

Radioembolization versus Standard Care of Hepatic Metastases: Comparative Retrospective Cohort Study of Survival Outcomes and Adverse Events in Salvage Patients

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ABSTRACT

Purpose: To retrospectively evaluate the safety and survival of patients with chemotherapy-refractory liver metastases treated with yttrium-90 (^{90}Y) resin microspheres, and to compare survival in this patient group versus survival after standard/supportive care to assess whether radioembolization contributes to survival gains in the salvage setting.

Materials And Methods: While 339 patients with chemotherapy-refractory liver metastases underwent ^{90}Y microspheres radioembolization at a single institution between 2006 and 2011, 51 patients were referred back to their treating physician for conservative treatment or best supportive care. Adverse events were assessed at the time of treatment and at 1 and 3 months after treatment. Overall survival (OS) was calculated by the Kaplan–Meier method for the radioembolization cohort (as a whole and according to two subcohorts: patients with colorectal primary cancer and patients with all other primary cancers, eg, breast or neuroendocrine) and the standard-care cohort.

Results: The median OS after ^{90}Y radioembolization (339 patients) was 12.0 months, versus 6.3 months for the standard-care cohort (51 patients; $P < .001$). The median OS times for the two subcohorts were 11.9 months and 12.7 months, respectively. At the 3-month follow-up, the incidence of more serious adverse events was low, with 11 cases (3%) of ulceration, 10 cases (2.9%) of radiation-induced liver disease, and six complications (1.8%) involving the gallbladder (eg, cholecystitis).

Conclusions: The present study suggests that radioembolization shows promise as an effective and safe treatment for patients with chemotherapy-refractory hepatic metastases and improves overall survival in a select population of patients in a salvage setting compared with best supportive care alone.

ABBREVIATIONS

CRC = colorectal cancer, ECOG = Eastern Cooperative Oncology Group, EHD = extrahepatic disease, HR = hazard ratio, OS = overall survival, RF = radiofrequency

Despite advances in systemic chemotherapy and biologic agents, liver metastases continue to present a life-limiting prognosis for patients with colorectal cancer (CRC) (1,2).

The liver is a common site of malignancies, the most common being metastatic from other primary tumors such as gastrointestinal tumors, CRC, neuroendocrine tumors,

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breast cancer, and pancreatic cancer (1). Secondary liver tumors have historically been managed by using systemic chemotherapy and/or surgical interventions (3). Regardless of the origin of metastatic lesions, they are associated with a poor prognosis, except for a limited number of patients who are suitable for surgical resection or ablation. Overall, only 10%–20% of patients who are diagnosed with hepatic metastases from CRC or other primary tumors are eligible for surgical resection (4,5). Modern chemotherapy regimens combined with biologic agents have substantially improved metastatic CRC median survival rates (currently ranging from approximately 12.8 to 24 mo) (6–9), and an increasing number of patients are able to undergo resection after neoadjuvant therapy (8). However, the recurrent nature of tumors such as metastatic CRC, particularly in the liver, remains a life-limiting factor for the majority of patients with advanced disease (2,10,11), and many patients eventually become insensitive to currently available chemotherapy. For such patients who experience a recurrence of their hepatic tumors after chemotherapy, or for those with low or no chemotherapy tolerance, alternative therapies must be examined. These alternative therapies include transarterial chemoembolization with or without drug-eluting beads, radiofrequency (RF) ablation, cryoablation, radioembolization, and combinations of these. (Chemoembolization with RF ablation is the most commonly combined treatment approach, but radioembolization has also been combined with local ablative therapy.) (12,13). The aim of these treatments and their integration into current treatment modalities is to impact the liver tumor burden to increase the proportion of patients whose disease is suitable for resection, extend the time to hepatic progression, and prolong overall survival (OS) (5).

The role of radioembolization for secondary liver tumors is promising, and according to Riaz et al (3), who conducted a comprehensive literature review of the complications and adverse events that may be associated with radioembolization, it has been shown to be safe and efficacious in patients with CRC, neuroendocrine tumors, or other polychemotherapy-refractory conditions (14–17). Data from randomized controlled trials on radioembolization with various chemotherapy regimens for the first- or second-line treatment of CRC hepatic metastases suggest particularly high tumoral responses and time to progression or progression-free survival (14,15,18). Results from phase II/III prospective clinical trials and retrospective studies also appear to show consistent therapeutic benefits in a salvage setting in patients with chemotherapy-refractory liver metastases, as demonstrated by low toxicity, high tumoral response rates, and increased survival times for a substantial proportion of patients (11,19–23).

In the present study, we report our experience with the use of yttrium-90 (^{90}Y) microspheres in a salvage setting in a population of patients presenting with chemotherapy-refractory liver metastases, primarily from CRC. Survival of this patient population was compared with that of a cohort of patients who received conventional therapy/sup-

portive care alone. The aim of the comparative study was to evaluate whether radioembolization contributes to survival gains in the salvage setting.

We also assessed adverse events at the time of treatment with radioembolization and at 1- and 3-month intervals after treatment for the evaluation of immediate and delayed toxicity to evaluate whether ^{90}Y microsphere radioembolization presents a safe treatment option for patients in a salvage setting who have previously undergone heavy pretreatment with chemotherapy.

MATERIALS AND METHODS

This retrospective study investigating the survival of patients who underwent ^{90}Y microsphere radioembolization was approved by our hospital's institutional review board, and data were supplied by cancer council and cancer registries. Informed consent was obtained from all patients to participate in this retrospective study. Patients entered into the retrospective analysis were all referred to our center for consideration of radioembolization with ^{90}Y resin microspheres (Sirtex Medical, Sydney, Australia). After the initial consultation when informed consent was obtained, patients underwent a preimplantation workup to determine eligibility. When the inclusion criteria had been met, as determined by the workup, the radioembolization procedure was performed, during which each patient received an individually calculated dose of ^{90}Y microspheres. Median survival was calculated from the time of implantation.

From February 2006 to February 2011, 417 patients were referred to our center to have their suitability for radioembolization to treat hepatic metastases investigated. All patients who were referred for evaluation had radiologic evidence of unresectable liver metastases from various primary tumors and no longer qualified for other treatment modalities, such as resection, cryoablation, RF ablation, or transcatheter arterial chemoembolization. Additionally, all patients presented with chemotherapy-refractory tumors, ie, patients had undergone failed multiple lines of chemotherapy with radiologically proven progressive liver disease or were known or anticipated to have a poor response to chemotherapy. Patients who fit these criteria are considered "salvage patients," who have exhausted or are ineligible for other therapies to treat hepatic metastases. Although patients with cholangiocarcinoma and hepatocellular carcinoma were also referred to our center for radioembolization, these cases were excluded from the study because we wanted to examine the effects of radioembolization on hepatic metastases from primary cancers outside the liver. Specific inclusion criteria used to determine patient eligibility for radioembolization at our center are outlined in **Table 1**. These criteria were assessed during the preimplantation workup for radioembolization, which involves laboratory tests, clinical factors, and imaging techniques, as detailed in **Table 1**.

If the inclusion criteria were met, patients returned

Table 1. Inclusion Criteria Considered for Determination of Patient Eligibility for Radioembolization with Yttrium-90 Microspheres**ECOG score ≤ 2**

Child–Pugh class A or B disease

Predicted life expectancy ≥ 3 mo

Salvage therapy

Liver metastases from primary of any origin

No contraindications (eg, renal insufficiency, thrombocytopenia)

Inoperable liver tumors

Sufficient hepatic reserve (bilirubin ≤ 2.0 mg/dL, AST and ALT < 5 times upper limit of normal, albumin > 3.5 mg/dL)Adequate renal function (creatinine ≤ 2.0 mg/dL)Adequate blood count (granulocyte count $\geq 1.5 \times 10^9/L$, platelets $\geq 75 \times 10^9/L$)

Liver-only or liver-dominant disease (evaluated by a recent abdominal CT scan)

Minor intraabdominal lymphadenopathy

Minor lung or bone metastases

Mesenteric angiography results

Delineation of hepatic vasculature with identification of aberrant or collateral vessels

Prophylactic embolization of gastroduodenal, right gastric and other extrahepatic arteries when deemed necessary to protect against nontarget delivery

CT hepatic angiography results

Determination of tumor volume and liver volume (tumor burden $\leq 75\%$ of liver volume)

Hepatic vessel anatomy favorable/additional embolization if extrahepatic perfusion detected

No/limited ascites and no obstruction of bile duct or extensive portal vein thrombosis

Hepatic artery perfusion scintigraphy using technetium-99m–labeled macroaggregated albumin

Identification of any nontargeted flow and percentage of hepatopulmonary shunting

Anticipated lung exposure to yttrium-90 radiation ≤ 30 Gy

Note.—ALT = alanine aminotransferase, AST = aspartate aminotransferase, ECOG = Eastern Cooperative Oncology Group.

7–10 days after the preimplantation workup procedure to undergo infusion of the individually calculated dose of ^{90}Y microspheres. Activity of ^{90}Y -labeled microsphere treatment was measured in GBq and adjusted to tumor volume and lung shunting fraction. Dosages were calculated according to body surface area and ^{90}Y microspheres were administered as described by Salem et al (24). Treatment for bilobar liver disease was performed in the same procedure as a single dose to both lobes of the liver or as a divided dose to the left and right lobes.

After infusion of the ^{90}Y microspheres via a femoral or brachial artery catheter, patients underwent a second nuclear medicine (ie, Bremsstrahlung) scan to validate the distribution achieved by radioembolization within the liver and to ascertain that no nontarget deposition of microspheres into other organs had occurred.

Adverse events were assessed at the time of treatment (0–24 hours) and at 1- and 3-month intervals after treatment. The primary outcome of the present study was OS. Among 417 patients who were assessed for eligibility to receive radioembolization, a total of 339 patients with chemotherapy-refractory liver metastases were considered suitable for radioembolization. Seventy-eight patients did not satisfy the inclusion criteria and were deemed unsuitable for radioembolization for reasons mentioned later. Fifty-one patients were referred back to their treating physician for conservative treatment or continued supportive care on

the basis of variant hepatic arterial anatomy with the potential for deposition of microspheres into the gastrointestinal tract that could not be corrected by embolization, extensive hepatopulmonary shunting with the potential for excess radiation exposure to the lungs (> 30 Gy), or reasons relating to patient consent (eg, refusal of consent or other treatment option chosen). These 51 patients excluded on the basis of hepatic arterial anatomy, lung shunting, refusal of consent, or choice of another treatment option (eg, bevacizumab) were unlikely to represent a patient group with more advanced disease, and were consequently used as a standard-care comparison cohort.

In addition to the 51 patients who would have been suitable for radioembolization except for the factors noted earlier, 27 patients were deemed unsuitable for radioembolization or elected not to proceed as a result of extensive extrahepatic metastases, an Eastern Cooperative Oncology Group (ECOG) score greater than 2, excessive hepatic tumor burden of more than 75%, and/or compromised residual liver function. These criteria are considered relative exclusion criteria for radioembolization that need to be reviewed on a case-by-case basis to evaluate whether they represent an inappropriate risk (25). As these 27 patients likely indicated a group with more advanced disease, they were excluded from radioembolization and referred back to their treating physician for continued supportive care, but were not included in the standard care cohort for analysis.

Table 2. Exclusion Criteria that Determined Patient Ineligibility for Radioembolization

Factor	No. of Pts.	
	Standard-care Cohort	Excluded from Analysis
Extensive extrahepatic disease	—	5
ECOG score of 3	—	3
Hepatic tumor burden > 75%	—	1
Evidence of liver failure		
High-volume ascites	—	2
LFT results outside normal limits	—	15
Lung shunting > 20%	3	—
Portal vein thrombosis	—	1
Variant hepatic arterial anatomy	10	—
Other treatment chosen by patient	38	—
Total	51	27

Note.— Patients deemed unsuitable based on these criteria became part of the standard-care cohort for analysis or were excluded from statistical analysis. ECOG = Eastern Cooperative Oncology Group, LFT = liver function test.

Table 3. Primary Cancers in CRC and Non-CRC Groups on a per-Treatment Basis

Primary Cancer	Treated	
	CRC Group	Non-CRC Group
CRC	224	—
Pancreatic	—	8
Neuroendocrine	—	40
Gastric	—	8
Breast	—	16
Other (eg, melanoma)	—	33
Unknown	—	10
Total	224	115

Note.— CRC = colorectal cancer.

Table 2 summarizes specific exclusion criteria that determined patient ineligibility for radioembolization at our center, as outlined earlier.

Statistical Analysis

For the analysis of the present data, all patients referred to the treatment center became part of the treated cohort or the standard-care cohort with the exclusions noted earlier. Treated cohort patients were further divided into two subcohorts: the primary CRC group and the non-CRC primary cancer group. **Table 3** summarizes the tumor types in each group.

For the overall treated cohort and the subcohorts, survival was calculated on a per-treatment basis and was measured from the date of radioembolization until death or the cutoff date, whichever came first. The cutoff date was the date on which data collection closed for this study (February 23, 2011). For the standard-care cohort, survival was measured from the time patients were consulted at our clinic to assess their potential eligibility for radioembolization until death or the cutoff date. Survival is presented

using the Kaplan–Meier method. The statistics package Analysis of Censored and Correlated Data, version 1.7.6 (Boffin Software, Sydney, Australia) was used to perform the analysis.

RESULTS

Patient Characteristics

The patient characteristics are summarized in **Table 4**. Of note, the median age of the 339 patients in the treated cohort was 67 years (range, 27–90 years), and 206 (61%) were men. The median age for the standard-care cohort patients was 66 years (range, 27–88 y), and 35 (69%) were men. Of all patients treated by radioembolization, 25 received multiple ^{90}Y microsphere treatments (the highest number of treatments for any one patient was four [26]), equating to a total of 364 treatments. For patients who received more than one treatment with radioembolization, only the first treatment was taken into consideration for the data analysis of this cohort. Overall, the median administered activity of ^{90}Y microspheres was 1.8 GBq (range, 0.42–2.55 GBq), with 67% of this cohort receiving a dose divided between lobes.

For the purposes of analysis, the treated cohort patients were compared to the standard-care cohort patients. Analysis of baseline characteristics revealed that there was no statistically significant difference between the two cohorts in all parameters assessed (**Table 4**). In particular, there were no significant differences between the two groups in the presence of extrahepatic disease (EHD) or hepatic tumor burden (**Table 4**).

CRC Group Characteristics

The CRC group included 224 patients with metastatic CRC (median age, 67 y; age range, 27–89 y; 142 men) who underwent 242 treatments with ^{90}Y microspheres. For pa-

Table 4. Patient Characteristics in Radioembolization-Treated and Standard-Care Cohorts

Variable	Patients		P Value
	Radioembolization	Standard Care	
Total	339 (100)	51 (100)	.2
Metastases from CRC	224 (66)	29 (57)	
Age			.98
≤ 65 y	159 (47)	24 (47)	
> 65 y	180 (53)	27 (53)	
Average age (y)	66	66	
Sex			.28
Male	206 (61)	35 (69)	
Female	133 (39)	16 (31)	
Extrahepatic disease			.65
Present	124 (37)	17 (33)	
Absent	215 (63)	34 (67)	
Previous systemic chemotherapy	290 (86)	47 (92)	.2
Previous local liver treatment	87 (26)	9 (18)	.21
Hepatic tumor burden*			.31
≤ 25%	172 (51)	22 (43)	
> 25%	167 (49)	29 (57)	
26%–50%*	134 (39)	17 (33)	
> 50%	33 (10)	12 (24)	

Note.—Values in parentheses are percentages. CRC = colorectal cancer.

* Both patient groups (ie, patients with 26%–50% hepatic tumor burden and patients with more than 50% tumor burden) have been summarized or included, or both, in the group of patients with hepatic tumor burden of more than 25% for analysis purposes.

tients who received more than one treatment with radioembolization, only the first treatment was taken into consideration for data analysis of this cohort. Patients in this subgroup presented primarily with an ECOG score of 0 (85%). Most patients had 0%–25% of liver volume replaced by tumor, presented with bilobar liver disease (87%), and did not have EHD (62%). Patients with concurrent EHD (38%) had minimal disease (eg, solitary lung metastases, bone metastases, or lymphadenopathy). No patients in the CRC group were found to have a lung shunt percentage of greater than 20%; however, nine patients had a lung shunt percentage greater than 10% but less than 20% that required a decrease in the dose of ^{90}Y microspheres. Vessel embolizations were performed in 51% of the CRC group patients so they could receive the ^{90}Y microspheres safely. Sixty-eight percent of this cohort received a split dose of ^{90}Y microspheres; the median activity of all doses administered to the CRC group was 1.8 GBq (range, 0.42–2.55 GBq).

Non-CRC Group Characteristics

The non-CRC group included 115 patients (median age, 65 y; age range, 31–90 y; 64 men) with liver metastases from primary cancers other than CRC. Patients of this cohort underwent 126 infusions of ^{90}Y microspheres; however, only the first treatment was considered for data analysis of patients who were treated more than once. Most patients in the non-CRC group presented with an ECOG

score of 0 (80%). The majority presented with 26%–50% of liver volume replaced by tumor, bilobar liver disease (85%), and no EHD (67%). Patients with concurrent EHD (33%) had minimal disease (eg, solitary lung metastases, bone metastases, or lymphadenopathy). Four patients in the non-CRC group were found to have a lung shunt percentage of greater than 20%, and balloon occlusion of the hepatopulmonary vasculature was successfully performed in these cases. Ten patients had a lung shunt percentage greater than 10% but less than 20% that required a dose reduction. Overall, 44% of patients in the non-CRC group required vessel embolization, and 64% of patients received a split dose of ^{90}Y microspheres. The median activity of all ^{90}Y microsphere doses administered to the non-CRC group was 1.72 GBq (range, 0.5–2.4 GBq).

Survival

At the time of analysis, 201 patients (59%) in the treated cohort had died (134 from the CRC group and 67 from the non-CRC group), and 39 patients (76%) from the standard-care cohort had died. OS was determined for the whole treated cohort and the standard-care cohort, as well as for the treated CRC group and the treated non-CRC group. For the whole treated cohort, the median OS after the first treatment with ^{90}Y microsphere radioembolization was 12.0 months (95% CI, 10.7–14.5 mo). For the standard-care cohort, the median OS was 6.3 months from the time patients were consulted at our clinic to assess potential eligibility for ra-

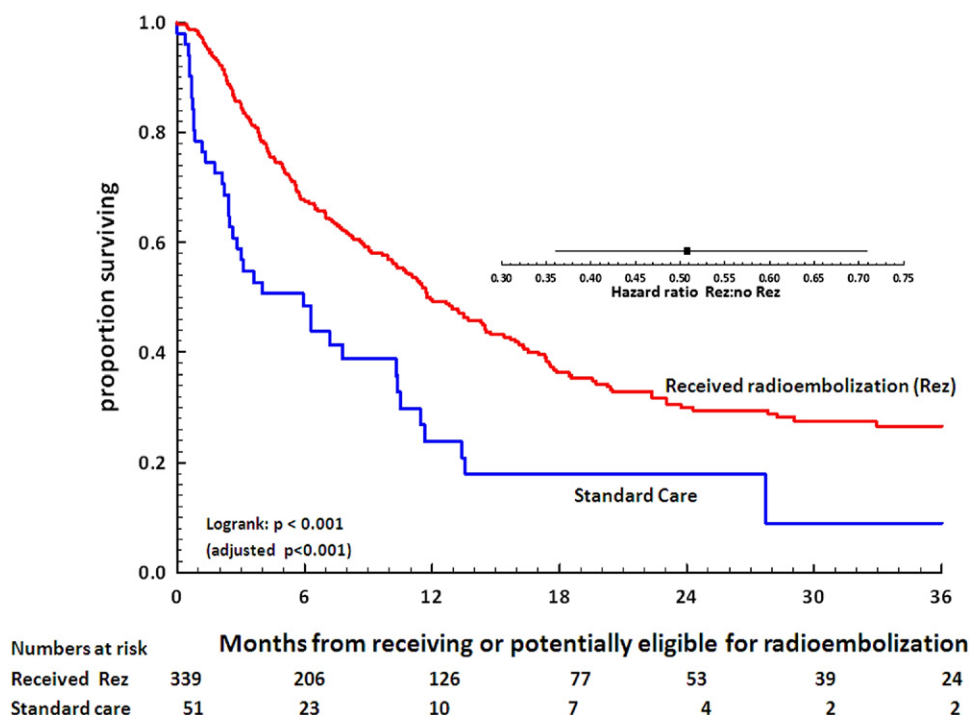


Figure 1. Median OS of all patients treated by radioembolization by Kaplan–Meier method. The median survival for this cohort was 12.0 months calculated from the date of radioembolization. By comparison, the median survival time for the standard-care cohort was 6.3 months calculated from the date patients were consulted at the authors’ institution to assess their potential eligibility for radioembolization. (Available in color online at www.jvir.org.)

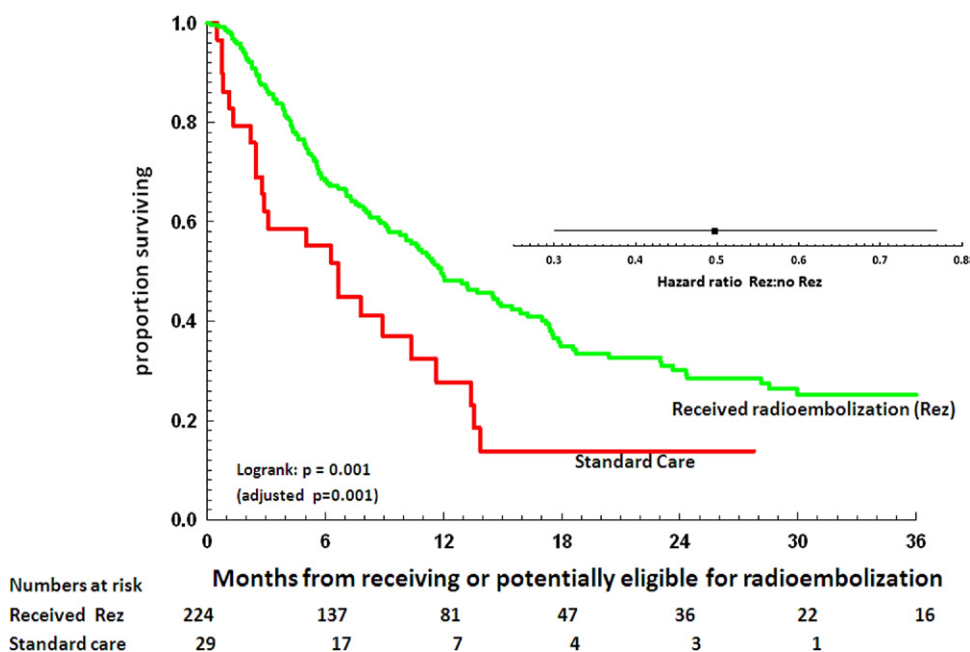


Figure 2. Median OS of the CRC cohort (ie, those with hepatic metastases from CRC) calculated from the date of radioembolization. The survival of this group as demonstrated by the Kaplan–Meier method was 11.9 months. (Available in color online at www.jvir.org.)

radioembolization (95% CI, 2.6–8.9 mo; **Fig 1**). The two cohorts were analyzed by using unadjusted log-rank analysis ($P < .001$). In the CRC radioembolization group, the median OS was 11.9 months (95% CI, 10.1–14.9 mo; **Fig 2**), which was significantly longer than the median OS of 6.6 months

in the standard-care cohort (log-rank test, $P = .001$). The OS in the non-CRC radioembolization group of 12.7 months (95% CI, 8.68–16.35 mo; **Fig 3**) was significantly longer than the OS of 3.6 months in the standard-care cohort (log-rank test, $P < .024$).

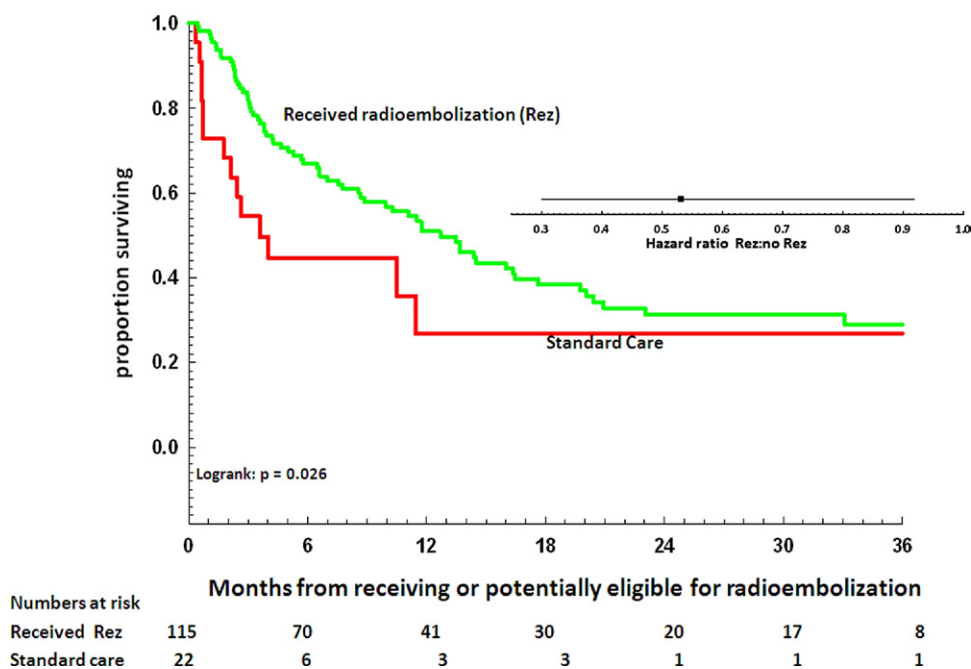


Figure 3. Median OS of the non-CRC group cohort (ie, those whose hepatic metastases were from non-CRC primary cancers) calculated from the date of radioembolization. The survival of this group as demonstrated by the Kaplan-Meier method was 12.7 months. (Available in color online at www.jvir.org.)

On multivariate analysis, radioembolization was a significant predictor of OS for the overall treated cohort ($P = .002$). There was a highly significant reduction of 43% in the hazard of death for patients who received radioembolization (hazard ratio [HR], 0.57; 95% CI, 0.41–0.82). The only other significant prognostic factors that impacted survival in a multivariate model were the extent of hepatic disease ($\leq 25\%$ vs $> 25\%$; HR, 1.82; 95% CI, 1.2–2.7) and previous chemotherapy (HR, 1.29; 95% CI, 1.5–3.5). The primary site of tumor was not a significant predictor of outcome.

Adverse Events

Overall, the incidence and severity of adverse events with radioembolization were low and readily medically manageable. The adverse events can be divided into immediate post-radioembolization (ie, 0–24 h) and delayed complications, which were categorized according to the Common Toxicity Criteria of Adverse Events. Adverse events at the time of radioembolization were minor (grade 1 abdominal pain, nausea, and vomiting) and occurred in 75 patients (22%; calculated based on adverse events occurring 0–24 h after radioembolization only). Grade 1 abdominal pain was the most commonly reported adverse event immediately after radioembolization and occurred in 51 of these patients (15%).

Grade 1 abdominal pain and lethargy were the most commonly reported minor adverse events 1 month after radioembolization. Abdominal pain was reported by 62 patients (18%), and lethargy was reported by 41 patients (12%). The other adverse events reported at the 1-month follow-up were of a moderate nature and included one case (0.3%) of mild (grade 2) radiation-induced liver disease, two cases (0.6%) of

gallbladder complications (grade 2 acalculous cholelithiasis), six cases (1.8%) of grade 2 gastritis, and two cases (0.6%) of grade 2 ulceration. Overall, at the 1-month follow-up after radioembolization, most adverse events were minor in nature and easily medically managed, including the case of radiation-induced liver disease.

At the 3-month follow-up after radioembolization, there were 11 reported cases (3.2%) of ulceration (duodenal or gastric), with three cases being severe (grade 3 ulceration) and eight cases being moderate (grade 2 ulceration); 10 cases (2.9%) of radiation-induced liver disease, with one case being severe (grade 3 radiation-induced liver disease, which was complicated by the development of high obstruction of the common bile duct) and the other cases being moderate (grade 2); and six (1.8%) reported adverse events (all grade 2) involving the gallbladder (eg, cholecystitis). Overall, for this 3-month follow-up period, the incidence of more serious adverse events was as follows: grade 2/3 ulcerations (3.2%), radiation-induced liver disease (2.9%), and gallbladder complications (1.8%). These adverse events were all medically managed, with no deaths within the 3-month follow-up period caused by the radioembolization procedure. There were no known cases of radiation pneumonitis.

DISCUSSION

Earlier studies have suggested that radioembolization with ^{90}Y microspheres represents a valuable treatment option for the management of secondary liver tumors. Therapeutic benefits appear to be greatest when radioembolization is

used as an earlier line of therapy or is combined with chemotherapy (14,15,18,27). Retrospective and prospective clinical studies have shown consistent clinical benefits with the use of radioembolization for chemotherapy-refractory hepatic metastases in the salvage setting, as demonstrated by low toxicity, high tumoral response rates, and increased survival times for a substantial proportion of patients (11,19–23). This is consistent with the findings from the present retrospective analysis, in which radioembolization with ^{90}Y microspheres produced a meaningful median OS of 12.0 months and an acceptable toxicity profile. The main aim of the present investigation was to compare survival outcomes of the patient population treated by radioembolization versus those of a cohort of patients who received conventional therapy/supportive care alone to assess whether radioembolization contributes to survival gains in patients with chemotherapy-refractory liver metastases in a salvage setting. This included patients with chemotherapy-refractory liver metastases that cannot be surgically resected or ablated with curative intent, for whom local/regional liver therapies provide a worthwhile and effective alternative. Patients in a salvage setting commonly are unsuitable for regional therapies such as RF ablation and cryoablation because of the number, morphology, extent, or distribution of the metastatic deposits (22,28). An advantage of radioembolization with ^{90}Y microspheres is that the treatment can be administered to patients with multiple and large-volume liver metastases. Even when used in a salvage setting, radioembolization has been reported to prolong survival and downstage tumors sufficiently to enable potentially curative surgical resection or ablation in some patients (13,23,26,29). Van den Eynde et al (29) and Cosimelli et al (23) reported cases of patients with unresectable liver CRC metastasis refractory to chemotherapy that was downstaged to allow resectability after radioembolization, which resulted in prolonged survival. Hoffmann et al (13) have demonstrated that, in selected patients with extensive hepatic metastases, radioembolization was able to downstage liver metastases to an extent that made subsequent RF ablation feasible in 11% of patients.

The present retrospective analysis suggests that radioembolization with ^{90}Y microspheres to preferentially deliver high-dose radiation to hepatic metastases may improve survival in a select population of patients in a salvage setting compared with standard/best supportive care alone. The median OS time for patients who received radioembolization in the present study was 12.0 months, compared with 6.3 months for patients who received standard care ($P < .001$).

The OS time for patients who received radioembolization in the present study compares favorably with survival times reported in the literature for other radioembolization studies, which range from 4.5 to 12.6 months for CRC and other primary cancers (19–23,28,30,31). Importantly, the present study also demonstrated that, in a contemporary treatment setting, radioembolization with ^{90}Y microspheres

was a significant independent predictor for prolonged OS on multivariate analysis ($P = .002$).

The similar survival outcomes in patients with CRC and non-CRC hepatic metastases (11.9 mo and 12.7 mo, respectively) suggests that the therapeutic effects of radioembolization are independent of the tumor origin and therefore support its role as a universal salvage therapy for hepatic metastases.

Given that the patients treated in the present cohort had undergone several failed lines of chemotherapy, the low rate of grade 2/3 adverse events at 3-month follow-up suggests that, despite the presence of hepatic parenchyma that had been heavily pretreated with chemotherapy, radioembolization is a safe treatment option with an acceptable low toxicity profile. Overall, the incidence of adverse events after radioembolization remained low, and adverse events were easily medically manageable. The majority of toxicities and side effects reported with radioembolization in the present study were relatively minor grade 1 gastrointestinal symptoms, including nausea, abdominal pain, and vomiting with lethargy. The small number of more serious adverse events after radioembolization treatment (eg, ulceration, radiation-induced liver disease, gallbladder complications) was comparable to the numbers reported by other groups that used ^{90}Y microspheres. The incidence of ulcerations (duodenal or gastric) in the literature ranges from 4% to 15% (3,13,18–22,28), which is in line with the number reported in the present study (3.2%). Gastric and duodenal ulceration associated with radioembolization treatment are most likely caused by inadvertent deposition of microspheres in the gastrointestinal tract through collateral vessels. In the present series, 10 patients (3%) developed radiation-induced liver disease after radioembolization, which is consistent with the 1%–10% incidences previously reported in the literature (3,19,28,32). In our institution, all these adverse events were able to be medically managed, with no deaths caused by the radioembolization procedure occurring within the 3-month follow-up period.

There are a number of limitations to the present study. This was a nonrandomized, retrospective investigation, and the findings ideally should be confirmed by a randomized prospective study. The treatment cohort was also a heterogeneous population, which limits the ability to generalize the findings. However, radioembolization treatment in similarly heterogeneous patients has been previously reported to provide survival benefits (17,20,22,30).

Despite these limitations, the results of the present study regarding survival in patients in whom other forms of treatment had been exhausted are encouraging. The median OS time for patients who received radioembolization in the present study of 12.0 months is superior to survival times reported in the literature for patients with metastatic CRC refractory to standard chemotherapy who received third-line agents (33,34). To date, we are aware of no substantial effective salvage chemotherapy regimens reported for progressive or relapsed advanced CRC, and radioembolization is likely to be better in inducing tumor response (11).

Consistent with previous studies in smaller proportions of patients in a salvage setting, our present research with large patient numbers confirms the acceptable safety profile of ^{90}Y microsphere embolization and the potential of this treatment to prolong survival of a substantial proportion of these patients.

In summary, the present study supports the findings that the use of ^{90}Y microspheres provides therapeutic benefits in the salvage setting for secondary liver tumors from any primary cancer, and suggests that radioembolization imparts a positive effect on the OS of patients in a salvage setting. Several studies have demonstrated the efficacy of ^{90}Y radioembolization for the treatment of liver metastases in chemotherapy-refractory disease (11,19–23). However, there is a paucity of literature comparing the outcomes of patients who were treated with radioembolization versus those who received conservative treatment or best supportive care. The present study, with a very strong cohort size, contributes to the provision of such data, and suggests that radioembolization contributes to survival gains in the salvage setting compared with best supportive care alone. Radioembolization with ^{90}Y microspheres in a salvage setting warrants increased use, as it is a therapy that appears to provide survival benefits available to patients who would otherwise have few treatment options and a poor prognosis.

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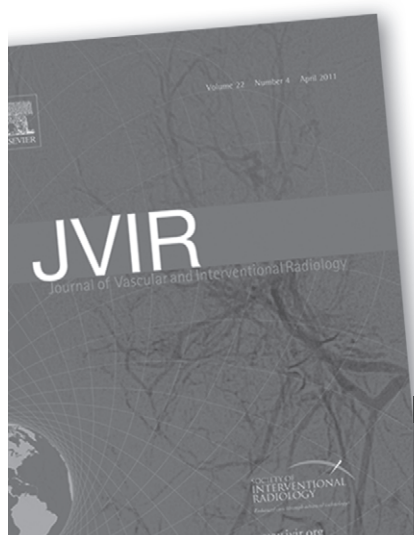
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