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工業工程與經營資訊學系
高階醫務工程與管理碩士在職專班

碩士論文

經肝動脈化療栓塞結合體外放射線療法治療晚期肝癌合併門靜脈血栓之成效

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The effectiveness of Combined Treatment of Transcatheter Arterial Chemoembolization (TACE) and External Beam Radiation Therapy (EBRT) for Patients of Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis

By

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摘　要

經肝動脈化療栓塞治療 (Transcatheter Arterial Chemoembolization)是肝癌中期患者的標準治療，它被認為是當病人符合下列臨床狀況:（1）合理肝功能；(2）大（> 5cm）或多顆腫瘤不阻塞門靜脈血管,(3)和沒有肝外擴散時的標準治療選擇。正如我們所知，肝門靜脈栓塞（PVTT）如果不及時治療平均僅有 3 個月存活的時間，此議題是重要存活預後因素。體外放射治療法（EBRT）是針對肝門靜脈栓塞給予更精準的治療、更高的劑量，安全治療控制肝腫瘤及減少正常肝臟組織的傷害，而不引起嚴重的併發症，因此本研究目的欲探討體外放射線療法合併經肝動脈化療栓塞對於治療門靜脈栓塞與肝臟腫瘤同時共存發生時，其治療成效與末期肝癌病人存活預後相關臨床因素分析。

本世代研究採用病歷回溯方式，從 2006 年 3 月至 2014 年 12 月，收集中部某醫學中心 255 位晚期肝癌患者 (BCLC stage C)，將 1)無治療前後放射影像，2) 無後續治療追蹤者排除，最後納入 96 位接受體外放射治療法與經肝動脈化療栓塞合併治療對於此病人存活情形進行研究分析，本研究中病人累積發生率(accumulative rate) 與存活率(survival cure) 採用 Kaplan-Meier 分析，而治療所造成病人死亡的風險，以 Cox 比例風險回歸分析 (Cox proportional hazard regression model)來計算危險比值(Hazard ratio)。

本研究共納入 96 位患者，平均整體存活為 14.8±0.9 個月，其中慢性 B 型肝炎是最常見的肝癌危險因素佔 41%，經肝動脈化療栓塞治療次數(HR:0.85; 95% 信賴區間:0.75-0.96)，肝癌腫瘤大小 (HR:1.15; 95% 信賴區間:1.02-1.17)，治療後有達到病變不惡化 (disease stabilization) (HR:0.15; 95% 信賴區間:0.07-0.33)為影響治療後存活的相關因素。

本研究發現肝腫瘤直徑較大且持續接受肝動脈栓塞與達到良好治療結果是影響晚期肝癌存活的預後因子。

關鍵字詞：晚期肝癌、肝門靜脈、經肝動脈化療栓塞、體外放射治療

The effectiveness of Combined Treatment of Transcatheter Arterial Chemoembolization (TACE) and External Beam Radiation Therapy (EBRT) for Patients of Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis

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ABSTRACT

The objective of our study is to evaluate the clinical efficacy and cost-effectiveness of combined treatment consisting of local radiotherapy for PVTT and TACE for advanced liver tumor.

We also examined and compared the cost-effctiveness of this treatment combination with other therapeutic modalities.

From March 2006 to December 2014, 96 patients with unresectable HCC complicated by Portal Vein Tumor Thrombosis (PVTT) were recruited as cases. All subjects received transarterial chemoembolization (TACE) and radiotherapy at Taichung Veterans General Hospital in Taiwan. Patient survival was estimated by Kaplan-Meier analysis. In multivariate analyses, the risk of patients' mortality was estimated by hazard ratio (HR) in Cox proportional hazard regression model.

HBV is the most common underlying hepatitis in the study population, with gender ratio favoring men over women. Multivariate analyses finds TACE treatment time (Hazard ratio [HR]:0.85; 95% confidence interval [CI]:0.75-0.96), maximum tumor diameter [HR: 1.10; 95% CI: 1.02-1.17], and post-TACE objective disease stabilization [HR:0.15; 95% CI:0.07-0.33] to be significantly associated with patients survival. And by combining these two therapeutic modalities we arrive at a mean total direct medical cost of NT133,000 for each patient.

In combination, transarterial chemoembolization (TACE) and external beam radiation therapy (EBRT) proved effective as a means of enhancing tumor control in HCC patients with Portal Vein Tumor Thrombosis (PVTT), and achieved a high response rate. This combined regimen shows promise as an effective and safe treatment modality. Transarterial chemoembolization (TACE) combined radiotherapy is both a clinically valuable as well as cost-effective treatment option for patients of HCC complicated with Portal Vein Tumor Thrombosis– (PVTT).

Keywords: Advance HCC, Portal vein tumor thrombosis, TACE, EBRT.

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1. INTRODUCTION

1.1 Background and Motivation

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related death in Taiwan, with hepatitis B virus (HBV) infection being its most well-known risk factor. There are more than 350 million chronic HBV carriers in the world, and 75% of them live in the Asia-Pacific regions including Taiwan (Liaw, Y., & Chu, C., 2009). The global incidence and mortality of HCC have continuously increased, notably in American and Asian countries (El-Serag, H. B., 2002). Patients suffering from chronic hepatitis B have a demonstrably increased tendency to develop HCC over the normal population. Other commonly cited risk factors include cirrhosis, hepatitis C, and aflatoxin B exposure. (Chen, C. P., Huang, K., & Roach III, M. 2010). The most widely used algorithm that classifies patients with HCC according to both prognosis and treatment allocation is the Barcelona Clinic Liver Cancer (BCLC) staging system, which classifies patients into five HCC stages (0, A, B, C and D) based on the extent of disease (tumor number, size, vascular invasion, nodal spread and extrahepatic metastases), liver function (Child-Pugh score), and ECOG performance status (PS). This enables accurate disease prognosis and informs the choice of first-line treatment.

According to the BCLC staging system and its recommended treatment strategy, transarterial chemoembolization (TACE) is the first-line therapy for intermediate stage HCC. In patients with reasonable liver function and the absence of extrahepatic involvement, TACE is considered the standard treatment for large (>5 cm) or multifocal tumors that do not occlude portal venous vessels. HCC with portal vein tumor thrombosis (PVTT) is an important survival prognostic factor, and median survival in such cases is only three months for untreated patients. It is commonly associated with portal vein hypertension, tumor dissemination, and deterioration of liver function, which then limits the application of surgical resection or TACE on HCC. Since PVTT compromises vascular supply to the liver, it is regarded as an absolute or relative contraindication to TACE by most researchers. Embolization of the

hepatic artery in patients with PVTT may result in hepatic infarction and/or acute hepatic failure, especially in patients with limited hepatic reserve.

On the other hand, the primary limitation of radiotherapy in treating HCC is the low hepatic tolerance to whole organ irradiation. Recent advances in radiotherapy techniques have enabled the use of external beam radiation therapy (EBRT) to apply localized tumoricidal doses of radiation to the target lesion, with much less systemic side-effects as compared to conventional radiotherapy. High-dose radiation can be safely delivered to liver tumors without serious complications, even in patients with coexisting PVTT.

Although intensive screening and early diagnosis of HCC means some patients can be treated curatively via surgical resection, radiofrequency ablation (RFA) or liver transplantation, the majority of patients present with intermediate (BCLC B) or advanced-stage disease (BCLC C) upon diagnosis. Only approximately 30–40% of patients are diagnosed at an early enough stage to benefit from curative therapies, and up to 70% of patients who undergo these procedures will have recurrent disease within five years that leads to a more advanced cancer stage. Therefore, palliative treatment modalities play a central role in the treatment of HCC for a majority of patients. Examples include TACE and radioembolization, as well as the orally administered multikinase inhibitor sorafenib.

The objective of our study is to evaluate the clinical efficacy and cost-effectiveness of combined treatment consisting of local radiotherapy for PVTT and TACE for advanced liver tumor, by analyzing the prognostic factors affecting survival following these procedures.

1.2 Objective

The aim of our study was to evaluate the outcome and survival rate of advanced stage HCC patients after combined treatment of TACE and EBRT. This analysis was also designed to identify independent prognostic factors for patients with advanced HCC in a multivariate analysis. We also examined and compared the cost-effectiveness of this treatment combination with other therapeutic modalities.

1.3 Keyword

1.3.1 Advanced stage HCC

Among of all the multiple staging systems for HCC; Barcelona Clinic Liver Cancer (BCLC) staging system is the only one to incorporate tumor burden, liver function assessment, and performance status into one prognostic classification. Advanced HCC (ie, BCLC stage C) is characterized by an Eastern Cooperative Oncology Group (ECOG) performance status of 1–2 and/or the presence of macroscopic vascular invasion (MVI) or extrahepatic metastasis. Any degree of vascular invasion (segmental or lobar or trunk) has the same implications in terms of tumor invasiveness and prognosis. Liver function is not well established as a prognostic predictor, but the presence of ascites and diuretic requirement as well as increased bilirubin level that qualify for Child–Pugh B status may imply a worse prognosis.

1.3.2 Portal vein tumor thrombosis (PVTT)

Portal vein tumor thrombosis (PVTT) arises in about 10%-40% of patients at diagnosis, with lower rates being reported when HCC is diagnosed early, usually as a consequence of screening (Cheung, T., Lai, C., Wong, B., Fung, J., & YUEN, M., 2006). By the end of life, it becomes apparent in up to 44% of patients with HCC (Pirisi M., Avellini C., Fabris C., Scott C., Bardus P., Soardo G. et al., 1998). PVTT has a profoundly adverse effect on prognosis.

The Liver Cancer Study Group of Japan proposed a macroscopic classification for HCC with PVTT in the General Rules for the Clinical and Pathological Study of Primary Liver Cancer. This classification is useful, because it is based on the clinical characteristics, imaging findings, pathological findings, and surgical outcomes. PVTT is classified into five grades: Vp0–Vp4. Each grade is defined as follows: Vp0, no tumor thrombus in the portal vein; Vp1, presence of a tumor thrombus distal to, but not in, the second-order branches of the portal vein; Vp2, presence of a tumor thrombus in the second-order branches of the portal vein; Vp3, presence of a tumor thrombus in the first-order branches of the portal vein; and Vp4, presence of a tumor thrombus in the main trunk of the portal vein or a portal vein branch

contralateral to the primarily involved lobe (or both) (Watanabe, T., Itabashi, M., Shimada, Y., Tanaka, S., Ito, Y., Ajioka, Y., Ishida, H., 2012).

Classification of PVTT

Types	Subtypes
Type I_0: Tumor thrombi formation found under microscopy	
Type I: Tumor thrombi involving segmental branches of portal vein or above	Type Ia: Tumor thrombi involving segmental branches of portal vein or above
	Type Ib: Tumor thrombi involving segmental branches of portal vein extending to sectoral branch
Type II: Tumor thrombi involving right/left portal vein	Type IIa: Tumor thrombi involving right/left portal vein
	Type IIb: Tumor thrombi involving both left and right portal veins
Type III: Tumor thrombi involving the main portal vein trunk	Type IIIa: Tumor thrombi involving the main portal vein trunk for no more than 2 cm below the confluence of the left and right portal veins
	Type IIIb: Tumor thrombi involving the main portal vein trunk for more than 2 cm below the confluence of the left and right portal veins
Type IV: Tumor thrombi involving the superior mesenteric vein	

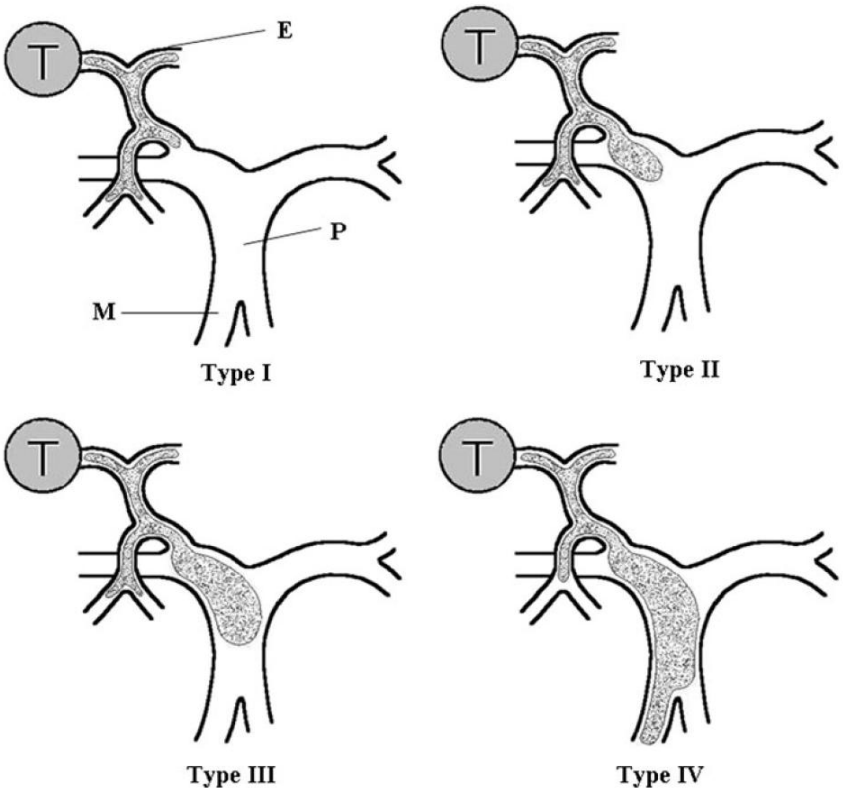

Fig 1.1 Patterns of tumor thrombus types system.

T = tumor, E = tumor embolus, P = main portal vein, M = superior mesenteric vein (Surgical Treatment of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus

(Shi,J.,Lai, E. C.,Li,N., Guo,W.X.,Xue,J.,Lau,W.Y.et al.,2010)

2. LITERATURE REVIEW

2.1 Cost Effectiveness

Although sorafenib, radioembolization, TACE and EBRT have all been shown to improve median overall survival in patients with advanced HCC; however, the financial burden for these therapeutic modalities are substantial. As almost everyone in Taiwan is covered by the single payer healthcare system, healthcare expenditures have become one of the most important issues from the perspective of the healthcare provider. A literature search enables a preliminary comparison of treatments that may be most cost-effective for patients with inoperable advanced HCC.

Sorafenib

Sorafenib is currently used as the most effective option for patients with advanced un-resectable HCC. The median overall survival of patients treated with sorafenib was 10.7 months. Most of the economic evaluation on sorafenib in unresectable HCC found it to be cost-effective when compared to best supportive care in the USA (Carr, B. I., Carroll, S., Muszbek, N., & Gondek, K., 2010). However, when taking into account its availability and accessibility, sorafenib was found not to be a cost-effective option for patients with advanced HCC in China (Zhang, P., Yang, Y., Wen, F., He, X., Tang, R.,Du, Z. et al.,2015). Promising new agents are at present beyond the reach of those who stand to benefit most, namely low-income countries with the largest population of HCC patients. For example, snapshot cost indicators of monthly pharmaceutical prices for sorafenib are: $7300 in China, $5400 in the USA, $5000 in Brazil, € 3562 in France, and & $1400 in Korea (Llovet, J. M., Ricci, S., Mazzaferro, V., Hilgard, P., Gane, E., Blanc, J., Forner, A., 2008) As the single payer Healthcare system in Taiwan, the high drug costs of sorafenib used for treating patients with advanced HCC have become one of its largest financial burdens. The price of sorafenib as reimbursed by the National Health Bureau was calculated based on the market price and negotiated with the manufacturer. The decision-maker is probably willing to pay for less expensive and high outcome treatment for these patients. If a case does not meet the requirements of health insurance payment, the patient may have to pay nearly 100000NT-150000NT a

month for sorafenib treatment in Taiwan. (Leung, H.W.C., Liu, C.F., Chan, A. L.F., 2016).

Transarterial radioembolization (TARE, Y-90)

Transarterial radioembolization (TARE) using yttrium-90 microspheres (also known as selective internal radiotherapy) are carried out by the administration of yttrium-90 microspheres into tumor-supplying hepatic arteries. Tumoricidal radiation doses are delivered with minimal toxicity to functional liver parenchyma, and preliminary studies in Taiwan are promising. However, because the technology remains in the hands of foreign corporations, the main disadvantage of this treatment is again its prohibitive cost. Patients with HCC who are considering this treatment often require a complex application procedure followed by substantial out-of-pocket expenses (陳健弘, 2013) during treatment. A course of treatment may entail fees ranging from 700,000 NT to 900,000NT in a medical center in Taichung.

TACE combined radiotherapy

In response to the uncertain efficacy of target drugs and the financial strain of novel therapeutic agents, it may be tempting to fall back on conventional treatment modalities such as TACE and externally applied radiation therapy. Unfortunately, the treatment response of TACE alone in HCC patients with PVTT is limited, and radiotherapy was thought to have a limited role in the treatment of HCC because of low hepatic tolerance for whole organ irradiation. Thus, it seems to be reasonable to combine these two modalities: TACE to treat the tumor in the hepatic parenchyma and radiotherapy specifically targeting the PVTT. Alternatively, repeat TACE treatments may be scheduled for much lesser cost based on therapy response. With Taiwan's National Health Insurance covering the cost of treatment for both TACE and radiotherapy, a combination of these two therapies is potentially safe and affordable. In this study, we assess the feasibility and efficacy of applying radiotherapy after TACE for patients with HCC with PVTT.

Due to advances in radiotherapy planning and imaging technologies, SBRT has been safely utilized in treating advanced localized or unresectable HCC, with a local control rate of 75–100 % at 1 to 2 years. Additionally, SBRT may

provide a better quality of life because of a more favorable toxicity profile. The result of this study may provide the healthcare payer with evidence in determining a reasonable reimbursement price for the effective treatment strategy for patients with advanced HCC.

To summarize, for patients of advanced HCC that meet the appropriate criteria, TACE combined with EBRT has been shown to be more cost-effective than sorafenib in Taiwan (Leung, H. W et al., 2016).

2.2 Overview of Hepatocellular Carcinoma (HCC)

2.2.1 Epidemiology

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and a major cause of mortality: it's the fifth most common cancer in men (523,000 cases, 7.9% of the total), the seventh in women (226,000 cases, 6.5% of the total) and the third leading cause of cancer death (Ferlay J, et al.,2010). In the last few decades, the management of HCC has changed significantly due to an improved diagnostic capacity, the development of evidence-based staging systems, and the availability of effective treatment. The major risk factor for HCC is chronic infection with HBV, which accounts for 52% of all HCC, followed by chronic infection with HCV and alcohol intake. The risk is highest among patients with cirrhosis (But, D.Y., Lai, C.L., & Yuen, M.F., 2008).

Risk factors

Hepatitis B

HBV affects approximately 350 million people around the world, with the majority found in Asia and Africa (But D.Y.et al., 2008). While in Europe, HCC in hepatitis B carriers occur mainly in patients with established cirrhosis (Fattovich, G., Brollo, L., Glustina, G., Noventa, F., Pontisso, P., & Realdi, G., 1991), hepatitis B carriers in Asia without cirrhosis are still at risk for HCC regardless of virus replication status (Yang, H.I., Lu, S.N., Liaw, Y.F., You, S.L.,Sun, C.A.,&Wang,L.Y.,2002). Nomograms based on clinical characteristics (sex, age, family history of HCC, alcohol consumption, serum ALT level, HBeAg serostatus, serum HBVDNA level, HBV genotype) can help predict the risk of hepatocellular carcinoma (Yang, H.I., Sherman, M., Su, J., Chen, P.J., Liaw, Y.F., & Iioeie, U. H.,2010).

Hepatitis C

The relationship between HCV infection and HCC development is well known. The risk is highest among patients with cirrhosis (Fattovich, G., Giustina,

G., Degos, F., Tremolada, F., Diodati, G., Almasio, P., 1997), while the cumulative 5-year incidence in non-cirrhotic patients is below 5% (Lok, A. S., Seeff, L. B., Morgan, T. R., Di Bisceglie, A. M., Sterling, R. K., Curto, T. M., Bonkovsky, H. L., 2009). Older age, African American race, lower platelet count, higher alkaline phosphatase, higher elastography values, esophageal varices, and biopsy stain showing high proliferative activity or large cell dysplasia are all indicators of higher risk for HCC. However, higher risk does not at present imply a specific surveillance strategy (Bruix, J., & Sherman, M., 2011).

Alcohol

Alcohol abuse is one of the major causes of liver cirrhosis and HCC in most Western countries (O'Shea, R. S., Dasarathy, S., & McCullough, A. J., 2010). Moreover, the combination of alcohol, chronic hepatitis virus infection, and other metabolic risk factors has been shown to have a synergistic carcinogenic effect (Velázquez, R. F., Rodriguez, M., Navascues, C. A., Linares, A., Perez, R., Sotorríos, N. G., Rodrigo, L., 2003). The 'Million Women Study' has demonstrated a 24% risk of liver cancer per 10 g a day increase in alcohol consumption (Allen, N. E., Beral, V., Casabonne, D., Kan, S. W., Reeves, G. K., Brown, A., Million Women Study Collaborators., 2009)

Aflatoxin (AF)

Aflatoxin B1 is a mycotoxin produced by *Aspergillus parasitics.* It was found in staple foodstuffs, such as grain, peanuts, and corn, most commonly in tropical regions of the world. It has been observed that globally, areas of high AF intake corresponded to areas of high HCC incidence (Groopman, J. D., Scholl, P., & Wang, J. S., 1996).

Cirrhosis

Cirrhosis refers to repeated inflammation of the liver that leads to progressive fibrosis of the hepatic parenchyma. A large proportion of people remain asymptomatic, while others present with abnormal liver function and eventually liver failure. While most hepatocellular carcinomas arise in cirrhotic individuals (about 85%), a minority of patients with HCC (about 15%) do not have concurrent cirrhosis (Health Promotion Administration, Ministry of Health and Welfare, 2015).

2.2.2 Diagnosis

The recall policy proposed by European Association for the Study of the Liver (EASL) is also prospectively applied. In nodules under 1 cm, which are malignant in less than half of the cases, close follow-up is recommended. In nodules of 1 to 2 cm, HCC diagnosis requires positive cyto-histology. However, there is a 30% to 40% false negative rate with fine-needle biopsy (Durand, F., Regimbeau, J. M., Belghiti, J., Sauvanet, A., Vilgrain, V., Terris, B., Valla, D., 2001). A negative result, therefore, does not rule out malignancy. In tumors more than 2 cm in diameter, non-invasive diagnostic criteria are applied in cirrhotic patients. HCC diagnosis is established by the concomitant finding of 2 imaging techniques showing a nodule of more than 2 cm with arterial hypervascularization or by a single positive imaging technique showing hypervascularization associated with α-fetoprotein more than 400ng/ml. It has to be pointed out, however, that in our unit a positive histological proof of HCC is required before liver transplantation in all cases. The low risk of fine-needle aspiration biopsy in our center (below 0.01%) favors the balance compared with transplanting a patient with a false-positive result by imaging techniques (Llovet, J. M., Fuster, J., & Bruix, J, 2004).

Diagnostic Imaging

Imaging studies play a key role in the diagnosis of HCC. Definitive diagnosis via non-invasive testing includes four-phase multidetector CT (unenhanced, arterial, venous and delayed) or dynamic contrast enhanced MRI. The presence of arterial hyper-enhancement with a venous or delayed phase washout of contrast medium, confirms the diagnosis of HCC (Bruix, J., & Sherman, M., 2011). Patients with atypical features for HCC either on CT or MRI should undergo the other imaging modality, or undergo lesion biopsy. Individuals with discordant CT/MRI findings or hepatic lesions without cirrhosis should also receive a liver biopsy (Fig 2.1) (Waghray,A., Murali,A.R., Menin.K.N,et al., 2015).

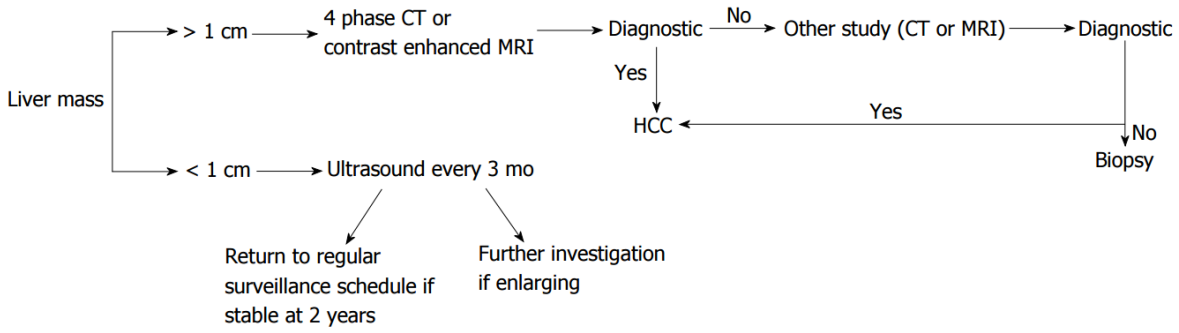

Fig 2.1. Diagnostic algorithm for hepatocellular carcinoma.
Reproduced from Bruix J. Hepatology. 2011. CT: Computed tomography; MRI: Magnetic resonance imaging; HCC: Hepatocellular carcinoma.

Liver biopsy

If contrast-enhanced cross-sectional imaging detects no characteristic contrast enhancement and washout behavior, and the hepatic focus is <2 cm in diameter, the current guideline recommends a fine-needle biopsy of the hepatic lesion. The reason for this is that in tumors between 1 and 2 cm a second imaging procedure fails to increase the sensitivity and specificity, and in 20% of cases even lead to false-negative findings (Khalili, K., Kim, T. K., Jang, H., Haider, M. A., Khan, L., Guindi, M., & Sherman, M., 2011). In contrast, histological confirmation is able to achieve sensitivity and specificity of over 90% (Caturelli, E., Bisceglia, M., Fusilli, S., Squillante, M. M., Castelvetere, M., & Siena, D. A., 1996).

Serum α-fetoprotein (AFP)

The only established serological marker for HCC is AFP. Measurements of AFP may be helpful in the diagnosis and management of HCC. AFP is elevated above 20 ng/mL in more than 70% of patients with HCC and may directly correlate with tumor size (Saar, B., & Kellner, W. F, 2008). Serum AFP is a glycoprotein produced by cells of the vitelline sac during fetal development but is usually absent in adults. AFP is also useful in monitoring response to treatment and detecting recurrence after treatment of HCC if the AFP was

elevated before treatment (Sato, Y., Nakata, K., Kato, Y., Shima, M., Ishii, N., Koji, T& Nagataki, S., 1993).

2.2.3 Treatment

The best therapy is determined based on the cancer stage at presentation. The Barcelona clinic liver cancer staging system, developed in 1999, is a common means to assess prognosis and select appropriate therapy for HCC, as shown in Fig 2.2.

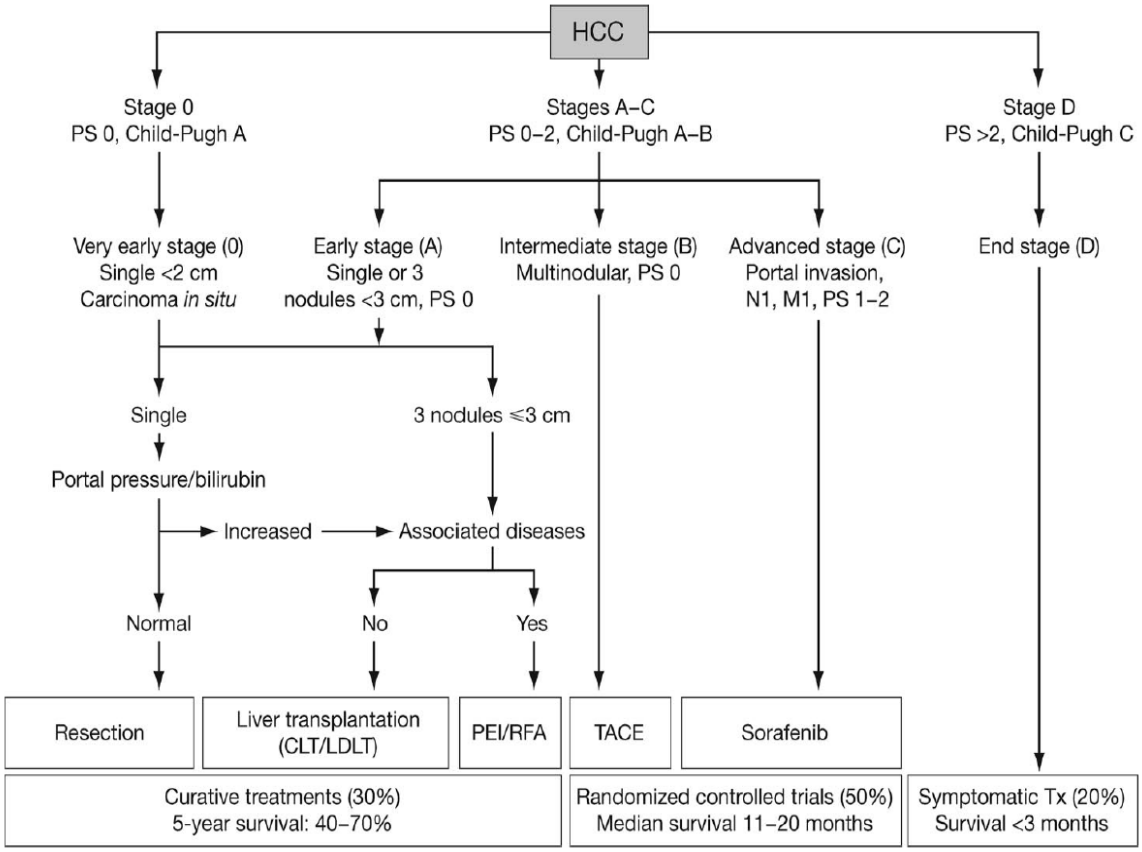

Fig 2.2. Design and endpoints of clinical trials in hepatocellular carcinoma.

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Early Stage (Stage A)

Surgical resection is the treatment of choice for patients with good performance status, preserved liver function, and no clinically significant portal hypertension (Lloved, J. M., Bru,C.,Bruix, J,1999). For patients that do not meet the criteria for resection, liver transplantation should be considered in patients with early HCC that is restricted to a solitary nodule <5 cm in diameter, or three nodules that is each smaller than 3 cm (Mazzaferro, V., Regalia, E., Doci, R., Andreola, S., Pulvirenti, A., Bozzetti, F,& Gennari, L, 1996).

These criteria (called the Milan criteria) lead to an expected 4-year overall survival of 85% and a recurrence-free survival of 93%. However, liver transplantation is hampered by the lack of organ availability and therefore is of limited value for large numbers of patients. Percutaneous ablation by radiofrequency ablation (RFA) and most widely used are percutaneous ethanol injection (PEI) is the best alternative treatment for patients with early HCC, who are ineligible for surgical resection, but still have well-preserved liver functions (Lin, S., Lin, C., Lin, C., Hsu, C., & Chen, Y., 2004). In fact, a recent randomized trial showed that RFA and surgical resection have similar overall survival for patients with early HCC (Livraghi, T., Meloni, F., Di Stasi, M., Rolle, E., Solbiati, L., Tinelli, C., & Rossi, S., 2008).

Intermediate Stage (Stage B)

Patients in the intermediate BCLC stage have preserved liver function and good performance status but suffer from either large or multifocal tumors, which make them ineligible for resection. Treatment of these patients using transarterial chemoembolization (TACE) have shown improved survival in randomized studies. Current guideline recommends TACE for patients in whom curative treatment is not an option and who display either solitary or multifocal HCC without extrahepatic involvement and Eastern Cooperative Oncology Group (ECOG) stage <2 with liver cirrhosis of Child–Pugh stage A or B (Lo, C., Ngan, H., Tso, W., Liu, C., Lam, C., Poon, R. T.,& Wong, J., 2002). It is known that HCC derives 80% of its blood supply from the hepatic artery, whereas the normal liver parenchyma is supplied by the portal vein. TACE exploits HCC's

preferential hepatic arterial blood supply to deliver chemotherapy without damaging the surrounding liver parenchyma, and can target HCC with specificity (Nakazawa, T., Adachi, S., Kitano, M., Isobe, Y., Kokubu, S., Hidaka, H., Saigenji, K., 2007). The intended purpose of embolization is to prevent the washout of treatment drugs at the site of the tumor and to induce ischemic necrosis. Usually, embolic particles are added following the injection of a chemotherapeutic mixture, in order to increase retention time within target tumors.

Advanced Stage (Stage C)

Advanced stage HCC includes patients with tumors that have vascular involvement and/or extrahepatic spread. Historically, systemic therapy in these patients was not shown to improve survival and was therefore neither recommended nor practiced clinically. This situation changed with the development of sorafenib. Sorafenib is an orally administered multikinase inhibitor with activity against Raf-1, B-Raf, VEGFR-2, PDGFR, and c-Kit receptors (Wilhelm SM, Adnane L, Newell P, Villanueva A, Loved JM, Lynch M,2008). BCLC guideline recommends treatment with sorafenib only in patients with good liver function (Child–Pugh stage A) and general good health (ECOG 0 to 2) (Llovet J et al., 2008).

2.3. Treatments of HCC with PVTT

Recent progress in imaging techniques has permitted the diagnosis of hepatocellular carcinoma (HCC) at an early stage. However, the portal venous invasion is still found in 12.5%-39.7% of patients with HCC (Stuart, K. E., Anand, A. J., & Jenkins, R. L., 1996). Portal venous invasion is a crucial factor that can worsen the prognosis of patients with HCC. It often leads to the extensive spreading of the tumor throughout the liver, and can increase portal venous blood pressure resulting in the fatal rupture of esophageal varies, and can decrease portal flow which causes ascites, jaundice, hepatic encephalopathy, and liver failure (Minagawa, M., & Makuuchi, M., 2006). To improve this short-term prognosis, various treatments have been applied; however, no standard treatment yet exists.

The best candidates for TACE are patients with unresectable and asymptomatic lesions, with preserved liver function and without vascular invasion or extrahepatic spread. The problem arises from the coexistence of inferior vena cava thrombosis (IVTT) and/or portal vein tumor thrombosis (PVTT). In these situations, TACE demonstrates a lack of treatment efficacy and a high risk of causing ischemic liver insufficiency. World-wide, although TACE remains the most widely accepted treatment of unresectable or intermediate-stage HCC, patients diagnosed at an intermediate stage often progress to the advanced stage after an initial therapeutic benefit.

Radioembolization (TARE) is a relatively novel treatment compared to TACE, with some preliminary antitumor activity being reported in the literature (Salem, R., Lewandowski, R. J., Mulcahy, M. F., Riaz, A., Ryu, R. K., Ibrahim, S.,& Miller, F.H.,2010). Finally, sorafenib is a targeted agent that has demonstrated a survival benefit as monotherapy in patients who are ineligible for or have progressed following surgery or locoregional therapy (TACE or TARE).

Despite the above-listed treatment options, previous studies have reported that the median survival time of patients with portal venous invasion is significantly reduced to 2-4 months if left untreated, as compared to those not accompanying PVTT, which is usually 10-24 months (Xi, M., Zhang, L., Zhao,

L., Li, Q., Guo, S., Feng, Z., Liu, M., 2013). The optimal treatment for HCC with PVTT has not been established, and only a few randomized controlled trails have been conducted. To date, while some treatments have been trialed for HCC with PVTT, such as TACE, radiation, and systematic chemotherapy, none of them have strong evidence-based support. BCLC staging guidelines recommend sorafenib for the patients with HCC with PVTT. Therefore, there are still unmet clinical needs in the treatment of patients with HCC accompanied by PVTT. Several studies reported that TACE could be safely performed even in HCC associated with occlusion of the main trunk of the portal vein owing to the presence of collateral circulation. (Yu, S. J., & Kim, Y. J., 2015) (Lee ,H.S.,Kim, J. S., Choi, I.J., Chung, J .W.,Park, J. H., Kim, C. Y. , 1997).

However, a retrospective study by Pinter et al. compared the efficacies of TACE and sorafenib in advanced stage HCC patients (35% of patients treated with TACE had PVTT) and found there was no significant difference between these two treatments in terms of overall survival. Notably, the median overall survival in TACE group was longer than that in sorafenib group (9.2 months versus 7.4 months) (Pinter, M., Hucke, F., Graziadei, I., Vogel, W., Maieron, A., Königsberg, R.,& Kölblinger, C., 2012).

Furthermore, several studies have shown that TACE could be safely performed in HCC patients with PVTT and might improve the survival (Cheung, T., Lai, C., Wong, B., Fung, J., & Yuen, M., 2006). More recently, a meta-analysis of 8 comparative studies, including 3 prospective and 5 retrospective studies, further confirmed the survival benefit for advanced HCC with PVTT, even with main portal vein obstruction (Xue, T. C., Xie, X. Y., Zhang, L., Yin, X., Zhang, B. H., & Ren, Z. G., 2013).

Another potential therapeutic tool is radiation therapy (RT). Advancements in RT techniques have increased its treatment efficiency in HCC. RT in HCC with PVTT tends to improve survival by 8~13 months. Although RT seems to provide an overall survival benefit, the prognostic influence of various factors is debatable. Our study was designed to evaluate the effectiveness of RT and to analyze the prognostic factors in HCC with PVTT (Park, S. G., Kim, J. H., Byun, S. J., Kim, O. B., Hwang, J. S., Oh, Y. K., & Choi, T. J., 2011). In our retrospective study, prognostic factors were analyzed in patients with HCC with

tumor thrombosis.

Imaging characteristics that affect survival were evaluated and the effects of the location and extent of PVTT were evaluated in association with long-term outcomes (Jia, L., Kiryu, S., Watadani, T., Akai, H., Yamashita, H., Akahane, M., & Ohtomo, K., 2012).

Although surgical resection is generally accepted as the most effective treatment for HCC, it has a limited role in the treatment of advanced disease. The majority of patients with advanced HCC are not suitable candidates for surgical treatment at the time of diagnosis, either due to poor liver function, extensive tumor involvement of the liver, PVT, or intrahepatic or extrahepatic tumor spreading. Various nonsurgical treatments have been attempted, including systemic or intra–arterial chemotherapy and hormonal or immunotherapy, but to our knowledge they have shown marginal survival benefits. Furthermore, the treatment of advanced HCC with PVTT often poses therapeutic difficulties (Chung, Y.H., Song, I. H., Song, B.C., Lee, G. C., Koh, M. S. et al., 2000). Recently, local liver radiotherapy (RT) as opposed to whole–liver RT has been attempted, and the results suggested that local RT can be effective in controlling the progression of HCC (Robertson, J. M., Lawrence, T. S., Dworzanin, L. M., Andrews, J. C., Walker, S., Kessler, M. L.,& Ensminger, W. D., 1993).

Recent investigations with a co-treatment regimen of TACE combined with radiotherapy have demonstrated superior results over TACE alone (Meng, M., Cui, Y., Lu, Y., She, B., Chen, Y., Guan, Y., & Zhang, R., 2009). In addition, a survival benefit has been reported in patients accompanying PVTT, who have been treated with TACE plus radiotherapy (Yoon, S. M., Lim, Y., Won, H. J., Kim, J. H., Kim, K. M., Lee, H. C.,& Park, J., 2012). It has also been hypothesized that high-dose radiotherapy might lead to sustained local control and possible cure of localized HCC (Cheng, S. H., Lin, Y., Chuang, V. P., Yang, P., Cheng, J. C., Huang, A. T., & Sung, J., 1999). Promising outcomes have also been observed in patients with PVT treated with radiotherapy.

Recently, Cho et al. conducted a retrospective study comparing TACE combined with radiotherapy (n = 67) with sorafenib (n = 49) in 116 patients accompanying PVTT and demonstrated that OS in the TACE plus radiotherapy group was significantly prolonged over the sorafenib group (14.1 mo vs. 3.3 mo,

P < 0.001). Even in the matched cohort by propensity score, the TACE combined with radiotherapy group demonstrated extended OS over the sorafenib group (6.7 mo vs. 3.1 mo, P < 0.001) (Cho, J., Paik, Y., Park, H. C., Yu, J. I., Sohn, W., Gwak, G., & Paik, S. W., 2014).

3. METHODS

3.1 Patient selection

We searched the patient records of a medical center in Taichung for primary hepatocellular carcinoma (ICD-9 155.0) from March 2006 to December 2014 and collected a total of 255 subjects with advanced stage HCC, who received radiotherapy treatment. After accounting for patients who had also undergone TACE, a final group of 96 subjects was eligible for our study.

Baseline patient data was collected upon initial cancer survey. Advanced HCC was defined as a hepatic lesion that was not eligible for curative treatment given the disease extent, or tumors that had recurred after local therapies. Exclusion criteria involved patients without dynamic CT or MRI images prior to EBRT, who had not received combination treatment of TACE or had inferior vena cava invasion, or lacked follow-up information after initial treatment.

3.2 Technique

3.2.1 TACE

All the interventional procedures were performed via INNOVA 4100 IQ digital subtraction angiography (DSA) (GE Company, United States) by well-experienced interventional radiologist at the Department of Interventional Radiology. After a routine preoperative preparation, TACE was performed under sterile conditions, with the patient under local anesthesia. The right femoral artery was cannulated using a 6 Fr vascular sheath by Seldinger's technique. Selective angiography of the celiac artery and superior mesenteric artery was performed using a 4 Fr hepatic artery catheter, inserted through the vascular sheath. Maximum catheter selectivity of the hepatic artery and some hepatic branches was achieved using a 3 Fr microcatheter (Progreat, Terumo Corporation, Japan), with drug administration from the afferent branch to the tumor lesion. Drug dosages per procedure varied, ranging from 10–40 ml for ethiodized oil (LIPIODOL® , Guerbet, USA), 10–40 mg of doxorubicin (Pfizer Pharmaceuticals Ltd, USA), depending on the size of the tumor lesion and laboratory results. Lipiodol-chemotherapeutic agents were administered until

stasis, minimizing reflux into non-target vessels. The injection was continued until near stasis was observed in the artery directly feeding the tumor (i.e., the contrast column should clear within 2–5 heartbeats). Gelatin sponge (Gelfoam, USP) cut into 1 x 1-mm particles was injected as a supplement when necessary. In the case of unilateral branch portal vein thrombosis, selective TACE for the feeding arteries of the tumor was performed. In cases where PVTT extended to the main portal vein, TACE was modified, for example by decreasing the amount of epirubicin hydrochloride or by not applying Gelfoam cubes. Additional TACE after the initiation of radiotherapy was allowed if adequate control of the intrahepatic tumor could not be maintained.

3.2.2 Radiotherapy

Radiation therapy in our study was delivered using linear accelerator equipped with 10-15MV photon beams. Radiation portals were designed to include the gross tumor thrombosis in the main portal trunk and/or major branches on CT scan with 1.5-2 cm margin for daily set-up variation and the respiratory motion of the liver. The hepatic tumor was included only if the tumor was located adjacent to PVTT. The technique of radiation therapy used in our study was 3DCRT or intensity-modulated radiotherapy (IMRT), and the accepted radiotherapy planning was designed to preserve liver function and to protect the uninvolved liver. The median dose of radiation therapy was 45Gy (range from 30Gy to 56Gy), with fraction size of 1.8-3Gy per day, 5 days per week.

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3.3 Tumor Assessment

In 2008, a group of experts convened by the American Association for the Study of Liver Diseases (AASLD) developed a set of guidelines aimed at providing a common framework for the design of clinical trials in HCC and adopted the concept of viable tumor–tumoral tissue showing uptake in arterial phase of contrast enhanced radiologic imaging techniques—to formally amend RECIST. These amendments are referred to in the current article as modified RECIST assessment (mRECIST) for HCC (Lancing.R & Loved.J.M., 2010). shown in Table 1.1.

Table 3.1 Radiographic Modified RECIST to assess tumor response

mRECIST for HCC	Definition
CR (complete response)	The disappearance of any intratumor arterial enhancement in all targets lesions.
PR (partial response)	At least 30% decrease in the sum of one-dimensional diameters of a viable portion of the target lesions, with the baseline sum of the diameters as a reference.
SD (stable disease)	Any case that does not qualify for CR, PR or PD.
PD (progressive disease)	At least 20% increase in the sum of the diameters of viable target lesions, with the lowest sum of the diameters recorded since the treatment started as a reference.

3.4. Data processing and statistical analysis

The present work is a retrospective study involving medical records, with raw data collected and archived via Microsoft Excel (2010) software. Data was decoded one by one and checked, then entered into the Chinese version of SPSS for Windows 22.0 software package for statistical analysis. According to the purpose and hypotheses, appropriate statistical methods were used to test the hypothesis and examine differences between each variable, with $p < 0.05$ as the significant level of the analysis methods described below.

3.4.1 Survival analysis:

The difference in two-year overall survival between potential prognostic subgroups in patients treated with HCC was assessed using the Kaplan-Meier method and tested for statistical significance by the log-rank test, with $P < 0.05$ as the threshold for statistical significance.

3.4.2 Cox proportional-hazards regression model

Demographic data including age, sex, hepatitis virus status, treatment response and complications, were examined in a regression model to identify independent prognostic factors.

4. RESULT

4.1 Baseline characteristics

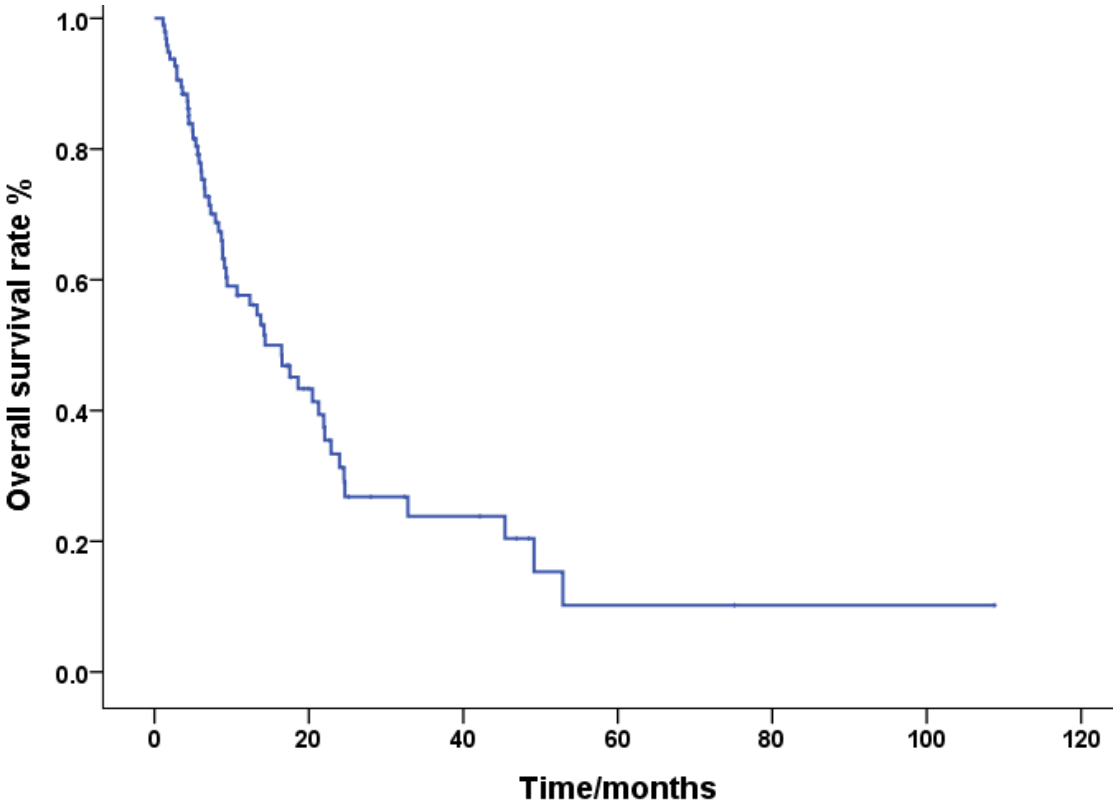
A total of 96 patients (70 males and 26 females) with a mean age 60±12.2 years (range, 53-69 years) were enrolled in the present study. Among these patients, the etiology of underlying liver disease included hepatitis B virus (HBV) in 40 patients (41.7%), hepatitis C virus (HCV) in 26 patients (27.1%), co-infection of hepatitis B (HBV) and hepatitis C (HCV) in 4 patients (4.2%), and non-B non-C hepatitis in 26 patients (27.1%). Median tumor diameter was 4.7 cm (range, 3.3-8.2 cm), while the mean number of TACE received by each patient from start of treatment was three (range, 2-6 times).

Table 4.1 Baseline characteristics of the study subjects

Variables	Total (n=96)
Age (years)	**60 ±12.2**
Gender, n (%)	
Male, n (%)	**70 (72.9)**
Female, n (%)	**26 (27.1)**
Hepatitis	
HBV only, n (%)	**40 (41.7)**
HCV only, n (%)	**26 (27.1)**
HBV+HCV, n (%)	**4 (4.2)**
Non-B non-C, n (%)	**26 (27.1)**
Tumor diamter	**4.7 (3.3-8.2)**
TACE times	**3 (2-6)**

4.2 The overall patient survival analysis in combined TACE and radiotherapy in patients with advanced stage HCC

During the follow-up period, the mean overall patient survival in advanced HCC patients was 14.8±0.9 months (median 14.3 mo), with 1-year and 2-year survival rate were 40.6% and 14.6%, respectively.



Patient at risk No	96	22	8	2	1	1	0

Fig4.1 Cumulative overall survival of the advancede-stage HCC after TACE and radiotherapy.

4.3 Effect of combined TACE and radiotherapy on patients with advanced stage HCC and the analysis of risk factors associated with mortality

During univariate analysis, it was found that subject age (HR: 0.98 95% CI=0.96-1.01; P = 0.13), gender (HR: 0.62 95% CI=0.42-1.68 P = 0.62), status of HBV (HR=0.95 95% CI = 0.50-1.83 P=0.89), HCV (HR=0.53 95% CI = 0.25-1.15 P=0.11) or concurrent HBV and HCV (HR=2.11 95% CI = 0.48-9.39 P=0.33), were not associated with overall patient mortality.

Tumor characteristics were also evaluated against mortality. A HR of 1.15 was found for maximum tumor diameter (95% CI = 1.08-1.23, P=<0.01), and severity of portal venous thrombosis in terms of Vp1-4 were also compared to mortality. Patients with Vp1 grade of PVTT had a HR of 0.48 (95% CI = 0.18-1.27, P=0.14), while HR is 0.29 for Vp2 (95% CI = 0.13-0.64, P=0.01) and 0.50 for Vp3 (95% CI = 0.25-1.01, P=0.05), respectively. An HR of 0.74 was calculated for number of TACE treatments (95% CI = 0.63-0.88, P=<0.01.), and achievement of objective disease stabilization (CR+PR+SD) had a HR of 0.15 (95% CI = 0.08-0.32, P=<0.01) in treatment responders.

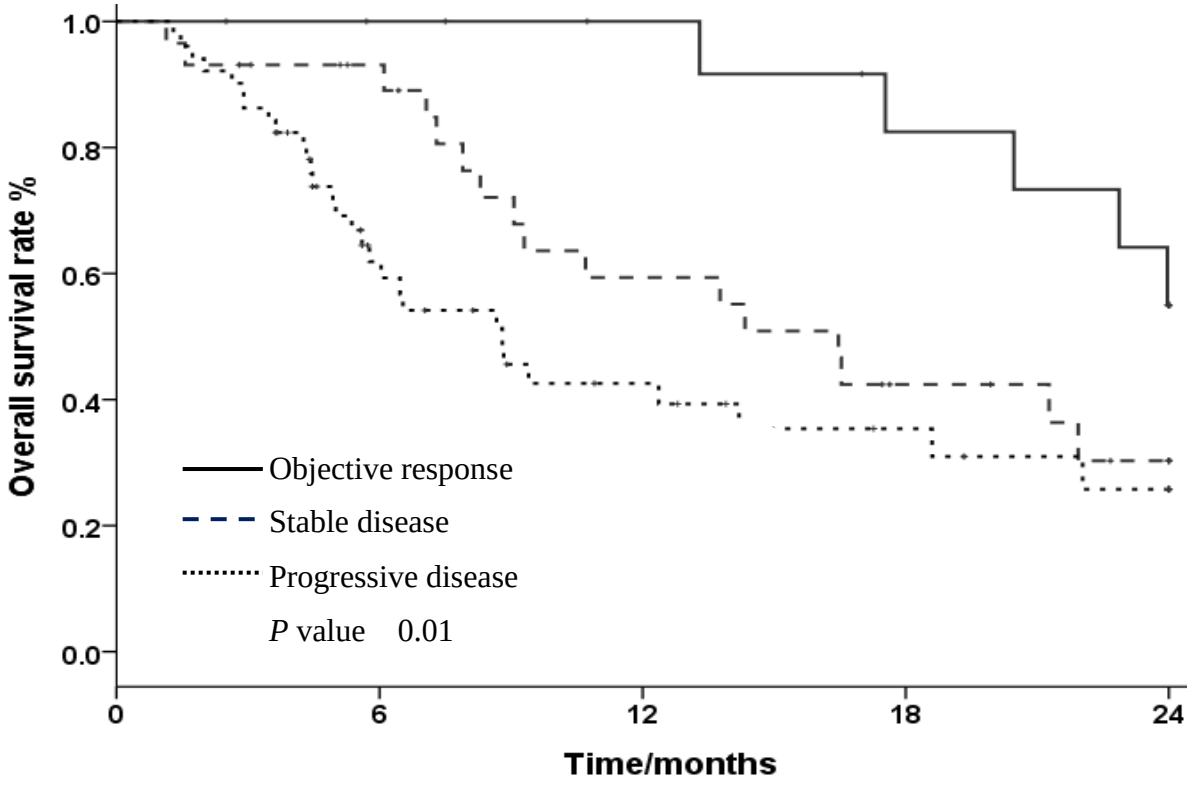
After adjusting for confounders, multivariate analysis demonstrated that maximum tumor diameter (HR=1.10 95% CI = 1.02-1.17 P=0.01), number of TACE treatments (HR=0.85 95% CI = 0.75-0.96 P=0.01) and achievement of objective disease stabilization (CR+PR+SD) after treatment (HR=0.15 95% CI = 0.07-0.33 P=<0.01) were significantly associated with patient survival. On the other hand, factors not significantly associated with mortality in patients with advanced HCC included PVTT of grade Vp1 (HR=0.56 95% CI = 0.19-1.65 P=0.29), Vp2 (HR=0.58 95% CI = 0.24-1.40 P=0.23) and Vp3 (HR=1.04 95% CI = 0.48-0.36 P=0.91).

Table4.2 Multivariate analysis for overall survival among patients receiving TACE and radiotherapy

		Univariate analysis			Multivariate analysis		
Variable	**Total(n=96)**	**HR**	**95%CI**	**P-value**	**HR**	**95%CI**	**P-value**
Age(year)	**96**	**0.98**	**0.96-1.01**	**0.13**			
Gender							
Female	**26**	**0.83**	**0.42-1.68**	**0.62**			
Male	**70**	**—**					
Chronic viral hepatitis							
Non-B non-C	**26**	**—**					
HBV only	**40**	**0.95**	**0.50-1.83**	**0.89**			
HCV only	**26**	**0.53**	**0.25-1.15**	**0.11**			
HBV+HCV	**4**	**2.11**	**0.48-9.39**	**0.33**			
Time to TACE	**96**	**0.74**	**0.63-0.88**	**<0.01****	**0.85**	**0.75-0.96**	**0.01***
Tumor diameter	**96**	**1.15**	**1.08-1.23**	**<0.01****	**1.10**	**1.02-1.17**	**0.01***
Portal venous thrombosis							
Vp1	**9**	**0.48**	**0.18-1.27**	**0.14**	**0.56**	**0.19-1.65**	**0.29**
Vp2	**27**	**0.29**	**0.13-0.64**	**0.01***	**0.58**	**0.24-1.40**	**0.23**
Vp3	**40**	**0.50**	**0.25-1.01**	**0.05***	**1.04**	**0.48-0.36**	**0.91**
Vp4	**20**	**—**			**—**		
TACE responder							
Objective disease stabilization	**36**	**0.15**	**0.08-0.32**	**<0.01****	**0.15**	**0.07-0.33**	**<0.01****
Progression	**60**	**—**			**—**		

4.4 Advanced stage HCC after combined TACE and radiotherapy responder between two-year survival differences

Overall survival rates for advanced HCC patients after combined treatment of TACE and EBRT within the 24-month study period is shown in Fig. 4.1, according to the patient's treatment response. The mean survival time is 22.1± 0.97 months of subjects with objective response (CR+PR) to treatment, with a significant difference between objective response, stable disease and progressive disease (*P*= 0.01).



Patient No					
Objective response	16	14	12	9	5
Stable disease	29	23	14	8	3
Progressive disease	51	24	13	8	4

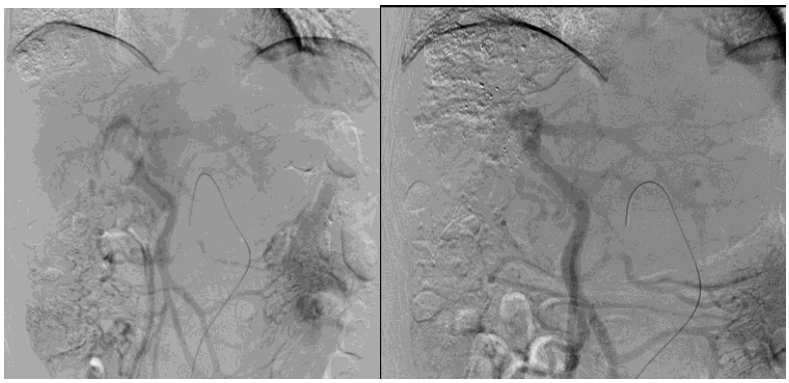
Fig4.2 Cumulative overall survival of the advanced-stage HCC after TACE and radiotherapy

4.5 Illustrative case

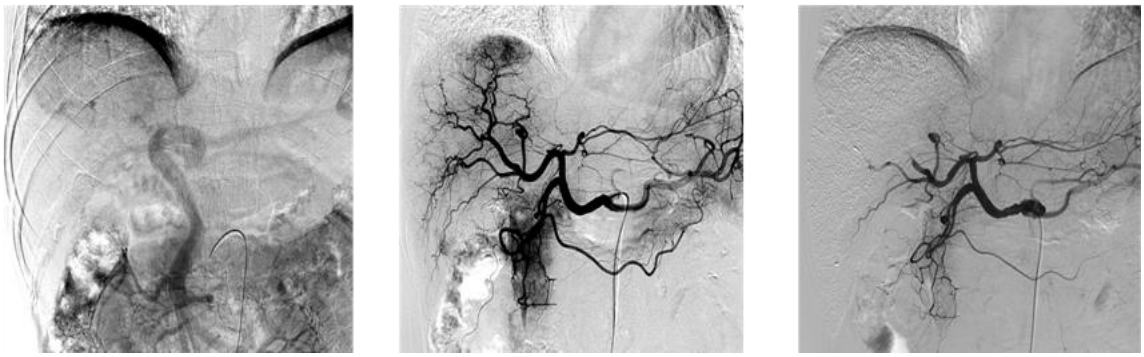
The angiography images from a 53-year-old male patient with history of chronic hepatitis B, treated with TACE one month later after radiotherapy.

A. Non-opacified of right portal branches and this may due to tumor thrombosis. B. Hypervascular tumor stain is noted over S8 of liver (black arrow). The TACE was performed through superselection of the right hepatic artery by 4.1Fr RC catheter with injection of 40mg Epirubicin, 7ml Lipiodol and some gelfoam cubes. C. The follow-up DSA showed complete obliteration of tumor stains in right lobe of liver.

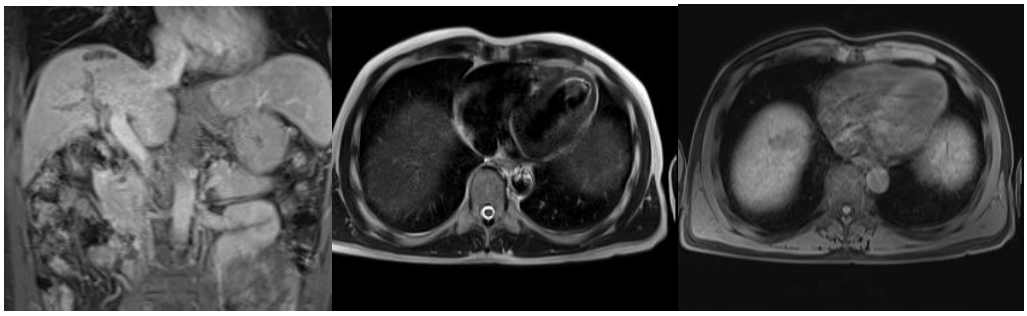
a.



b.



c.



4.6 The cost effectiveness of combined treatment of TACE and radiotherapy

Three major types of medical expenditure are associated with treatment of HCC with PVTT: acquisition costs for TACE and EBRT, outpatient visits and hospitalization. Costs for TACE include initial purchase and yearly depreciation expenses for the equipment involved, overnight patient hospitalization expenses, as well as parts and labor cost for the superselective embolization procedure itself. Total direct costs approached NT17,000 for each TACE, with repeat procedures increasing the overall cost of treatment. As each patient received TACE three times on average, the total cost of TACE therapy for advanced HCC patients amounts to NT 51,000 per patient. In contrast, total direct medical costs of radiotherapy for patients with PVTT varied to a greater extent, and depended strongly on the selection of portal arrangements along with frequency of planning and treatment sessions. In this study, mean costs for radiotherapy was estimated to be NT 82,000 for each patient. Therefore, by combining these two therapeutic modalities we arrive at a mean total direct medical cost of NT133,000 for each patient.

Table4.3 Estimated cost of TACE with radiotherapy (NT dollar)

Treatment	TACE (Health care of points: 21042*0.9=18937.8 NT dollar)	EBRT
Equipment depreciation	6200	2500
Personnel cost	4000	1600
Hospitalization cost	1800	—
Medical supplies	5000	—
Average time per patient	3	20
Per patient cost total	51,000	82,000
Sub total	133,000	

5. DISSCUSSION

HCC is distributed unevenly worldwide, and morbidity and mortality are particularly high in Asia, including China, Japan, and Korea. According to the Barcelona Clinic Liver Cancer (BCLC) guideline based on evidence from randomized clinical trials, advanced HCC with PVTT can only be treated with sorafenib-targeted therapy (Llovet J et al., 2008). As Sorafenib is the first targeted agent with survival benefits proven by two large-scale RCT, it is the standard of care for patients with advanced stage disease (Cheng, A., Kang, Y., Chen, Z., Tsao, C., Qin, S., Kim, J. S.,& Yang, T., 2009). However, sorafenib for available HCC is still not easy for Asian physicians to prescribe due to high costs (Lee, J. M., & Han, K. H., 2010). For the management of advanced HCC, sorafenib has not yet been covered for reimbursement in most Asian countries due to a big burden on the national insurance budget. Although, HCC with PVTT have poor prognosis median survival 2.7-4.0 months if untreated (Llovet et al., 1999). There are still several other therapeutic modalities to improve the outcome, such as a surgical approach, hepatic arterial infusion chemotherapy (HAIC), external beam radiation, locoregional strategies (TACE and TARE) and the combination of treatments based on clinical experiences for intermediate and advanced stage HCC. We review recent data for the various treatment strategies for the patients with HCC accompanying PVTT.

Therefore, we review recent data for the various treatment strategies for the patients with HCC complicated with PVTT.

Multikinase Inhibitors (Sorafenib)

Sorafenib is the first systemic agent shown to improve overall survival in patients with unresectable HCC, including PVTT, and it is currently the only therapy specifically recommended for HCC with PVTT in BCLC guidelines. However, the average median survival is only 8.1 months with common adverse events. In the phase III Sorafenib HCC Assessment Randomized Protocol (SHARP) trial (Llovet J et al., 2008), 602 patients with HCC were randomly assigned to treatment with sorafenib or placebo. The patients were ineligible for or had progressed following surgery or locoregional therapy, and had an Eastern

Cooperative Oncology Group (ECOG) PS score of 0 –2 and Child-Pugh class A liver function. The study was terminated at the second planned interim analysis because of a significant difference in the survival time between the two treatment arms in favor of sorafenib (median survival time, 10.7 months versus 7.9 months for sorafenib and placebo, respectively; HR, 0.69; 95% CI, 0.55–0.87; $p < .001$). In the sub-group analyses of the Asia-Pacific trial, patients with macroscopic vascular invasion (MVI) and/or extrahepatic spread who received sorafenib (n = 118) showed only a marginal survival benefit for sorafenib over placebo (n = 61) median OS (5.6 mo vs 4.1 mo), TTP (2.7 mo vs 1.3 mo) and disease control rate (30.5% vs 11.5%), respectively (Cheng, A.L., Guan, Z., Chen, Z., Tsao, C.J., Qin ,S., Kim ,J.S et al., 2012).

TACE

PVTT is generally considered a contraindication for TACE because of concerns that interruption to hepatic arterial blood supply could result in an enormous segment of hepatic necrosis in patients whose blood supply is already compromised (Jelic, S., Sotiropoulos, G. C., & ESMO Guidelines Working Group., 2010). Nevertheless, there is evidence that selected patients with PVTT can tolerate a modified delivery of TACE provided they have good liver function and collateral blood flow around the obstructed portal vein. In more recent years, several groups have reported that subselective and superselective TACE can be performed safely in some patients with PVTT, and is associated with improved overall survival (Pinter, M., Hucke, F., Graziadei, I., Vogel, W., Maieron, A., Königsberg, R., Kölblinger, C., 2012). Overall survival among PVTT patients treated with TACE in these studies ranged from 7.0 to 10.2 mo. In a large nonrandomized study, Luo and colleagues prospectively treated 164 patients with PVT with either lipiodol TACE or conservative treatment. Twelve and 24 mo survival rates in the TACE group were significantly prolonged (30.9% and 9.2%, vs 3.8% and 0%), and the benefit was consistent across patients with segmental and main PVTT (Luo, J., Guo, R., Lai, E. C., Zhang, Y., Lau, W. Y., Chen, M., 2011). In most Asian countries, TACE is still used routinely for patients with PVTT. Consensus has been reached recently based on the guidelines from the main Asian countries with high HCC morbidity (Han, K. H., Kudo, M., Ye, S. L., Choi, J. Y., Poon, R. T., Seong, J., Cheng, A. L., 2011).

However, a clear evidence base for TACE in patients with PVTT is still lacking. The present meta-analysis indicated that TACE was a safe choice for advanced HCC with PVTT. The presence of a portal vein thrombosis at the initial diagnosis of the HCC is not an absolute contraindication for TACE treatment, but patients have to be elected carefully with critical regard to their liver function.

Radiotherapy

Radiotherapy for HCC has infrequently been used in the treatment of HCC because the liver has a low tolerance to whole-organ irradiation (Ingold, J. A., Reed, G. B., Kaplan, H. S., & Bagshaw, M. A., 1965).With advances in radiotherapy techniques, high-dose conformal radiotherapy, including proton irradiation, has allowed selective delivery of increased radiation doses to tumors with minimal doses to normal tissue. (Hawkins, M. A., & Dawson, L. A., 2006) Some retrospective studies have examined the use of these new technologies in selected patients accompanying PVTT: median OS (6.7-11 mo), and 1-, 2-, and 5-year survival rates 30%-40%, 20%-30%, and 5.1%-24%, respectively (Yu,S.J.&Kim,Y.J, 2015). More recently, Nakazawa et al. did a retrospective study comparing the survival benefits of sorafenib vs. radiotherapy in unresectable HCC patients accompanying PVTT (Vp3 or Vp4). Median OS did not differ significantly between the sorafenib and the radiotherapy group 4.3 mo vs. 5.9 mo, respectively; P = 0.115 (Nakazawa, T., Hidaka, H., Shibuya, A., Okuwaki, Y., Tanaka, Y., Takada, J., Koizumi, W., 2014).

TACE combined radiotherapy

In recent years, radiotherapy has been utilized for treatment of HCC patients with major PV invasion, and combined treatment for liver tumors consisting RT for PVTT and TACE was found to have a better response rate (Yamada, K., Izaki, K., Sugimoto, K., Mayahara H., Morita Y., Yoden E. et al.,2003). Although TACE has frequently been used in patients with unresectable HCC, its efficacy has been unsatisfactory in most patients with PVTT, especially those having HCC with first or main portal vein invasion (Kim, J., Yoon, H., Kim, S., Kim, K., KO, G., Gwon, D., & Sung, K., 2009).

Radiotherapy alone also has had limited efficacy, although most studies have been small series with a retrospective design. Due to recent improvements in radiotherapy techniques, the combination of TACE with radiotherapy has resulted in improved outcomes for these patients. Local radiotherapy combined with TACE has also been investigated as a means of enhancing tumor control (Le Pechoux, C., Akine, Y., Tokita, N., Sumi, M., Churei, H., Takayasu, K , & Hasegawa, H., 1994). Because TACE has a limited effect on PVTT and the pericapsular invasion of the tumor. The recent advances with a co-treatment modality of TACE combined with radiotherapy have demonstrated superior results over TACE alone. PVTT is a major obstacle to performing TACE, focal field radiotherapy targeting the PVTT, before or immediately after TACE for the tumor, may be a good treatment option. The rationale for this combined approach was that radiotherapy focused on PVTT may decrease intravascular tumor growth and maintain portal blood flow, allowing the maintenance of normal liver function, limiting intrahepatic tumor spread, and thereby allowing additional TACE (Yoon et al., 2012). In addition, the survival benefit has been reported in patients accompanying PVTT, who have been treated with TACE plus radiotherapy (Shim, S. J., Seong, J., Han, K. H., Chon, C. Y,& Suh, C. O., 2005).

Nagashima reported that 7 of 11 patients with HCC with PVTT showed partial response by this combined-modality treatment (Nagashima et al., 1989). According to the report by Chen et al. 5 of 10 patients showed complete response and the rest partial response, with a median survival time of 7.5 months. These reports suggest that this combination of modalities may become a potential treatment of choice for patients with HCC with PVTT. Recently, Cho et al. conducted a retrospective study comparing TACE combined with radiotherapy (n = 67) with sorafenib (n = 49) in 116 patients accompanying PVTT and demonstrated that overall survival in the TACE plus radiotherapy group was significantly prolonged over the sorafenib group (14.1 mo vs. 3.3 mo, $P < 0.001$). Even in the matched cohort by propensity score, the TACE combined with radiotherapy group demonstrated extended OS over the sorafenib group 6.7 mo vs. 3.1 mo, $P < 0.001$ (Chen, S., Lian, S., & Chang, W., 1994).

Hepatic arterial infusion chemotherapy (HAIC)

HAIC has been applied to treat advanced HCC patients with tumors that are unresectable, refractory to TACE in single or multiple tumors, the infiltrative type or those with portal vein thrombosis. Theoretically, HAIC shows better efficacy than systemic chemotherapy in advanced HCC because the infusion of the chemotherapeutic agents through the hepatic artery provides direct delivery of high concentrations of drugs to the feeding arteries of HCC. In addition, HAIC also minimizes systemic toxicities through a greater first-pass effect in the liver, reflecting the lower the systemic levels of the drugs compared to the systemic infusion (Song, M.J., Bae,S.H., Chung,W.J., Jang,J.Y., Kim,Y.S., Lee,S.H.et al., 2015). Kim et al. showed a better long-term outcome of high dose HAIC. During the follow-up period, overall survival and time to progression were 9.5 and 6.0 mo, respectively. These results seem comparable to the reported outcome of sorafenib. (Kim, B. K., Park, J. Y., Choi, H. J., Ahn, S. H., Kim, J. K., Lee, K. H., & Han, K., 2011). The results were obtained by Ando et al., who treated 48 patients with Vp2 to Vp4 PVTT by HAIC with cisplatin plus 5-fluorouracil. The 5-year overall survival rate was 11.0 %, and the median survival time was 10.2 months in that study (Ando, E., Tanaka, M., Yamashita, F., Kuromatsu, R., Yutani, S., Fukumori, K., Sata, M., 2002). Recently, Nouso et al. evaluated the efficacy of HAIC of 5-FU and cisplatin for advanced HCC in a nationwide survey in Japan. The outcome of 476 patients with HCC who underwent HAIC was compared with 1466 patients who did not receive active therapy. In propensity score-matched analysis, median survival in patients with HAIC was longer than that in patients with supportive care (14.0 vs. 5.2 mo, respectively, $P < 0.0001$). (Nouso, K., Miyahara, K., Uchida, D., Kuwaki, K., Izumi, N., Omata, M., Kokudo, N., 2013). Many of the other studies reported overall survival of up to 3 years, but the long-term outcomes remain largely unclear.

Transarterial radioembolization (TARE)

Radioembolization (TARE) using yttrium-90 microspheres for treating HCC in the following scenarios, down staging/bridging to transplantation or

resection, advanced disease and HCC with portal vein thrombosis. Studies reported the improvement of median survival with intermediate- to advanced-stage HCC, and the median survival is 7-41.6 months with objective response rates from 20 to 77% (Sangro, B., Salem ,R., Kennedy, A., Coldwell ,D., Wasan, H ,2011). TARE is proved to have more well-tolerated and associated with favorable overall survival. Moreover, there is increasing evidence that TARE can be delivered safely and effectively in suitable HCC patients with PVTT, with several studies reporting median OS rates of approximately 10 months following the procedure in these patients (Kooby, D. A., Egnatashvili, V., Srinivasan, S., Chamsuddin, A., Delman, K. A., Kauh, J., Kim, H. S., 2010).

Hepatectomy

Most patients with HCC with Vp4 are considered technically unsuitable for curative resection, and the presence of PVTT is usually considered a contraindication for liver transplantation due to higher tumor recurrence rates. (Lau, W. Y., Sangro, B., Chen, P. J., Cheng, S. Q., Chow, P., Lee, R. C,& Poon, R. T., 2013). However, throughout the Oriental area, the operation is considered a potentially curative treatment in suitable patients with PVTT as reflected in the consensus recommendations of Asia-Pacific Association for the Study of the Liver, (Omata, M., Lesmana, L. A., Tateishi, R., Chen, P., Lin, S., Yoshida, H., Poon, R. T., 2010). Although only about 10% of patients undergoing surgery has PVTT. (Chen, X.P., Qiu, F.Z., Wu, Z.D., Zhang, Z.W., Huang, Z.Y., Chen ,Y.F. et al., 2010). Published data indicate median survival outcomes ranging from 8.9 to 33 months for various surgical procedures in highly selected patients with varying degrees of portal vein involvement. However, surgery can only be performed for highly selected patients, and the indications for surgery have not been clearly demonstrated.

Other combination strategies

TACE combined hepatectomy

In a controlled trial 126 patients with HCC and PVTT were randomly assigned to hepatectomy alone (control group) or hepatectomy followed by

TACE (TACE group). The median survival time was 13 months in the TACE group and 9 months in the control group. The estimated survival rates at 5 years were also better in the TACE group (21.5 %) than in the control group (8.5 %). This randomized controlled study of multimodality treatment was considered to be a key clinical trial. The available evidence indicates that hepatectomy-based interdisciplinary therapy is effective and should be explored in further trials (Peng, B., He, Q., Li, J., & Zhou, F., 2009).

CCRT combined HAIC

There are also studies for combined treatments such as localize chemoradiation therapy (CCRT) followed by HAIC plus localized EBRT in patients with locally advanced HCC with PVTT, which shows the objective response rate approximately 45%, actuarial 3-year overall survival rate, 24.1% and median survival time, 13.1 months.

In the recent sorafenib trial with Asia-Pacific patients with advanced HCC, only 5 of 150 patients (3.3%) in the sorafenib group achieved a PR, and the median survival of the sorafenib group was 6.5 months (Cheng, A., Kang, Y., Chen, Z., Tsao, C., Qin, S., Kim, J. S., Yang, T., 2009). Compared with the previous study, our results demonstrated that the objective response rate after combined treatment regimen approximated 16.7 % and 14.8±0.9 months in mean survival time was observed in patients with advanced HCC which is remarkable longer patient survival time than that in the previous study with sorafenib therapy only. Although these results cannot be directly compared among studies, the better tumor response rates are suggested to be significantly associated with better overall survival in patients with advanced HCC.

In multivariate analysis, our results showed that only two factors including tumor diameter and the frequency of TACE treatment were significantly associated with the risk factors for patient survival. Accordingly, our findings suppose that the degree of PVTT and the type of hepatitis accidentally were not significantly contributed to the risk of mortality for HCC. It is reasonably that patients who had larger tumors may eventually experience worse outcome. Theoretically, the higher degree of PVTT seems to have worse prognosis; however, our findings showed that the obstruction level of the portal vein was

not associated with the therapeutic outcome. These findings might suggest that radiotherapy combined with multiple interventions of TACE would attain a better outcome regardless of the severity of PVTT in advanced HCC. Our study provides information to recognize the factors that can affect survival and design tailored treatment for advanced HCC in the future. Understanding these factors may help identify optimal treatment regimens and establish more detailed treatment guidelines in patients with HCC combined with PVTT.

Based on these findings, we recommend that combined treatment consisting of EBRT for PVTT and TACE for liver tumor could reach a higher response rate (objective response rate, 16.7 %) and median survival (14.3 months) as compared with other modalities including hepatectomy, systemic chemotherapy, sorafenib, and HAIC.

Table 5.1 Comparing various treatment strategies for hepatocellular carcinoma patients accompanying portal vein tumor thrombosis

Treatment	Author	Number	Response rate,%	Median survival time,mo
Sorafenib	Loved et al	602	Sorefenib (PR 2,SD 71) Placebo (PR 1, SD 67)	Sorefenib 10.7 Placebo 7.9
HAIC	Kim et al	138	CR 2.2, PR 21, SD 39.1	9.5
TARE	Mazzaferro et al.	35	OR 34.3, SD 40	13
Sorafenib +TACE	Choi et al.	192	Sorafenib+TACE (CR 1,PR 11,SD 64) Sorafenib (PR 5.2,SD 48)	Sorafenib+TACE 9.1 Sorafenib 6.7
TACE+RT	Yoon et al.	412	CR 3.6,PR 24.3	10.6
TACE+RT	Our study	**96**	**OR 16.7,SD 30.2**	**14.3**

HAIC: Hepatic arterial infusion chemotherapy; **RT**: rediotherapy

TACE: Transarterial chemoembolization; **TARE**: Transarterial radioembolization;

(Llovet et al., 2008, Kim et al.,2011, Mazzaferro et al.,2013, Yoon et al.,2011)

As health-care costs continue to rise, understanding the economic trends in health care and identifying contributing factors in increased treatment costs will be important in planning for financially and clinically appropriate treatment. Considering the high worldwide healthcare costs for advanced HCC, our results determined that TACE with radiotherapy for HCC with PVTT patients incurs significantly lower medical expenses, longer survival and better outcome.

In Taiwan, advanced HCC is a prevalent cancer with poor prognosis. In view of this, understanding the therapeutic outcomes of HCC with PVTT is vital for optimizing health insurance coverage. Our findings suggest that TACE combined radiotherapy is a good choice for patients with advanced HCC.

Table 5.2 Comparing cost-effectiveness of various treatment strategies for HCC with PVTT

Treatment	Advantages	Disadvantages	Mean Cost (NT)
Sorafenib	Showing survival benefit in infiltrative.	Hand-foot skin reaction.	1,080,000/year
TARE	Down staging allowing liver transplantation.	Requiring additional lung shunt study due to the risk of lung injury.	700,000-800,000
Surgery	Less expensive technic better Outcome than other patients who with HCC are BCLC stage C and Child-A liver function.	Invasive and expensive technic Potential risk liver failure	>150,000
TACE with Radiotherapy	Widen dictation/Combined to multimodal strategies.	Post TACE syndrome Potential risk liver failure.	133,000

Although our results are significantly positive, some points need to be addressed further. First, the response of PVTT after TACE and radiotherapy is difficult to determine, because of the tumor configuration and PVTT region. As we know, HCC can be assessed by mRESICT criteria, which means we should only measure the hypervascular part of treated HCC, but there is no proper radiologic response guideline for the portal thrombus to determine a more objective response to radiotherapy. We can only assess response by measuring size reduction of PVTT compared with initial size; however, substantial portions of responding HCC with PVTTs showed the disappearance of contrast enhancement without an actual reduction in tumor and thrombus size, followed by no increase in thrombus size during long-term follow-up (Yoon et al., 2012). Second, thirty-three patients in our study received various treatments before and after TACE, including Sorafenib, RFA, and surgery, these treatments could have influenced the obtained results.

We do our best to elaborate the study as possible, but some limitations cannot avoid it. Firstly, it was a retrospective study and not a randomized control prospective study, which led to bias. Secondly, although many studies have reported on the use of TACE in patients with HCC, several unresolved issues remain. There is a lack of consensus among interventional radiologists regarding the ideal chemo embolic regimen, procedure end points, the degree of vascular stasis to be achieved, and the ideal time interval between treatment sessions. Third, the fractionated radiation dose might have influenced the PVT response to RT due to the wide range of biologic properties of HCC, but a standard dose fractionation schedule has not been established for RT for patients with HCC with PVTT until now. Therefore, further studies are needed to evaluate the standard dose fractionation schedule. At last, the sample size was too small to postulate the benefits of TACE in patients with PV thrombosis. Further investigation, long-term follow-up, and prospective clinical trials are warranted to determine the exact role of this treatment method in the management of advanced HCC.

6. CONCULSION

Combined treatment consisting of radiotherapy for PVTT and TACE for hepatocellular carcinoma was found to be an effective treatment regimen which achieved a higher response rate and better patient outcome as compared with single-agent modalities such as systemic chemotherapy, sorafenib, radiotherapy or HAIC.

Our findings suggest that in patients diagnosed with advanced HCC, continuous application of TACE treatment results in better response and increased survival rate regardless of the severity of portal vein tumor obstruction.

In conclusion, TACE combined radiotherapy is both a clinically valuable as well as cost-effective treatment option for patients of HCC complicated with PVTT.

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