies. Though TAE has been used to treat HCC since it was first reported in 1974 (19), the use of TACE to treat HCC really began after Lipiodol was introduced as a drug carrier and an embolic agent in the early 1980s (20). When injected into the hepatic artery, Lipiodol selectively remains more in tumor nodules for several weeks to over a year due to a siphoning effect from hypervascularization of the tumor vessels and an absence of Kupffer cells inside tumor tissues (21, 22). This results in the embolic effects on smaller vessels. However, Lipiodol injected into the hepatic artery of normal liver parenchyma accumulates in the portal venules by arteriportal communication and is gradually released into the systemic circulation via the hepatic sinusoids or undergoes phagocytosis by Kupffer cells and is usually cleared within a week (17, 21, 23). Lipiodol has another role as a vehicle to carry and localize chemotherapeutic agents inside a tumor. Anticancer drugs used in conjunction with Lipiodol include doxorubicin, epirubicin, aclarubicin, 5-fluorouracil, mitomycin, cisplatin and SMANCS (styrene maleic acid neocarzinostatin). The anticancer drugs are vigorously mixed with the Lipiodol through the use of a pumping method to prepare an emulsion, and when the emulsified Lipiodol and drug mixture is injected into a tumor supplying vessels, the anticancer drug is slowly released from Lipiodol and remains in high concentrations within the tumor for a prolonged period (24).

There have been concerns that such emulsions may not be stable and anticancer drugs are released too quickly into the systemic circulation. In a study done by Johnson et al. (25), there was no difference with regard to pharmacokinetic parameters or toxicity of intraarterial administration of doxorubicin with or without Lipiodol compared to intravenous doxorubicin. However, this study appears technically flawed as the volume of normal saline (25 ml) used to dissolve doxorubicin was excessive compared to the volume of Lipiodol (10 ml). How to make a stable emulsion with water-based preparations for anticancer drugs and oil (Lipiodol) has been a major issue as the stability of the mixture can greatly influence the pharmacokinetic characteristics of the anticancer drugs; hence, the clinical benefits of TACE. Studies have found that the stability of the emulsion is greatly influenced by the volume ratio between Lipiodol and the contrast medium used to dissolve the anticancer agents, and the highest stability for Lipiodol and contrast medium was obtained at a ratio of 2-4:1 (26, 27). An experimental study demonstrated that an excess volume of Lipiodol over contrast medium results in water-in-oil emulsions with

increased tumor uptake of Lipiodol while minimizing non-tumor or lung uptake of Lipiodol compared to an oil-in-water type emulsion (28). A clinical study by Nakamura et al. (24) has shown that doxorubicin was released slowly from a water-in-oil emulsion resulting clearly in a lower blood doxorubicin concentration compared to intraarterial injection of the drug without Lipiodol. From the results of these studies, it is assumed that improved pharmacokinetic outcomes of TACE can be obtained by adjusting the mixing volume of Lipiodol and doxorubicin to a 2-3:1 ratio (Lipiodol/doxorubicin solution) (24). Another study that used a water-in-oil emulsion investigated the effect of concurrent use of gelfoam and found that the pharmacokinetic ameliorations were even more pronounced after gelfoam embolization. It was concluded that from a kinetic standpoint, the use of a doxorubicin-Lipiodol-gelfoam combination provided the best effect (29). This study implied that gelfoam embolization functions to release doxorubicin more slowly from Lipiodol, hence further increasing the drug concentration inside the tumor by preventing washout of the emulsion as well as increasing the embolization effect. The stability of the emulsion could even be more enhanced by adjusting the specific gravity of the contrast medium by adding a small amount of distilled water so it is close to the specific gravity of Lipiodol (24, 27).

Another advantage of using Lipiodol is that Lipiodol can reach the portal veins around tumors because of arteriportal communication through the peribiliary vascular plexus, the vasa vasorum of the portal vein and drainage routes from a tumor itself (17, 30). While encapsulated nodular HCCs receive its blood supply almost exclusively from the hepatic artery, the periphery of HCC nodules or advanced HCCs with extracapsular invasion or early HCCs have a dual blood supply both from the hepatic artery and the portal vein leading to resistance to TACE and incomplete tumor necrosis after TACE (31, 32). The deposition of Lipiodol in the portal veins around a tumor has been reported to strengthen anti-tumor effects and conventional embolizations without Lipiodol did not produce such strengthened antitumor effects (33). Local tumor recurrence was significantly lower when a greater degree of portal vein visualization with Lipiodol was demonstrated during TACE (10) (Fig. 2).

In summary, Lipiodol has several functions. Lipiodol functions as a microvessel embolic agent, as a carrier of chemotherapeutic agents and as an augmentor of antitumor effects of TACE by efflux into the portal veins. Though the use of Lipiodol in TACE has been challenged (4), there is substantial evidence that confirms the efficacy of the use of Lipiodol. Lipiodol is still widely adopted in

## Transarterial Chemoembolization for Hepatocellular Carcinoma Treatment

TACE protocols.

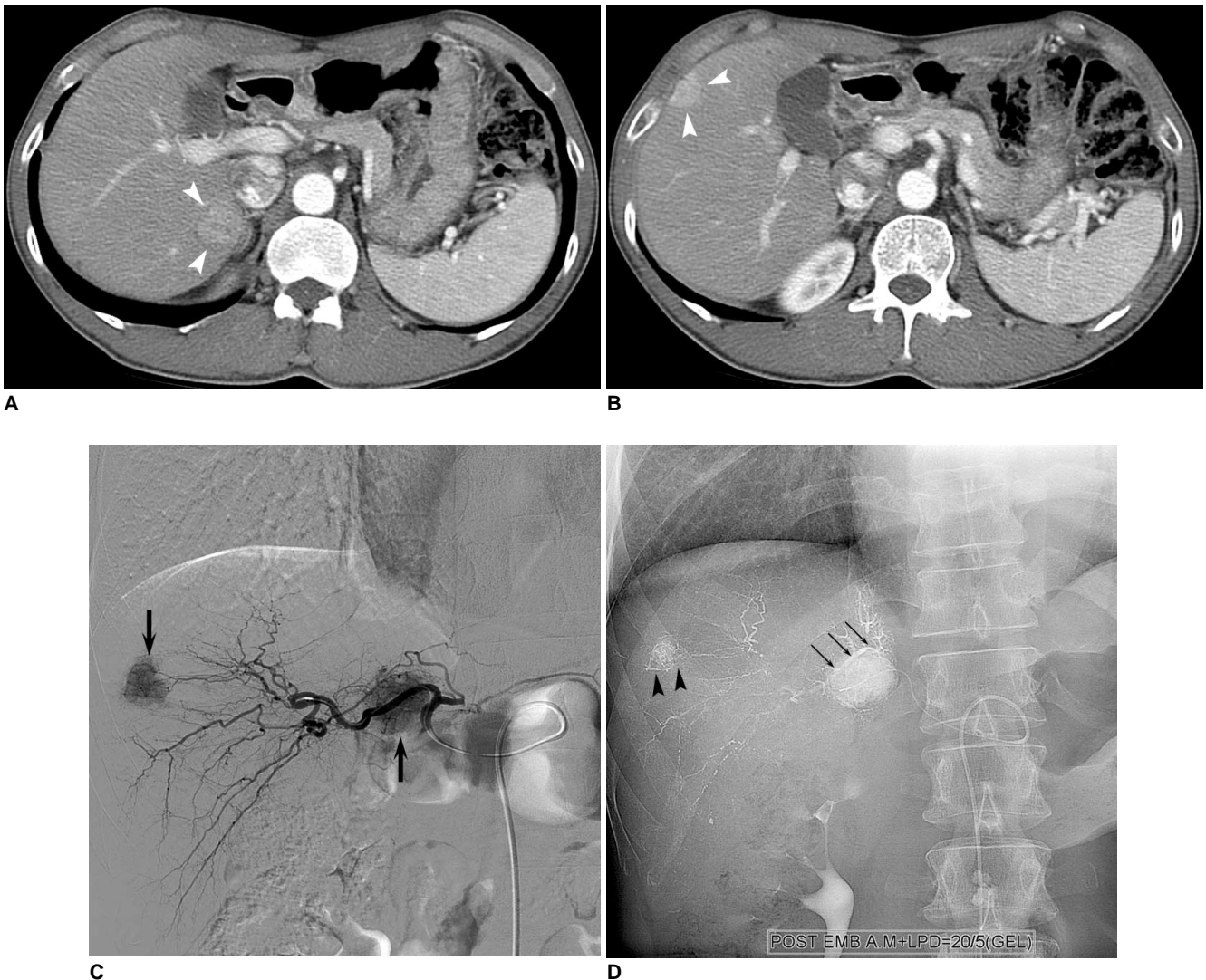
### Chemotherapeutic Agents

Chemotherapeutic agents are usually suspended in iodized oil and are delivered as close to a tumor as possible followed by the embolization process. Several chemotherapeutic agents have been used with doxorubicin and cisplatin being the most common. The usual dose for doxorubicin and cisplatin per session is 10–70 mg and 10–120 mg respectively (4, 34). The criteria to determine the dosages of chemotherapeutic agents are variable and not standardized: some authors refer to patient's body surface

area, weight, tumor burden or bilirubin level, and some used a fixed dose. A few RCTs have failed to show significant differences in survival between the use of doxorubicin and other drugs such as cisplatin or epirubicin (35–37), and to date, there is no evidence of the superiority of any single chemotherapeutic agent over other drugs or for mono-drug chemotherapy versus combination chemotherapy (4).

### Therapeutic Efficacy of Transarterial Chemoembolization

Transarterial chemoembolization can induce extensive



**Fig. 2.** 56-year-old man with hepatocellular carcinoma.

**A, B.** Contrast enhanced CT scans show two enhancing nodules (arrowheads) in liver segment 7 (**A**) and segment 8 (**B**). Serum  $\alpha$ FP level was 5826.7 ng/ml.

**C.** Hepatic arteriogram shows two hypervascular tumor nodules (arrows) in corresponding segments. Segmental transarterial chemoembolization was performed with mixture of 5 ml of Lipiodol and 20 mg of doxorubicin followed by gelfoam embolization.

**D.** Post-transarterial chemoembolization plain radiograph shows better deposition of Lipiodol in portal vein around tumor in segment 7 (arrows) when compared to tumor in segment 8 (arrowheads).



**Fig. 2.** 56-year-old man with hepatocellular carcinoma.

**E.** Follow-up CT scan one month later shows residual tumor enhancement in segment 8 (arrowheads). In contrast, CT reveals compact Lipiodol retention in tumor of segment 7 without evidence of viable tumor (not shown). Serum  $\alpha$ FP level was 177.9 ng/ml.

**F.** Hepatic arteriogram for second session transarterial chemoembolization shows tumor staining in segment 8 (arrows) in agreement with CT findings. No tumor staining is noted in segment 7 tumor.

**G.** After subsegmental transarterial chemoembolization, Lipiodol deposition appears better in portal vein around segment 8 tumor (arrows) when compared with that of previous transarterial chemoembolization.

**H.** Four months after second transarterial chemoembolization, follow-up CT scan shows compact Lipiodol uptake in both of tumors without any viable tumor portion. Serum  $\alpha$ FP level returned to normal (2.9 ng/ml).

tumor necrosis in most patients and this has been substantiated by the pathological identification of tumor necrosis, by a reduction in tumor burden as seen on contrast enhanced CT scans and by a decrease in tumor marker concentrations after the procedure (9, 38). The objective response rate of TACE has been reported between 15% and 61% (39–45) and TACE appeared to prevent significant tumor progression compared with conservative or inactive treatments (39, 40).

However, the ability of TACE to induce tumor necrosis does not necessarily mean longer survival rates for HCC patients. Almost 70–80% of patients treated with TACE die due to tumor progression during follow-up because of

the eventual regrowth of the residual tumor cells after regaining a vascular supply or the remote recurrence of tumors in other areas of the liver. The most reliable way to confirm a survival benefit is through the use of large RCTs that compare treatment versus no treatment; however, small RCTs have failed to show a survival advantage of TACE (39, 40, 42–44) and until recently, the use of TACE was controversial in HCC patients not indicated for curative therapies.

In 2002, two RCTs from Hong Kong (45) and Spain (41) showed the survival benefits of TACE compared to the best conservative treatment. Llovet et al. (41) compared TACE to the use of gelatin sponges and doxorubicin

## Transarterial Chemoembolization for Hepatocellular Carcinoma Treatment

**Table 1. Response and Survival Rates of HCC Patients in Randomized Controlled Trials Comparing TACE/TAE versus Inactive Treatments**

Author	Journal, Year	Treatment Arms (No. of Patients)	Objective Response (%)	Survival (%)		Risk Factors for Survival
				1-year	2-year	
Lin et al. (42)	Gastroenterology, 1988	TAE (21)	62	42	25	NR
		TAE + IV 5-FU (21)	48	20	20	
		IV 5-FU (21)	9.5	13	13	
Pelletier et al. (43)	J Hepatol, 1990	TACE (21)	33	24	NR	NR
		Control (21)	0	33	NR	
GETCH (40)	N Engl J Med, 1995	TACE (50)	16	62	38	Performance, liver function, tumor mass, PVT, $\alpha$ FP
		Control (46)	5	43	26	
Bruix et al. (39)	Hepatology, 1998	TAE + coils (40)	55	70	49	Performance, bilirubin
		Control (40)	0	72	50	
Pelletier et al. (44)	J Hepatol, 1998	TACE + tamoxifen (37)	24	51	24	Child-Pugh class
		Tamoxifen (36)	5.5	55	26	
Lo et al. (45)	Hepatology, 2002	TACE (40)	27	57	31	TACE, PVT
		Control (39)	2.6	32	11	
Llovet et al. (41)	Lancet, 2002	TAE (37)	43	75	50	TACE, symptom
		TACE (40)	35	82	63	
		Control (35)	0	63	27	

Note.— HCC = hepatocellular carcinoma, TACE = transarterial chemoembolization, TAE = transarterial embolization, IV = intravenous, NR = not reported, 5-FU = 5-fluorouracil, PVT = portal vein tumor thrombosis,  $\alpha$ FP = alpha-fetoprotein

dissolved in Lipiodol and TAE to the use of gelatin sponges and conservative treatment. An interim analysis showed that TACE had survival benefits compared to the conservative treatment (hazard ratio of death, 0.47; 95% confidence interval, 0.25–0.91), and the survival probabilities at one and two years were 82% and 63% for TACE, 75% and 50% for TAE and 63% and 27% for conservative treatment, respectively (TACE versus conservative treatment,  $p = 0.009$ ). In addition, treatment allocation was the only variable independently related to survival. Another RCT from Hong Kong compared the use of TACE to an emulsion of cisplatin in Lipiodol and gelatin sponges and symptomatic treatment (45). The study showed that survival was better in patients treated with TACE (1-year survival, 57%; 2-year survival, 31%; 3-year survival, 26%) than in patients that received symptomatic treatment (1-year survival, 32%; 2-year survival, 11%; 3-year survival, 3%;  $p = 0.002$ ).

These RCTs were followed by cumulative meta-analyses which included all published RCTs (46, 47) showing that TACE significantly reduced the overall 2-year mortality rate compared to control patients who received conservative or inactive treatments (odds ratios, 0.53 and 0.54; 95% confidence interval, 0.32–0.89 and 0.33–0.89;  $p = 0.015$  and 0.017, respectively). However, two RCTs presented contrary results for a comparison between TACE and TAE and one study failed to show any evidence

that TACE was more effective than TAE (46). The results of RCTs that have compared the use of TACE or TAE versus inactive treatments are summarized in Table 1.

In one prospective study that compared the use of TACE and hepatic resection (48), there was no significant survival difference between TACE and hepatic resection for advanced HCCs (UICC [Union Internationale Contre Le Cancer] stage T3 N0 M0), and even in patients with UICC stage T1-2 N0 M0 HCC when Lipiodol was compactly retained, the survival rate after TACE was comparable to the survival rate after hepatic resection. The extent of Lipiodol retention translates into response to treatment.

### Complications

Transarterial chemoembolization can cause a variety of complications. However, the procedural complications usually arise from underlying causative factors or an application of inadvertent techniques. The causative factors include compromised liver function, main portal vein obstruction, biliary tract obstruction, a previous history of bile duct surgery, Lipiodol overdosage, hepatic artery occlusion due to repeated TACE and nonselective TACE (49). Therefore, the presence of any of these factors should be identified prior to performing TACE and an adjustment of the dosage for the drug and the application of a meticulous technique must be implemented accord-

ingly.

The most common complication of TACE is post-embolization syndrome that consists of transient abdominal pain and fever occurring in 60–80% of the patients after TACE. Elevation of the level of hepatic transaminases typically accompanies post-embolization syndrome (50). Whether post-embolization syndrome reflects damage to the normal liver parenchyma or tumor necrosis is uncertain. Though prolonged hospitalization may be required to monitor a patient and to control pain, post-embolization syndrome is self-limiting within 3–4 days, and the use of antibiotics is not necessary to treat the fever (51).

Hepatic failure after TACE is related to TACE-induced ischemic damage to the non-tumorous liver tissue and several risk factors have been identified including portal vein obstruction, the use of a high dose of anti-cancer drugs and Lipiodol, a high basal level of bilirubin, a prolonged prothrombin time and advanced Child-Pugh class (49, 52). Because the definitions of TACE-induced hepatic failure are different in each study, the reported incidence of hepatic failure has varied widely from 0–49%, with a median incidence of 8% (4). Though deterioration of liver function recovers to the pretreatment level before the next session of TACE in most patients and only 3% of patients had irreversible hepatic decompensation (4), TACE should be performed with extreme caution in patients having risk factors for hepatic failure.

Other TACE-related complications occur in less than 10% of treatment sessions and include ischemic cholecystitis, hepatic abscesses and biliary strictures (34). Cholecystitis or gallbladder infarction frequently occurred after inadvertent injection of the Lipiodol mixture or embolization of the cystic artery; however, most cases are asymptomatic and rarely require intervention with percutaneous drainage or a cholecystectomy (53, 54). Song et al. (55) reviewed the risk of liver abscesses in 6,255 TACE procedures and found a 0.2% incidence rate of liver abscesses. Development of a liver abscess has been linked to previous intervention in the biliary system being prone to an ascending biliary infection (55). The prophylactic use of antibiotics and a bowel enema could be considered in these patients.

Bile duct injury including a subcapsular biloma, focal strictures of the common hepatic or bile duct and diffuse dilatation of the intrahepatic ducts has been reported with a 0.5–2% incidence (56, 57). Bilomas seem to be associated with the use of Lipiodol and focal strictures of large bile ducts with the use of gelatin sponge particles (56). Therefore, careful use of these agents with a meticulous level of embolization may reduce bile duct injury.

Upper gastrointestinal complications such as gastritis, ulceration and bleeding can occur after TACE caused by the regurgitation of embolic agents into the gastric arteries, by the presence of anatomic variants (e.g., an accessory left gastric artery arising from the left hepatic artery) and by the development of stress ulcers. Upper gastrointestinal bleeding occurred in 3% (median) of the patients (range, 0–22%) in 23 trials that involved 2,593 patients (4). It is essential to recognize the presence of any of the anatomic variants and to prevent the efflux of a drug into the gastrointestinal organs.

## Conclusion and Future Perspectives

It has been shown that TACE is the only palliative treatment that can benefit HCC patients ineligible for curative treatment in terms of survival, and TACE has been widely accepted as standard therapy in selected patients. However, several important issues remain to be clarified including what is the best chemotherapeutic drug to employ, what is the best embolization agent to utilize and what is the most appropriate retreatment schedule. Most importantly, the survival gain of TACE seems to be marginal, partly due to HCCs having tumor portions supplied by the portal vein such as the periphery or the extracapsular portion of an advanced HCC though the use of Lipiodol has a theoretical advantage as it can reach the portal vein (31, 32). Recent advancement in microcatheter technology has made it possible to perform ultraslective catheterization of tumor feeding arteries. Miyayama et al. (10) used a newly designed 2-Fr tip microcatheter to facilitate superselective catheterization of tumor feeders and the overflow of Lipiodol emulsion into the portal vein. With the use of this technique, marked visualization of the portal veins due to overflowed Lipiodol emulsion was noted in almost half of the tumors and a greater grade of portal vein visualization was associated with lower local tumor recurrence. Another strategy to improve the therapeutic effect of TACE may be the use of DEB (18). DEB consists of PVA beads and doxorubicin, and PVA beads loaded with doxorubicin is supposed to act as a drug carrier capable of releasing doxorubicin in a slow and controlled manner. In a recent study, the pharmacokinetic profiles of injected doxorubicin were significantly better in TACE using DEB than in conventional TACE and the reported 1-year and 2-year survival after TACE using DEB was 93% and 89%, respectively (18). There have been efforts to improve therapeutic efficacy of TACE by combining TACE with other modality treatments such as radiofrequency ablation (RFA). Cheng et al. (58) recently showed that the use of combined TACE-RFA was superior



to the use of TACE alone or RFA alone in selected patients reporting that the median survival time of the patients treated with TACE-RFA was 37 months while median survival times of TACE alone and RFA alone were 24 months and 22 months, respectively. Through these investigations, the limitations of TACE are expected to be overcome, and it is hoped to expand the indications and clinical benefits of TACE.

## References

- Breedis C, Young G. The blood supply of neoplasms in the liver. *Am J Pathol* 1954;30:969-977
- Nakashima T, Kojiro M. Pathologic characteristics of hepatocellular carcinoma. *Semin Liver Dis* 1986;6:259-266
- Lee JM, Kim IH, Kwak HS, Youk JH, Han YM, Kim CS. Detection of small hypervascular hepatocellular carcinomas in cirrhotic patients: comparison of superparamagnetic iron oxide-enhanced MR imaging with dual-phase spiral CT. *Korean J Radiol* 2003;4:1-8
- Marelli L, Stigliano R, Triantos C, Senzolo M, Cholongitas E, Davies N, et al. Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. *Cardiovasc Intervent Radiol* 2007;30:6-25
- Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology* 2005;42:1208-1236
- Chung JW, Kim HC, Yoon JH, Lee HS, Jae HJ, Lee W, et al. Transcatheter arterial chemoembolization of hepatocellular carcinoma: prevalence and causative factors of extrahepatic collateral arteries in 479 patients. *Korean J Radiol* 2006;7:257-266
- Chung JW, Park JH, Han JK, Choi BI, Kim TK, Han MC. Transcatheter oily chemoembolization of the inferior phrenic artery in hepatocellular carcinoma: the safety and potential therapeutic role. *J Vasc Interv Radiol* 1998;9:495-500
- Ji SK, Cho YK, Ahn YS, Kim MY, Park YO, Kim JK, et al. Multivariate analysis of the predictors of survival for patients with hepatocellular carcinoma undergoing transarterial chemoembolization: focusing on superselective chemoembolization. *Korean J Radiol* 2008;9:534-540
- Matsui O, Kadoya M, Yoshikawa J, Gabata T, Takashima T, Demachi H. Subsegmental transcatheter arterial embolization for small hepatocellular carcinomas: local therapeutic effect and 5-year survival rate. *Cancer Chemother Pharmacol* 1994;33:S84-S88
- Miyayama S, Matsui O, Yamashiro M, Ryu Y, Kaito K, Ozaki K, et al. Ultrasensitive transcatheter arterial chemoembolization with a 2-f tip microcatheter for small hepatocellular carcinomas: relationship between local tumor recurrence and visualization of the portal vein with iodized oil. *J Vasc Interv Radiol* 2007;18:365-376
- Park SH, Cho YK, Ahn YS, Park YO, Kim JK, Chung JW. Local recurrence of hepatocellular carcinoma after segmental transarterial chemoembolization: risk estimates based on multiple prognostic factors. *Korean J Radiol* 2007;8:111-119
- Doppman JL, Dunnick NR, Girton M, Fauci AS, Popovsky MA. Bile duct cysts secondary to liver infarcts: report of a case and experimental production by small vessel hepatic artery occlusion. *Radiology* 1979;130:1-5
- Makuuchi M, Sukigara M, Mori T, Kobayashi J, Yamazaki S, Hasegawa H, et al. Bile duct necrosis: complication of transcatheter hepatic arterial embolization. *Radiology* 1985;156:331-334
- Nakamura H, Tanaka T, Hori S, Yoshioka H, Kuroda C, Okamura J, et al. Transcatheter embolization of hepatocellular carcinoma: assessment of efficacy in cases of resection following embolization. *Radiology* 1983;147:401-405
- Coldwell DM, Stokes KR, Yakes WF. Embolotherapy: agents, clinical applications, and techniques. *Radiographics* 1994;14:623-643
- Chung JW. Transcatheter arterial chemoembolization of hepatocellular carcinoma. *Hepatogastroenterology* 1998;45:S1236-S1241
- Kan Z, Sato M, Ivancev K, Uchida B, Hedgpeth P, Lunderquist A, et al. Distribution and effect of iodized poppyseed oil in the liver after hepatic artery embolization: experimental study in several animal species. *Radiology* 1993;186:861-866
- Varela M, Real MI, Burrel M, Forner A, Sala M, Brunet M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. *J Hepatol* 2007;46:474-481
- Doyon D, Mouzon A, Jourde AM, Regensberg C, Frileux C. Hepatic, arterial embolization in patients with malignant liver tumours (author's transl). *Ann Radiol (Paris)* 1974;17:593-603
- Nakakuma K, Tashiro S, Hiraoka T, Uemura K, Konno T, Miyauchi Y, et al. Studies on anticancer treatment with an oily anticancer drug injected into the ligated feeding hepatic artery for liver cancer. *Cancer* 1983;52:2193-2200
- Kan Z, McCuskey PA, Wright KC, Wallace S. Role of Kupffer cells in iodized oil embolization. *Invest Radiol* 1994;29:990-993
- Ohishi H, Uchida H, Yoshimura H, Ohue S, Ueda J, Katsuragi M, et al. Hepatocellular carcinoma detected by iodized oil. Use of anticancer agents. *Radiology* 1985;154:25-29
- Okayasu I, Hatakeyama S, Yoshida T, Yoshimatsu S, Tsuruta K, Miyamoto H, et al. Selective and persistent deposition and gradual drainage of iodized oil, Lipiodol in the hepatocellular carcinoma after injection into the feeding hepatic artery. *Am J Clin Pathol* 1988;90:536-544
- Nakamura H, Hashimoto T, Oi H, Sawada S. Transcatheter oily chemoembolization of hepatocellular carcinoma. *Radiology* 1989;170:783-786
- Johnson PJ, Kalayci C, Dobbs N, Raby N, Metivier EM, Summers L, et al. Pharmacokinetics and toxicity of intraarterial adriamycin for hepatocellular carcinoma: effect of coadministration of Lipiodol. *J Hepatol* 1991;13:120-127
- Heresbach D, Raoul JL, Bentue-Ferrer D, Bretagne JF, Van den Driessche J, Gastard J. Chemotherapy combined with Lipiodol. In vitro study of the kinetics of release of adriamycin. *Gastroenterol Clin Biol* 1989;13:775-778
- Sakaguchi H, Uchida H, Nishimura Y, Guo QY, Yoshimura H, Ohishi H. Pharmacokinetic study of adriamycin in the emulsion mixed with Lipiodol-difference resulting from composition and methods of preparation, and behavior after mesenteric arterial injection in rat. *Gan To Kagaku Ryoho* 1991;18:1349-1355
- de Baere T, Zhang X, Aubert B, Harry G, Lagrange C, Ropers J, et al. Quantification of tumor uptake of iodized oils and emulsions of iodized oils: experimental study. *Radiology* 1996;201:731-735
- Raoul JL, Heresbach D, Bretagne JF, Ferrer DB, Duvauferrier

- R, Bourguet P, et al. Chemoembolization of hepatocellular carcinomas. A study of the biodistribution and pharmacokinetics of doxorubicin. *Cancer* 1992;70:585-590
30. Nakamura H, Hashimoto T, Oi H, Sawada S. Iodized oil in the portal vein after arterial embolization. *Radiology* 1988;167:415-417
  31. Takayasu K, Shima Y, Muramatsu Y, Moriyama N, Yamada T, Makuuchi M, et al. Hepatocellular carcinoma: treatment with intraarterial iodized oil with and without chemotherapeutic agents. *Radiology* 1987;163:345-351
  32. Kuroda C, Sakurai M, Monden M, Marukawa T, Hosoki T, Tokunaga K, et al. Limitation of transcatheter arterial chemoembolization using iodized oil for small hepatocellular carcinoma. A study in resected cases. *Cancer* 1991;67:81-86
  33. Sasaki Y, Imaoka S, Kasugai H, Fujita M, Kawamoto S, Ishiguro S, et al. A new approach to chemoembolization therapy for hepatoma using ethiodized oil, cisplatin, and gelatin sponge. *Cancer* 1987;60:1194-1203
  34. Bruix J, Sala M, Llovet JM. Chemoembolization for hepatocellular carcinoma. *Gastroenterology* 2004;127:S179-S188
  35. Kasugai H, Kojima J, Tatsuta M, Okuda S, Sasaki Y, Imaoka S, et al. Treatment of hepatocellular carcinoma by transcatheter arterial embolization combined with intraarterial infusion of a mixture of cisplatin and ethiodized oil. *Gastroenterology* 1989;97:965-971
  36. Kawai S, Tani M, Okamura J, Ogawa M, Ohashi Y, Monden M, et al. Prospective and randomized trial of Lipiodol-transcatheter arterial chemoembolization for treatment of hepatocellular carcinoma: a comparison of epirubicin and doxorubicin (second cooperative study). The Cooperative Study Group for Liver Cancer Treatment of Japan. *Semin Oncol* 1997;24:S6-38-S6-45
  37. Watanabe S, Nishioka M, Ohta Y, Ogawa N, Ito S, Yamamoto Y. Prospective and randomized controlled study of chemoembolization therapy in patients with advanced hepatocellular carcinoma. Cooperative Study Group for Liver Cancer Treatment in Shikoku area. *Cancer Chemother Pharmacol* 1994;33:S93-S96
  38. Bartolozzi C, Lencioni R, Caramella D, Falaschi F, Cioni R, DiCoscio G. Hepatocellular carcinoma: CT and MR features after transcatheter arterial embolization and percutaneous ethanol injection. *Radiology* 1994;191:123-128
  39. Bruix J, Llovet JM, Castells A, Montana X, Bru C, Ayuso MC, et al. Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized, controlled trial in a single institution. *Hepatology* 1998;27:1578-1583
  40. A comparison of Lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire. *N Engl J Med* 1995;332:1256-1261
  41. Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002;359:1734-1739
  42. Lin DY, Liaw YF, Lee TY, Lai CM. Hepatic arterial embolization in patients with unresectable hepatocellular carcinoma—a randomized controlled trial. *Gastroenterology* 1988;94:453-456
  43. Pelletier G, Roche A, Ink O, Anciaux ML, Derhy S, Rouquier P, et al. A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. *J Hepatol* 1990;11:181-184
  44. Pelletier G, Ducreux M, Gay F, Luboinski M, Hagege H, Dao T, et al. Treatment of unresectable hepatocellular carcinoma with Lipiodol chemoembolization: a multicenter randomized trial. Groupe CHC. *J Hepatol* 1998;29:129-134
  45. Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, et al. Randomized controlled trial of transarterial Lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002;35:1164-1171
  46. Camma C, Schepis F, Orlando A, Albanese M, Shahied L, Trevisani F, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. *Radiology* 2002;224:47-54
  47. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology* 2003;37:429-442
  48. Lee HS, Kim KM, Yoon JH, Lee TR, Suh KS, Lee KU, et al. Therapeutic efficacy of transcatheter arterial chemoembolization as compared with hepatic resection in hepatocellular carcinoma patients with compensated liver function in a hepatitis B virus-endemic area: a prospective cohort study. *J Clin Oncol* 2002;20:4459-4465
  49. Chung JW, Park JH, Han JK, Choi BI, Han MC, Lee HS, et al. Hepatic tumors: predisposing factors for complications of transcatheter oily chemoembolization. *Radiology* 1996;198:33-40
  50. Wigmore SJ, Redhead DN, Thomson BN, Currie EJ, Parks RW, Madhavan KK, et al. Postchemoembolisation syndrome—tumour necrosis or hepatocyte injury? *Br J Cancer* 2003;89:1423-1427
  51. Castells A, Bruix J, Ayuso C, Bru C, Montanya X, Boix L, et al. Transarterial embolization for hepatocellular carcinoma. Antibiotic prophylaxis and clinical meaning of postembolization fever. *J Hepatol* 1995;22:410-415
  52. Chan AO, Yuen MF, Hui CK, Tso WK, Lai CL. A prospective study regarding the complications of transcatheter intraarterial Lipiodol chemoembolization in patients with hepatocellular carcinoma. *Cancer* 2002;94:1747-1752
  53. Takayasu K, Moriyama N, Muramatsu Y, Shima Y, Ushio K, Yamada T, et al. Gallbladder infarction after hepatic artery embolization. *AJR Am J Roentgenol* 1985;144:135-138
  54. Miyayama S, Matsui O, Nishida H, Yamamori S, Minami T, Shinmura R, et al. Transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma fed by the cystic artery. *J Vasc Interv Radiol* 2003;14:1155-1161
  55. Song SY, Chung JW, Han JK, Lim HG, Koh YH, Park JH, et al. Liver abscess after transcatheter oily chemoembolization for hepatic tumors: incidence, predisposing factors, and clinical outcome. *J Vasc Interv Radiol* 2001;12:313-320
  56. Kim HK, Chung YH, Song BC, Yang SH, Yoon HK, Yu E, et al. Ischemic bile duct injury as a serious complication after transarterial chemoembolization in patients with hepatocellular carcinoma. *J Clin Gastroenterol* 2001;32:423-427
  57. Wang MQ, Shao RH, Ye HY, Wang ZQ, Wang ZP, Liu FY. Investigation of bile duct injury after transcatheter arterial chemoembolization. *Zhonghua Zhong Liu Za Zhi* 2005;27:609-612
  58. Cheng BQ, Jia CQ, Liu CT, Fan W, Wang QL, Zhang ZL, et al. Chemoembolization combined with radiofrequency ablation for patients with hepatocellular carcinoma larger than 3 cm: a randomized controlled trial. *JAMA* 2008;299:1669-1677