Review Article

Transarterial chemoembolization for hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is common cancer in the world. Hepatitis B/C or alcoholic cirrhosis is usually underlying condition. Surgical resection is curative treatment for small HCC, however most patients usually present when advanced or inoperable disease. Transarterial chemoembolization (TACE) is most common alternative treatment for early and advanced HCC. Curative treatment is possible in some selected cases. Multiple techniques of treatment are now developed with improving result. Different chemotherapeutic drugs or embolic agents are now available without complication or less toxicity. Some limitation such as portal vein thrombosis or hepatoportal/hepatovenous shunt can be treated with TACE in selected cases. Multimodality or combined therapy improves survival for complicated cases. Complication rate is low when carefully perform with good knowledge. We found that TACE is feasible and effective treatment for inoperable HCC.

Key words: Hepatocellular carcinoma (HCC), Hepatitis B/C, Transarterial chemoembolization (TACE)

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Introduction

Hepatocellular carcinoma (HCC) is common tumor in the world. Hepatitis B or C is usually underlying disease associated with or without liver cirrhosis. When liver cirrhosis is developed, dysplastic nodule will be risk for transformation to HCC with diversion of portal venous blood supply to hepatic arterial supply. This characteristic of HCC provides a basic rationale of transarterial therapy as an effective treatment for inoperable HCC.

Many techniques of treatment from transarterial therapy are developed, including transarterial embolization (TAE), intraarterial chemoinfusion therapy (IA), chemoembolization with or without drug-eluting beads and radioembolization using yttrium 90 (90Y).

Transarterial embolization (TAE) are performed for treated liver malignancy by occluding its blood supply that was introduced in 1950s and continued to be the basis of transarterial embolization in the treatment of unresectable disease, goal of completely occluding the tumor-feeding arterioles. Although particles smaller than 40 mm. preferentially (6-12 folds) accumulate in tumor vasculatures, they may pass through sinusoids and tumor related arteriovenous shunts into the systemic circulation, and may produce serious embolic complications. Embolization of the feeding arteries has been shown to induce tumor necrosis and cell death; however recent research has shown that tumor ischemia and hypoxia may actually result in stimulating neoangiogenesis and providing a mechanism for resisting apoptosis. Brown *et al*[1] retrospectively evaluated survival outcomes in 46 patients with HCC treated with transarterial embolization over a 4 year period, underwent 86 sessions of transarterial embolization, in which 81% experienced postembolization syndrome. They concluded that particle embolization for HCC was well tolerated and demonstrated actuarial survivals of 50% and 33% at 1 and 2 years, respectively.

Intra-arterial chemoinfusion is another treatment with rationale for regional chemotherapy to maximize drug concentrations and tumor drug uptake in the target organ and minimize systemic toxicity. The concept is that regional delivery of a drug leads to increased local drug concentration to increased therapeutic response and decreased systemic exposure of that drug. Okusaka *et al*[2] published a randomized phase III trial comparing transarterial chemoembolization and infusion chemotherapy for the treatment of patients with unresectable HCC. In this prospective 161-patient study, there was no significant difference when the median overall survival time was compared between these two therapies.

Transarterial chemoembolization (TACE) with using of anticancer drugs followed by gelfoam are conventional techniques for treatment of HCC in many centers, introduced by Yamada *et al* in the late 1970s. Chemoembolization is currently defined as the infusion of a mixture of chemotherapeutic agents with or without iodized oil, followed by embolization with particles. The concept of chemoembolization is to administer potent chemotherapeutic agent (s) into the hepatic arteries supplying the tumor. This is followed by embolization of the target vessels with agents such as gelfoam, polyvinyl alcohol, or acrylic copolymer gelatin particles. Two purpose of embolization are preventing washout of the drug at the site of the tumor and inducing ischemic necrosis. Several variations of this technique have been demonstrated with difference in the characteristics of the patients treated, the choice of the embolizing agents used, the choice and/or dose of the anticancer agents used, embolization end-points, and the schedule and/or interval of retreatment[3]. For treatment of HCC, single-agent Doxorubicin is commonly used worldwide, whereas the combination of Mitomycin-C, Doxorubicin, and Cisplatin is preferred in the United States. However in Thailand, we prefer combination of Mitomycin-C and 5-FU emulsified in lipiodol, an oily contrast agent believed to increase intratumoral retention of the cytotoxic agent. Iodized oil acts as a carrier of chemotherapeutic agents, which are released slowly from the lipiodol mixture and remain selectively in the neovasculature and extravascular spaces of liver tumors when injected into the hepatic artery, and persists selectively in the tumor for few weeks or months. In 2006, Takayasu *et al*[4] published data from a

large cohort study of 8,510 HCC patients treated with transarterial chemoembolization (lipiodol, chemotherapy, gelatin sponge). The overall median survival was 34 months and 1, 3, 5 and 7-year survival rates were 82%, 47%, 26%, and 16%, respectively.

Drug eluting beads are new mechanism of enhancing the delivery of potent anticancer agents to the site of the tumor. The concept of drug-eluting beads is to load polyvinyl alcohol–based microspheres with various types of chemotherapeutic agents and deliver them intra-arterially allowing for fixed dosing and release the anticancer agents in a sustained and controlled manner. Significant reductions of peak plasma concentrations have been observed with drug-eluting beads when compared with conventional chemoembolization. An example of drug-eluting beads is the Doxorubicin-capable bead or DC bead, loaded with Doxorubicin to 25 mg/ml. on hydrated beads by immersing them in a drug solution for 1 to 120 minutes. Varela *et al*[5] reported on the applicability, safety and efficacy of drug eluting beads in 27 patients with HCC. Objective responses of 66.6% were reported by using the European Association for the Study of the Liver (EASL). Malagari *et al*[6] have reported on 71 patients prospectively enrolled and treated segmentally with drug-eluting beads. The overall survival at 30 months was 88.2%. Poon *et al*[7] reported a phase I and II study in which drug-eluting beads were used for patients with incurable HCC and Child-Pugh class A cirrhosis. The phase I study was a dose-escalation study, from 25 to 150 mg of Doxorubicin. The 150-mg dose was used for the phase II study. According to the modified RECIST criteria, by taking into account the extent of tumor necrosis, 63% of patient had a partial response and 7% had a complete response.

Radioembolization is another new treatment which can deliver radiation doses as high as 150 Gy without developing the clinical complications. Two radioembolic devices are commercially available. The first one is TheraSphere (glass microsphere) that was approved in 1999 by the Food and Drug Administration for the treatment of unresectable HCC. Another is SIR-Spheres (resin microsphere) that were approval in 2002 from the Food and Drug Administration for the treatment of colorectal metastases in conjunction with intrahepatic FUDR. 90 Y is a pure beta emitter that decays to stable zirconium 90. Its physical half-life is 64.2 hours. Resin microspheres (20–60 micron in diameter) differ from glass microspheres (20–30 micron in diameter) in that they have a lower specific activity, lower specific gravity, and higher number of particles per treatment. Geschwind *et al*[8] reported findings in 80 patients with inoperable HCC treated with 90 Y microspheres by using segmental, regional and whole-liver approach. Median survival for Okuda stage I (68%) and stage II (38%) was 628 and 324 days, respectively. Salem *et al*[9] published their 291 patient single-center experience on the role of radioembolization in patients with HCC. They found that patients with HCC in Child-Pugh class A disease with or without vascular invasion benefited most from radioembolization.

Conventional TACE

For inoperable HCC, chemoembolization are still effective alternative treatment for palliative or curative purpose. Common indication/contraindication for TACE are usually mentioned in many centers including;

Indication

- solitary or multiple lesions in patients with Child-Pugh A and B
- diffused disease of HCC in one lobe with Child-Pugh A and B
- bleeding or intractable pain due to tumor
- postoperative recurrence

Absolute contraindications

- extensive disease with Child-Pugh C
- intractable systemic infection

Relative contraindications

- extrahepatic metastasis
- Child-Pugh C
- diffused disease in both lobes
- intractable arteriovenous fistula
- severe main portal vein thrombosis
- tumor invasion to IVC and right atrium
- biliary-enteric anastomosis

TACE is well established for treatment of hepatoma, especially in cases of solitary of multiple lesions in one lobe with patient status in Child-Pugh classification A or B[10]. Effectiveness of treatment is documented when performed in segment TACE and collateral TACE. Superselective catheterization with coaxial technique is mandatory for segmental TACE. Several types of small catheters and guide wires are introduced through a 5-6 Fr angiographic catheters. Lipiodol is indispensable material for segmental TACE to mix with anticancer drug. Using of non-ionic contrast media, anticancer drug and lipiodol to make water-in-oil emulsion. Optimal dose of lipidol is estimated individually in each case according to the size of the tumor. Diverse anatomical variation in celiac axis and superior mesenteric arteries may be found. Evaluation of vascular anatomy before TACE is essential for a perfect procedure. In the cases with celiac axis stenosis or occlusion, collateral pathways develop in different ways. A through knowledge for the anatomical variations and major collateral pathways are important for TACE. It is essential to determine whether extrahepatic supply to tumor is presented. Signs of direct invasion into adjacent organs or extrahepatic collaterals in the initial CT or MRI examination may present. Tumor with exophytic growth patterns prone to have collaterals. The location of tumor near to ligaments or bare area also suggests extrahepatic supply. In a postoperative recurrence at the surgical margin, omental collaterals should be suspected. There are a variety of arteries as extrahepatic collaterals in patients with HCC including inferior phrenic artery, omental artery and internal mammary artery. TACE through the collaterals such as inferior phrenic or internal mammary artery are essential for the complete embolization of the tumor and it may improve the therapeutic effect resulting in longer survival.

CT or MRI is essential to evaluate nature of tumor, arterial anatomy of hepatic blood supply and extrahepatic collateral pathways, tumor response after treatment and follow up study for detection of recurrent tumor. Using new developed machine, we can find small foci of satellite nodules before perform TACE for pre-procedural planning and possible perform complete chemoembolization in single session or follow up study before next treatment session. Angiographic findings with new technology of DSA (digital subtraction angiography) provide clearly detail of feeding artery and extrahepatic blood supply. With microcatheter system (2-3 Fr), we can select microcatheter to small feeding arteries more distally to perform TACE in segmental or subsegmental techniques for purpose of more tumor staining and less staining in normal parenchyma by using infusion of mixture of lipiodol and chemotherapeutic agents. Embolization feeding artery by embolic agents at peripheral portion of hepatic artery as much as possible is preferred for prevention of washout of chemotherapeutic agents and induction of ischemic necrosis at tumor. Purpose of lipiodol (Gyerbet Labolatory, Roissy France) use for TACE are mandatory for drug carrier and localized chemotherapeutic agent in tumor, microvessel embolic agent and augment antitumor effect by efflux of mixed lipiodol and chemotherapeutic agent into portal vein. Usual dose of lipiodol is upon size of tumors; however dose 1-10 ml of lipidol for conventional TACE is usually adequate for each session of treatment. Several chemotherapeutic agents are commonly used for TACE, these agents are Doxorubicin, Epirubicin, Aclarubicin, 5-Fluorouracil, Mitomycin, Cisplatin, Strene maleic acid neocarzinostatinetc[11]. For our practice, common agents that we use for TACE are Mitomycin-C and 5-Flurouracil with varying dose up to 20 mg of Mitomycin-C and 500 mg. of 5-Flurouracil *per* session depended on tumor size and number of tumor intended to treat. Embolization by using embolic material agents are performed with many embolic agents available such as gelatin sponges (most commonly use), polyvinyl alcohol (PVA), microsphere, steel coil, autologous blood clot etc. However in our practice, we prefer gelatin sponges in pellet or fragment mixed with diluted non-ionic contrast medium for occluded peripheral blood supply to tumor after infusion of mixed chemotherapeutic drug and lipiodol (Figure 1)

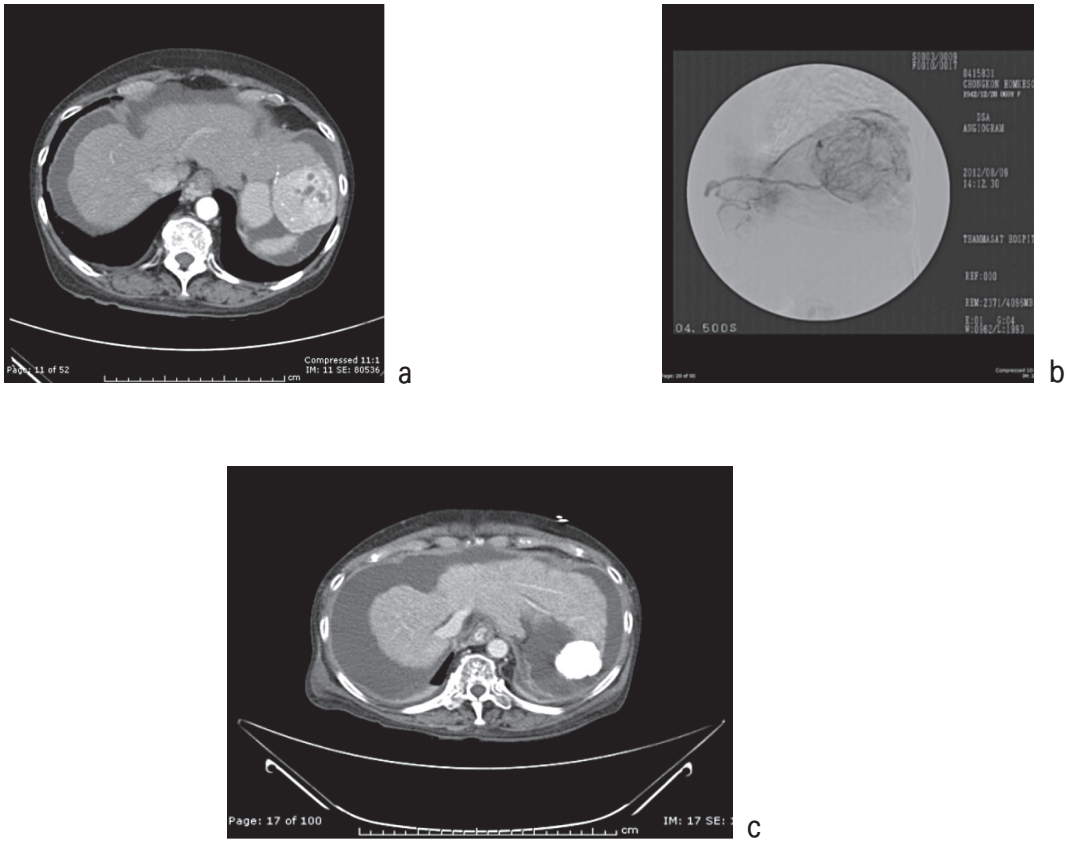

Figure 1 (a) Multiple HCC at right hepatic lobe after multiple session of TACE at right hepatic artery, presented with recurrent HCC at left lobe on follow up CT. (b) During segmental TACE showed feeding vessel from left hepatic artery. and (c) CT follow up 5 months after 2nd session of TACE showed no residual tumor at left lobe HCC.

We usually perform TACE in segmental or subsegmental techniques for improving survival in compensated liver cirrhosis with inoperable HCC. Silvia *et al*[12] performed segmentally or subsegmentally TACE at 56 patients with inoperable HCC and compensated cirrhosis (Child-Pugh class A or B) by using mixture of Epirubicin (30-80 mg.), lipiodol (4-16 ml.) and gelfoam embolization. They compared between treated groups and control groups that showed 3-year survival rate were 56% and 50%, respectively. They found that survival in patients with compensated cirrhosis and inoperable HCC did not appear to improve with the use of TACE therapy. However another report of superselective TACE by Shiro *et al*[13] showed better result. They published data of ultraselective TACE with 2-Fr tip microcatheter for small HCC compared between local tumor recurrence and visualization of the portal vein with iodized oil. 123 tumors smaller than 5 cm in diameter were treated with TACE by using a 2-Fr tip microcatheter at a distal portion of the subsegmental artery of the liver. Portal vein visualization at spot radiography during TACE was divided into three grades (0: not visualized, 1: limited near the tumor, 2: whole or extended to the embolized area). Local recurrent rates of each grade groups were compared. The local recurrent rates for the grade 2, 1 and 0 groups were 7.9%, 24.8%, and 85.7%, respectively at 12 months and 17.7%, 38.9%, and 85.7% at 24 months. Recurrent rates in the grade 2 group were significantly lower than those in the grade 1 and 0 groups. They concluded that ultraselective TACE was safe and effective. In particular, local recurrence was significantly lower when a greater degree of portal vein visualization was demonstrated during TACE.

Extrahepatic collateral route

Extrahepatic collateral vessels commonly supply HCC if tumors are large or peripherally located. We suspected extrahepatic collateral vessels when *(a)* a tumor grew exophytically or invaded adjacent organs, *(b)* a tumor was in contact with the ligaments and bare area of the liver, *(c)* a hypertrophied extrahepatic collateral vessel was observed on a computed tomographic (CT) scan, *(d)* a peripheral defect of iodized oil retention within a tumor was seen during chemoembolization or on a follow-up CT scan, *(e)* a local recurrence developed at the peripheral portion of the treated tumor during follow-up, or *(f)* a sustained elevation in serum alpha-fetoprotein level was noted despite adequate embolization of the hepatic artery.

Multiple extrahepatic collateral vessels are described by Hyo-Cheol Kim *et al*[14]. The right inferior phrenic artery was found to be the most common extrahepatic collateral vessel that supplies HCC (Figure 2). The right and the left inferior phrenic arteries usually originate from the celiac trunk or directly from the aorta as a common trunk or independent origins and less frequently from the renal arteries. When the tumor is located in liver segment S7 and is in contact with the right hemidiaphragm, selective angiography of the right inferior phrenic artery is mandatory. When the tumor is located in liver segments S2 or S3 and abuts the left hemidiaphragm, the possibility of a collateral blood supply from the left inferior phrenic artery should be considered.

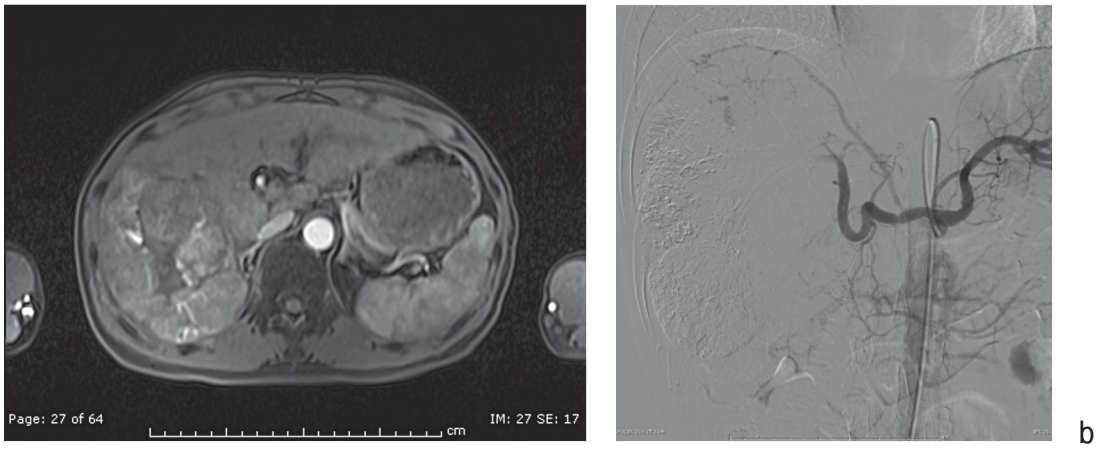

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Figure 2 HCC supply by multiple collateral vessels. (a) MRI obtained after six sessions of TACE shows residual tumor. (b) Right inferior phrenic artery supply superior part of tumor after 7th TACE at right hepatic artery.

When a HCC is located in ventral hepatic areas, abutting the diaphragm and anterior abdominal wall, the internal mammary arteries may serve as feeding arteries. HCCs located in liver segments S8 or S4 are fed by the right internal mammary artery, whereas those located in the left lateral segment are fed by the left internal mammary arteries. HCCs abutting the inferolateral aspect of the diaphragm are frequently supplied by the posterior intercostal arteries (Figure 3). HCCs invading the abdominal wall were also found to be supplied by the lower intercostal, subcostal, or lumbar arteries. A microcatheter should be advanced beyond the diaphragmatic insertion to the thoracic cage, where a sharp upward turn is seen, to avoid possible complications such as skin necrosis and spinal infarction[15]. The common levels of the intercostal arteries that supply HCCs are T10, T9, and T11, in order of frequency.

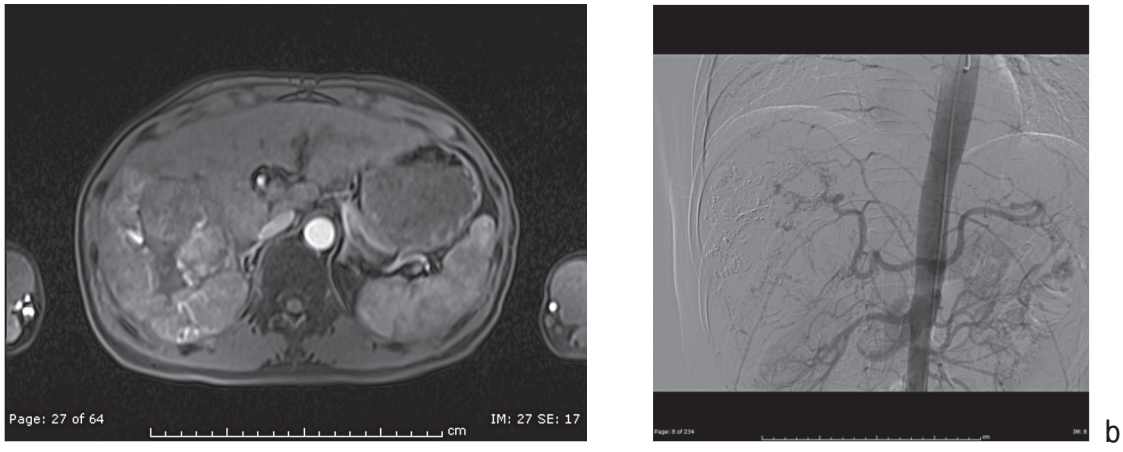

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Figure 3 HCC supply by multiple collateral vessels (same patient in Figure 2). (a) MRI obtained after six sessions of TACE shows residual tumor. (b) Multiple posterior intercostal artery (9^{th}-11^{th}) supply posterior part of tumor are found on aortogram.

Omental branches usually are small and branch at an acute angle from the gastroepiploic artery. Several omental branches exist in healthy patients, but they are hardly recognized on angiograms. However, when an omental branch supplies an HCC, it becomes sufficiently dilated to be recognizable at celiac angiography. The anatomic location of the tumor adjacent to the bare area and suspensory ligaments of the liver and direct invasion of or adhesions to adjacent organs seem to be primary causes. Other vessels with possibility of extrahepatic collateral vessels are adrenal artery, renal and renal capsular artery, superior mesenteric artery, gastric artery and cystic artery (Figure 4).

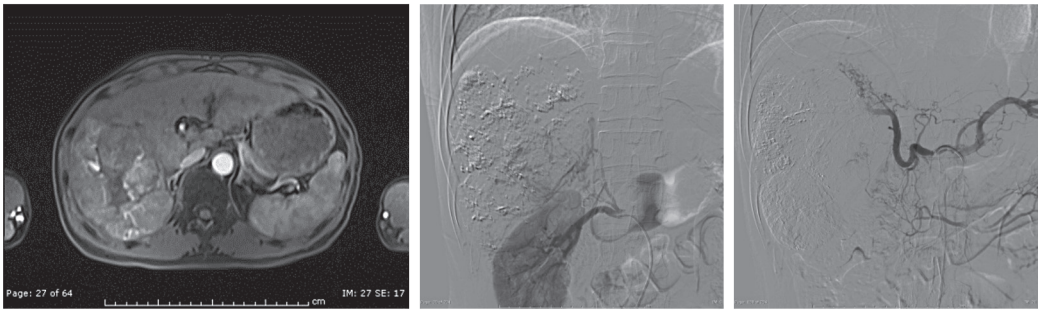

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Figure 4 HCC supply by multiple collateral vessels (same patient in Figure 5). (a) MRI obtained after six sessions of TACE shows residual tumor. (b) Right inferior adrenal artery from right renal artery and (c) Omental branch of gastroduodenal artery (GDA) supply inferior part of tumor.

CT scan provides useful information, and CT signs of direct invasion into adjacent organs or extracapsular infiltration indicate the presence of extrahepatic collateral vessels. Tumors with an exophytic growth pattern are prone to collateral vessels development. If a tumor is in contact with the ligaments and bare area of the liver, there is a high chance of parasitic supply from extrahepatic collateral vessels even in small tumors.

The correlation of CT and angiographic findings is essential. If a tumor observed at CT is not demonstrated at

hepatic angiography, collateral vessels must be investigated. When collateral vessels are chemoembolized, there is a risk of embolizing normal branches, which can lead to a variety of complications. To avoid these complications, selective catheterization should be achieved by placing the catheter tip as close as possible to the specific branch or branches supplying a neoplasm.

Vascular invasion

A known complication of HCC is tumor or bland portal vein thrombus (PV) which are considered relative contraindication to TACE or at least to represent an increased risk for complication after procedure, including acute liver failure or infarction[16, 17]. It is well-established that patients with unresectable HCC and portal vein thrombosis have a worse prognosis than those without PV thrombosis irrespective of disease stage or treatment[18 - 21]. However report from Christos *et al*[22] with prospective study in 32 consecutive patients with unresectable. HCC and PV thrombosis who underwent treatment with TACE. Using microcatheter for selective catheterization of the right or left hepatic artery, followed by infusion of 7–10 ml of a solution containing Cisplatin 100 mg (Bristol Myers Squibb, Princeton, NJ), Doxorubicin 50 mg (Pharmacia & Upjohn) and Mitomycin-C 10 mg (Bedford Laboratories, Bedford, OH) mixed with Ethiodol (Savage Laboratories, Melville, NY) in a 1:1 volume ratio or a 2:1 ratio, with twice as much chemotherapeutic agent as Ethiodol, depending on flow characteristics, to avoid complete stasis within the selected hepatic artery. This was followed by infusion of 1–2 ml of Embosphere particles (Biosphere Medical, Rockland, MA) measuring 300–500 micron in size to slow down arterial inflow and prevent washout of the chemotherapeutic agents. Repeated TACE was performed every 6 weeks unless patients developed a contraindication or MR imaging showed complete response. Median overall survival was 9.5 months (range 3–50 months). Child-Pugh numerical disease stage was the prognostic factor most strongly related to survival. The 30-day mortality rate was zero and there was no evidence of TACE-related hepatic infarction or acute liver failure. The 6, 9, 12 and 18 month survival rates were 60%, 47%, 25% and 12.5% respectively. They concluded that PV thrombosis should not be considered a contraindication to TACE. Compared with historical control subjects who received traditional forms of treatment, the patients in the present study had extended survival. In my experience both hepatic and portal vein thrombus could be treated carefully by methods of chemoembolization which could prolong survival in these patient groups (Figure 5).

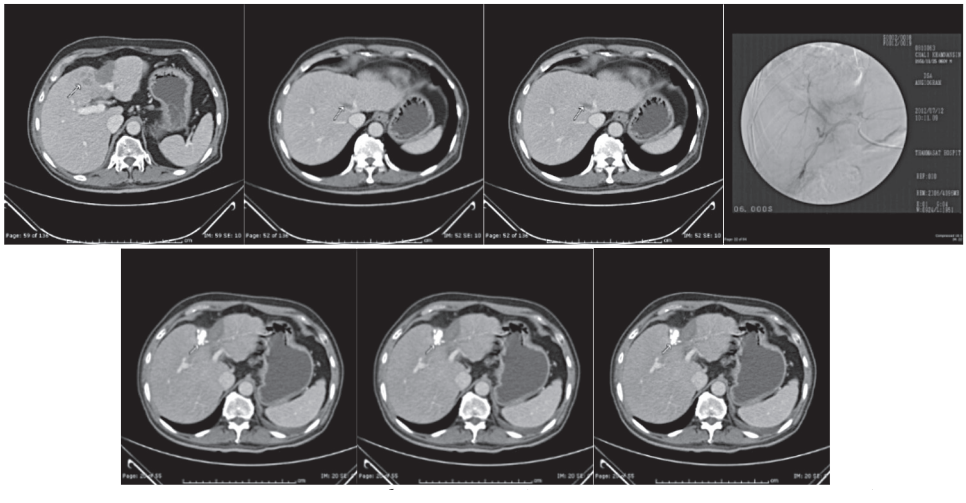

Figure 5 Recurrent HCC at left hepatic lobe after RFA 8 months present with recurrent HCC at left lobe and middle hepatic vein, IVC tumor thrombus on follow up CT (upper row). Segmental TACE showed feeding vessel from left hepatic artery with hepatic vein/IVC shunting (left top) and CT follow up 6 months after 3rd session of TACE/IA showed minimal residual tumor at hepatic vein (lower row).

Other problems are arteriovenous shunting from hepatic artery to portal vein and/or hepatic vein, which are relative contraindication for TACE. However, we can occlude shunt before TACE for preventing post-procedural complication. Retrospective report of Chan *et al*[23] in 11 patients with significant arteriovenous shunts during performance of pre TACE hepatic angiogram for HCC were treated by different types of embolic agents depended on angio-architecture of the shunt and operator's experience. They classified the shunts according to their angio-architecture. Simple shunts were defined as those with a single feeding artery and a single draining vein, essentially arteriovenous fistula. Complex shunts were defined as those with multiple arterial feeders and/or multiple venous outflows. The embolic agents are included coils, PVA particles (PVA, Ivalon Contour 350-500 emboli; Boston Scientific, Mississauga [ON], Canada), Histoacryl (NBCA, N-butyl cyanoacrylate; B Braun, Melsungen, Germany) mixed with lipiodol (Laboratory Guerbet, Roissy, France) at a ratio of 1:2, and absolute alcohol (dehydrated alcohol BP, DBL; Mayne Pharma Pty, Melbourne, Australia). For simple shunt, they used coil embolization for shunt embolization and used liquid (ethanol or glue) or particulate agents (e.g. PVA) for complex shunt. Amount of absolute ethanol injection are ranged from 2.5-7.5 ml per embolization. Then subsequent TACEs were successfully performed without complications.

Although not common, hepatic artery to hepatic vein shunt may be presented during angiogram. Transcatheter arterial chemoembolization (TACE) using iodized oil in hepatocellular carcinoma with AV shunt has the potential risk of pulmonary embolism or infarction because the iodized oil can pass through the shunt[24, 25]. Generally pulmonary complications after TACE are usually asymptomatic or self-limited, with reported incidence of 0.17%[24]. But the incidence of pulmonary oil embolization increases to 43% when a large amount of iodized oil is used for TACE[26]. However TACE can perform safely by using balloon occlusion at hepatic vein reporting by Lee *et al*[27]. They performed TACE in 11 patients with HCC and angiographic finding of AV shunt, with occlusion of the shunt-draining hepatic veins using temporary occlusion balloon catheters. All tumors were in the right lobe, and all AV shunts were between the right hepatic artery and right hepatic vein. The occlusion balloon was inserted via femoral or jugular venous access. The balloon diameter ranged from 8.5 to 11.5 mm and time of ballooning was 3 to 15 minutes. TACE was performed using emulsion of iodized oil and Doxorubicin, followed by gelfoam embolization. The balloon was deflated immediately after chemoembolization, and then physical examination and chest radiography were performed. The technical success rate was 100% with no symptom, sign, or radiographic evidence of pulmonary complication. Follow-up computed tomography revealed complete iodized oil uptake by the tumor without iodized oil uptake in the lungs. Temporary balloon occlusion of the hepatic vein in hepatocellular carcinoma with AV shunt allowed completion of TACE using conventional method while preventing pulmonary complications.

Embolic and chemotherapeutic agents

About chemotherapeutic agent, there are many chemotherapeutic regimens as protocols. Doxorubicin[28, 29], 5-fluorouracil[30], Cisplatin[29, 31], Mitomycin-C[29, 32], Epirubicin[33, 34], and Neocarzinostatin[35] have been used at different doses alone or in various combinations. One comparative study[36] with use of Cisplatin (CDDP), lipiodol (LPD) suspension (CDDP/LPD) compared with that use of Doxorubicin hydrochloride (ADM), lipiodol (LPD) emulsion (ADM/LPD) in patients with unresectable hepatocellular carcinoma (HCC). CDDP/LPD was given at a dose of 15–70 mg, whereas ADM/LPD was given at a dose of 20–100 mg throughout the study period. The survival rates in the CDDP/LPD group were 81% at 1 year, 41% at 3 years, 19% at 5 years, and 13% at 7 years, whereas those in the ADM/LPD group were 67% at 1 year, 18% at 3 years, and 0% at 5 years. The CDDP/LPD group showed significantly better survival than the ADM/LPD group ($p < 0.05$). The study concluded that TACE with use of low-dose CDDP was efficacious for unresectable HCC and had few complications. TACE with use of CDDP may contribute to prolongation of the life span of patients with HCC versus TACE with use of ADM.

For occlusion of peripheral blood supply at tumor after infusion of mixed chemotherapeutic drug, we can use any embolic material agents such as gelatin sponges (most commonly use), polyvinyl alcohol (PVA), microsphere, steel coil, autologous blood clot etc. However in series of Brown *et al*, compared outcomes of TACE for HCC with gelfoam powder and polyvinyl alcohol (PVA) by using same chemotherapeutic drugs with 50 mg Cisplatin, 20 mg Doxorubicin, 10 mg Mitomycin-C in both groups. The groups were statistically similar in all categories regarding liver function, Child-Pugh score, tumor size, hepatitis status, and percentage of patients with Child class A, B, and C disease. Overall survival was similar between groups (519 days in gelfoam powder, 511 days in PVA groups) and found that survival after treatment of HCC with TACE by using gelfoam powder or PVA were similar[37].

Drug eluting beads (DEB-TACE) for inoperable hepatocellular carcinoma (HCC) are more commonly performed in recent day. Retrospective study in 130 patients[38], with inoperable HCC was treated with DEB-TACE by using 100-300 micron LC beads loaded with 100 mg of Doxorubicin (Adriamycin). DEB-TACE was technically successful in all (100%) with mean hospital stay at 2 days. Thirty day mortality was 0.8% and response on EASL was 68%. Survival at 6, 12 and 24 months were 75%, 52% and 32%. They concluded that DEB-TACE is safe and effective in the treatment of inoperable HCC. Study of other drug eluting bead[39], using HepaSphere™ microspheres (Bio Sphere Medical, Rockland, Maryland) loaded with Doxorubicin (Adriamycin RDF, Rubex) in patients with unresectable hepatocellular carcinoma and compared this series with traditional TACE [TACE with Lipiodol and Spongostan (Johnson & Johnson Medical, New Brunswick, New Jersey)], showed immediate technical success rate 100%. Survival at 6 months was 94.1% in HepaSphere™, 91.3% in Embosphere and 77% in Spongostan group; survival at 12 months was 83.3% in HepaSphere™, 73.9% in Embosphere and 59.1% in Spongostan group. TACE using HepaSphere™ is feasible, with low complication rate and promising efficacy. The results seem to be better than standard TACE with Embosphere and gelfoam.

In our experiences, we usually use drug eluting bead in patients with receiving systemic toxicity of conventional TACE or underlying poor liver function. We found that drug eluting bead provided better result and short hospital stay with less systemic toxicity. However, long term benefits are still controversy (Figure 6, 7).

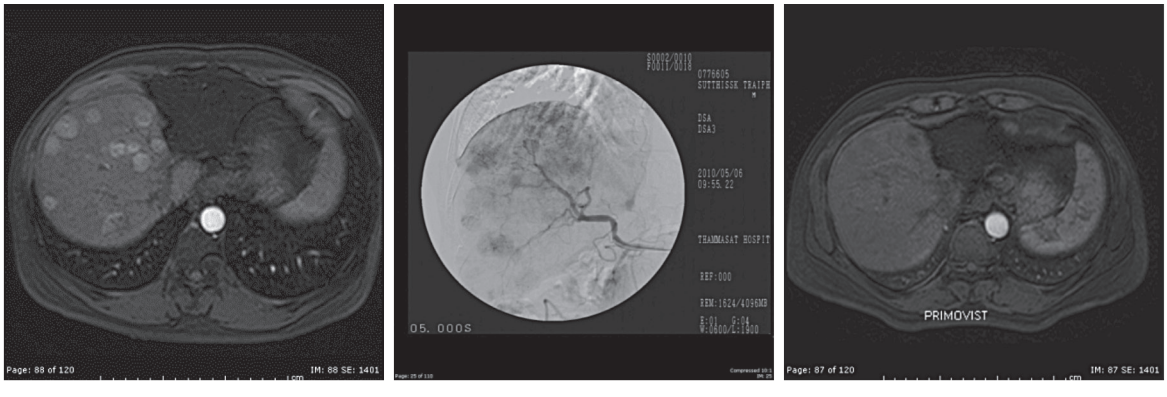

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Figure 6 (a) Recurrent HCC at right hepatic lobe after left hepatectomy 2 years for left lobe HCC presented with multiple recurrent HCC at right lobe on follow up CT. (b) During DC bead infusion, right hepatic angiogram showed small feeding vessels from right hepatic artery and (c) MRI follow up 4 months after 2nd session of DEB-TACE showed no residual tumor at right lobe.

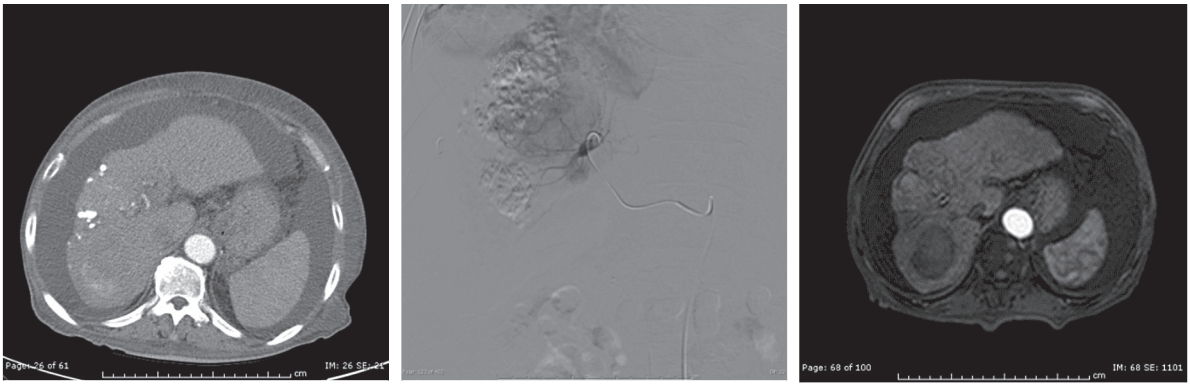

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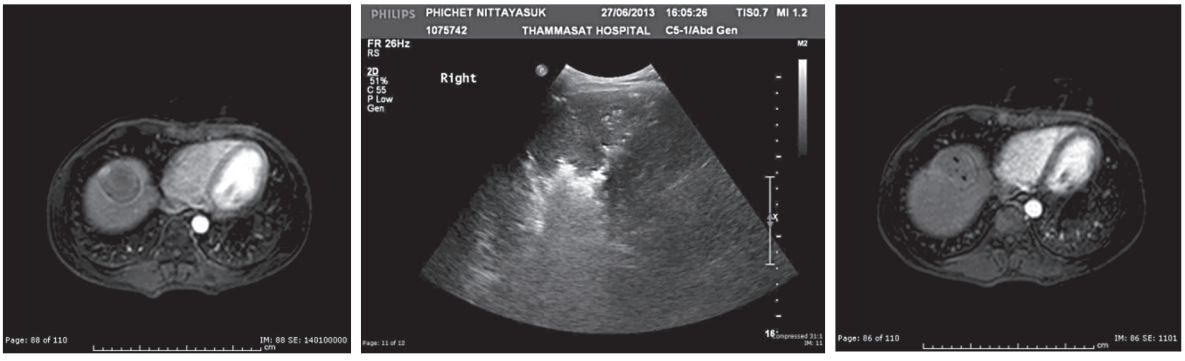
Figure 7 (a) Diffused HCC at right hepatic lobe after 2nd TACE with residual HCC at posterior aspect of right lobe on follow up CT (b) During HepaSphere bead infusion, right hepatic angiogram showed small feeding vessels from posterior branch of right hepatic artery and (c) MRI follow up 1 month after HepaSphere infusion showed no residual tumor at posterior segment of right lobe.

Combined therapy

In advanced disease or complex HCC or residual/ recurrent tumor after multiple sessions of TACE, combination with other treatment modalities seem to be benefit and prolong survival in these patients such as combination of TACE with ablation or systemic therapies[40]. Maluccio *et al*[41] published findings of a comparative study of surgical resection *versus* transarterial embolization with ablation in patients with HCC. The authors concluded that transarterial embolization in combination with ablation is effective for treatment of solitary HCC tumors up to 7 cm and achieved overall survival rates similar to those of surgical resection in selected patients. Morimoto *et al*[42] published findings of a randomized study of 37 patients with solitary HCC 3–5-cm in size, treated with either chemoembolization and radiofrequency ablation or chemoembolization alone. They concluded that radiofrequency ablation combined with chemoembolization is more effective than radiofrequency ablation alone for extending the ablated area in fewer treatment sessions and for decreasing the local tumor progression rate.

Transcatheter therapies, combined with systemic therapies, particularly in those with metastatic disease, are also likely to improve survival. Hendlisz *et al*[43] reported that radioembolization with 90 Y resin microspheres plus 5-fluorouracil is well tolerated and significantly improves time-to-liver progression and time to progression than does 5-fluorouracil alone.

In our experiences, combination of TACE and RFA are commonly performed in cases of residual tumor after TACE or high risk group for organs complication after TACE (e.g. complication at gallbladder or GI tract). TACE can perform with additional RFA for purpose of complete tumor necrosis without complication (Figure 8).



a b c

Figure 8 Multiple HCC at right hepatic lobe after 4th TACE : (a) residual HCC at anterior margin of segment 8 HCC on MRI follow up (b) During RFA by ultrasound guidance and (c) MRI follow up 1 month after RFA showed no residual tumor at anterior part of right lobe.

Complication

The most common complication of TACE is postembolization syndrome that consists of transient abdominal pain and fever occurring in 60-80% of the patients after TACE[44]. Elevation of the level of hepatic transaminases typically accompanies post-embolization syndrome[45]. Whether post-embolization syndrome reflects damage to the normal liver parenchyma or tumor necrosis is uncertain. 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[45, 46]. 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%[47]. 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[48]. 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 such as percutaneous drainage or a cholecystectomy[49, 50]. Development of a liver abscess has been linked to previous intervention in the biliary system being prone to an ascending biliary infection[51]. 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 diffused dilatation of the intrahepatic ducts has been reported with a 0.5-2% incidence[52, 53]. Bilomas seem to be associated with the use of lipiodol and focal strictures of large bile ducts with the use of gelatin spongse particles[54]. 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. 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

Transarterial chemoembolization (TACE) is now common treatment modality for HCC. Curative aim is possible in some selected cases. Multiple techniques of treat-

ment are now developed with improving result and survival rate. Different chemotherapeutic drugs and embolic agents are now available without complication or less systemic toxicity. Some limitation such as portal vein thrombosis or hepatoportal/hepatovenous shunt can be treated with TACE in selected cases without complication. Multimodality or combined therapy improves survival for complicated cases. Complication rate is low when carefully perform with good knowledge. We found that TACE is feasible and effective treatment for HCC.

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บทคัดย่อ

การรักษามะเร็งตับด้วยการให้ยาเคมีบำบัดทางหลอดเลือดแดง

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มะเร็งตับเป็นมะเร็งที่พบบ่อย โดยมักพบในผู้ป่วยที่มีภาวะตับอักเสบเรื้อรังชนิด B หรือ C หรือเป็นตับแข็ง สำหรับการรักษาด้วยการผ่าตัด สามารถรักษาหายขาดได้ในกลุ่มที่ก้อนมะเร็งยังมีขนาดเล็ก แต่ผู้ป่วยส่วนใหญ่มักมาพบแพทย์เมื่อก้อนมะเร็งมีขนาดใหญ่ หรือเป็นระยะลุกลามที่ไม่สามารถผ่าตัดให้หายขาดได้ ดังนั้นการรักษาทางเลือกอื่นที่ได้ผลดี จึงมีการนำมาใช้ในผู้ป่วยกลุ่มนี้มากขึ้น โดยการรักษาที่ได้ผลค่อนข้างดี คือ การให้ยาเคมีบำบัดทางหลอดเลือดแดง (transarterial chemoembolization) และอาจรักษาหายขาดได้ในผู้ป่วยที่โรคมะเร็งยังไม่ลุกลามมาก โดยเทคนิควิธีการรักษาดังกล่าว ได้มีการศึกษาและพัฒนามาอย่างต่อเนื่องจนเป็นที่ยอมรับในปัจจุบัน ในส่วนของยาเคมีบำบัดหรือสารที่ใช้ทำการรักษาก็ได้มีการพัฒนาจนมีประสิทธิภาพมากขึ้นในปัจจุบันและมีผลข้างเคียงหรือความเสี่ยงน้อยลงเป็นลำดับ สำหรับผู้ป่วยบางรายที่มะเร็งมีการลุกลามไปที่หลอดเลือดดำ (portal vein thrombosis) หรือมีการรั่วของหลอดเลือดดำ (arteriovenous shunt) ก็สามารถรักษาได้ในรายที่ยังมีการลุกลามไม่มากนัก นอกจากนั้นการรักษาด้วย transarterial chemoembolization ร่วมกับการรักษาด้วยวิธีอื่น (radiofrequency ablation or systemic chemotherapy) พบว่า สามารถช่วยเพิ่มประสิทธิภาพในการรักษาและโอกาสหายขาดมากขึ้น ดังนั้นการรักษาด้วย transarterial chemoembolization จึงเป็นการรักษาทางเลือกที่มีประสิทธิภาพสำหรับผู้ป่วยมะเร็งตับที่ไม่สามารถผ่าตัดรักษาได้และอาจหายขาดได้ในผู้ป่วยที่ยังมีการลุกลามของโรคมะเร็งไม่มาก

คำสำคัญ: มะเร็งตับ, ภาวะตับอักเสบเรื้อรังชนิด B หรือ C, เคมีบำบัดทางหลอดเลือดแดง