A Systematic Review on the Safety and Effectiveness of yttrium-90 Radioembolization for Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis

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ABSTRACT

Background/Aim: Over the past two decades, several advances have been made in the management of patients with hepatocellular carcinoma (HCC) and portal vein tumor thrombosis (PVTT). Yttrium-90 (^{90}Y) radioembolization has recently been made a treatment option for patients with HCC and PVTT. However, there is still a need to systematicly evaluate the outcomes of ^{90}Y radioembolization for HCC and PVTT. We aimed to assess the safety and effectiveness of ^{90}Y radioembolization for HCC and PVTT. We performed a systematic review of clinical trials, clinical studies, and abstracts from conferences that qualified for analysis. **Materials and Methods:** PubMed, EMBASE, Cochrane Database of Systematic Review, CINAHL, and the "gray" literature (Google Scholar) were searched for all reports (1991-2016) related to ^{90}Y radioembolization for HCC and PVTT. **Results:** A total of 14 clinical studies and three abstracts from conferences including 722 patients qualified for the analysis. The median length of follow-up was 7.2 months; the median time to progression was 5.6 months, and median disease control rate was 74.3%. Radiological response data were reported in five studies, and the median reported value of patients with complete response, partial response, stable disease, and progressive disease were 3.2%, 16.5%, 31.3%, and 28%, respectively. The median survival was 9.7 months for all patients, including the median overall survival (OS) were 12.1, 6.1 months of Child–Pugh class A and B patients, and the median OS were 6.1, 13.4 months of main and branch PVTT patients, respectively. The common toxicities were fatigue, nausea/vomiting, abdominal pain, mostly not requiring medical intervention needed no medication intervention. **Conclusions:** ^{90}Y radioembolization is a safe and effective treatment for HCC and PVTT.

Key Words: Hepatocellular carcinoma, portal vein tumor thrombosis, radioembolization, toxicity, yttrium-90

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Portal vein tumor thrombosis (PVTT) occurs in a substantial portion of hepatocellular carcinoma (HCC) patients and in approximately 10%–40% of patients at diagnosis.[1,2] PVTT has a profound adverse effect on prognosis, with the median survival time of patients who have unresectable HCC with PVTT being significantly reduced (2–4 months) compared with those without PVTT (10–24 months).[1,3]

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The presence of PVTT also limits the treatment options, with HCC treatment guidelines often considering PVTT a contraindication for transplantation, curative resection, and transarterial chemoembolization (TACE).[4,5] Although the presence of PVTT poses a challenging treatment dilemma,[1] many treatments of HCC with PVTT have been reported, including surgical,[2] TACE,[4-9] external beam radiotherapy,[10] gamma-knife radiosurgery,[4] TACE combined with endovascular implantation of an iodine-125 seed strand,[11] and transarterial radioembolization.[12]

However, the optimal treatment for patients with HCC and PVTT remains largely controversial.[7] 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 results in tumor necrosis, including HCC and PVTT.[13] It was reported that ^{90}Y radioembolization is a safe and effective treatment for patients with HCC and PVTT.[6] However, there is still a need to systematically evaluate the outcomes of this treatment modality.

The purpose of this study was to comprehensively review the safety and effectiveness of ^{90}Y radioembolization for HCC and PVTT.

MATERIALS AND METHODS

Search strategy

PubMed, EMBASE, Cochrane Database of Systematic Review, CINAHL and the "gray" literature (Google Scholar) were searched from January 1, 1991 (the first commercial availability of the ^{90}Y products) to January 25, 2016, for the full text describing ^{90}Y in the treatment of HCC and PVTT (keywords: (Liver cancer or liver tumor or primary liver cancer or hepatocellular carcinoma); (portal vein tumor thrombosis or portal vein thrombosis); and (yttrium-90 or ^{90}Y or TheraSphere or SIR-Spheres) and English language). We retrieved potentially relevant articles and reviewed their reference lists to find studies that our search strategy may have missed. Clinical trials, clinical studies, and abstracts from conferences that qualified for analysis were included in this review.

The primary objective of this study was to determine the overall survival (OS), and the secondary objectives were to identify the radiological response and clinical toxicity.

Inclusion criteria

The inclusion criteria were (1) clinical trials, clinical studies, or abstracts from conferences; (2) describing ^{90}Y in the treatment of PVTT; (3) at least include the primary objective: OS. Exclusion criteria were as follows: (1) Review articles, animal studies, laboratory investigations, case reports, and case series; (2) any duplicated clinical studies. All the clinical trials, clinical studies, and abstracts from conferences were reviewed for qualification according to our study criteria.

Data extraction

A standardized data extraction database was created by tabulating the following information: First author, year of publication, prospective or retrospective design, quality criteria, number of patients, patient characteristics, assessment criteria (European Association for the Study of the Liver [EASL]; Response Evaluation Criteria in Solid Tumors [RECIST]; World Health Organization [WHO]), time to progression (TTP), disease control rate, radiological response, OS, and clinical toxicity. Two members of the research team conducted the literature search independently to verify data accuracy and completeness, with a third one resolving any discrepancy. Studies were classified into three levels of evidence as follows: Level I, randomized controlled trials (RCTs); level II, non-RCTs or well-designed cohort studies; and level III, observational studies, as described by the U.S. Preventive Services Task Force.

Definitions

OS was calculated in months for all subjects from the date of radioembolization treatment to the date of death or last follow-up. Disease control rate was defined as the percentage of patients who have achieved complete response (CR), partial response (PR), and stable disease (SD) to ^{90}Y radioembolization.[14]

RESULTS

The initial search yielded 225 English reports from January 1, 1991, to January 25, 2016. An additional search using Google Scholar found no additional relevant articles. Of the 225 reports, a total of 208 reports were excluded due to unqualified studies (n = 182), review articles (n = 21), and duplicated clinical studies (n = 5) [Figure 1]. Ultimately, a total of 17 reports, including 14 studies (five prospective and nine retrospective) and three abstracts from conferences were included in this study (Kokabi N, *et al.*;[15] Mazzaferro V, *et al.*;[16] Memon K, *et al.*;[17] Woodall CE,

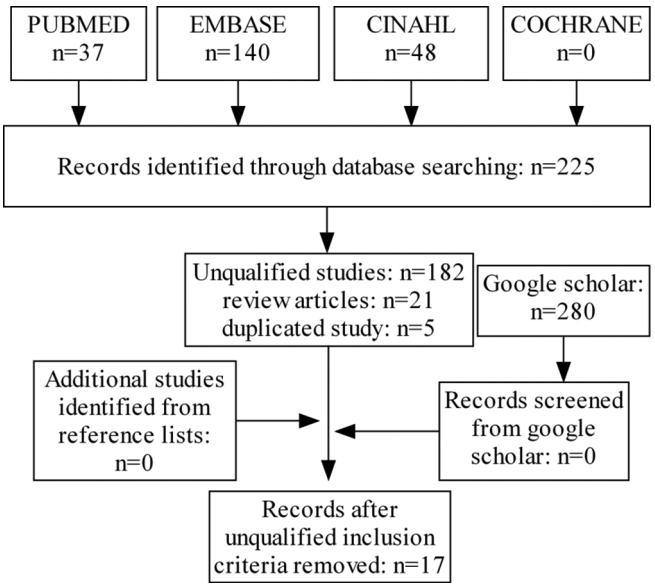

Figure 1: Flow diagram of literature search

et al.;[18] Kulik LM, *et al*.;[19] Salem R, *et al*.;[20] Garin E, *et al*.;[21] Sangro B, *et al*.;[22] Inarrairaegui M, *et al*.;[23] Salem R, *et al*.;[24] Tsai AL, *et al*.;[25] Hilgard P, *et al*.;[26] Akinwande O, *et al*.;[27] Lee VH, *et al*.;[28] Biederman DM, *et al*.;[29] Kim YH, *et al*.;[30] El Fouly A, *et al*.[31]). The quality of evidence was as follows: level II, n = 6, and level III, n = 11.

Table 1 summarizes the patient demographic characteristics of the included reports. A total of 722 cases were included in the final analysis. The median value of the percentage of male patients was 80.5% (range 70%–94.2%) with a median age of 64 years (range 56–67 years). The median percentage of the reported main PVTT was 42.1% (range 0%–100%), and the extrahepatic metastases were present in a median of 12% cases (range 0%–31.9%). The median percentage of Child–Pugh class A, B, C were 67% (range 20%–92.7%), 33% (range 7.3%–62%), and 0 (0%–27%), respectively. The median value of the radioactivity delivered was 2.6 GBq (range 1.4–3.1 GBq). Of the 722 cases, glass microspheres were used in 540 cases, resin microspheres were used in 160 cases, and the other 22 cases were unspecified.

Table 2 summarizes the effectiveness of ^{90}Y treatment of the included studies. The median length of follow-up was 7.2 months (range 6–36 months), the median TTP was 5.6 months (range 4.9–9 months), and the median disease control rate was 74.3% (range 16.7%–94%). Radiological response data were reported in five studies; the median reported value of patients with CR, PR, SD, and progressive disease (PD) were 3.2% (range 0%–12.2%), 16.5% (range 5%–73.2%), 31.3% (range 5%–64%), and 28% (range 0%–80%), respectively. OS results were reported in all studies, with the median survival being 9.7 months (range 3–23.7 months).

The Child–Pugh class A (n = 70) and B (n = 85) patients were reported in four studies (only two studies identified the total patients number), with median OS being 12.1 months (7.4–23.7 months) of Child–Pugh class A patients, and 6.1 months (3.6–7 months) of Child–Pugh class B patients [Table 2]. The main PVTT (n = 70) and branch PVTT (n = 100) patients were reported in three studies, with median OS being 6.1 months (4.5–12 months) of main PVTT patients, and 13.4 months (6.5–21.5 months) of branch PVTT patients [Table 2].

Table 3 presents a thorough overview of the toxicity associated with ^{90}Y radioembolization. Although toxicities were not available for most of the included studies, the common toxicities were fatigue (range 2.9%–67%), abdominal pain (range 2.9%–57%), and nausea/vomiting (range 5.7%–28%).

DISCUSSION

This review demonstrated the median disease control rate as 74.3%, and median survival as 9.7 months following ^{90}Y radioembolization for HCC and PVTT patients. The median OS were 12.1 and 6.1 months of Child–Pugh class A and B patients, respectively, and the median OS were 6.1 and 13.4 months of main and branch PVTT patients, respectively.

^{90}Y radioembolization treatment, a form of intraarterial brachytherapy, is a technique in which glass or resin particles

Table 1: Summary of the characteristics of the included studies

References	Study type	Level of evidence	Number of cases	Male	Age	Main PVTT	Extra-hepatic metastases	Child-Pugh A/B/C (%)	Mean activity (Gbq)	^{90}Y Products
Kokabi N.[15] 2015	Pro	II	30	77%	62	20%	23%	67/33/0	2.9	Glass
Mazzaferro V.[16] 2013	Pro	II	35	94.2%	64	17.1%	0	80/20/0	2.6	Glass
Memon K.[17] 2013	Pro	II	35	75%	65	46%	N/A	55.6/44.4/0	N/A	Glass
Woodall CE.[18] 2009	Pro	II	15	73%	67	71%	N/A	20/53/27	N/A	Glass
Kulik LM.[19] 2008	Pro	II	37	N/A	N/A	32.4%	N/A	N/A	N/A	Glass
Salem R.[20] 2004	Re	III	15	73.3%	56	0	26.7%	N/A	N/A	Glass
Garin E.[21] 2015	Re	III	41	80.5%	64.4	29.2%	0	92.7/7.3/0	3.1	Glass
Sangro B.[22] 2011	Re	III	76	N/A	N/A	42.1%	N/A	N/A	N/A	Resin
Inarrairaegui M.[23] 2010	Re	III	25	88%	66	24%	N/A	N/A	1.8	Glass
Salem R.[24] 2010	Re	III	92	N/A	N/A	50%	0	38/62/0	N/A	Glass
Tsai AL.[25] 2010	Re	III	22	91%	57.5	45.5%	14%	N/A	2.7	N/A
Hilgard P. [26] 2010	Re	III	33	N/A	N/A	36.4%	N/A	N/A	N/A	Glass
Akinwande O.[27] 2015	Re	II	20	70%	67.1	100%	10%	35/55/10	1.9	Glass
Lee VH.[28] 2015	Re	III	12	91.7%	64	66.7%	N/A	83.3/16.7/0	1.4	Resin
Biederman DM.[29] 2015	Re	III	97	81%	63	N/A	N/A	N/A	N/A	Mixed
Kim YH.[30] 2014	Re	III	47	N/A	N/A	N/A	31.9%	87.2/12.8/0	N/A	Resin
El Fouly A.[31] 2014	N/A	III	90	N/A	N/A	54%	N/A	67/33/0	N/A	Glass

Re: Retrospective, Pro: Prospective, N/A: Not avalible, PVTT: Portal vein tumor thrombosis

Table 2: Summary of the outcomes of the included studies

References	No. of evaluable patients	Assessment criteria	Median FU (months)	TTP (months)	Disease control rate	Response rates CR/PR/SD/PD (%)	Overall survival (months)
Kokabi N.	30	mRECIST	17.4	9	N/A	N/A	13 (4.4-22)
Mazzaferro V.	35	RECIST	36	7	74.3%	N/A	13 (9-17)
Woodall CE.	15	N/A	N/A	N/A	N/A	N/A	3.2
Salem R.	15	N/A	7.2	N/A	N/A	N/A	16.5
Memon K.	35 (CP A cases)	WHO	N/A	5.6 (3.5-7.5)	86%	0/49/37/14	13.8 (9-18.8)
	28 (CP B cases)	WHO	N/A	4.9 (2.2-6.3)	89%	0/25/64/11	6.5 (5-7.5)
Kulik LM.	12 (main PVTT)	WHO	N/A	N/A	N/A	N/A	4.5
	25 (branch PVTT)	WHO	N/A	N/A	N/A	N/A	10.2
Salem R.	35 (CP A, PVTT mixed)	WHO	N/A	N/A	N/A	N/A	10.4
	16 (main PVTT)	WHO	N/A	N/A	N/A	N/A	7.7
	19 (branch PVTT)	WHO	N/A	N/A	N/A	N/A	16.6
	57 (CP B, PVTT mixed)	WHO	N/A	N/A	N/A	N/A	5.6
	30 (main PVTT)	WHO	N/A	N/A	N/A	N/A	4.5
	27 (branch PVTT)	WHO	N/A	N/A	N/A	N/A	6.5
Garin E.	41 (total)	EASL	N/A	N/A	85%	12.2/73.2/14.6/0	18
	12 (main PVTT)	EASL	N/A	N/A	N/A	N/A	12
	29 (branch PVTT)	EASL	N/A	N/A	N/A	N/A	21.5
	N/A (CP A, PVTT mixed)	N/A	N/A	N/A	N/A	N/A	23.7
	N/A (CP B, PVTT mixed)	N/A	N/A	N/A	N/A	N/A	7
Sangro B.	76	N/A	N/A	N/A	N/A	N/A	10
Inarrairaegui M.	24	RECIST	8	N/A	94%	N/A	10 (6.6-13.3)
Tsai AL.	22	RECIST	9	N/A	58%	0/8/50/42	7 (4.5-6.7)
Hilgard P.	33	RECIST	N/A	N/A	N/A	N/A	10
Akinwande O.	20	mRECIST	22	N/A	20%	10/5/5/80	3
Lee VH.	12	N/A	N/A	N/A	16.7%	N/A	4.4
Biederman DM.	97 (total)	mRECIST	N/A	N/A	N/A	N/A	9.3
	72 (glass)	mRECIST	N/A	N/A	N/A	N/A	15 (8.6-19.5)
	25 (resin)	mRECIST	N/A	N/A	N/A	N/A	4.1 (2.7-6.6)
Kim YH.	47	mRECIST	6	N/A	48.9%	6.4/6.4/25.5/51.1	10.3 (5.7-14.8)
El Fouly A.	90 (total)	N/A	N/A	4.9	N/A	N/A	6.1 (5.4-6.8)
	N/A (CP A, PVTT mixed)	N/A	N/A	N/A	N/A	N/A	7.4 (5.1-9.8)
	N/A (CP B, PVTT mixed)	N/A	N/A	N/A	N/A	N/A	3.6 (2.7-4.4)

CP: Child-Pugh class, PVTT: Portal vein tumor thrombosis, EASL: European association for the study of the liver, RECIST: Response evaluation criteria in solid tumors, mRECIST: Modified response evaluation criteria in solid tumors, WHO: World health organization, FU: Follow-up, N/A: Not avalible, TTP: Time to progression, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease

are labeled with ^{90}Y. The radioisotope ^{90}Y is a pure β-emitter with no primary gamma radiation. HCC and PVTT are fed mainly by hepatic arterial system rather than portal venous blood. Therefore, the dominant arterial flow of malignant tissue allows the delivery of high doses of radiation to tumors while keeping the exposure of the healthy liver at minimum with selective ^{90}Y microsphere distribution. It was reported that ^{90}Y internal radiation therapy can provide tumor doses as high as 50–150 Gy, in contrast to traditional whole liver external beam radiation where the radiation dose has been limited to 30 Gy to prevent adjacent organ injury.[32,33] To date, the published reports documented in this sample demonstrate that ^{90}Y treatment can be used safely in patients with portal circulation compromised at the level of the first-order portal branches.[12,17,34] Also, Tsai *et al.*[10] reported that ^{90}Y treatment is tolerated in patients with HCC and major PVTT, and the median OS (7 months) is promising.

Most of the studied patients had end-stage disease, reflected by the high proportion of patients with Child–Pugh class B or C and main PVTT. The median disease control rate in the review of studies was 74.3%, with a median TTP of 5.6 months, and median survival of 9.7 months. It demonstrates that ^{90}Y radioembolization is an effective treatment for HCC and PVTT. ^{90}Y may also lead to tumor downstaging, which might allow for subsequent surgical resection or radiofrequency ablation.

From this study, the median OS of patients in Child–Pugh class A was longer than patients in Child–Pugh class B (12.1

Table 3: Summary the toxicity of patients in the included studies

References	No. of evaluable patients	Total	Fatigue	Abdominal pain	Nausea/ vomiting	Fever	Ascites	Elevated bilirubin
Kokabi N.	30	N/A	67%	57%	N/A	N/A	N/A	27%
Mazzaferro V.	35	17.2%	2.9%	2.9%	5.7%	2.8%	2.9%	N/A
Memon K.	63	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Woodall CE.	15	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Kulik LM.	N/A	50%	22%	N/A	28%	N/A	N/A	N/A
Salem R.	15	20%	N/A	N/A	N/A	N/A	N/A	20%
Garin E.	41	6%	N/A	N/A	N/A	N/A	N/A	N/A
Sangro B.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Inarrairaegui M.	25	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Salem R.	92	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Tsai AL.	22	38%	N/A	38%	N/A	N/A	N/A	N/A
Hilgard P.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Akinwande O.	20	31%	N/A	N/A	N/A	N/A	N/A	N/A
Lee VH.	12	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Biederman DM.	97	N/A	30%	28%	17%	N/A	7%	54%
Kim YH.	47	N/A	N/A	19.1%	17%	N/A	N/A	N/A
El Fouly A.	90	N/A	N/A	N/A	N/A	N/A	N/A	N/A

N/A: Not avalible

vs 6.1 months); and the median OS of patients in branch PVTT was longer than that in main PVTT patients (13.4 vs 6.1 months). It shows that tumor progression was slower in patients with Child–Pugh class A and branch PVTT than patients with Child–Pugh class B and main PVTT.

Although embolization with ^{90}Y does results in permanent vascular blockade with glass or resin particles, the smaller caliber of the particles (20–30 μm glass, 20–60 μm resin) impart the theoretical advantage of a lesser degree of macroscopic arterial occlusion. It was reported that the ^{90}Y treatment exerts less of an ischemic effect compared with TACE (threefold lower incidence of postembolization syndrome).[35]

Overall, ^{90}Y treatment is a well-tolerated procedure, especially when compared with TACE. The most frequently encountered toxicities are symptoms of the post-radioembolization syndrome, including fatigue, abdominal pain, nausea/vomiting, and fever. Although the incidence of symptoms of post-radioembolization syndrome was not reported in most of the included studies, the common toxicities were abdominal pain, nausea/vomiting, and fatigue. Fortunately, postembolization syndrome can be managed with medication and the symptoms generally subside within a week post-radioembolization.

Study limitation

This study was limited by the small number and quality of included studies, as only 14 studies and three abstracts were included and the overall evidence was level II or III by the U.S. Preventive Services Task Force, and all the included studies were not specifically focused on and lacked details related to the etiological factors (especially hepatitis B- and hepatitis C-related HCC). Also, the number of patients and the observation time was short in the included studies, all of which may bias the results. Furthermore, only four studies mentioned the OS of different Child–Pugh class (A/B) and three studies mentioned the OS of different PVTT location (main/branch), which may also bias the results. Lastly, we cannot prove which ^{90}Y product (glass/resin) is better due to the small studied sample of only 160 cases that used resin microsphere.

CONCLUSIONS

^{90}Y radioembolization is a safe and effective treatment for HCC and PVTT. However, this study lacks adequate power to draw definitive conclusions based on the presented data. A larger cohort might allow more meaningful conclusions and more robust survival data.

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Conflicts of interest

There are no conflicts of interest.

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