

Chemoembolization for Hepatocellular Carcinoma (HCC)

Sobhonslidsuk A

ABSTRACT

Liver cancer is the most common cause of cancer death in Thailand. The majority of hepatocellular carcinoma (HCC) is diagnosed in the intermediate, advanced or terminal stage in which curative treatment is not feasible. The survival benefit of chemoembolization in intermediate HCC and some selected cases of advanced HCC was confirmed from two randomized controlled trials and meta-analysis studies. Predictors of outcome are tumor burden, degree of liver impairment, performance status and treatment response. The ideal candidates for chemoembolization are those with well-preserved liver function, multinodular tumors without vascular and distant metastasis. Post-embolization syndrome was found in nearly 80% of patients. New techniques of chemoembolization with the purpose of reducing the side effects of chemoembolization and increasing efficacy are under investigation.

Key words : Hepatocellular carcinoma, Chemoembolization, Liver transplantation, Resection, Ablation

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INTRODUCTION

Liver cancer is the leading cause of cancer death in Thailand. Hepatocellular carcinoma (HCC) and cholangiocarcinoma constitute the majority types of primary liver cancer.⁽¹⁾ HCC ranks the fifth most common cancer in the world. Regular alcoholic drinking and chronic hepatitis B viral infection are the most frequent causes of HCC in many countries in Asia-Pacific regions including Thailand.⁽¹⁾ Japan is a particular country in this region that has chronic hepatitis C as its primary cause of HCC. Comparing to HCC reported from western countries, the lower survival rate of HCC in this area is a unique feature.⁽²⁾ Lack of na-

tional policy and appropriate screening system may result in lower chance of detection of early stage HCC. The treatment of HCC should follow the staging of HCC and other relating factors although a large cohort study recently showed that only 40% of patients with early stage HCC received curative treatments that is liver transplantation, resection and percutaneous ablation.⁽³⁾

Staging of HCC and choices of treatment

Liver cirrhosis, chronic hepatitis B and hepatitis B carrier increases the risk of HCC development. The survival of HCC patients is associated with tumor stage

Division of Gastroenterology, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

Address for Correspondence: Abhasnee Sobhonslidsuk, M.D., Division of Gastroenterology, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand
Telephone: (66) 02-201-1304, (66) 081-349-8438 Fax: (66) 02-201-1387, E-mail: teasb@hotmail.com

and status of cirrhotic liver. Other factors that may affect the prognosis of patient survival are performance status, treatment efficacy and treatment response.⁽⁴⁾ The attempt to stratify patients with HCC according to tumor characteristics and underlying liver status was made by several HCC staging systems such as Okuda system, the Cancer of the Liver Italian Program (CLIP), the American Joint Committee on Cancer Tumor-Node-Metastasis (AJCC TNM). The emerging of Barcelona Clinic Liver Cancer (BCLC) staging system results in the prognostic stratification of HCC and the selection of suitable treatment according to the relevant stage of the disease. The BCLC staging system incorporates tumor characteristics, the status of liver cirrhosis categorized by Child-Pugh classification and performance status of patients.⁽⁴⁾ However, there is nothing perfect since the BCLC staging system lacks the consideration of age and other medical co-morbidities. According to the BCLC staging system, patients with very early stage or stage 0 (= a single tumor with diameter less than 2 cm) and early stage HCC or stage A (= a single tumor with diameter less than 5 cm or 2-3 tumors with the maximal diameter of 3 cm), the treatments of choice with the aim for curative treatment are resection, liver transplantation and percutaneous ablation (: radio-frequency ablation and percutaneous alcohol injection).⁽⁴⁻⁸⁾ The outcome of the curative treatment of this stage is quite impressive with 5-year survival approaching 75%.⁽⁴⁻⁸⁾ For intermediate stage HCC or stage B (= multinodular tumors without portal vein invasion

or distant metastasis) and advanced stage HCC or stage C (= multinodular tumors with portal vein invasion or worsening of performance status), the goal of management is for palliative therapy to prolong patient survival with good quality of life. The 3-year survival without treatment for intermediate stage HCC (or stage B) was about 50%.⁽⁴⁻⁸⁾ Chemoembolization is recommended for those with intermediate stage HCC.⁽⁴⁻⁸⁾ For advanced stage HCC (or stage C), the choice of treatment is limited; there is only molecular targeted therapy that was proved to extend patient survival and control progression of HCC temporarily.^(9,10) Chemoembolization may be beneficial in selected cases of advanced stage HCC.⁽⁶⁾ Lastly, symptomatic treatment is recommended for those who have terminal stage HCC (or stage D).⁽⁴⁻⁸⁾ The treatment algorithm of HCC with underlying liver cirrhosis is summarized in Figure 1.

Chemoembolization for HCC

Types and techniques of chemoembolization

Chemoembolization is proposed to be one of the treatments for HCC owing to a basic principle that liver cancer with a diameter greater than 2 cm receives blood supply mainly from hepatic artery, not from portal vein.⁽¹¹⁾ Theoretically, arterial embolization leads to ischemic necrosis of the liver cancer. Chemoembolization for HCC is aimed to deliver a very high dose of anticancer drugs directly to tumor cells, then prolong the exposure of anticancer drugs and the liver tumors by the process of hepatic arterial embolization.⁽¹²⁾

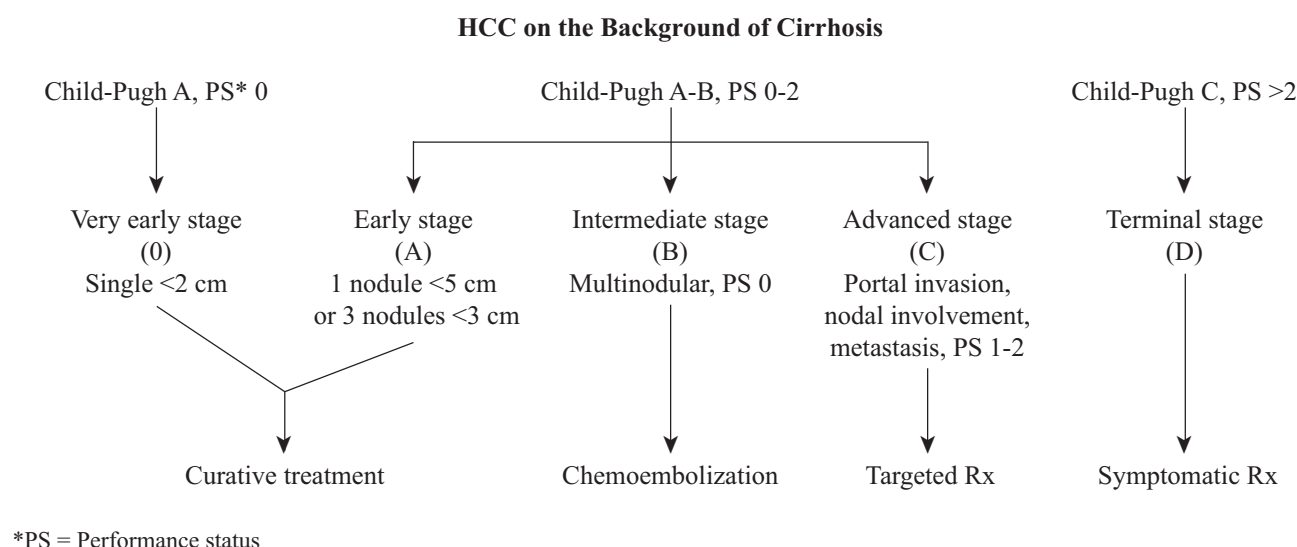


Figure 1. Algorithm of HCC treatment according to BCLC staging (adapt from Verslype C et al, 2009⁽⁵⁾).

Chemoembolization should also minimize systemic side effects of chemotherapeutic agents.⁽¹²⁾ For the treatment of HCC, chemoembolization is divided, by definition, into 4 types and techniques as following:⁽¹³⁾

I. Transarterial Embolization (TAE) - Only hepatic arterial occlusion is performed.

II. Transarterial Chemoembolization (TACE) - Hepatic arterial occlusion is performed after the infusion of chemotherapeutic drugs, with or without lipiodol as a vehicle

III. Transarterial Oily Chemoembolization (TOCE) - Infusion of chemotherapeutic drugs with lipiodol as a vehicle; it is not designed to achieve hepatic arterial occlusion

IV. Transarterial Chemotherapy (TAC) - Infusion of chemotherapeutic drugs alone through hepatic artery without hepatic arterial occlusion

So far, the survival benefit of TACE over TAE has never been confirmed even from a recent systematic review.⁽¹³⁾ Doxorubicin, cisplatin and mitomycin C are usually the anti-cancer drugs of choices used in TACE as a single or a combination regimen.⁽¹¹⁾ Some centers prefer a mixture of chemotherapeutic agents with lipiodol (iodinized poppy seed oil), an oily contrast medium or a vehicle to trap chemotherapeutic agents in HCC.^(11,14,15) After that, hepatic arterial embolization will prevent the washout of the chemotherapeutic agents from the tumor. Gelfoam, starch microparticles, polyvinyl chloride and collagen are used as occluding agents.^(11,14,15) Gelfoam, the most common occluding agent utilized in hepatic arterial embolization, blocks the artery temporarily, with recanalization in 2 weeks.⁽¹⁵⁾ Polyvinyl chloride or collagen particles are permanent occluding agents.^(11,15,16) There has been no evidence that one occluding agent works better than the others.

Complication of chemoembolization

Post-embolization syndrome such as fever, abdominal pain, nausea, vomiting, headache is founded in 32-80% of patients.^(11,14-16) Because fever after chemoembolization is often the consequence of tumor necrosis, prophylactic antibiotic is not routinely necessary except in high risk patients (: Child class C).⁽¹⁷⁾ Chemoembolization may cause gastric ulcer, gastric erosion, cholecystitis, pancreatitis and bile duct injury.⁽¹⁶⁾ A low volume of liver tumor and large volume of embolizing agents are associated with post-embolization syndrome.⁽¹⁵⁾ The most fatal complication of chemoembolization is hepatic decompensation that is

predisposed by advanced cirrhosis, high baseline level of bilirubin, prolong prothrombin time and high dose of cisplatin use.⁽¹⁵⁾ Other rare complications are cerebral lipiodol embolism and pulmonary embolism.⁽¹⁵⁾

Indications and contraindications of chemoembolization

Chemoembolization is recommended for patients with unresectable and non-infiltrative HCC who have preserved liver function (Child class A and B), good performance status and without distant metastasis.⁽¹¹⁾ The recommended staging of HCC to receive chemoembolization is intermediate stage. Chemoembolization can be an alternative modality in early stage HCC who cannot undergo curative treatment that is resection, liver transplantation or percutaneous ablation. Absolute contraindications for TACE are sepsis, Child class C, performance status 3 or 4, Okuda stage 3, infiltrative HCC, active GI bleeding, hepatic encephalopathy, main or both branches of portal vein thrombosis, extrahepatic metastases, hepatofugal portal flow and unable to perform peripheral arterial catheterization (: platelet count lower than 50,000 /mm³, prothrombin activity less than 50%).^(11,16)

Issue with proven benefit of chemoembolization

- *Chemoembolization for palliative treatment of unresectable HCC* - In 2002, two large randomized controlled trials (RCTs) published (almost at the same time) from western and Asian countries, then followed by a meta-analysis study of 7 RCTs confirmed the benefit of chemoembolization over supportive treatment.⁽¹⁸⁻²⁰⁾ Objective response of the tumor assessed 1 to 6 months after chemoembolization was 35% (range, 16%-61%).⁽¹⁸⁻²¹⁾ The meta-analysis study revealed a significant improvement in 2-year survival in chemoembolization group (OR, 0.53; 95%CI, 0.32-0.89).⁽²⁰⁾ Predictors of outcome after chemoembolization of HCC are tumor burden (size, portal vein thrombosis or invasion, AFP level), liver function status (Child-Pugh class, bilirubin, ascites), performance status and response to treatment.^(14,15,21) A study of TOCE in Thai patients with HCC suggested that the outcome of treatment depended on tumor size, stage of disease and completeness of TOCE of extrahepatic collateral vessels.⁽²²⁾ The best candidates for chemoembolization are those with well-preserved liver status (Child class A), multinodular liver tumors without vascular invasion and distant metastasis.⁽¹⁹⁻²¹⁾ Chemoembolization can lower the risk of portal vein invasion at 2 years

(17% versus 58%, $p = 0.005$).⁽¹⁸⁾ Although a single branch of portal vein thrombosis is not the absolute contraindication for chemoembolization, unilobar portal vein obstruction is a poor prognostic factor that can increase the risk of mortality by 3 times.⁽¹⁹⁾ Hence, survival benefit may not derive from chemoembolization for HCC with thrombosis of a portal vein branch.⁽¹⁹⁾

Issues with unproven benefit of chemoembolization

- Chemoembolization before hepatic resection -

Strong evidence to support pre-operative chemoembolization has been shortage so far.⁽²³⁾

- Chemoembolization pre-liver transplantation -

There is no definite evidence of the benefit of TACE pre-liver transplantation and no evidence of improvement in drop-out rate, survival rate or recurrence rate.^(17,23,24)

- Chemoembolization for down-staging HCC -

The proven benefit of down-staging of HCC pre-liver transplantation is limited.^(15,23-25) The successful result and excellent outcome after liver transplantation of down-staging HCC was reported from a center.⁽²⁴⁾ At this stage, chemoembolization for down-staging HCC before liver transplantation cannot be accepted as a standard recommendation.^(15,17,23-25)

Hot topics in chemoembolization: Time to come

- *The combinations of TACE with molecular targeted therapy such as sorafenib are being evaluated.*^(17,26) Chemoembolization results in hypoxic ischemia that can stimulate proliferation, angiogenesis and metastases by enhancing the expression of angiogenic factors (: VEGF and IGF).⁽¹⁷⁾ Combining TACE with antiangiogenic drugs may inhibit tumor recurrence and tumor progression.⁽¹⁷⁾

- *TACE with drug-eluting beads (DEB), a novel system, is based on the concept of slowly release of the chemotherapeutic agents from DEB in the liver.* It aims to reduce the systemic side effects of anti-cancer drugs and prolong the uptake of the drugs in the tumor cells.⁽¹¹⁾ A recent study that compared TACE with doxorubicin-eluting bead versus conventional TACE with doxorubicin showed similar responses of both groups but fewer side effects in DEB group.⁽²⁷⁾

CONCLUSIONS

The survival benefit of HCC patients with inter-

Chemoembolization for Hepatocellular Carcinoma (HCC)

mediate and advanced stage receiving chemoembolization was confirmed from well-designed studies. The outcome of the treatment depends on tumor burden, liver function and patient status. Although the rationale of combining chemoembolization with other treatment modalities (: resection, liver transplantation) lacks supporting evidence so far, the application of the rationale in clinical practice in individual patient showed attractive results. The new technology and modification of chemoembolization has been under development and investigation.

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