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**Transarterial chemoembolization for hepatocellular carcinoma: A review of techniques**

Imai N *et al.*TACE techniques for HCC

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**Abstract**

Hepatocellular carcinoma (HCC) is one of the most common malignant diseases worldwide. While curative therapies, including resection, liver transplantation, and percutaneous ablation (percutaneous ethanol injection and radiofrequency ablation), are applicable for only a portion of the HCC population, transcatheter arterial chemoembolization (TACE) has been recognized as an effective palliative treatment option for patients with advanced HCC. TACE is also used even for single HCCs in which it is difficult to perform surgical resection or locoregional treatment due to systemic co-morbidities or anatomical problems. TACE has become widely adopted in the treatment of HCC. By using computed tomography-angiography, TACE is capable of performing diagnosis and treatment at the same time. Furthermore, TACE plays an important role in the multidisciplinary treatment for HCC when combined with other treatment. In this review, we first discuss the history of TACE, and then review the previous findings about techniques of achieving a locoregional treatment effect (liver infarction treatment, *e.g.,* ultra-selective TACE, balloon-occluded TACE), and the use of TACE as a drug delivery system for anti-cancer agents (palliative, e.g., platinum complex agents, drug-eluting beads) for multiple lesions.

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**Key words:** Hepatocellular carcinoma; Transcatheter arterial chemoembolization; Balloon-occluded transcatheter arterial chemoembolization; Drug-eluting bead

**Core tip:** Transcatheter arterial chemoembolization (TACE) has become widely adopted in the treatment of hepatocellular carcinoma (HCC). By using computed tomography-angiography, TACE is capable of performing diagnosis and treatment at the same time. Furthermore, TACE plays an important role in the multidisciplinary treatment for HCC when combined with other treatment. In this review, we first discuss the history of TACE, and then review the previous findings about techniques of achieving a locoregional treatment effect (liver infarction treatment, e.g., ultra-selective TACE, balloon-occluded TACE), and the use of TACE as a drug delivery system for anti-cancer agents (palliative, *e.g.,* platinum complex agents, drug-eluting beads) for multiple lesions.

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**INTRODUCTION**

Hepatocellular carcinoma (HCC) accounts for one-third of cancer-related deaths worldwide, and has become the fourth leading cause of cancer death in Japan and the seventh leading cause of cancer death in the US. In recent years, liver cancer deaths have decreased due to remarkable progress in the treatment of viral hepatitis in Japan, while HCC deaths remain high in the United States[1].

Underlying liver disease is present in most HCC cases. Development of HCC in a healthy liver is rare; the majority of patients who develop HCC have a background of chronic hepatitis/cirrhosis viral hepatitis, alcohol abuse, and/or NASH. HCC frequently recurs after primary treatment due to the underlying liver disease[2,3].

With advances in diagnostic imaging and treatment in recent years, adaptation of radical treatment strategies such as surgical resection and radiofrequency ablation therapy is increasing. However, even in cases in whom curative treatment is selected as initial treatment, a high recurrence rate due to multi-centric carcinogenesis and intrahepatic metastasis makes it difficult for cure to truly be achieved. Transarterial chemoembolization (TACE) has been widely performed as a treatment for multifocal HCC in patients in whom curative treatment is difficult to perform[4-11].

In the BCLC staging system, TACE is indicated for patients with intermediate-stage HCC (four or more tumors), and in the 2010 Japan Society of Hepatology consensus-based treatment algorithm for HCC, TACE is recommended for patients with a Child-Pugh score A or B, tumor diameter of more than 3 cm, or four or more tumors. However, in real clinical conditions, TACE is selected even for single HCCs in which it is difficult to perform surgical resection or locoregional treatment due to systemic co-morbidities or anatomical problems[12,13].

TACE has been widely adopted in the treatment of HCC. Through the use of CT-angiography, diagnosis and TACE can be performed at the same time. TACE also plays an important role in the multidisciplinary treatment of HCC as it is often combined with other treatments (*e.g.*, with radiofrequency ablation, with percutaneous ethanol injection, with radiation therapy).

In this review, we discuss the history of TACE and review previous findings about techniques for achieving a locoregional treatment effect (liver infarction treatment) and the use of TACE as a drug delivery system for anti-cancer agents (palliative) for multiple lesions.

**CHANGES IN HEPATIC ARTERY CHEMOEMBOLIZATION FOR HCC**

TACE induces tumor necrosis through “starvation tactics”. It takes advantage of the fact that advanced HCCs are fed only by the hepatic artery and is intended to embolize the distal portion of the hepatic artery. The liver receives blood from the portal vein and hepatic artery at a ratio of 3:1 in the normal liver. Although this ratio varies in cirrhosis, the cirrhotic liver still receives blood flow from both of these vessels. In contrast, classical HCC (moderately-differentiated type) tumors receive nutritional blood flow through the hepatic artery only, and do not depend on portal vein blood flow. By utilizing this property of HCC, TACE was developed by Yamada *et al*[4]. TACE has become widely used for the treatment of HCC since the 1980s. Embolization using adriamycin or mitomycin C and gelatin sponges has been carried out since the first half of the 1980s. Intraarterial injection of lipiodol with anti-cancer drugs before embolic agent results in enhanced embolic effects[14,15]. It also became apparent that using a water-in-oil type emulsion is highly effective for embolization and tumor uptake, and this method is also widely used[16].

Microcatheter insertion into the first three to four branches of the hepatic artery became easily available starting around 1990. Through the use of microcatheter injection of lipiodol into the peripheral branches of the hepatic artery, segmental TACE/subsegmental TACE became a standard treatment. Segmental TACE/subsegmental TACE allows for strong locoregional embolization while stopping the portal blood flow, thereby improving the local treatment effects of TACE[17,18]. In the 2000s, platinum complex agents became available, and treatment effects could be obtained even in HCCs that developed TACE resistance through repeat TACE[19]. Cone beam CT and flat-panel detectors have advanced imaging as they enable more accurate TACE treatment[20,21].

**CONVENTIONAL TACE**

Intra-tumor concentrations of drugs (particularly polymer drugs) are much higher than those of normal tissue and blood due to the characteristics of blood vessels in solid tumors[14]. In hypervascular HCC, blood returns to the sinusoidal or portal vein; in addition, HCC tissue does not have associated lymph vessels. These features allow stasis of viscous liquid such as lipiodol in the sinusoidal or portal vein in or around HCCs. Nakamura *et al*[22] reported that liver necrosis occurs following injection of lipiodol into the hepatic artery until it is visualized in the portal vein branch. Based on this discovery, Uchida *et al*[15] and Matsui *et al*[18] developed segmental and subsegmental TACE[15,18,22].

The use of water-soluble anti-cancer drugs along with lipiodol as water-in-oil type therapy has been reported to be good for distribution of anti-cancer drugs in HCC[16,23]. Therapy involving selective infusion into tumor vessels of an anti-cancer drug/lipiodol mixture and an embolic agent (gelatin sponge) is generally called conventional TACE (cTACE), and it is widely used as standard treatment worldwide (Table 1).

In 1983 Yamada *et al*[4] reported a 1-year survival rate of 44% for TACE. The 3-year survival rate of segmental TACE reported by Uchida *et al*[15] in 1990 was 67%, Matsui *et al*[18] reported a 4-year survival rate of 67% in 1993, and Takayasu *et al*[24] reported a 3-year survival rate of 77% using IVR-CT in subsegmental TACE in 2001. Thus, therapeutic outcomes of TACE have improved rapidly along with advances in TACE techniques, drugs, microcatheters, and the adaption of IVR-CT[25].

**ULTRA-SELECTIVE TACE**

It has recently become possible to insert microcatheters into the distal hepatic artery more safely due to progress in microcatheter and guidewire technology. Ultra-selective TACE aims to achieve a local therapeutic effect through liver infarction. This technique involves insertion of a microcatheter selectively into a peripheral rather than subsegmental branch (subsubsegment artery), thereby wedging the tumor-feeding vessels, and then injecting lipiodol under high pressure into the tumor and surrounding sinusoids.

The local recurrence rate of ultra-selective TACE has been reported to be 7.9% at 12 mo and 17.7% at 24 mo[26]. Ultra-selective TACE allows injection of lipiodol even into hypovascular lesions in well-differentiated HCC, and is reported to have a local control rate of 53.2% in such cases[27].

With respect to pathological background, in a study of patients who underwent liver resection after undergoing ultra-selective TACE through peripheral branches, necrosis of the tumor as well as the surrounding liver parenchyma was observed[28]. With the spread of fine microcatheters as a treatment aimed at liver infarction, injection of lipiodol in the peripheral rather than the subsegmental branches is becoming a standard treatment[29].

**BALLOON-OCCLUDED TACE**

Irie *et al*[30] reported in 2008 that better lipiodol deposition was obtained by performing selective TACE while preventing the backflow of embolic material proximally using a micro-balloon catheter, called balloon-occluded TACE (B-TACE)[30]. In conventional TACE, lipiodol suspended with an anti-cancer drug is present in the bloodstream. The blood flow may slow before sufficient lipiodol and drug have reached the tumor, and may even stop flowing. This may occur because when the arterial blood flow is reduced, the backflow of blood to the tumor occurs from the sinusoidal and portal veins. In addition, lipiodol inflow restriction to the normal liver parenchyma is caused by a reduction in peripheral arterial pressure.

In B-TACE, hemodynamic changes caused by balloon occlusion reduce the arterial blood flow by closing the hepatic artery, thereby pushing lipiodol into the tumor under high pressure and enabling the drug to be intensively administered to the tumor, allowing for an enhanced therapeutic effect. In recent years, since micro-balloon catheters with small diameters have become more available, B-TACE has been widely used, primarily in Japan (Figure 1). In performing B-TACE, evaluation of the collateral circulation of the tumor is essential, as a good response rate is obtained if the catheter tip pressure is equal to 64 mmHg or less; the collateral circulation pressure increases above that in many cases[31].

**PLATINUM COMPLEX AGENTS**

In advanced HCC treatment, it is critical that TACE functions as an efficient drug delivery system. Platinum complex agents are anti-cancer agents that cause DNA damage. Unlike anthracyclines, which are excreted from the bile, platinum complex agents are not metabolized by P450, and are excreted primarily in the urine. Thus, platinum complex agents are considered to be advantageous for patients with liver cirrhosis. Cisplatin, a first-generation platinum complex, and miriplatin, a third-generation platinum complex, are both used in the treatment of HCC[32-39].

Kawamura *et al*[19] reported that a 19.6% response rate was obtained by switching the anti-cancer agent used in TACE to a platinum complex agent in cases in which the tumor number or size increased despite administration of more than one TACE treatment. Use of a platinum complex agent also resulted in a survival benefit in responders[19]. Furthermore, Maeda *et al*[40] also reported the efficacy of TACE using cisplatin in patients with HCC that had not responded to TACE using epirubicin, with a response rate of 27.5%[40].

However, cisplatin is associated with serious side effects, including renal failure and anaphylaxis. Kawaoka *et al*[33,41] reported that anaphylaxis occurs more frequently during performance of three or more than three TACE procedure with cisplatin. In recent years, miriplatin has been administered as a third-generation platinum complex that has been developed for hepatic arterial infusion therapy particularly for HCC. Miriplatin (cis-[(1R,2R)-1,2-cyclohexanediamine-N,N’)bis(myristato)]-platinum(II)monohydrate; Dainippon Sumitomo Pharma Co., Ltd., Osaka, Japan) is a novel lipophilic cisplatin derivative that can be suspended in lipiodol. Miriplatin/lipiodol suspension is a stable colloidal emulsion that is deposited within HCC tumors, where active derivatives of miriplatin are gradually released. Also, in a cisplatin-resistant rat hepatoma cell line model, miriplatin did not show cross-resistance with cisplatin[37].

Despite clinical expectations, it is difficult to obtain adequate deposition of miriplatin in HCC, and local recurrences, particularly intra-tumoral recurrences, frequently develop using selective TACE[42]. This may be due to the higher viscosity of miriplatin, since it is suspended in lipiodol; miriplatin may be retained within the artery, so a sufficient amount of the drug does not reach the tumor through narrow blood vessels.

Seko *et al*[43] reported that reduction of the miriplatin/lipiodol suspension viscosity resistance can be obtained by warming it to 40 ℃. Compared to ordinary (room temperature) miriplatin treatment, which has a response rate of 44.3%, efficiency is improved to 70.1% for warmed miriplatin treatment[43]. Kora *et al*[44] also reported similar treatment outcomes for warmed miriplatin.

Miriplatin is known to have less serious side effects and a lower incidence of renal failure compared to other platinum complex agents. Thus, miriplatin is considered to be suitable for repeat treatments, patients with complications, and elderly patients[45,46].

**DRUG-ELUTING BEAD**

In recent years, beginning in western countries, permanent spherical embolic material (*i.e.,* beads) have been used in TACE with the aim of more efficient drug delivery[47-49]. Unlike conventional gelatin sponges, the particle size of this material is uniform. Prediction of the level of embolism is straightforward, and a sustained embolic effect can be obtained. It is also possible to impregnate anti-cancer drugs into the beads, and the anti-tumor effect is improved due to the slow release of anti-cancer agents into the tumor.

Two formulations of drug-eluting beads (DEB) are available in Japan: Hepasphere[50] and DC Bead[51] are widely used and each have unique features. DC Bead is a raw material derived from polyvinyl alcohol that is capable of impregnation of positively-charged drugs (*e.g.,* epirubicin, doxorubicin, or irinotecan). Its size is slightly decreased, and its hardness is increased by impregnation of anti-cancer drugs. Meanwhile, Hepasphere is a raw material derived from a polymer with high water absorption and can thus be impregnated with water-soluble anti-cancer agents. The size of Hepasphere increases following impregnation, it expands to about four times its size in the blood, and the resulting embolus is highly flexible and molds to the shape of the target vessel.

In a randomized controlled trial (PRECISION V) that compared TACE using lipiodol (cTACE) to TACE using DC Bead, the complete response rate, objective response rate, and disease control rate were superior in the DC Bead group compared to the cTACE group, although these differences were not statistically significant. In addition, response rates were significantly higher in certain sub-groups, such as in patients with a Child-Pugh score B and in those with HCC in bilateral lobes[52]. Vogl *et al*[53] also reported that the incidence of decreased left heart ejection fraction, post-embolization liver enzyme elevation, and hepatobiliary system adverse events were lower in the DC Bead group compared to the cTACE group[53]. Sacco *et al*[54] reported similar results from a randomized controlled trial of DEB-TACE versus cTACE for unresectable HCC: post-treatment elevation of ALT was frequently observed in the cTACE group. However, time to progression and survival did not significantly differ between the two groups: the cumulative 2-year survival rates were 86.8% in the DEB-TACE group and 83.6% in the cTACE group[54].

For TACE with epirubicin-eluting Hepasphere, Seki *et al*[55] reported a 1-mo response rate of 56.3% and a 6-mo response rate of 52.6%, using response rates as defined by the EASL criteria[55]. For the treatment of HCCs that became refractory to TACE with epirubicin-eluting Hepasphere, changing the impregnated anti-cancer drug to cisplatin resulted in a response at 6 months in 40% of patients[56].

Several retrospective studies showed the safety and efficacy in DEB-TACE group were significantly higher than in cTACE group (Table 1)[57-59].

However, clear evidence of DEB-TACE superiority compared to cTACE has not been established to date.

**LIMITATIONS**

There are limitations in this review. First, this is not a systemic review. Therefore, this article may have the potential biases of the authors. Second, we mostly described Japanese history of TACE for HCC in this review.

**CONCLUSION**

Improvement of the therapeutic effects of TACE treatment for HCC has been obtained by progression in techniques, drugs, and therapeutic equipment. In a variety of TACE treatments, selecting the anti-cancer agents, treatment methods and equipment for the best therapeutic effect is becoming more important. In the future, it is necessary to clarify the optimal treatment choices for each HCC patient.

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**Figure 1 A patient with unresectable hepatocellular carcinoma who received balloon-occluded TACE with miriplatin.** A:Micro balloon catheter was inserted into A8. Feeding artery was occluded using micro balloon (arrow). Miriplatin/lipiodol suspension and 1-mm gelatin sponge particles were administrated slowly under balloon occlusion; B: Treated lesion showed a dense accumulation of lipiodol (arrow head).

**Table 1 Summary of key prospective trials and retrospective studies for the treatment of hepatocellular carcinoma**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  | Overall survival (%) |
| 　 | Ref. | Year | Analysis | No. of patients | Objective response (%) | 1 yr | 2 yr | 3 yr |
| cTACE |  |  |  |  |  |  |  |  |
|  | Llovet *et al*[7] | 2002 | Prospective | 40 | 35 (at 6 mo) | 82 | 63 | 29 |
|  | Lo *et al*[8] | 2002 | Prospective | 40 | 39 (at 3 mo) | 57 | 31 | 26 |
|  | Takayasu *et al*[10] | 2006 | Prospective | 8510 | NA | 82 | 63 | 47 |
| DEB-TACE |  |  |  |  |  |  |  |  |
|  | Lammer *et al*[52] | 2010 | Prospective | 102 | 51.6 (at 6 mo) | NA | NA | NA |
|  | Sacco *et al*[54] | 2011 | Prospective | 33 | 100 (at 1 mo) | NA | 86.8 | NA |
|  | Song *et al*[57] | 2012 | Retrospective | 60 | 81.6 (at 3 mo) | 88 | NA | NA |
| 　 | Wiggermann *et al*[58] | 2011 | Retrospective | 22 | 22.7 (at 8 mo) | 70 | NA | NA |
|  |  |  |  |  |  |  |  |  |

TACE: Transcatheter arterial chemoembolization; DEB: Drug-eluting bead.

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