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ORIGINAL RESEARCH

Utility of Yttrium-90 Radioembolization for the Treatment of Fibrolamellar Hepatocellular Carcinoma: A Tertiary Cancer Center Experience

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Purpose: To describe the safety and efficacy of Yttrium-90 transarterial radioembolization (Y90-TARE) in patients with fibrolamellar hepatocellular carcinoma (FL-HCC).

Patients and Methods: This is a retrospective study of patients with FL-HCC treated with Y90-TARE in a single tertiary cancer center. Y90-TARE was performed using Y90 glass or resin microspheres. Treatment response was evaluated at 1, 3, and 6 months using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) guidelines. Electronic medical records were retrospectively reviewed to evaluate clinical outcomes, complications, tumor response on imaging, overall survival (OS), and progression-free survival (PFS). MIM Software (v7.1, Cleveland, OH) was used for dosimetry analysis and contouring.

Results: Seven patients (5 females, 2 males; median age at the time of Y90-TARE: 24, range: 16–77 years) with FL-HCC underwent nine Y90-TARE procedures. The median progression-free survival (PFS) was 9.0 months, and the median overall survival (OS) was 15.8 months. Partial response (PR) was observed in 86% of patients at 3 months and 100% of evaluable patients at 6 months. One patient underwent successful liver transplantation, and another received hepatectomy after treatment. No adverse events grade 3 or greater were reported within 30 days. One patient developed a hepatic abscess two months post-procedure, and another developed a tumor to duodenum fistula three months after Y90-TARE. The median absorbed tumor dose was 405 Gy (mean: 579 ± 442 Gy; range: 109–1362 Gy), and the median absorbed dose to perfused normal liver was 83 Gy (mean: 96 ± 41 Gy; range: 63.5–190 Gy). The median administered activity was 3.85 GBq, with a median lung shunt fraction of 4.59% and a median lung dose of 6.4 Gy. The study is limited by its retrospective design and small sample size in this rare tumor cohort.

Conclusion: Treatment of FL-HCC patients with unresectable tumors with 90Y-TARE is safe and shows a favorable response to treatment.

Plain Language Summary: Fibrolamellar hepatocellular carcinoma (FL-HCC) is a rare type of liver cancer that usually affects young people without underlying liver disease. Because it is rare, there is limited information on multidisciplinary treatment approaches, especially when surgery is not feasible.

In this study, we report seven patients with FL-HCC who were treated with Yttrium-90 transarterial radioembolization (Y90-TARE) . The treatment delivers radiation directly to liver tumors through the hepatic arteries, which can help control tumor growth with acceptable side effects.

The study found that the treatment was generally safe and well-tolerated and induced promising anti-tumor effects and survival outcomes. In two cases, the treatment allowed patients to undergo surgery for treatment.

These findings suggest that Y90-TARE may be a valuable multidisciplinary treatment option for select patients with FL-HCC, particularly those with unresectable disease. Our study warrants further investigation through future multicenter studies to validate this

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approach in patients with FL-HCC.

Keywords: Yttrium-90 radioembolization, transarterial radioembolization, TARE, fibrolamellar hepatocellular carcinoma, FL-HCC, locoregional therapy, tumor dosimetry, liver-directed therapy, resin microspheres, glass microspheres, hepatic malignancy

Introduction

Fibrolamellar hepatocellular carcinoma (FL-HCC) is a rare type of primary liver cancer, occurring in young adults without underlying liver disease, and accounts for up to 1% of all primary hepatic malignancies in the US.[1,2] It is characterized by different biological profiles from other forms of hepatocellular carcinoma (HCC), which requires a tailored treatment strategy.[3,4] Surgical resection is often the first line of treatment; however, for those with unresectable disease, the median survival is only 12 months, with no reported five-year survivors.[5]

Beyond HCC, Yttrium-90 transarterial radioembolization (Y90-TARE) has emerged as an effective treatment for different types of liver malignancies.[6–8] Y90-TARE has been shown to control tumor growth and improve survival in patients with unresectable liver tumors.[9,10] In recent years, dosimetry has emerged as a necessary component of Y90-TARE, transitioning from fixed-activity prescriptions toward personalized treatment planning. With modalities such as Y-90 SPECT/CT and PET/CT, voxel-level dosimetry allows for more accurate quantification of the absorbed radiation dose delivered to both tumor and normal liver tissue. In addition, evidence from resin microsphere cohorts of patients with large unresectable HCC, where higher mean tumor-absorbed doses (≥150 Gy) were associated with improved overall survival, further emphasized the importance of quantitative dosimetry in Y90-TARE. This personalized approach has been associated with improved prediction of treatment response and toxicity, resulting in increased emphasis on dosimetric endpoints in clinical studies.[11–13]

The application of Y90-TARE in FL-HCC remains less documented due to the rarity of the disease, and is mostly limited to case reports.[14,15] Given the limitations of resection and the challenges of large, centrally located FL-HCC in young, non-cirrhotic patients, durable control must be balanced with preservation of functional liver parenchyma. In this context, other liver-directed therapies such as ablation and TACE are often less appealing.[16,17] Y90-TARE, by contrast, enables high radiation doses to extensive or anatomically complex tumor burden with relative sparing of uninvolved liver and has shown promising local control, downstaging, and safety in HCC when compared against other liver-directed therapies.[18–20] There remains a gap to explore the use of Y90-TARE in the treatment of FL-HCC. This study aims to evaluate treatment outcomes, safety profiles, and the role of Y90-TARE, along with quantitative dosimetry, in the treatment of FL-HCC.

Materials and Methods

Study Design and Patient Selection

This retrospective study was conducted at a tertiary cancer center following approval by the Institutional Review Board and in accordance with the Declaration of Helsinki and the Health Insurance Portability and Accountability Act (HIPAA), where applicable. Because only previously collected clinical data were used, the requirement for written informed consent was waived by the Institutional Review Board.The institutional database was searched to identify patients with histopathologically confirmed FL-HCC who underwent Y90-TARE between January 2010 and December 2024. Patients were eligible if they had unresectable diseases (multifocal or bilobar disease not amenable to resection, anticipated insufficient liver remnant, involvement of major vascular structures, extrahepatic disease precluding curative surgery, or significant comorbidities) and received Y90 treatment with either glass or resin microspheres. Patient demographics, clinical imaging, and treatment details were retrieved from electronic medical records.

TARE Y90 Procedure

All patients underwent pre-procedural hepatic angiography and mapping to explore vascular anatomy, identify and embolize extrahepatic branches if needed, and evaluate lung shunt fraction via technetium-99m macroaggregated albumin (99mTc-MAA) imaging. Tc-99m MAA SPECT/CT images were used to delineate tumor and perfused normal liver compartments, and projected absorbed doses were estimated using a compartment-based model to estimate mean absorbed doses to tumor, non-tumoral liver, and lungs; activity was adjusted to achieve the tumor dose goal while respecting normal-tissue constraints to avoid toxicity. Delivered tumor-absorbed doses were calculated from Y-90 Bremsstrahlung SPECT/CT which were generally in agreement with the planned Tc-99m MAA–based tumor doses.

Y90-TARE treatment planning was performed based on tumor burden and lung shunt fraction. Y90-TARE and all aspects of the procedures were performed by Interventional radiologists with 4–15 years of experience using glass microspheres (TheraSphere, Boston Scientific, Marlborough, MA, USA) in 6 patients and resin microspheres (SIR-Spheres, Sirtex Medical, Woburn, MA, USA) in one patient. Patient details and disease characteristics are described in Table 1.

The choice of microspheres and prospective dosimetry approach (Medical Internal Radiation Dose [MIRD], partition dosimetry, or body surface area [BSA] method) was based on physician preference, tumor burden, type of microspheres, and planned treatment volume.

Chemotherapy Regimens

All patients had received systemic chemotherapy prior to Y90-TARE. Front-line regimens included PIAF (a combination of cisplatin, interferon alpha-2b, doxorubicin, and 5-fluorouracil (5-FU)) or GemOx (Gemcitabine and oxaliplatin) plus lenvatinib, while second- and third-line therapies included agents such as sorafenib, 5-FU, interferon, nivolumab, and bevacizumab. Chemotherapy data, including type and sequence of regimens, are detailed in Table 1 and Table 2.

Dosimetry

The delivered doses after Y90-TARE to each patient were calculated using 90Y-SPECT/CT-based voxel dosimetry by a medical physicist with specialties in Y90-TARE (S.C.K). The 90Y-SPECT/CT imaging protocol has been described elsewhere.[21] Briefly, SPECT/CT imaging (SymbiaT-16, Siemens Healthineers, Hoffman Estates, IL) was acquired using an imaging energy window 90–125 keV, for 128 views over 360 degrees, with 22 seconds/view, and with medium energy low-penetration collimation. The images were reconstructed in isotropic 4.8 mm voxels using the 3D-OSEM algorithm (8 iterations, 16 subsets), incorporating a CT-based attenuation correction, a vendor-specific resolution recovery algorithm, and an empirical scatter compensation model.[22]

For each patient segmentations were done by a post-doctoral fellow (M.M.K), and an interventional radiologist with more than 10 years of experience (PH) contoured total perfused and tumor volumes of interest (VOIs) on the computed tomography (CT) of the Y90-SPECT/CT, with the registered diagnostic images aiding in tumor localization. The liver VOI was based on the anatomic treatment volume (whole liver or lobes) and was further refined according to the degree of perfusion observed on the 90Y-SPECT/CT for lobar treatments.

Following VOI segmentation, post-procedure dosimetry was performed in MIM via the LDM_{KA} dosimetry algorithm. In this formalism, the 90Y-SPECT/CT voxel values were scaled by the ratio of Admin to the summation of the 90Y-SPECT/CT counts within PV.[21]

Then, as in standard LDM dosimetry, the Y-90 activity distribution is scaled by a Y-90 self-dose constant and voxel mass. Voxel-based mean and median doses to the tumor and perfused normal liver VOIs were calculated.

Imaging and Response Assessment

A representative case demonstrating long-term imaging response to TARE-Y90 is shown in Figure 1. Baseline imaging, including CT or MRI, was conducted within 4–6 weeks before the Y90 procedure to assess tumor size and extent. Post-treatment imaging was performed at approximately 3 and 6 months. Pre- and post-procedure CT or MRI images were reviewed by an interventional radiologist with more than 10 years of experience (P.H.) using the established modified Response Evaluation Criteria in Solid Tumors (mRECIST) to categorize outcomes as partial response (PR), stable disease (SD), or progressive disease (PD), where applicable.[23] The observed responses post-treatment was recorded.

Table 1 Patient Demographics and Disease Characteristics

Patient	Age at Y90 Treatment	Gender	Disease Stage (TNM)	Front-line Chemotherapy	Second-line Chemotherapy	Third-line Chemotherapy	Tumor Extent at the Time of Y90	Primary Tumor Size (cm^2)	Distant Metastases (Yes (Y)/No (N))	Vascular Invasion (Yes (Y)/ No (N))	Prior Surgery
1	48	F	IVB	PIAF	Nexavar		Segment IV target lesion 3.1×2.3 cm; 5 additional lesions from 0.6 to 1.1 cm; 2 subcentimeter nodules in left lower lobe concerning for mets	3.1×2.3	Y	Y	Right hepatectomy
2	31	F	IIIA	GemOX + Lenvatinib	5FU + Pegasys + Nivolumab	GemOX + Lenvatinib	3 mass regions: 10.5×7.6 cm (primary region seg 4b), 2.2×2.2 cm, 1.0×0.8 cm	14.3×8	N	N	
3	24	F	IVA	5-FU + interferon	Xeloda + avastin		Large central liver tumor 7.4×4.5 cm, infiltrated tumor thrombus in SMV	5.2×3.2	Y	Y	
4	17	F	IVA	Sorafenib	5-FU + interferon		Numerous liver masses. Primary mass (inferior liver) measures 12.3×9.8 cm. Portal vein tumor thrombi of the main PV, main R and L PV branches. Lymphadenopathy	12.3×9.8	Y	Y	
5	77	M	IIIA	Carbo/taxol (for lung carcinoma)			Multifocal tumor. Large involvement of seg IV, V, and VIII. Primary lesion measures 11.5×9.5 cm. L lobe involvement, >4 lesions 2.2–3.6 cm of seg II, VI, and VII.	11.5×9.5	Y	Y	

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6	16	F	IVB	PLADO	5-FU + interferon		Large mass (13 x 10.4 cm) in seg VIII, VII, VI, and I. Periportal and retroperitoneal adenopathy is present, concerning for mets.	9.7×10.4	Y	N	
7	16	M	IVB	Cyclophosphamide, sorafenib, bevacizumab	PIAF + 5FU		Primary: R lobe segment V & VI extending into IV, 14.3×8.3 cm; 2 segment VII lesions, 1.8×1.3 cm, 2.5×2.1 cm; stable middle diaphragmatic, periportal and portacaval lymphadenopathy likely malignant	14.3×8.3	Y	N	

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Table 2 Treatment Properties

Patient	Line of Chemotherapy at the Time of Y90 Treatment	Disease Status at the Time of Y90	Y90 Device	Extent of Treatment	Number of Sessions
1	Second	Post-surgical recurrence in the Left hepatic lobe	Glass	Left hepatic lobe lesions	1
2	First	Mild progression	Resin	Left and right anterior liver	2 (re-treatment)
3	Second	Progressive disease	Glass	Bilobar treatment	2 (sequential right and left lobes)
4	Second	Progressive disease	Glass	Right liver	1
5	First line for concurrent lung cancer	Stable disease	Glass	Bilobar	1
6	Second	Stable disease	Glass	Right liver	1
7	Second	Stable disease	Glass	Right liver and segment 4	1

Clinical Outcomes and Follow-Up

PFS was defined as the time from Y90-TARE completion until disease progression at the last imaging follow-up.

OS was measured from the date of Y90 therapy until death or last known follow-up. Surgical interventions post-Y90 were noted. Causes of death were determined from medical records when available.

Statistical Analysis

Given the small sample size, descriptive statistics were used to summarize baseline demographics, tumor characteristics, procedural details, adverse events, and causes of death. OS was calculated from the date of Y90-TARE to the date of death, and progression-free survival PFS was defined as the interval from the procedure to the first documented radiographic or clinical evidence of disease progression. Using the Kaplan–Meier method, survival curves were

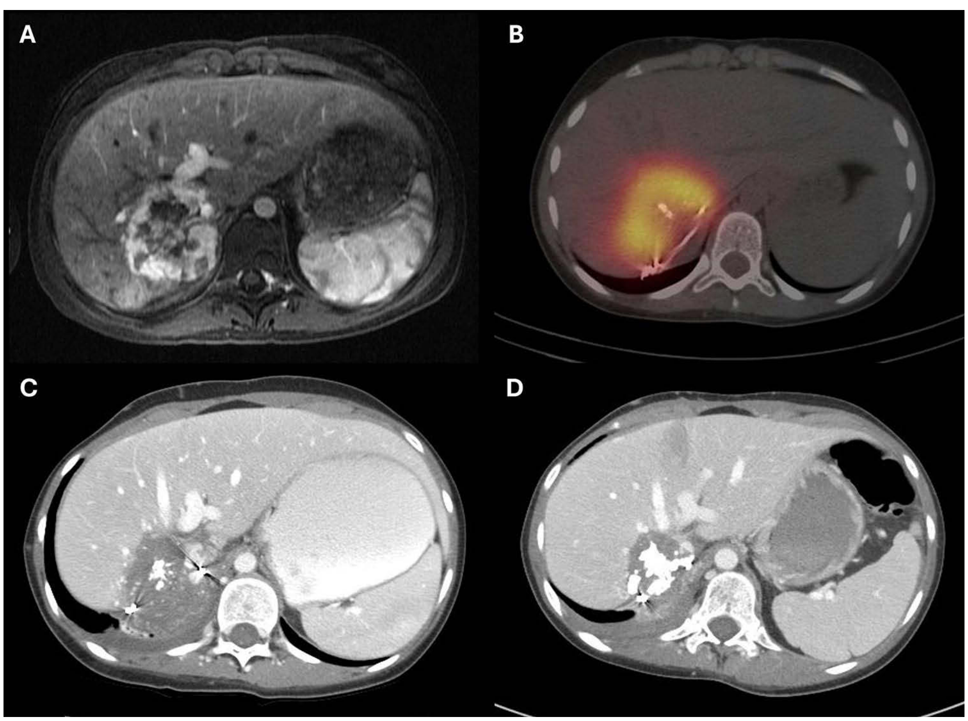

Figure 1 MRI image of a patient with a large FL-HCC centered in the right lobe of the liver prior to treatment with TARE-Y90 (**A**). Post-treatment SPECT-CT image shows deposition of Yttrium-90 microspheres within the tumor (**B**). A follow-up CT at 6 months shows a marked treatment response with decreased enhancement and size reduction, which is consistent with a partial imaging response (**C**). CT images obtained 11 years later demonstrate further tumor shrinkage, calcification, and lack of enhancement, consistent with a sustained complete response and no evidence of recurrence (**D**).

generated for both OS and PFS. Continuous variables were summarized using both median and mean values, and categorical variables were reported as frequencies and percentages.

Results

A total of 7 FL-HCC patients (5 female, 2 males; median age at the time of Y90-TARE: 24, range: 16–77 years) who underwent 9 Y90-TARE procedures were reviewed for the study. Patient demographics and disease characteristics are shown in Table 1.

Treatment Characteristics and Dosimetry Analysis

A total of 9 Y90-TARE procedures were performed. At the time of treatment, one case (patient 1) had post-surgical recurrence, three patients (patients 2, 3, and 4) exhibited progressive disease, while patients 6 and 7 had stable disease patterns, and patient 5 had stable disease in the context of concurrent malignancy (lung cancer).

Two patients received an additional procedure. One (Patient 2) was re-treated due to left hepatic lobe recurrence, and another (Patient 3) underwent planned sequential lobar treatments for bilobar disease. All patients were treated with glass microspheres (Thera Sphere), except for Patient 2, who received resin microspheres (SIR-Spheres) for both procedures. Patient 2 underwent two separate Y90-TARE procedures, performed 7 months and 12 days apart. Due to the extent of disease and the increase in the size of hepatic metastases, complete tumor coverage could not be achieved in a single session, necessitating a re-treatment. The patient remains alive at the time of study conclusion.

The extent of treatment ranged from targeting at least a single lobe to bilobar treatments for more widespread disease (Table 2).

Details on administered activity, lung shunt fraction (LSF), lung dose, and post-treatment voxel-based dosimetry are summarized in Table 3. The median whole liver volume was 1981 mL (mean: 1946 ± 554 mL). The median LSF was 4.59% (mean: 4.56 ± 1.94%), and the median lung dose was 6.4 Gy (mean: 8.2 ± 6.1 Gy). For the single patient treated with resin microspheres, two staged lobar treatments were performed. The first treatment to the right lobe and segment 4 delivered 7.07 GBq, with a total tumor volume of 463.3 mL receiving a mean absorbed dose of 282.2 Gy and 245.7 mL of perfused non-tumoral liver receiving 190.1 Gy. The second treatment to the left lobe and segments 5/8 delivered 3.85 GBq, with tumor segments in the left lobe totaling 72.5 mL (11.7, 13.3, and 47.5 mL) receiving mean absorbed doses of 1362.5–1095.7 Gy, and 339.8 mL of perfused non-tumoral liver receiving 288.4 Gy. Across all patients, the median administered activity was 3.85 GBq (mean: 4.13 ± 1.63 GBq). The median treated tumor volume was 198 mL (mean: 284 ± 341 mL), and the median volume of perfused normal liver (pNL) was 1008 mL (mean: 944 ± 451 mL). The median absorbed dose to tumor was 405 Gy (mean: 579 ± 442 Gy; range: 109–1362 Gy), and the median absorbed dose to pNL was 83 Gy (mean: 96 ± 41 Gy; range: 63.5–190 Gy).

Survival and Causes of Death

The median OS was 479 days (95% CI: 159 days – upper limit not reached), with OS rates of 83% at 6 months and 67% at 1 year (Figure 2). Among patients, the median PFS was 9 months, with 57% of patients, progression-free at 6 months and 43% at 1 year (Figure 3). Patient deaths were attributed to renal failure (patient 3), rapid disease progression (patient 4), and progression leading to hospice care (patient 5). Patient 6 passed away more than 11 years after Y90-TARE due to complications from gastrointestinal bleeding. As for the remaining patients, one remained alive without evidence of disease progression and received hepatectomy, one had successfully undergone Orthotopic Liver Transplantation (OLT) and remained without evidence of disease on chest and abdominal CT performed 9.5 months post-transplant, and one was lost to follow-up.

Imaging Response

Follow-up imaging for response assessment at approximately 1, 3, and 6 months after treatment is detailed in Table 4. At one month, imaging response data were available for five patients. Among the evaluable patients (n = 5), the objective response rate was 80%, with PR in 4 patients and SD in one patient. Patient 1 and Patient 4 had no imaging available at this time point. At three months, the response rate was 85.7%, with PR in 6 patients and SD in one patient (Patient 4). At

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Table 3 Results of the Dosimetry Analysis for Patients and Treated Tumors

Patient	Procedure	Territory	LSF (%)	Lung Dose (Gy)	Net GBq	VOI	Mean (Gy)	Median (Gy)	Volume (mL)	Percentage of Normal Liver Treated
1		WL	4.18%	4.7	2.2	Tumor 1 (T1)	1315.1	1265.4	9.75	
						Tumor 2 (T1)	611.1	564.6	4.28	
						perfused Normal Liver (pNL)	77.3	51.9	1162.1	100
						Whole liver (WL)			1180	
2	1st Y90	RL+Seg4	1.30%	4.6	7.07	T1	421.6	418.7	17.5	
						T2	379.1	376.8	394.2	
						pNL	190.1	179.9	245.7	56.57
						WL			1981	
	2nd Y90	LL+Seg5/8	4.50%	8.7	3.8	Tseg2	1362.5		11.7	
						Tseg3	1092.9		13.3	
						Tseg4	1095.7		47.5	
						Tright	288.4		339.8	26.98
						Whole liver (WL)			1528	
3	1st Y90	RL	6.51%	16.8	5.2	T	311.2	290.6	365.21	
						pNL	98.9	92.8	1330.5	77.71
						WL			2182	
	2nd Y90	LL	6.51%	3.9	1.2	T	398.2	334.0	63.4	
						pNL	63.5	50.5	503.8	34.29
						WL			1654	
4		RL	6.10%	15.5	5.1	T	137.3	135.6	930.2	
						pNL	83.8	85.3	1353	72.64
						WL			3143	
5		WL	7.77%	20.0	5.1	T	190.9	189.4	688.8	
						pNL	77.0	72.0	1464.5	100
						WL			2153	
6		RL	4.59%	6.4	2.9	T	391.9	381.8	441.1	
						pNL	114.7	84.4	699.6	54.8%
						WL			1276	
7		RL	1.17%	2.0	3.3	T	109.5	106.8	932.2	
						pNL	64.6	58.9	872.4	73.90
						WL			2442	

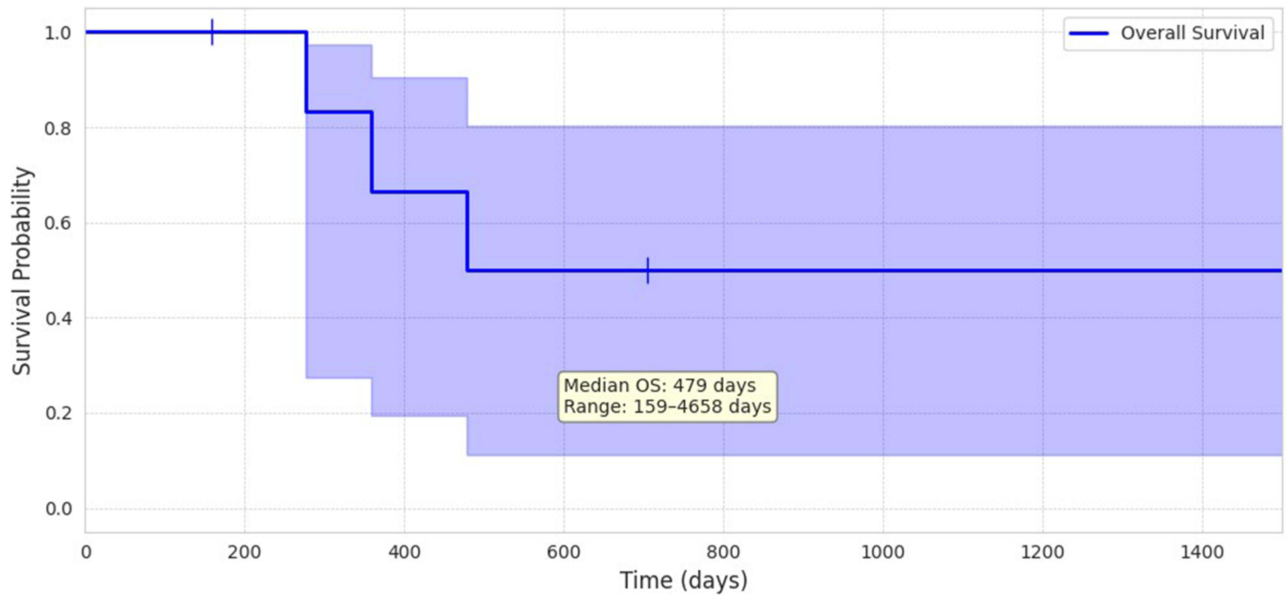

Figure 2 Kaplan–Meier Curve for Overall Survival. The Kaplan–Meier curve shows OS after TARE-Y90 treatment. Median OS was 479 days (range, 159–4658 days).

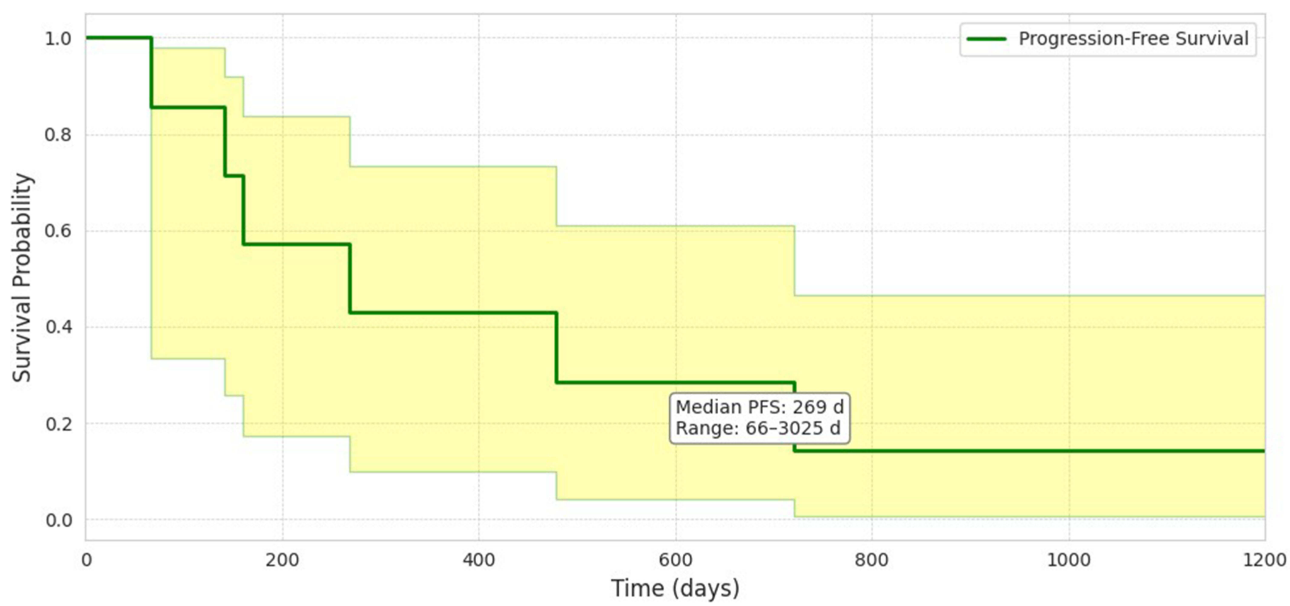

Figure 3 Kaplan–Meier Curve for Progression-Free Survival. The Kaplan–Meier curve illustrates PFS for the cohort following TARE-Y90 treatment. Events were defined as either radiologic or clinical progression, whichever occurred first. Median PFS was 269 days (range, 66–3025 days).

six months, Imaging was not available for patient 2 (underwent liver transplantation) and Patient 4. Among the evaluable patients (n = 5), the objective response rate was 100%, with PR observed in all 5 patients.

Safety and Adverse Events

No procedural complications or grade >3 adverse events, as defined by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, were reported within 30 days of Y90-TARE in any of the 7 patients attributable to the procedure. Treatment was well tolerated; reported complications included fatigue and fever in one patient, which resolved within less than a week. Beyond the first month post-procedure, one patient (patient number 1, who had prior hepaticojejunostomy) developed hepatic abscess (CTCAE grade 3) in segment III measuring 1.1×0.6 cm, which was treated with antibiotics and underwent CT-

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Table 4 Response Assessment and Outcomes

	Procedural Complications	Imaging Response			PFS *	OS *	Surgical Interventions Post-Y90	Death	Cause of Death
		1-mon	3-mon	6-mon					
1	Hepatic abscess	N/A	PR	PR	2.2	Lost to follow up		Lost to follow up	Unknown
2 1st Y90	Pain and fatigue	PR	PR	PR	4.7	***28.3		No	–
2 2nd Y90		PR	PR	NA, patient got OLT	–	–	OLT	–	–
3**		PR	PR	PR	5.3	11.79		Yes	Renal failure
4		N/A	S	N/A	16	15.7		Yes	Rapid progression
5		S	PR	PR	9	9.07		Yes	Death in hospice care
6		PR	PR	PR	24	152.7		Yes	Disease progression leading to GI bleeding
7		PR	PR	PR	***99.4	***99.4	Trisegmentectomy of the liver	No	

Notes: *Months. ** Two Y90-TARE treatments were 4 weeks apart; response assessment was done after the second treatment. *** Censored.

guided percutaneous drainage. Another patient (patient number 2) developed epigastric pain, fatigue, and cough after both procedures, which resolved with conservative management. Given that this patient received the highest prescribed activity and was treated with resin microspheres, these acute post-procedural symptoms were consistent with an embolic phenomenon related to the radioembolization. Subsequent CT imaging performed 3 months after the second Y90-TARE treatment demonstrated a tumor to duodenal fistula, representing a Grade 3 adverse event. She needed a blood transfusion to manage bleeding secondary to the fistula, and it was ultimately managed by Whipple procedure at the time of orthotopic liver transplantation.

Discussion

FL-HCC is a rare and unique type of primary liver tumor, with an incidence rate of approximately 0.02 per 100,000 individuals per year in the United States.[24] Surgical resection is currently the first-line potentially curative treatment and is the standard of care for patients with resectable disease.[25,26] For patients with unresectable tumors, management remains challenging, since no universally accepted standard of care exists given the rarity of the disease. Alternative treatment strategies, such as intra-arterial therapies, have not been widely explored, and literature on this topic remains sparse. Early experiences were limited to individual case reports. The current study evaluated the role of Y90-TARE in treating FL-HCC in 7 patients (the largest data set to the best of the authors' knowledge), who were deemed to have an unresectable tumor. The current data show that Y90-TARE is safe and effective in patients with FL-HCC and could result in a high rate of objective tumor response, and in one patient, it led to durable disease control up to 11 years after treatment. Historically, small case series suggested that FL-HCC might be radiation-sensitive, and clinicians have attempted modalities like external beam radiotherapy or stereotactic body radiation in select cases.[27] Transarterial approaches, including chemoembolization (TACE) and radioembolization, have likewise been used experimentally as definitive or bridging therapies to surgery in FL-HCC.[27] For example, a 2018 case report by Mafeld et al described the first use of Y-90 resin microspheres in an unresectable FL-HCC, in a 52-year-old male. This treatment led to a reduction in tumor volume from 350 cm^3 to 20 cm^3 over seven months, ultimately leading to liver resection.[15] This study also demonstrates the potential advantage of Y90-TARE as a tool to downstage tumors to potentially allow curative treatments such as liver transplantation and tumor resection, as shown in patients 2 and 7. In the current study, 6 out of 7 patients demonstrated PR at 3 months, and all assessed patients showed PR at 6 months following Y90-TARE, based on mRECIST criteria, corresponding to objective response rates of 86% and 100%, respectively. One patient (Patient 4) had stable disease and was on sorafenib for 9 months before developing rapid progression. The patient ultimately passed away 15.7 months after treatment.

Our results suggest that Y90-TARE can be an effective locoregional therapy, especially in patients without tumor thrombus. Three patients in our study who did not have any tumor thrombus did better than the rest of the patients with tumor thrombosis. One of these patients was the one who successfully underwent liver transplantation after 2 sequential TARE Y90. The other two had durable responses for 8 and 11 years after treatment.

Nonetheless, outcomes have been variable. A multi-institution pediatric series (10 children/adolescents with primary liver malignancies, including 3 FL-HCC) reported a median survival of only 4 months after Y-90 treatment, using resin-based microspheres. The three patients with FL-HCC treated with Y90-TARE had survival times of 20, 17, and 2 months following treatment.[28] The LSFs for cases in the mentioned report were 3%, 4% (29% for the second treatment), and 5%, comparable to the median LSF of 4.59% (mean: 4.56 ± 1.94%) in our study. This study discussed the potential for Y90 therapy to achieve localized tumor control, in conjunction with systemic treatments for managing extrahepatic metastatic disease. There are other reports discussing the utility and outcomes of Y90-TARE in patients with FL-HCC who had multiple treatments. In a reported case of a pediatric patient, Y90-TARE was initially performed for a massive FL-HCC tumor in the right hepatic lobe. Follow-up imaging at 4 months demonstrated areas of tumor necrosis and a slight reduction in the tumor size, though new metastases in the left lobe were observed. The patient was treated with another Y90-TARE procedure 6 months later. Despite achieving stability in the liver tumor patient developed new extrahepatic disease unresponsive to systemic therapy and passed away at 20 months after the initial diagnosis.[29]

In addition to outcomes, understanding dosimetric parameters is an important aspect for treatment efficacy and therapeutic planning in Y90-TARE. Tumor and liver absorbed doses were highly variable in our study. This is most likely attributable to the use of different Y90 devices (resin vs glass, and different calibrations for glass Y90 microspheres) and the evolution of personalized dosimetry over time. Therefore, we cannot make strong dosimetry recommendations based on these results for FL-HCC. However, at our institution, we follow the dosimetry principles based on prospective or retrospective studies evaluating the impact of dosimetry on imaging and pathological response in patients with HCC.[30,31]

Limitations of the current study include being a retrospective study with a small number of patients. However, it represents one of the largest series of FL-HCC reporting on Y90-TARE, given the rare incidence of this tumor type. Our study did not report a formal local time-to-progression analysis because some tumors were only partially treated, so response assessments by mRECIST (which also accounts for extrahepatic progression) served as our endpoint. The heterogeneous use and timing of systemic therapy around Y90-TARE, which reflects evolving real-world practice, can confound survival outcomes and limit our ability to isolate the effect of Y90-TARE alone.

Additionally, variability in dosimetric practices and the use of different Y-90 microsphere types (resin vs. glass) across cases could have influenced treatment responses and survival outcomes. This study is limited by the lack of a formal comparison between Tc-99m MAA–based planned doses and delivered doses, and by reliance on Y-90 Bremsstrahlung SPECT/CT rather than PET for post-treatment dosimetry. While substantial progress has been made in refinement of dosimetry calculations, dose quantification, and response/toxicity assessment, there is a critical need to improve standardization of dosimetry models, imaging, and reporting when interpreting clinical outcomes. Despite these limitations, we believe that, given the current state of the FL-HCC literature, these data offer value for clinicians and researchers to further explore the role of Y90-TARE in this patient population in future multicenter studies.

Conclusion

In conclusion, this retrospective case series suggests that Y90-TARE is safe, effective, and has potential for achieving tumor control in patients with unresectable FL-HCC. In carefully selected patients, Y90-TARE may lead to durable responses, extended survival, or even facilitate downstaging to curative options such as liver transplantation.

Abbreviations

FL-HCC, Fibrolamellar Hepatocellular Carcinoma; TARE, Transarterial Radioembolization; Y-90, Yttrium-90; PR, Partial Response; SD, Stable Disease; PFS, Progression-Free Survival; OS, Overall Survival; OLT, Orthotopic Liver Transplantation; mRECIST, Modified Response Evaluation Criteria in Solid Tumors; CTCAE, Common Terminology

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Criteria for Adverse Events; VOI, Volume of Interest; LSF, Lung Shunt Fraction; GBq, Gigabecquerel; CT, Computed Tomography; MRI, Magnetic Resonance Imaging; SPECT, Single Photon Emission Computed Tomography; PET, Positron Emission Tomography.

Data Sharing Statement

The authors are willing to make their data, analytical methods, and study materials available to other researchers upon reasonable request to the corresponding author, in accordance with ethical and institutional regulations.

Ethics Approval and Informed Consent

This retrospective study was conducted following approval by the Institutional Review Board of The University of Texas MD Anderson Cancer Center, and in accordance with the Declaration of Helsinki and the Health Insurance Portability and Accountability Act (HIPAA), where applicable. Because only previously collected clinical data were used, the requirement for written informed consent was waived by the Institutional Review Board.

Consent for Publication

No identifiable personal information or images are included in this manuscript.

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Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. All authors took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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