

Transportal Radioembolization as Salvage Hepatocellular Carcinoma Therapy to Maintain Liver Transplant Candidacy

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ABSTRACT

A 53-year-old woman with chronic hepatitis B and multifocal hepatocellular carcinoma was unable to receive transarterial radioembolization and had disease progression despite multiple chemoembolizations and systemic chemotherapy. Transportal radioembolization (TPRE) to maintain transplant candidacy was performed. Two lesions (1.7 cm, 1.4 cm) were treated with a single session of TPRE. Imaging performed at 4 months after TPRE demonstrated complete response in one lesion and stable disease in the other. This case illustrates TPRE as a salvage therapy for hepatocellular carcinoma in select patients.

ABBREVIATIONS

HCC = hepatocellular carcinoma, OPTN = Organ Procurement and Transplantation Network, PET = positron emission tomography, TARE = transarterial radioembolization, TPRE = transportal radioembolization

Transarterial radioembolization (TARE) is a well-tolerated and effective therapy for the management of primary and metastatic liver tumors (1,2). Use of supra-therapeutic yttrium-90 as a means of arterial-based liver ablation continues to gain acceptance and provides high doses of tumor radiation with minimal exposure to uninvolved hepatic tissue (3,4). As experience with TARE has increased, newer limitations to optimal treatment have been identified. Variations in liver arterial anatomy and tumor supply may not always provide optimal treatment coverage (5–7). Lesions with a high degree of refractory pulmonary shunting may preclude ideal dosing of radioembolic agents. Targeted agent therapy, such as bevacizumab (Genentech/Roche, South San Francisco, California), may predispose treatment arteries to injury requiring discontinuation before TARE (8). Additionally, prior arterial embolic based therapies,

such as transarterial chemoembolization, may attenuate hepatic arteries limiting a future tumor conduit.

Following is a case report of a patient with multifocal hepatocellular carcinoma (HCC) who could not receive TARE, sustained advanced arterial pruning after multiple sessions of transarterial chemoembolization, and did not tolerate full-dose systemic chemotherapy. Transportal radioembolization (TPRE) as a salvage therapy to maintain transplant candidacy was performed targeting two lesions. Imaging response at 4 months after TPRE demonstrated complete response in one lesion and stable disease in the other per modified Response Evaluation Criteria In Solid Tumors (9).

CASE REPORT

Institutional review board approval was not required for this case report. A 53-year-old woman, Eastern Cooperative Oncology Group 0, Child-Pugh class A, with chronic hepatitis B presented with a biopsy-confirmed 6-cm HCC in segment 6. After starting antiviral therapy, she underwent hepatic resection with negative margins and a final oncologic stage of T3aNxM0 (American Joint Committee on Cancer, 7th edition).

Magnetic resonance (MR) imaging performed 9 months after resection demonstrated a 1.6-cm Organ Procurement and Transplantation Network (OPTN) (10) class 5A

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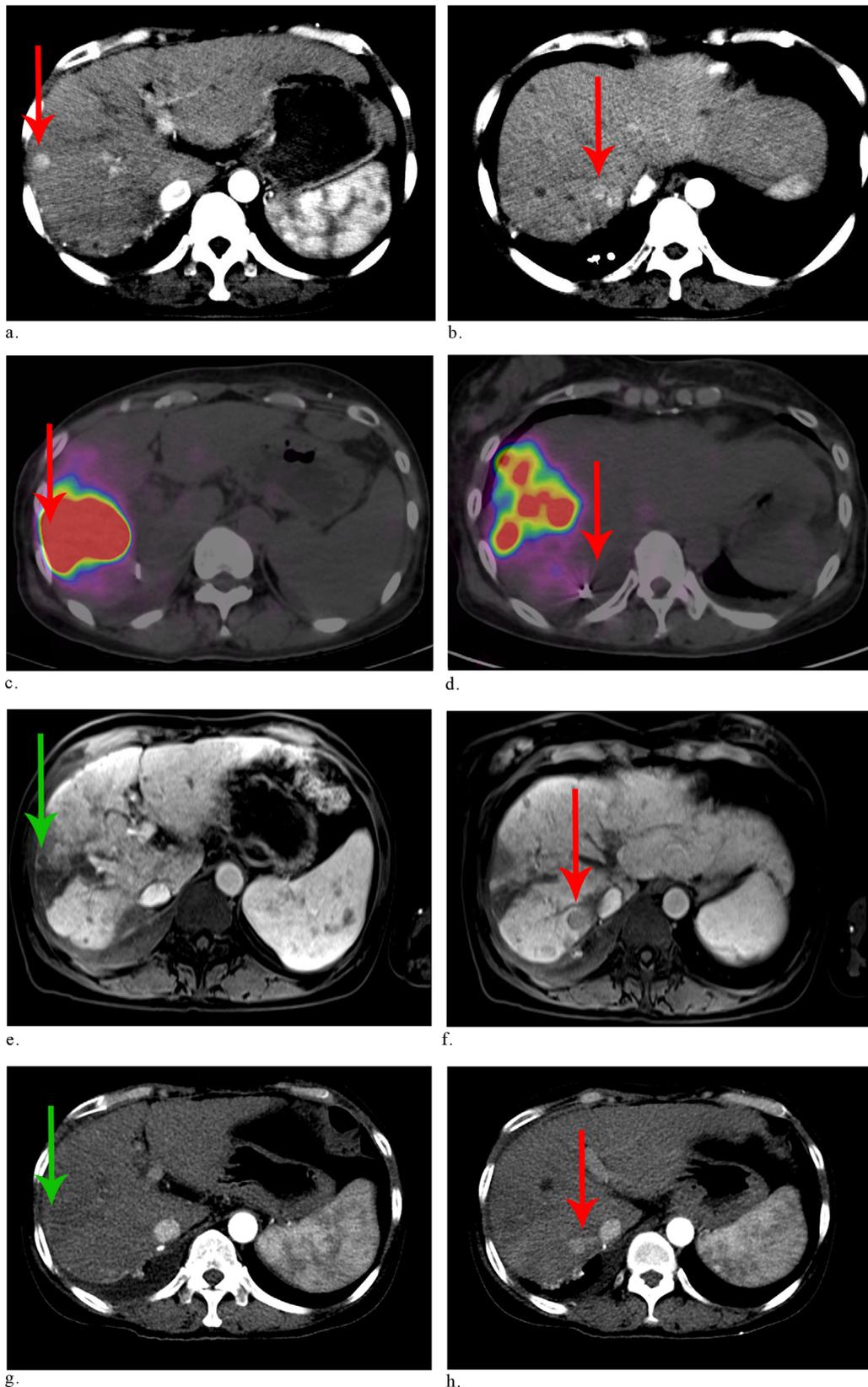


Figure 1. OPTN class 5A lesions (arrows) and imaging after TPRE. Two right hepatic lobe lesions were targeted for TPRE. (a) A lesion of 1.4 cm in segment 8. (b) A lesion of 1.7 cm in segment 7. Positron emission tomography (PET)/CT scan performed 1 day after TPRE corroborated with procedural angiograms (Fig 3) and demonstrated uniform radioisotope delivery in segment 8 (c) and uneven peripheral delivery in segment 7 (d). MR imaging performed 1 month after TPRE demonstrated complete response in segment 8 (e) and stable disease in segment 7 (f). CT scan performed 4 months after TPRE demonstrated complete response maintained in segment 8 (g) and stable disease in segment 7 (h).

lesion in segment 7 and additional bilateral lesions not meeting OPTN HCC criteria. She was referred for liver transplant evaluation and locoregional therapy. The patient underwent transarterial chemoembolization targeting the segment 7 lesion using epirubicin-laden QuadraSphere Microspheres (Merit Medical Systems, Inc, South Jordan, Utah). A 3-month surveillance computed tomography (CT) scan demonstrated new OPTN class 5A lesions in segment 8 (1.4 cm) (**Fig 1a**), segment 5 (1.4 cm, not shown), and segment 2 (1.2 cm, not shown), with no treatment response of the segment 7 lesion (1.7 cm) (**Fig 1b**). Given the suboptimal outcome, TARE was offered.

Subsequent mapping angiography demonstrated partial arterial supply to the segment 7 lesion from a right inferior phrenic artery to pulmonary artery shunt, which, in addition to the gastroduodenal and right gastric arteries, was coiled to redistribute flow. Technetium 99m-labeled macroaggregated albumin (^{99m}Tc MAA) scintigraphy identified duodenal activity secondary to small-caliber right hepatic artery collaterals, which could not be mitigated despite multiple devices and techniques.

Given the inability to proceed with TARE, the lesions were treated with four additional sessions of transarterial chemoembolization. During the fifth transarterial chemoembolization session, less than 2 mL of QuadraSpheres could be administered secondary to pruning of intrahepatic arteries (**Fig 2**). The patient was started on 400 mg of sorafenib (Bayer HealthCare, Whippany, New Jersey) twice daily but developed a

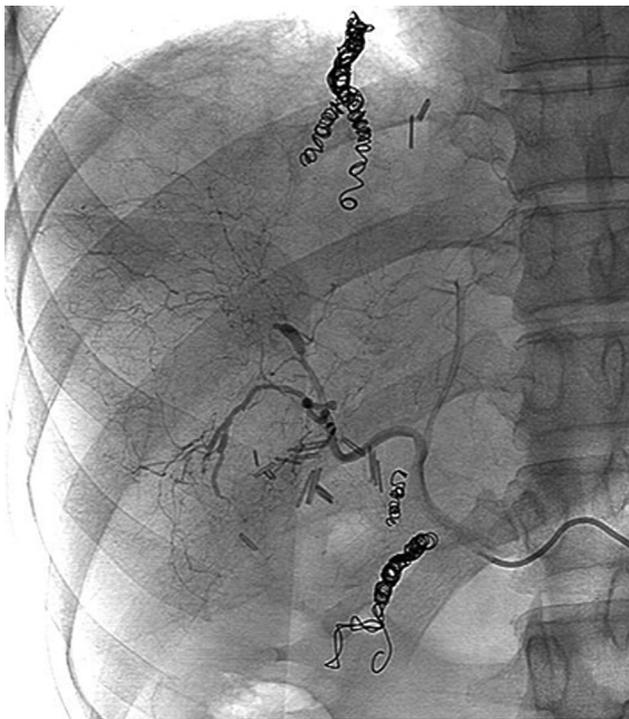


Figure 2. Advanced hepatic arterial pruning seen during the fifth transarterial chemoembolization session. Previous coiling of the phrenic shunt, gastroduodenal artery, and right gastric artery is seen.

debilitating hand and foot skin reaction requiring a 200-mg dose reduction. A CT scan performed 2 months after the final transarterial chemoembolization demonstrated persistent disease in all four OPTN class 5A lesions.

The patient had systematically failed the institutional standard of care. The concept of providing brachytherapy via the portal vein in similar fashion to an arterial-based radiation segmentectomy was agreed on after a multidisciplinary tumor board consensus. The patient was informed of the treatment plan, including the reasoning, risks, benefits, alternatives, and lack of data to support this approach, to which she provided informed consent. Humanitarian deviation from protocol was granted by the Western Institutional Review Board for off-label use of a radioembolic agent. Therapy was condensed to a single session, which has been successfully adopted for TARE (11). The yttrium-90 written directive established a dose of 2.44 GBq for 750 mL of the remaining right hepatic lobe.

Under general anesthesia, portal venous access was established from the left hepatic lobe with a 6-F sheath; direct portal pressure measured 10 mm Hg. Portovenography demonstrated hepatopetal flow without varix formation (**Fig 3a**). The right portal vein was selected with a 5-F Mariner MPA catheter (AngioDynamics, Latham, New York), and venography revealed separate hepatic segment 7 and 8 branches (**Fig 3b**). A 2 mCi/30 μm range ^{99m}Tc MAA dose was administered to the right portal vein. Scintigraphy confirmed radiotracer uptake confined to the liver and a lung shunt fraction of 3% (**Fig 3c**).

The segment 7 portal branch was selected and imaged using a Renegade HI-FLO microcatheter (Boston Scientific, Marlborough, Massachusetts), which demonstrated dense contrast accumulation surrounding the catheter end-hole and poor peripheral perfusion (**Fig 3d**). Cone-beam CT revealed delayed enhancement of the portal segment, which was not demonstrated with angiography. The segment 7 portal branch was treated with a 4-GBq dose vial of glass microspheres.

Next, the segment 8 portal branch was selected with the 5-F MPA catheter; the microcatheter was not used given the incomplete peripheral perfusion witnessed during segment 7 treatment. Angiography demonstrated complete and uniform segmental perfusion (**Fig 3e**), and the 3-GBq dose vial was administered. The liver access was closed using sequential occlusion with absorbable gelatin sponge, and the patient was observed overnight. The ^{99m}Tc MAA pool in the portal vein resulted in residual equipment activity, which cleared after a 24-hour quarantine. A PET/CT scan performed the following morning demonstrated uniform radioisotope delivery within the 5-F catheter distribution (segment 8) (**Fig 1c**) but uneven peripheral delivery in the microcatheter territory (segment 7) (**Fig 1d**). There was no activity outside the liver.

The patient resumed reduced dose sorafenib 3 days after TPRE. Contrast-enhanced MR imaging performed

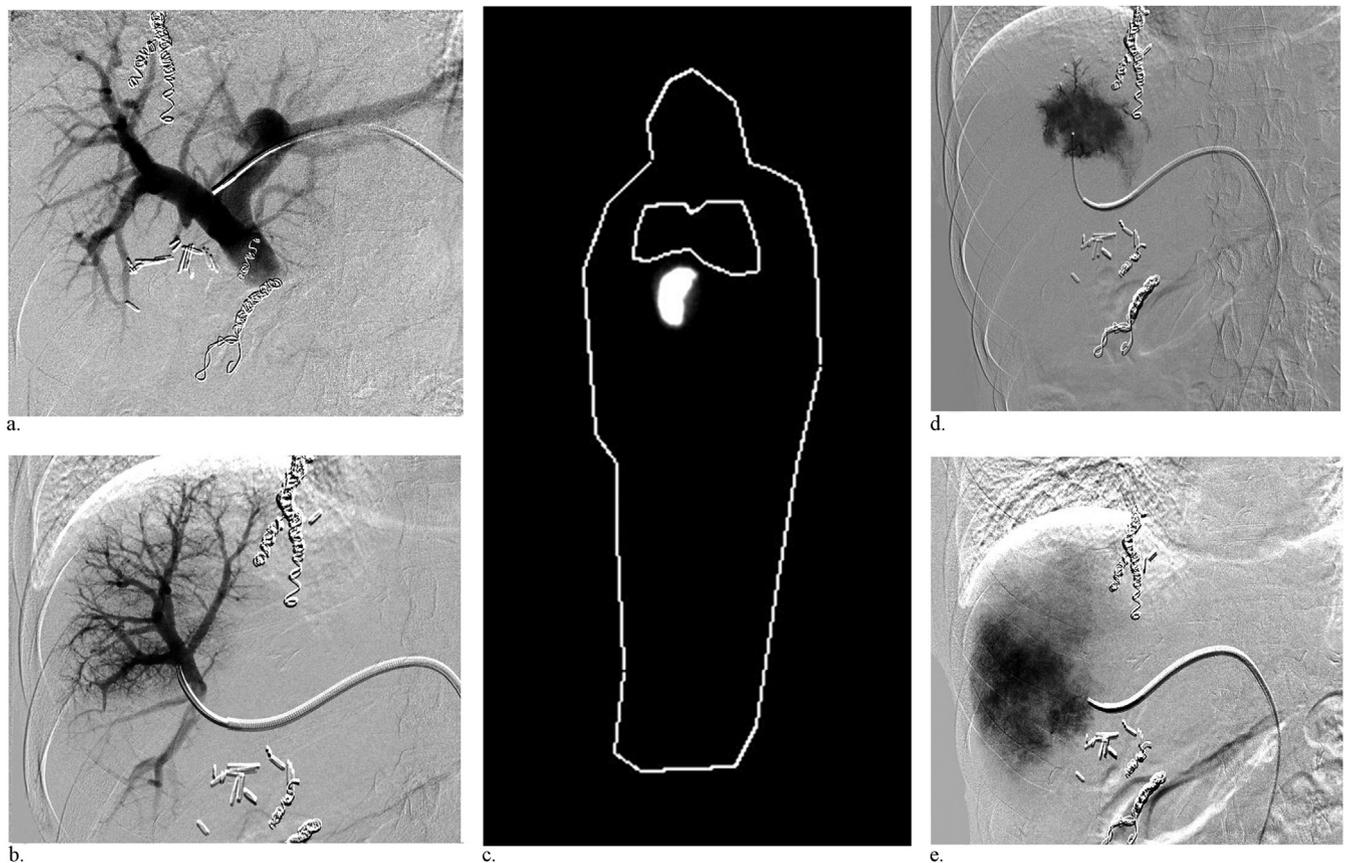


Figure 3. TPRE. (a) Portovenography demonstrating hepatopetal flow without varix formation. (b) Right portovenogram demonstrating supply to segments 7 and 8. (c) Right portal vein ^{99m}Tc MAA injection with 3% lung shunt fraction. (d) Segment 7 portovenogram with a Renegade HI-FLO microcatheter demonstrating dense accumulation of contrast material surrounding the catheter end-hole and poor peripheral perfusion. (e) Segment 8 portovenogram with 5-F MPA Mariner catheter demonstrating complete and uniform perfusion.

1 month (Fig 1e, f) and multiphase CT performed 4 months (Fig 1g, h) after TPRE demonstrated a complete response in segment 8 and stable disease in segment 7. The untreated lesions in segments 2 and 5 demonstrated progressive disease (1.5 cm and 1.7 cm, respectively; not shown).

The patient's course after TPRE included transient loss of energy, right upper quadrant pain, decreased appetite, mild nausea, and hypogeusia. All symptoms improved within 1 month. The patient also experienced temporary hair loss and an asymptomatic right pleural effusion 1 week after the procedure. There was no change in performance status or liver function 4 months after TPRE. Imaging showed findings similar to a transarterial radiation segmentectomy with segment 8 fibrosis and HCC necrosis. She had no evidence of radiation-induced liver disease and currently awaits liver transplantation.

DISCUSSION

This case describes radioembolization performed via the portal vein when TARE could not be performed and

multiple chemoembolizations precluded further transarterial therapy. TPRE offers several conceptual benefits when TARE cannot be safely administered owing to nontarget collaterals, suboptimal arterial supply, persistent hepatopulmonary shunting, or attenuated hepatic arteries from prior therapies as in this case. In these instances, the portal venous approach provides alternative access. Although targeted agent therapy has unknown effects on the portal vein, TPRE may offer a second route of treatment for patients who have sustained an associated arterial injury.

Disadvantages of TPRE include lack of data, hypothesized contraindication in severe portal hypertension, more invasive procedural technique, and flow diversion in the setting of portal vascular invasion or compression. A complete radiologic response was observed in the segment 8 lesion despite its avid arterial phase enhancement. Although portal contribution to tumor can be variable (12), bracket radiation of lesions with arterial dominant supply in the range of 20 mm is conceivable given a 10-mm maximum beta-particle penetration of liver tissue (4). TPRE efficacy was based solely on imaging, and an eventual histologic analysis is required.

The angiographic and PET/CT findings after TPRE demonstrated uneven peripheral delivery when administered using a microcatheter (segment 7), but uniform radioisotope delivery when using a 5-F catheter (segment 8); this was likely related to a flow velocity mismatch. We hypothesize the low portal venous perfusion velocity did not sustain laminar flow during the higher velocity microcatheter injection, whereas turbulence was minimized during the more commensurate 5-F catheter injection (13,14).

In conclusion, TPRE provided a salvage catheter-directed treatment for HCC to downstage multifocal disease and maintain candidacy for liver transplant. Based on the preservation of patient performance status, liver function, and treatment effects at 4 months after TPRE, further investigation of this technique is encouraged.

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