Research Article

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Radioembolization for hepatocellular carcinoma with portal vein thrombosis: Impact of liver function on systemic treatment options at disease progression

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Background & Aims: Yttrium-90 (^{90}Y) radioembolization is a microembolic procedure. Hence, it is commonly used in hepatocellular carcinoma (HCC) patients with portal venous thrombosis (PVT). We analyzed liver function, imaging findings, and treatment options (local/systemic) at disease progression following ^{90}Y treatment in HCC patients with PVT.

Methods: We treated 291 HCC patients with ^{90}Y radioembolization. From this cohort, we included patients with liver-only disease, PVT and Child–Pugh (CP) score $\leqslant$7; this identified 63 patients with HCC and PVT (CP-A:35, CP-B7:27). Liver function, CP status, and imaging findings at progression were determined in order to assess potential candidacy for systemic treatment/clinical trials. Survival, time-to-progression (TTP), and time-to-hepatic decompensation analyses were performed using Kaplan–Meier methodology.

Results: Of 35 CP-A and 28 CP-B7 patients, 29 and 15 progressed, respectively. Median survival and TTP were 13.8 and 5.6 months in CP-A and 6.5 and 4.9 months in CP-B7 patients, respectively. Of the 29 CP-A patients who progressed, 45% maintained their CP status at progression (55% decompensated to CP-B). Of the 15 CP-B7 patients who progressed, 20% improved to CP-A, 20% maintained their CP score and 60% decompensated.

Conclusions: Knowledge of liver function and CP score of HCC with PVT progressing after ^{90}Y is critically relevant information, as these patients may be considered for systemic therapy/clinical trials. If a strict CP-A status is mandated, our study demonstrated that 64% of cases exhibited inadequate liver function and were ineligible for systemic therapy/clinical trials. An adjuvant approach using local therapy and systemic agents prior to progression should be investigated.

Keywords: Hepatocellular carcinoma; Portal venous thrombosis; Progressive disease; Yttrium-90; Liver function.

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Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CI, 95% confidence interval; CP, Child–Pugh; CT, computed tomography; EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma; LRT, locoregional therapy; MRI, magnetic resonance imaging; PD, progressive disease; PVT, portal venous thrombosis; SIRveNIB, phase III multicenter open-label randomized trial of selective internal radiation therapy versus sorafenib in locally advanced hepatocellular carcinoma; SORAMIC, evaluation of sorafenib in combination with local microtherapy guided by Gd-EOB-DTPA enhanced MRI in patients with inoperable hepatocellular carcinoma; SPACE, sorafenib or placebo in combination with transarterial chemoembolization for intermediate-stage hepatocellular carcinoma; STOP-HCC, phase III clinical trial of intra-arterial TheraSphere in the treatment of patients with unresectable hepatocellular carcinoma; TACE, trans-arterial chemoembolization; TTP, time-to-progression; UNOS, United Network for Organ Sharing; WHO, World Health Organization; ^{90}Y, yttrium-90 radioembolization; YES-p, a prospective randomized clinical trial of ^{90}Y radioembolization *vs.* sorafenib for the treatment of advanced HCC with portal vein thrombosis.

Introduction

Hepatocellular carcinoma (HCC) is the 6th most common malignancy diagnosed worldwide [1]. Its incidence is increasing, and it is the 3rd most common cause of cancer-related mortality [2]. Late stage presentation, comorbidities, and limited donor availability enable only 10% of the patients to receive curative therapies [3]. ^{90}Y radioembolization plays an important palliative role in the management of HCC by inducing tumor necrosis and delaying progression [4–10].

One of the common indications for ^{90}Y that has emerged since its introduction, is HCC in the presence of portal venous thrombosis (PVT). This is a clinically relevant scenario, as 26–35% of HCC patients demonstrate vascular invasion at transplantation [11]. ^{90}Y is a microembolic procedure and causes minimal occlusion of hepatic arteries; hence, it can be safely used in the setting of PVT without compromising blood flow to the hepatic parenchyma [12]. A recent study has suggested that the presence of

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PVT significantly increases the chances of extrahepatic spread of the tumor and decreases overall survival [13]. Assessing outcomes in this situation is therefore important; treating underlying PVT may theoretically translate into a lower rate of extrahepatic metastases. Unfortunately, despite promising response rates in PVT patients treated with ^{90}Y, most patients will progress. This setting of disease progression represents a challenging clinical scenario as treatment options are scarce. The role of systemic agents was historically limited until two randomized trials demonstrated survival benefit with sorafenib [14,15]. Both of these studies enrolled patients with advanced HCC who were ineligible for or had progressed on previous surgical/locoregional therapies. Interestingly, >95% of patients in these studies had Child–Pugh (CP) class A liver function. These trials led a consensus panel to recognize sorafenib as a standard-of-care for patients progressing on locoregional therapy (LRT) [16,17].

The primary purpose of this study was to assess clinical/imaging progression of HCC patients with PVT treated with ^{90}Y (Barcelona Clinic Liver Cancer [BCLC] C disease), as well as to investigate their candidacy for systemic treatment at disease progression. This analysis is of relevance since it explores the commonly stated (but suboptimally studied) notion that patients with PVT may receive an LRT (in this case ^{90}Y) followed by systemic agents at progression. This concept assumes that patient liver function (and CP score) at progression will be sufficiently maintained to permit use of systemic agents which, by 3 major consensus guidelines, should be reserved for CP-A patients [16,18,19].

Materials and methods

This analysis was approved by the Northwestern University Institutional Review Board and is Health Insurance Portability and Accountability Act complaint. The study is a subset analysis of a 291-patient cohort of consecutive HCC patients who were treated with ^{90}Y radioembolization at our institution [5]. Patients were considered candidates for ^{90}Y if they exhibited unresectable HCC (determined by transplant surgery) and bilirubin <3.0 mg/dl. For the purpose of isolating the appropriate cohort, we excluded patients who: (1) did not exhibit PVT, (2) demonstrated extrahepatic metastases, and (3) had a CP score of ⩾8 (Fig. 1). We excluded patients with ⩾CP-B8 and extrahepatic disease in order to reduce the confounding effect of liver function and extrahepatic metastases on survival, respectively. This resulted in the identification of a homogeneous 63 patient cohort who had PVT at baseline and preserved liver function (⩽CP-B7). The patient population was further subdivided into two groups on the basis of CP status (CP-A and CP-B7). CP-B7 patients were included since this is a commonly used cut-off for clinical trials in HCC. Although patients were initially enrolled between January 2004 and December 2008, they have since then been prospectively followed and imaging findings updated; imaging/survival data were closed on December 28, 2011 to report mature outcomes. The data reported herein comply with research reporting standards for ^{90}Y [20].

Evaluation and staging

Diagnostic criteria for HCC included biopsy or radiographic findings as defined by guidelines [16]. Enhancing portal vein thrombus (on imaging) associated with an HCC was deemed to represent malignant vascular invasion. Baseline staging was performed by CP (liver function), United Network for Organ Sharing (UNOS TNM) (tumor size/number), and BCLC classification systems (composite of liver function, tumor size/number and symptoms). The decision to treat with ^{90}Y was consensus-based during the weekly HCC conference represented by medical oncology, hepatology, transplant surgery, and interventional radiology.

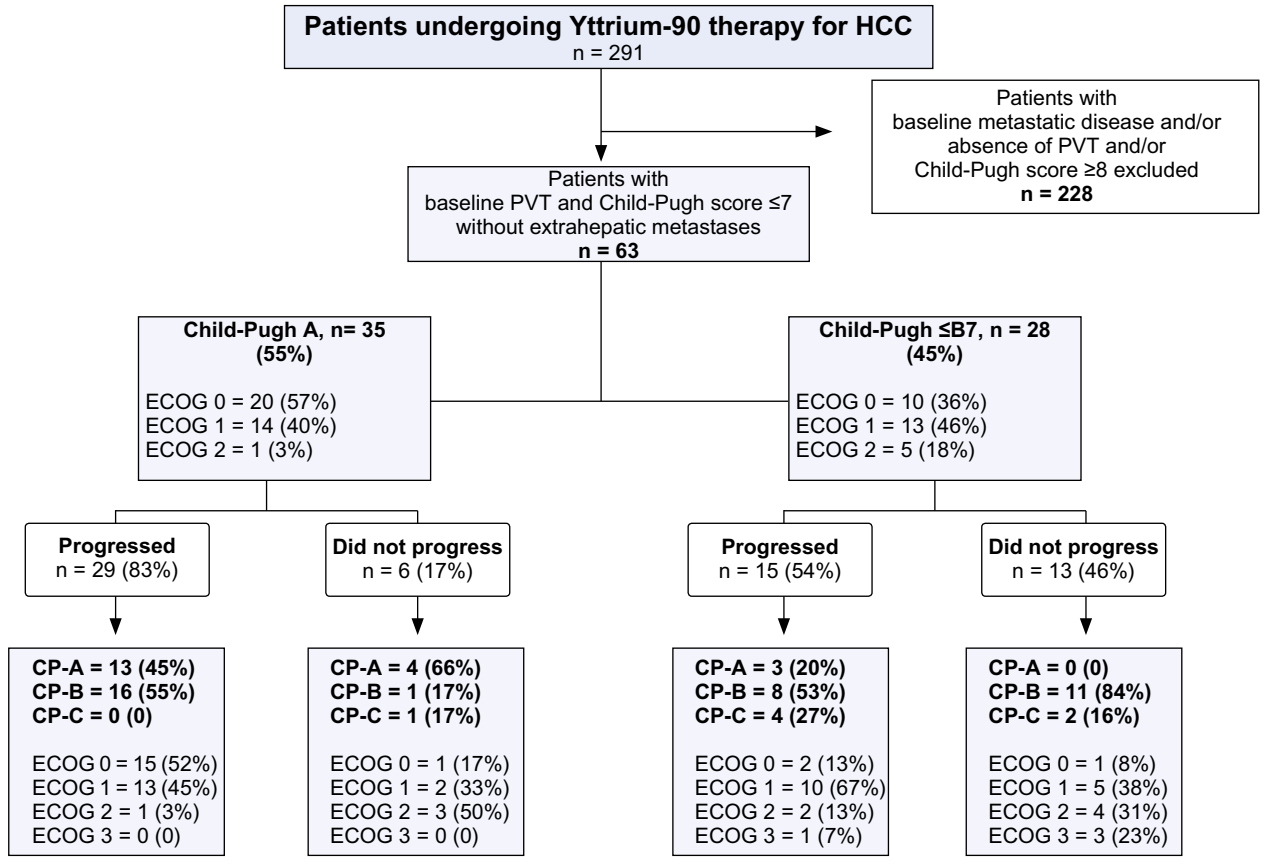

Fig. 1. Study flow chart.