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Radioembolization in Treatment of Hepatocellular Carcinoma with Portal Vein Invasion

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ABSTRACT

Aim of work: this study aimed assess the efficacy of radioembolization (Yttrium-90) therapy in Hepatocellular carcinoma (HCC) patients with portal vein thrombosis.

Patients and methods: this study included 24 patients diagnosed with HCC and portal vein invasion to be treated with Transarterial Radioembolization (TARE). They were 17 males and 7 females. Patients received a single course of treatment.

Results: tumor radiological response assessment revealed that the tumor was controlled in 92% of the patients. Complete response was observed in 21 % of the patients, partial response in 29 % of the patients, stable disease in 42 % of the patients and progressive disease in 8% of the patients.

Conclusion: Yttrium-90 radioemblization appeared to be an effective, safe and feasible treatment option for patients with hepatocelluar carcinoma with portal vein invasion.

Keywords: radioembolization, Yttrium-90, hepatocellular carcinoma, portal vein thrombosis.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common cancers. Overall incidence is more than a million cases every year and it is increasing over the last decade [(1)]. Portal vein tumor thrombosis (PVTT) is a poor prognostic factor for HCC. PVTT is present in 10%-40% of HCC at the time of diagnosis[(2)].

Management of hepatic malignancy is a challenging clinical problem involving several different medical and surgical disciplines. Because of the wide variety of potential therapies, treatment protocols continue to evolve. Consequently, development of appropriate therapeutic algorithms necessitates consideration of medical options, such as systemic chemotherapy; surgical options, such as resection or transplantation; and locoregional therapies, such as thermal ablation and transarterial embolization. Internal radiation therapy through transarterial delivery of beta-emitting yttrium-90 (90Y)-loaded microspheres, is an emerging technique for the treatment of patients with unresectable primary liver tumors**.**

The microspheres lodge preferentially within the neovessels of the tumor(s) and deliver high-energy radiation over a limited range (mean penetration of radiation into tissues is 2.4 mm), thereby minimizing the radiation exposure to normal liver parenchyma[(2)]. Radioembolization may be used for the treatment of unresectable HCC in patients with branch/partial portal vein thrombosis [(3)].

PATIENTS AND METHODS

This study included 24 patients diagnosed with HCC with portal vein invasion to be treated with Transarterial Radioembolization (TARE). Patients provided written informed consent before treatment.

Inclusion criteria

patients with: (1) HCC by imaging or pathology (2) nonsurgical candidate; not fit for radiofrequency or TACE (3) noncompromised pulmonary function (assessed by the history of severe chronic obstructive pulmonary disease, physical examination); (4) able to undergo angiography and selective visceral catheterization; (5) Portal vein thrombosis (6) tumor less than 70% of the total liver volume (7) adequate hematology (granulocytes count $\geqslant 1.5 \times 10^9$/L, platelets $\geqslant 50 \times 10^9$/L), renal function (serum creatinine $\leqslant$ 2.0 mg/dL); (8) liver function (serum total bilirubin $\leqslant$ 2.0 mg/dL).

Exclusion criteria

(1) other planned therapy systemic/locoregional therapy for their HCC (2) liver cell failure (serum total bilirubin > 2.0 mg/dL); (3) evidence of any uncorrectable flow to the gastrointestinal tract observed on angiography or technetium-99m macroaggregated albumin scan; (4) greater than 30 Gy (16.5 mCi) estimated to be delivered to the lungs in a single administration or 50 Gy on

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multiple administrations; and (5) significant extra hepatic disease.

Procedure

Patient selection:

1- Full history taking, physical examination and clinical laboratory tests.
2- All patients had portal vein thrombosis according to baseline imaging CT/MRI.

Method

All patients underwent single session of Transarterial radioembolization using Y-90 resin microspheres.

Dose was calculated according to the following table

Table1. Recommended microspheres dose.

Percent of the Tumor in the Liver	Recommended microspheres dose (Gbq)
>50	3.0
25-50	2.5
<25	2.0

The study was approved by the Ethics Board of Ain Shams University.

Table 2 showed the base line characteristics of the studied population.

Table 2. Base line characteristics of the studied population

characteristic	Value
Mean age (years)	63
Sex ratio M/F	7/3
Portal vein thrombosis (branch)(n)	17
Protal vein thrombosis (Trunk or Trunk and Branch)	7
Child-Pugh score(n)	
A	16
B	8

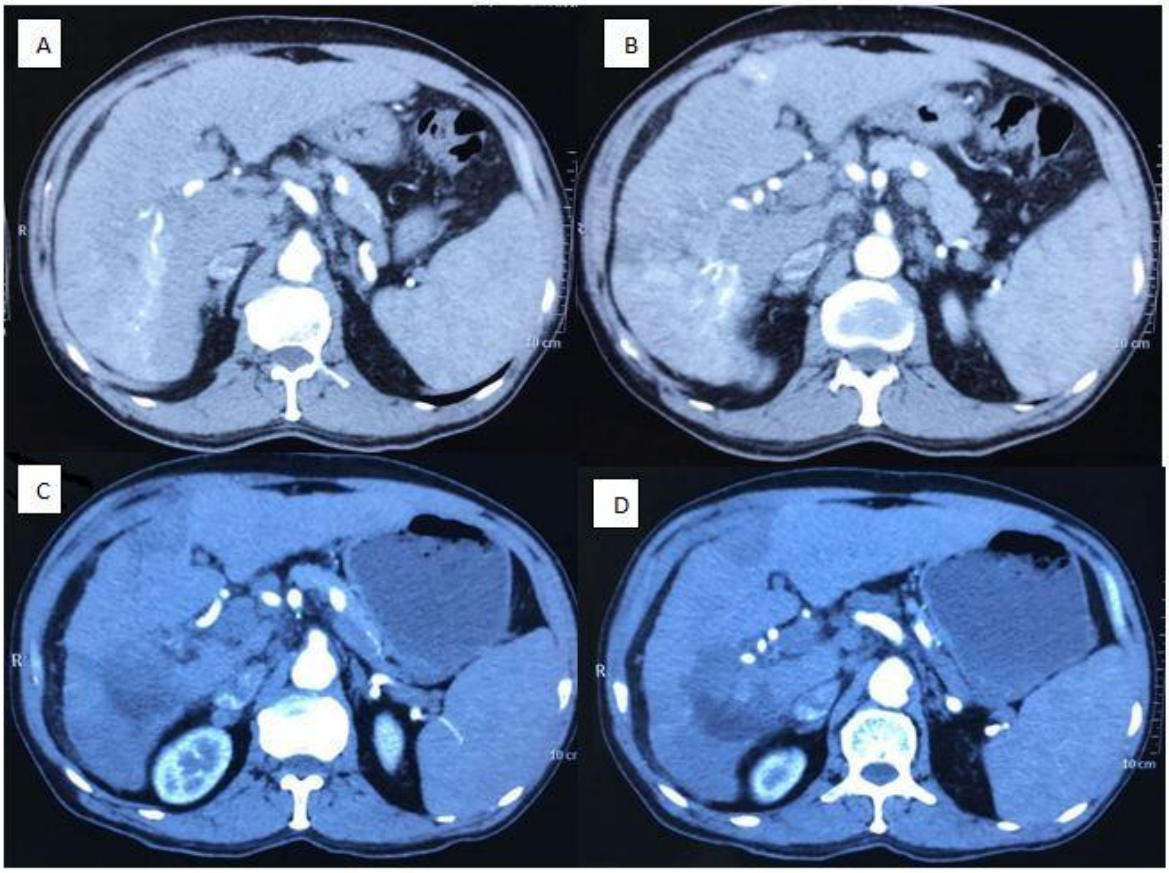
Child-Pugh score is calculated were according to the patients' Bilirubin, Albumin, INR, Ascites and enchapelopathy and given a score. Patient is classified to 3 groups A,B and C where A (5-6 points, least severe disease), B (7 to 9 points, Moderatelty severe disease) and C 10 to 15 points (most severe liver disease).

The study was done after approval of ethical board of Al Azhar university and an informed written consent was taken from each participant in the study.

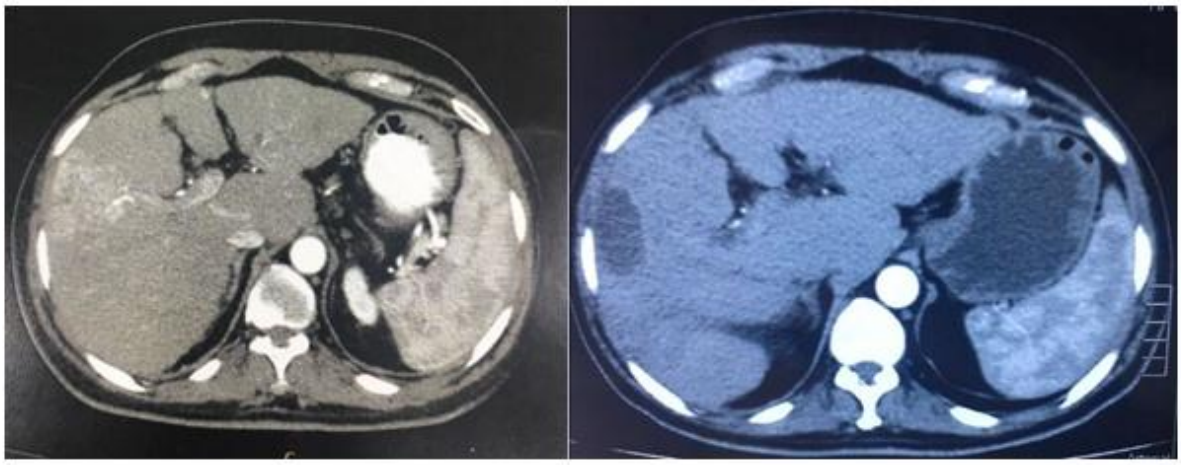
RESULTS

The tumor response was classified into the controlled and progressive disease. Disease control rate was set as the percentage of patients who have attained complete response (CR), partial response (PR) and stable disease (SD) to 90 Y radioembolization.

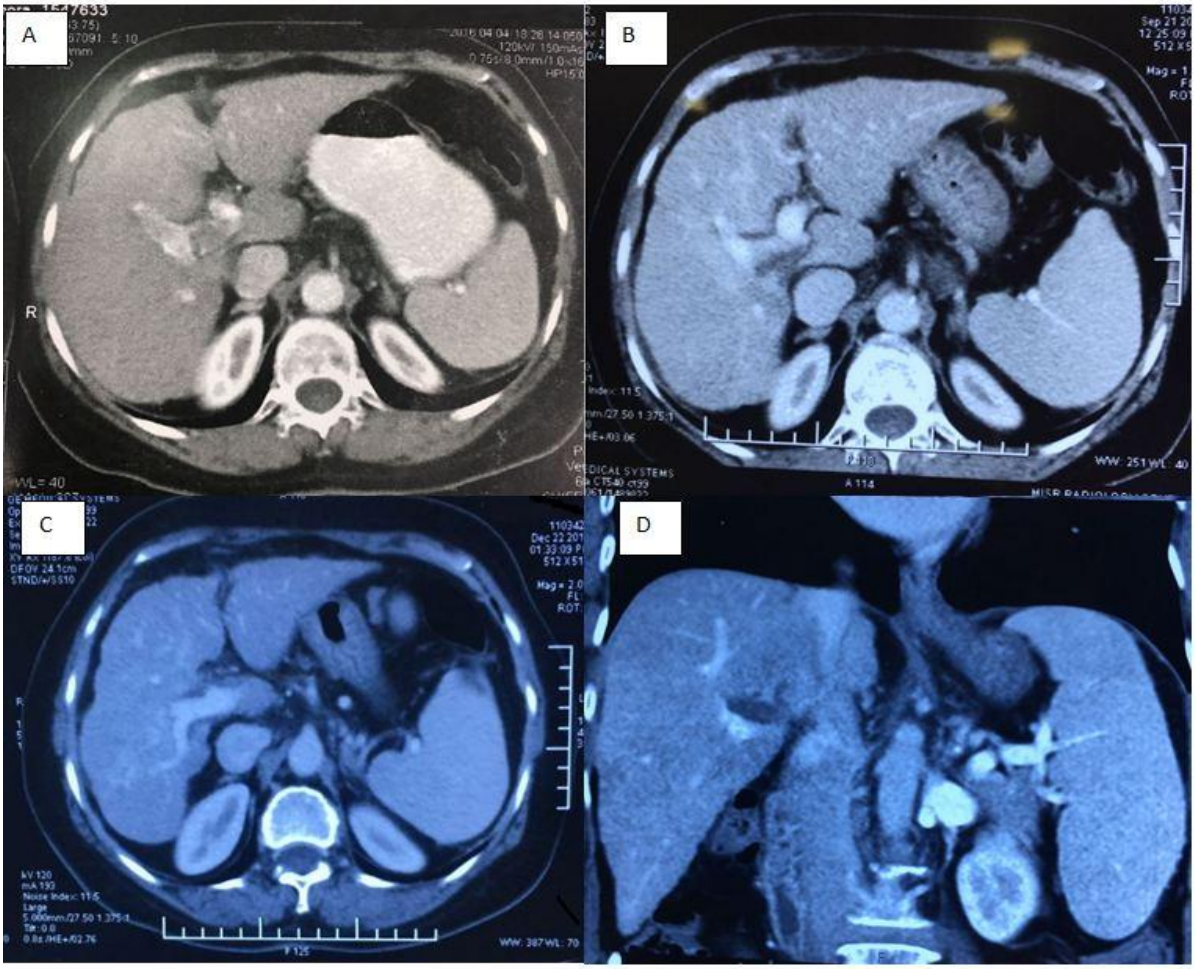
WHO criteria and the subsequent Response Evaluation Criteria in Solid Tumors (RECIST) assessed change in tumor size; however, these criteria generally neglect tumor necrosis and therefore might underestimate treatment responses. So, a panel of experts of the European Association for the Study of Liver (EASL) altered the response criteria to account for tumor necrosis. The modified RECIST (mRECIST) was established, which consider both the concept of tumor viability based on arterial enhancement and single linear summation.



Case:1 65 year old male showing right love infiltrative HCC with contrast enhancement in the arterial phase (A,B). After radioembolization the tumor is hypodense and decreased in size (C,D)



Case 2: 68 year old male showing right lobe infiltrative HCC with contrast enhancement in the arterial phase (A). After radioembolization the tumor is hypodense and decreased in size



Case 3: 67 year old female showing right love infiltrative HCC with contrast enhancement in the arterial phase (A). After radioembolization the tumor is hypodense and decreased in size (B). Persistent response in 6-month follow-up (C,D)

According to the WHO tumor response evaluation criteria Complete or partial response was present in 21 % of the patients, stable disease was presented by 71 % of the patients and progressive disease in 8 % of the patients.

According to the EASL modification complete response was noted in 21 % of the patients, partial response in 29 % of the patients, stable disease in 42 % of the patients and progressive disease in 8% of the patients.

The most common recorded treatment-related complication was transient fatigue, which was reported by 30% of the cases; this was followed by nonspecific mild abdominal pain. Both symptoms were resolved within the first 3 weeks after treatment with no related hospitalization needed. **Table 3** showed tumor radiological response 30 days after Y-90 microspheres

Table 3. Tumor radiological response 30 days after Y-90 microspheres

Treatment outcome	n (%)
Controlled disease	22 (92%)
Progressive disease	2 (8%)
WHO criteria	
Complete response	1 (4%)
Partial response	4 (17%)
Stable disease	17 (71%)
Progressive disease	2 (8%)
WHO with EASL modification	
Complete response	5 (21%)
Partial response	7 (29%)
Stable disease	10 (42%)
Progressive disease	2 (8%)

DISCUSSION

Portal vein tumor thrombosis (PVTT) is a poor prognostic factor for HCC. PVT is present in 10%-40% of HCC at the time of diagnosis. Portal vein tumor thrombosis has a serious adverse effect on prognosis, with the median survival time of cases that have unrespectable HCC with portal vein tumor thrombosis being greatly reduced (2-4 months) compared to those without PVTT (10-24 months). The presence of PVTT also limits the treatment options, with HCC treatment guidelines usually considering PVTT a contraindication for curative resection, transplantation and transarterial chemoembolization (TACE) [(4)]. A recent study showed that HCC with PVTT represented heterogeneous classes with different prognoses. Several classifications have been suggested to gauge the prognoses of PVTT. For selected cases with less severe PVTT, surgery with curative intent was possible with favorable outcomes. Also, broadening treatment options, such as radiotherapy, radioembolization and systemic treatment may improve the outcomes of cases with more severe forms of PVTT [(5)]. Systemic administration of sorafenib may result in significant improvement in survival: median 8.1 months versus 4.9 with placebo for BCLC C patients with macrovascular invasion. But, Sorafenib cannot be considered as a curative treatment because there have been no recorded cases of downsizing. The objective response rate with sorafenib was very low, less than 3% with the RECIST criteria [(6)]. The efficacy of SIRT in unrespectable HCC was compared to sorafenib in a recent study. **Edeline *et al.*** retrospectively reviewed the records of 151 HCC patients with PVTT. The overall survival of 34 patients managed with SIRT was compared with 117 patients treated with sorafenib only. SIRT was associated with a higher median overall survival compared to sorafenib (18.8 mo vs 6.5 mo, $P < 0.001$) [(7)].

Over the past two decades, progress has been made in the management of patients with hepatocellular carcinoma (HCC) and portal vein tumor thrombosis (PVTT). Yttrium-90 (90 Y) radioembolization has been made a treatment option for those patients.

Yttrium-90 (90 Y) radioembolization is a locoregional liver-directed therapy that involves transcatheter delivery of particles embedded with the radioisotope 90 Y. In addition to obliteration of the arterial blood supply, the 90 Y results in a 50-150 Gy dose of radiation to the tumor tissue, which leads to tumor necrosis, including HCC and PVTT? It was reported that 90 Y radioembolization is a safe and effective treatment for patients with HCC and PVTT[(8)]. The introduction of radioembolization for the treatment of cases with HCC and PVT has been tempered by concerns regarding the potential increased risk of liver failure, complications and death as a result of impairment of hepatic vascular supply in the presence of compromised portal blood flow. These concerns have been guided by the previous experience with intense embolic therapies such as chemoembolization. A randomized studies including chemoembolization had mainly excluded patients with vascular invasion, including segmental portal obstruction, in view of the increased risk of compromised hepatic arterial flow. A randomized study of chemoembolization versus untreated controls found the relative risk of death for patients with unilobar (ie, branch) portal vein obstruction managed with chemoembolization was 2.71 (P.004) compared to patients without PVT [(9)]. By contrast, a recent study suggested that 90Y resin microspheres can be used with a decreased risk of complication and can provide some clinical benefit in this challenging patient population[(10)].

The present study aimed to explore the safety and feasibility of 90Y radioembolization in patients with HCC and PVT

This study showed that 90Y radioembolization is a viable treatment option for HCC with PVT in the outpatient setting, with a good safety profile as previously approved by several guidelines for HCC with PVT.

Similar to previously published data, the most common clinical symptoms experienced by the cases were transient fatigue syndrome and nonspecific mild abdominal pain, both of which were resolved within 2 to 3 weeks after the therapy with no hospitalization needed.

Mosconi *et al.* [(10)] studied the safety and efficacy of glass 90Y microspheres in intermediate to advanced HCC with or without PVT, 90Y therapy and they showed a low incidence of moderate/severe complications with a 14% rate of grade 3 to 4 bilirubin toxicity at 3 months.

Our series confirmed the efficacy of this treatment and the tumor was controlled in 92% of our patients.

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