Yttrium-90 Radioembolization of Renal Cell Carcinoma Metastatic to the Liver

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ABSTRACT

Purpose: To investigate the safety and efficacy of yttrium-90 (^{90}Y) hepatic radioembolization treatment of patients with liver-dominant metastatic renal cell carcinoma (RCC) refractory to immunotherapy and targeted therapies.

Materials and Methods: Between March 2006 and December 2010, six patients with metastatic RCC underwent eight radioembolization treatments with ^{90}Y-labeled resin microspheres for unresectable liver-dominant metastases. All six patients had previous hepatic tumor progression despite targeted therapies or immunotherapies. All had bilobar disease and required whole-liver treatment. Clinical and biochemical toxicities were recorded, and tumor response was assessed every 2–3 months after treatment by cross-sectional imaging.

Results: The median dose delivered was 1.89 Gbq (range 0.41–2.03 Gbq). Grade 1 and 2 toxicities were noted in all patients, primarily fatigue. Follow-up imaging was available for five patients. In follow-up periods from 2–64 months (mean 25 months), three patients showed complete responses, and 1 patient showed a partial response by standard imaging criteria, and these patients are alive at 64 months, 55 months, 17 months, and 7 months after treatment. Two patients with rapid progression of disease died within 2 months of treatment, although hepatic malignancy or failure was not the cause of death in either patient.

Conclusions: ^{90}Y radioembolization is a promising option for liver-dominant metastatic RCC with potential for providing long-term survival in patients refractory to or intolerant of targeted therapies.

ABBREVIATIONS

MAA = microaggregated albumin, mRECIST = modified Response Evaluation Criteria in Solid Tumors, PET = positron emission tomography, RCC = renal cell carcinoma, RECIST = Response Evaluation Criteria in Solid Tumors, ^{90}Y = yttrium-90

Renal cell carcinoma (RCC) is the most common malignancy of the kidney, accounting for 92% of renal cancers (1). In the United States, 58,000 people are diagnosed annually. This figure represents 3% of all adult cancers, which result in 13,000 deaths. Although the survival rate is very high after curative nephrectomy, the 5-year survival rate in patients with metastatic RCC historically was only 10% (1). Hepatic involvement is seen in only a minority of patients with metastatic RCC(2), but those patients are particularly difficult to treat. Select patients may benefit from metastasectomy (3,4), but very few are candidates for resection (5). Conventional therapies such as systemic chemotherapy and external beam radiation do not have a significant influence on progression of hepatic metastases, and immunotherapy, although associated with improved survival, has limited efficacy in patients with hepatic metastases (6–8). Promising results have been

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Figures 1(c) and 1(d) are available online at *www.jvir.org*.

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Table. Patient Characteristics, Toxicities, and Response

Patient No./ Age (y)/Sex	No. Treatments	Tumor Replacement of Liver (%)	Lung Shunt Fraction (%)	Extrahepatic Metastases	Prior Systemic Therapies and Results	Performance Status (ECOG)	Baseline Serum Creatinine (mg/dL)/ Estimated GFR (mL/min/1.73m^2)
1/61/F	1	25	6.5	Pancreas, kidney	Sorafenib: Extrahepatic stability, intrahepatic progression, grade 3–4 toxicities	2	1.3/44
2/64/M	2	60	4.9	Lung	Sunitinib: Extrahepatic response, intrahepatic refractory disease	0	1.5/49
		10	5.3	Lung	Sunitinib: Extrahepatic stability, intrahepatic recurrence after radioembolization	0	1.3/57
3/64/M	1	15	14.0	Renal fossa	Interferon-α, sorafenib, bevacizumab: Extrahepatic stability, intrahepatic progression	1	1.4/54
4/61/M	1	15	5.9	Bone	Sunitinib: Intrahepatic and extrahepatic progression, grade 3–4 toxicities	1	2.2/31
5/65/M	2	20	8.3	Lung	Interleukin-2, interferon-α: Extrahepatic response, intrahepatic progression	0	1.8/38
		5	—	Lung	Residual intrahepatic disease after radioembolization	0	1.8/38
6/69/F	1	40	40.5	—	Sunitinib, sorafenib: intrahepatic progression	0	0.9/65

CR = complete response; CTCAE-NCI = Common Terminology Criteria for Adverse Events of the National Cancer Institute; ECOG = Eastern Cooperative Oncology Group; GFR = glomerular filtration rate; mRECIST = modified Response Evaluation Criteria in Solid Tumors; NA = not available; PD = progressive disease; PR = partial response.

* Only an unenhanced CT scan was obtained because of azotemia, so mRECIST criteria could not be applied. Lesions showed enlargement sufficient to be PD by Response Evaluation Criteria in Solid Tumors (RECIST) criteria, but no information on lesion viability was available.

† Patient expired without undergoing follow-up imaging.

achieved with various systemically delivered targeted therapies, including tyrosine kinase inhibitors (sunitinib, sorafenib, pazopanib), antiangiogenic agents (bevacizumab), and mammalian target of rapamycin inhibitors (everolimus, temsirolimus). These targeted therapies have led to a significant improvement in clinical outcome and are now standard of care treatment for metastatic RCC; however, the 5-year overall survival is still only approximately 20% (6,9,10).

Radioembolization using the beta particle emitter yttrium-90 (^{90}Y) can deliver very-high-dose intraarterial radiation brachytherapy, capitalizing on the dual blood supply of the liver and the hypervascularity of most neoplasms. Radioembolization is gaining acceptance as a treatment option for unresectable primary and metastatic hepatic neoplasms, including metastases from colorectal, neuroendocrine, and breast carcinomas; melanoma; and cholangiocarcinoma (11,12). RCC does not commonly cause liver-dominant metastasis and is known to be resistant to radiation, requiring doses too high to apply to the liver (13). However, metastatic RCC lesions are typically hypervascular owing to overexpression of hypoxia-inducing factor-1α and other downstream genes regulated by it (14). Tumor hypervascularity may allow for more effective concentration of injected microspheres and resultant delivery

Iodinated Contrast Used, Preparatory Angiography/ Treatment (mL)	Laboratory Toxicities Baseline/after Treatment (CTCAE-NCI Grade)			Clinical Toxicities (CTCAE-NCI Grade)		Best Tumor Response (mRECIST)
	Creatinine	Alkaline Phosphatase	Bilirubin	Fatigue	Nausea/Vomiting	
93/52	1/0	0/1	1/0	1	0	CR
85/82	1/1	0/0	1/0	1	0	CR
117/25	1/1	0/0	0/0	1	0	CR
43/25	1/2	2/1	1/0	1	0	?PD*
105/35	2/1	1/1	1/1	2	0	NA†
30/35	1/1	0/1	0/0	1	1	PR (−67%)
—/40	1/1	1/1	0/0	0	0	CR
75/80	0/0	1/1	0/0	1	0	PR (−78%)

of a radiation dose greater than what is feasible via external beam treatment. We present our experience with six patients with liver-dominant metastatic RCC refractory to other treatments who were treated by radioembolization.

MATERIALS AND METHODS

Patients

Between March 2006 and December 2010, six patients (four men, two women) with metastatic RCC (all clear cell subtype) underwent eight treatments for liver-dominant metastases. Clinical response data were retrospectively reviewed. All data were handled in compliance with the Health Insurance Portability and Accountability Act.

Patient demographics are provided in **Table 1**. The mean age was 65 years (range 61–69 years). All patients had undergone unilateral radical nephrectomy for local control and developed metastatic disease after resection. All patients had bilobar disease with estimated 15%–60% replacement of hepatic volume and normal hepatic synthetic function. Only one patient underwent biopsy for confirmation of diagnosis. Four of six patients had active extrahepatic metastasis. Three patients received prior treatment

with one targeted agent (bevacizumab, sorafenib, or sunitinib), and two patients received treatment sequentially with two agents. The remaining patient received treatment with only high-dose interleukin-2 and interferon-α. Four of the five patients with extrahepatic disease exhibited extrahepatic response to systemic therapies, but all six patients showed intrahepatic progression. Mean time elapsed between diagnosis of RCC and radioembolization treatment was 29.8 months (range 5–54 months), and mean time elapsed between diagnosis of hepatic metastases and radioembolization was 18.3 months (range 2–54 months). Performance status using Eastern Cooperative Oncology Group criteria was 0 (n = 3), 1 (n = 2), or 2 (n = 1).

Treatment Planning and Dosimetry

A recovery period of 1–2 weeks was advised between the last dose of antiangiogenesis therapy and the treatment planning angiogram to decrease the theoretical risk of bleeding. A mean of 2.5 hepaticoenteric anastomotic arteries per patient required embolization. In addition, two patients underwent consolidation of the hepatic arterial inflow by embolization of variant hepatic arteries (15). No parasitized extrahepatic arteries were prospectively identified. Baseline serum creatinine levels ranged from 0.9–2.2 mg/dL, corresponding to estimated glomerular filtration rates of 31–65 mL/min/1.73 m^2 (mean 47). Carbon dioxide was used adjunctively as contrast medium in three patients to minimize the use of iodinated contrast medium in these azotemic patients with solitary kidneys. A mean of 78 mL of iodinated contrast agent was used for the preparatory angiogram (range 30–117 mL), and a mean of 47 mL was used for the treatment angiogram (range 25–82 mL).

Scintigraphy was performed with injection of 1 mCi of technetium-99m microaggregated albumin (MAA) to calculate lung shunt fraction, to characterize the intrahepatic distribution of injected tracer, and to detect extrahepatic perfusion. A smaller than conventional dose was used to allow for fusion MAA–sulfur colloid imaging (16). Dosimetry was prescribed according to the body surface area formula (11). The median lung shunt was 6.5% (range 4.9%–40.5%).

Radioembolization Treatment Procedure

When patients returned for treatment, embolization of all residual or newly identified collateral hepaticoenteric vessels was performed before administration of the microspheres (17). The median prescribed dose was 1.98 Gbq (range 0.48–2.14 Gbq), and the median delivered dose was 1.89 Gbq (range 0.41–2.03 Gbq). All patients underwent whole-liver resin microsphere (SIR-Spheres, Sirtex Medical, Lane Cove, Australia) treatment in a single session with administration in the proper hepatic artery except for one patient in whom the dose was split between a proper and a large replaced right hepatic artery. All the prescribed doses were successfully administered without reaching stasis of flow. All patients were discharged on the day of treatment without overnight hospitalization and received a 10-day course of corticosteroids, 30-day course of prophylactic proton pump inhibitor, and analgesics and antiemetics if needed.

High lung shunt fractions from arteriovenous shunting were present in two patients. For one patient, the prescribed dose was decreased by 20% as per the manufacturer's recommendations. For the patient with the higher shunt fraction, temporary balloon occlusion of the right and middle hepatic veins was performed, and bland embolization material (Embospheres, 100–300 μm, 300–500 μm, 500–700 μm; BioSphere/Merit Medical, South Jordan, Utah) was administered simultaneously with the radioembolic microspheres through a parallel second microcatheter. No recalculation of shunt fraction was performed (18–20).

Outcome Measures

Hematologic, coagulation, and serum metabolic laboratory tests were obtained at baseline and at 2 weeks, 4 weeks, 8 weeks, and 12 weeks after treatment. Clinical follow-up was obtained at 1 month and 3 months and approximately every 3 months thereafter. Laboratory and clinical toxicities were graded by Common Terminology Criteria for Adverse Events of the National Cancer Institute (version 4.03).

Tumor response on cross-sectional imaging by computed tomography (CT), positron emission tomography (PET)/CT, or magnetic resonance (MR) imaging was evaluated on all surviving patients 2–3 months after treatment and approximately every 3 months thereafter. Tumor response was categorized according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) (21) or the European Organization for Research and Treatment of Cancer criteria for PET for a maximum of four measurable lesions each $>$ 1 cm in diameter (22).

Statistical Analysis

All statistical analyses were performed using commercial software (SPSS v. 17.0.0; SPSS, Chicago, Illinois).

RESULTS

Biochemical and Clinical Toxicity

None of the patients developed gastrointestinal or pulmonary complications after the procedures. Grade 1 and 2 toxicities were encountered in all patients, but there were no grade 3, 4, or 5 toxicities (**Table 1**). Laboratory toxicities resolved in 4–12 weeks in surviving patients, but the two patients who died within 9 weeks experienced toxicities that were sustained until the time of death. Clinical toxicities, mainly fatigue and anorexia, resolved in 2–5 weeks. Three patients started or restarted systemic therapies within 1–6 weeks after resolution of radioembolization toxicities (sunitinib [n = 1], bevacizumab [n = 1], pazopanib [n = 1]).

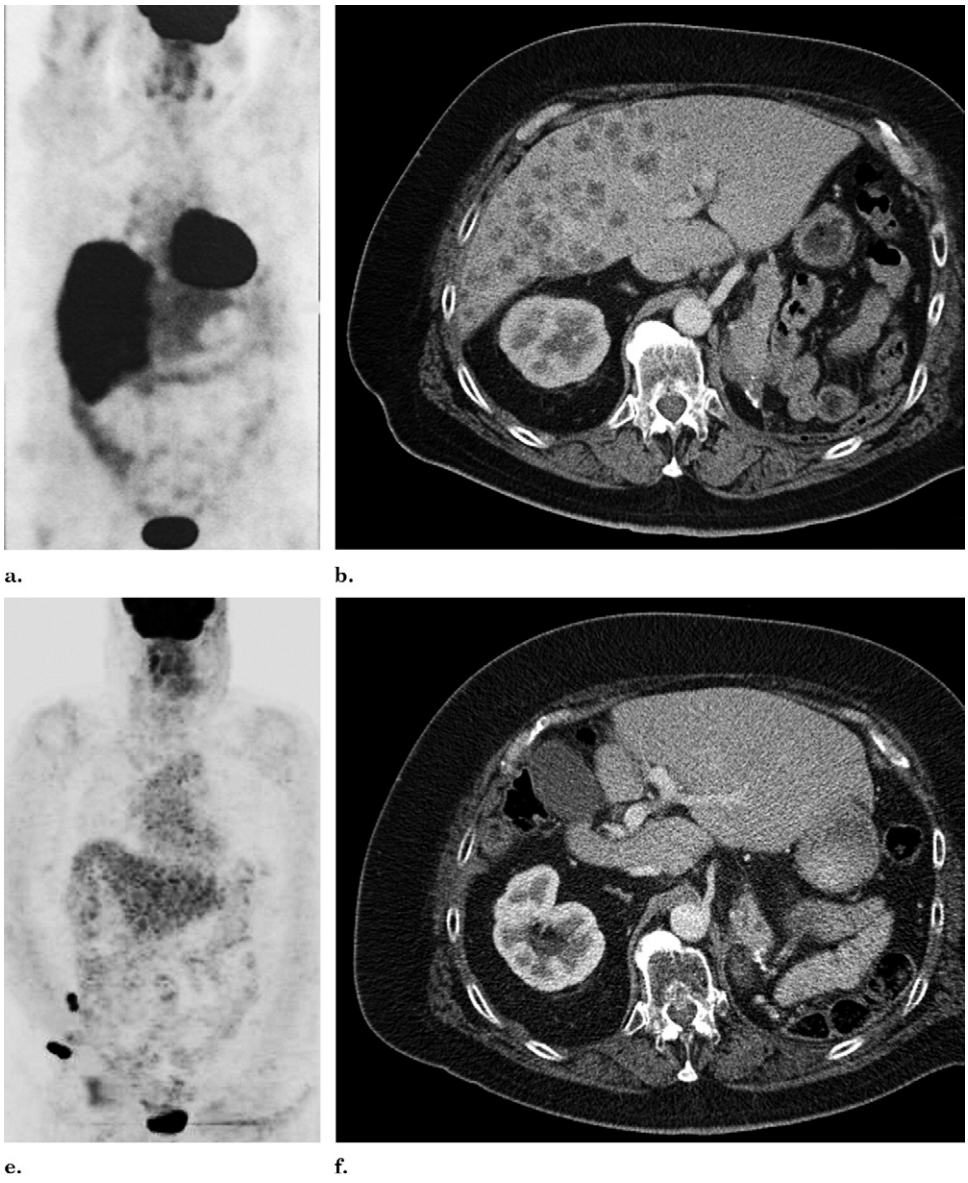

Figure 1. A 63-year-old man underwent left radical nephrectomy and adrenalectomy, followed 1 year later by resection of a retroperitoneal recurrence involving the tail of the pancreas, the spleen, the lymph nodes, and the diaphragm. He developed a lung nodule and metastatic disease replacing the right lobe and segment 4 of the liver 1 year later and underwent radioembolization. Fluorodeoxyglucose-PET scan before treatment (**a**) showed diffuse hypermetabolic activity in segments 4–8. CT scan at the level of the left portal vein (**b**) showed confluent masses with hypoattenuating centers and hypervascular rims. Follow-up PET scan (**c**, available online at *www.jvir.org*) 18 months after treatment showed resolution of hepatic hypermetabolic activity, atrophy of the right lobe, and hypertrophy of the left lobe. A small region of hypermetabolic activity (**d**, available online at *www.jvir.org*) was detected in the medial dome (arrow) 26 months after treatment, prompting a second radioembolization treatment. Follow-up PET scan (**e**) and CT scan (**f**) 13 months after the second treatment (39 months after first treatment) showed no hypermetabolic activity in the liver. Even the celiac axis had diminished in size. The patient was treated with systemic sunitinib starting 5 months before the first radioembolization treatment and throughout the entire follow-up period.

Tumor Response and Imaging Findings

Follow-up imaging was available for five patients; three were followed by CT, one by CT and PET, and one by CT and MR imaging. The mean imaging follow-up period was 25 months (range 2–67 months). Best tumor responses according to mRECIST criteria are listed in **Table 1**. Patient 2 showed a complete response by mRECIST and European Organization for Research and Treatment of Cancer criteria but developed a recurrent lesion at the medial hepatic dome 26 months after treatment that required a second treatment, resulting in a complete response again (**Fig 1a–f** [**c** and **d** available online at *www.jvir.org*]). This patient developed metastatic lesions in the pancreatic head and recurrence in the hepatic dome 23 months after the second treatment, for which he is undergoing pazopanib therapy. Patient 5 underwent chemoembolization (ethiodol,

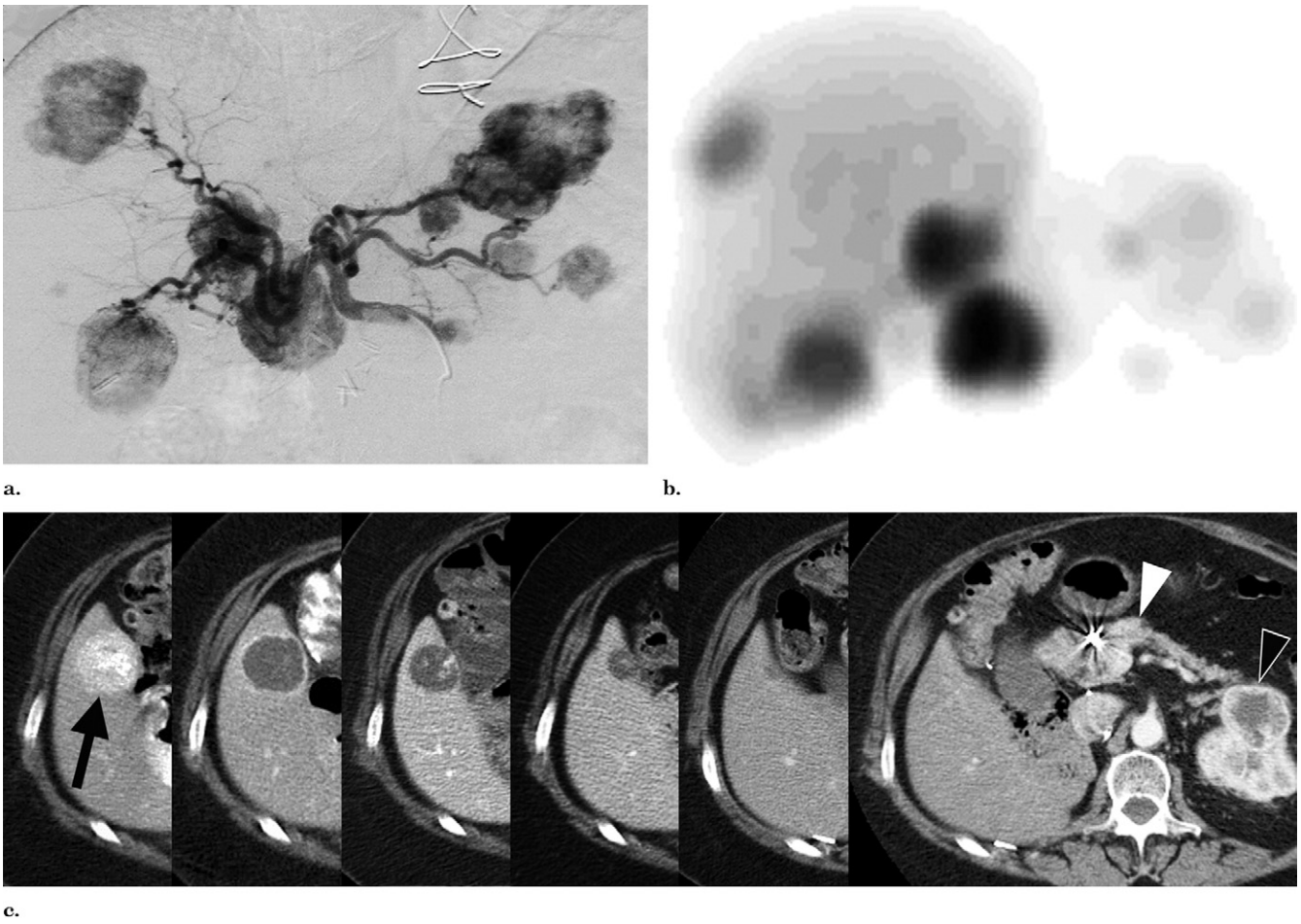

Figure 2. A 61-year-old woman who had undergone right radical nephrectomy with extraction of tumor thrombus from the inferior vena cava developed hepatic metastases 3 years later. The metastases progressed despite systemic sorafenib therapy. Proper hepatic arteriography (**a**) showed numerous hypervascular lesions throughout the liver. Technetium-99m MAA scintigraphy (**b**) predicted high tumor uptake. CT images (**c**) show a representative lesion in segment 5 before treatment (arrow) and at 3-month, 6-month, 19-month, 50-month, and 59-month follow-up. Apparent complete necrosis with pronounced rim enhancement was replaced by an appearance of coarse linear enhancing internal septations, which slowly resolved. Progressive enlargement of extrahepatic metastases in the pancreas (white arrowhead) and contralateral kidney (black arrowhead) were noted, despite systemic therapy with bevacizumab, sunitinib, and pazopanib.

doxorubicin) of an undetected parasitized inferior phrenic artery for residual disease (only 67% decrease in sum of diameters of enhancing tumor tissue). A second segment 7 radioembolization treatment 7 months after the first treatment resulted in complete response by mRECIST criteria. One patient had only an unenhanced CT scan for follow-up imaging at 2 months owing to azotemia; mRECIST criteria could not be applied, but increased overall tumor sizes suggested progressive disease by Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Three (50%) patients had a radiographic complete response, one (16.7%) had an early partial response at 3 months and 6 months, one (16.7%) had probable progressive disease, and one (16.7%) died without imaging follow-up. All three patients with a complete response showed initial rim enhancement after treatment with some lesions showing enhancing coarse internal septations before eventual disappearance of all enhancement, and the patient with progressive disease at the present time is following the same imaging course with a 78% decrease in diameter of enhanced tumor at 6-month follow-up (**Fig 2a–c**).

Survival

Four (66.7%) patients are alive, and two (33.3%) patients have died. Mean and median survivals are 25 months and 12 months so far. One patient died without imaging follow-up 58 days after treatment from rapidly progressive bony metastases and complications of vertebral compression fractures; one patient died of abdominal trauma 61 days after treatment but showed signs of intrahepatic progression before the trauma.

DISCUSSION

Metastatic RCC is one of the most treatment-resistant malignancies, resulting in poor outcomes and a historical me-

dian survival of < 1 year (3,6,10). Frequent sites for metastasis include the lung (50%–60% of patients with metastases), bone (30%–40%), liver (30%–40%), brain (5%), and pancreas (0.3%–3%) (2). Metastasis to the liver is associated with especially poor outcomes (8,23). Most patients are not candidates for resection, and metastases are notoriously refractory to systemic cytotoxic chemotherapy and external beam radiotherapy (3,6). Immunotherapy drugs (ie, cytokines such as interleukin-2 and interferon-α) have proven modestly effective at delaying disease progression but are highly toxic (7,8). Better results are now achieved with therapies targeted against angiogenesis, tyrosine kinases, or mammalian target of rapamycin, which have led to significant improvements in survival. However, the objective response rates are low, and dose-limiting toxicity is high (6,9,10). Regardless of the treatment modality, the unique microenvironment of the liver may compromise the efficacy of systemic therapies for treatment of hepatic metastases.

Various hepatic locoregional therapies for metastatic disease are available, but only a few have been applied to metastatic RCC. Thermal and chemical ablation (24) and stereotactic radiosurgery (25) are technologies applicable only to patients who have limited number and size of metastatic foci. For patients with liver metastases that are too large, too numerous, or spatially inaccessible, hepatic arterial infusion or chemoembolization may be more appropriate. The largest published study described 22 patients with RCC metastatic to the liver treated by chemoembolization using lipiodol, mitomycin C, gemcitabine, and degradable starch microspheres (26). Partial responses by RECIST criteria were achieved in 13.7% of patients, and stable disease was achieved in 59%. However, mean and median survivals from the start of chemoembolization were only 10 months and 6.6 months. Similarly, hepatic arterial infusion of immunotherapy (interferon-α, activated monocytes, or interleukin-2) appears to have very limited benefit, with only one patient of three treated surviving > 3 months (27).

Despite its known resistance to radiation, metastatic RCC may be a good target for radioembolization because its typical hypervascularity allows for very high intratumoral accumulation of microspheres. Conventional radiation dose limitations were developed in the context of external beam radiotherapy and may not be pertinent in this scenario (13). Early attempts at systemically administered biochemically selective radionuclide treatment of metastatic RCC targeting the G250 antigen were unsuccessful, with only a 6% response rate (28). The selectivity of radioembolization differs in that it is spatial and vascular rather than biochemical. The severe atrophy of the right lobe of one of our patients (**Fig 1f**) illustrates how pronounced intrahepatic flow differentiation can be in the presence of hypervascular tumors.

Our results show that radioembolization may be an effective option for treating patients with hepatic involvement of metastatic RCC, with an acceptable overall toxicity profile and promising tumor response and overall survival. However, the early death of two patients in our cohort emphasizes the importance of patient selection and the finite window of opportunity for potential benefit. Patients with hepatic metastases may also have extensive extrahepatic disease, and differential growth rates and morbidity from hepatic and extrahepatic metastases are difficult to calculate and even more difficult to predict. Temporarily withholding systemic treatment during and after radioembolization treatment may allow unrestricted growth of extrahepatic tumors. Our study was limited by small number of subjects and retrospective analysis, so these issues need to be clarified in larger treatment cohorts and future trials. In addition, our patients were treated an average of 18 months after diagnosis of hepatic metastases, suggesting a possible selection bias for relatively indolent or responsive disease.

In conclusion, our initial experience of treating patients with hepatic involvement of metastatic RCC refractory to other types of treatment shows that ^{90}Y radioembolization appears to be a safe and effective option with promising tumor response and survival outcomes in selected patients.

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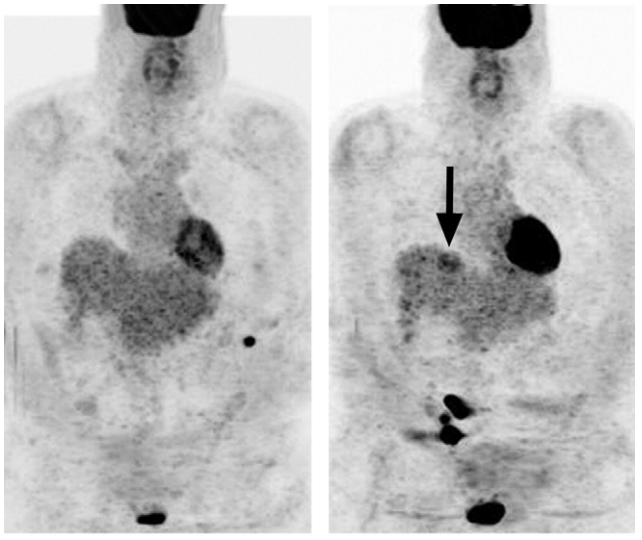

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Figure 1.